An Overview of Liver Directed Locoregional Therapies

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KEYWORDS

• Liver metastasis • Uveal melanoma • Cutaneous melanoma • Mucosal melanoma
• Systematic review • Surgery • Local therapy • Liver directed therapy

KEY POINTS

- A minority of patients diagnosed with melanoma liver metastasis are eligible for local therapy with curative intent (approximately 5%).
- For cutaneous melanoma liver metastasis, systemic therapy with immune checkpoint inhibition or targeted therapy should be considered as first-line treatment of choice.
- Uveal melanoma is the only melanoma liver metastasis type with data to support complete local/surgical intervention (5-year overall survival approximately 30%).
- Aggressive strategies with surgical tumor load reduction and adjuvant therapy in uveal melanoma have not been shown to improve survival.
- No recommendations for any liver-directed regional therapy in the treatment of mucosal melanoma liver metastasis can be made.

INTRODUCTION

Besides the skin, malignant melanomas also can originate within the uveal tract and from mucosal surfaces.[1,2] Malignant melanoma of cutaneous, uveal, and mucosal origin should be regarded as separate entities, each with distinct biology, epidemiology, and disease characteristics.[1,2] Of the malignant melanomas, cutaneous melanoma is the most common (227/1,000,000/y [Fig. 1A]). When cutaneous melanoma

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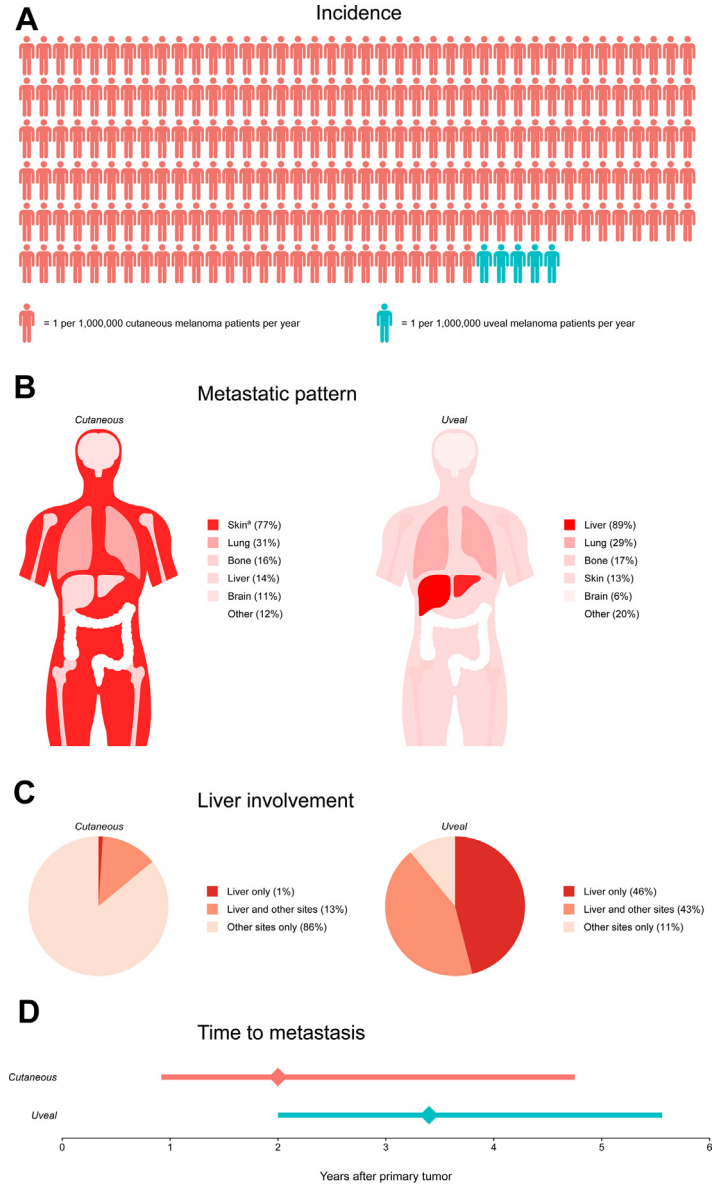

Fig. 1. (*A*) Incidence of cutaneous melanoma and uveal melanoma in the United States. (*B*) Metastatic pattern of cutaneous[3] and uveal[5] melanoma (*C*) Degree of liver involvement in metastatic cutaneous[3] and uveal[5] melanoma. (*D*) Time to metastasis in cutaneous[4] and uveal[6] melanoma. The diamond shape represents the median and the line represents the corresponding interquartile range. [a] Including subcutaneous tissue and regional lymph nodes.

metastasizes, it most often (77%) is to the locoregional skin and approximately 14% to the liver (**Fig. 1**B).[3] Liver metastases from cutaneous melanoma almost always are seen in combination with metastases at other sites (13%) and only rarely are confined to the liver (1% [**Fig. 1**C]).[3] The median time to metastasis of cutaneous

melanoma is 2 years (Fig. 1D).[4] Compared with cutaneous melanoma, uveal melanoma is rare (5.1/1,000,000/y [Fig. 1A]). Uveal melanoma often metastasizes to the liver, which is involved in 89% of patients with metastatic uveal melanoma and represents the only site of metastasis in 46% (Fig. 1B, C).[5] The median time to metastasis of uveal melanoma is 3.4 years (Fig. 1D).[6] If uveal melanoma is rare, mucosal melanoma is extremely rare (2.3/1,000,000/y).[2] Mucosal melanoma has a metastatic pattern more comparable to cutaneous melanoma, with the lung the most frequent metastatic site (40%).[7] Metastases in the liver are seen in approximately 36% of metastatic mucosal melanoma patients, with 26% of patients presenting with liver-only metastases.[7] The median time to metastasis of mucosal melanoma is 3.5 years.[8] This article provides a systematic review (Fig. 2) of all liver-directed locoregional therapies, including surgical resection for melanoma liver metastases (MLMs), and briefly discusses current efficacy of systemic therapy in order to aid evidence-based clinical decision making in the surgical oncologists' and clinicians' practice.

PARTIAL LIVER RESECTION

Treatment Specifics

The study details, demographics, and treatment specifics of 37 studies investigating surgical treatment of MLMs are reported in Supplementary Data [Table 1].[9–45] Based on 12 studies that reported the complete diagnostic work-up,[12,14,15,21,23,25,26,28,32,35,36,41] a total of 5859 patients were diagnosed with MLMs. Of 5859 patients, 343 patients (6%) diagnosed with MLMs eventually were treated with curative intent resection (Rx). An important reason for patients not undergoing Rx was extrahepatic disease and more extensive liver involvement discovered during surgery compared with preoperative assessments, especially miliary disease in patients with MLMs from uveal origin. Large heterogeneity existed between studies concerning preoperative and postoperative treatment strategies; systemic therapy of any

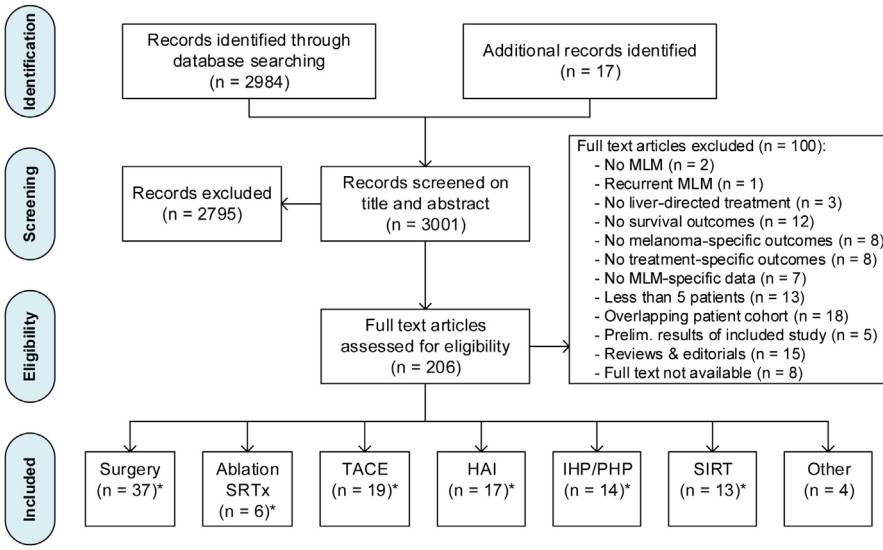

Fig. 2. Overview and flowchart of the article screening and selection process. Prelim, preliminary. * Three studies reported on multiple treatments: one on surgery and HAI, one on surgery and ablation, and one on TACE, SIRT, and IHP.

kind (SYS), hepatic arterial infusion chemotherapy (HAI), and/or transarterial chemoembolization (TACE) were administered both preoperatively and postoperatively across studies. Concurrent ablation was not often utilized (overall 9%, range 0%–31%), whereas major hepatectomy frequently was performed (overall 44%, range 0%–85%).

Outcomes

All 37 studies investigated Rx for MLMs,[9–45] with 7 studies additionally reporting on debulking for MLMs Supplementary Data [Table 2].[11,14,15,25,27,28,43] A total of 947 patients treated with Rx are described, 302 (32%) with MLMs from cutaneous, 489 (52%) with MLMs from uveal, 3 (<1%) with MLMs from mucosal, and 16 (2%) with MLMs from unknown primary origin. In the remaining 137 (14%) patients treated with Rx, MLM origin was not (clearly) reported. The 7 studies reporting on debulking describe a total of 221 patients, 6 (3%) patients with MLMs from cutaneous and 187 (86%) patients with MLMs from uveal origin; MLM origin was not (clearly) reported for 28 (13%) patients. This discrepancy in MLM origin between patients treated with Rx and debulking can be attributed to debulking (with adjuvant HAI/SYS) being standard of care treatment of disseminated liver disease in 2 dedicated uveal melanoma centers, whose series together account for all 187 patients with MLMs from uveal origin treated with debulking. Complete microscopic resection of all MLMs (R0) was achieved in 83% (range 40%-100%) of patients treated with Rx. Perioperative mortality and morbidity after surgical treatment of MLMs (both Rx and debulking) were approximately 2% (range 0%–8%) and 14% (range 0%–36%), respectively. In the patients rendered free of disease after Rx, recurrent disease was observed in a majority of patients (overall 75%, range 40%–100%). Median progression-free survival (PFS) (range of medians) for Rx was 12 (range 5–20) months. Median overall survival (OS) was 26 (range 10–100) months after Rx versus 11 (range 5–18) months after debulking. All but 1 of the studies that reported a median OS of greater than 36 months after Rx were small, highly selected series of less than 20 patients.[14,18,21,26,28,40,44] The study by Groeschl and colleagues,[30] which reported a median OS of 39 months in 31 patients, is a pooled multicenter retrospective analysis of 4 major liver centers, making it highly unlikely that 20 or more patients were treated in a single center. Three of the 4 studies comparing Rx to SYS/best supportive care (BSC) reported improved survival after Rx,[32,35,36] with the study that did not find a survival benefit comparing only 5 patients treated with Rx to 12 treated with SYS/BSC.[13] Similarly, all studies that compared Rx to debulking with or without adjuvant HAI or SYS reported an improved survival for Rx.[11,14,15,25,27,28,43] The only study that directly compared Rx (with HAI), debulking with HAI and SYS/BSC found OS for Rx (with HAI) to be significantly improved compared with the other treatments, with no difference observed between debulking with HAI and SYS/BSC.[15] Four studies directly compared patients with MLMs from cutaneous and uveal origin, with 3 reporting no survival differences between cutaneous and uveal origin[17,33,38] and 1 suggesting improved survival for patients with MLMs from uveal origin.[20] Lastly, 30 of the 37 studies reported long-term survivors (longer than 5 years) after Rx, suggesting possibility of cure.[9,11,12,14–20,23–26,28–31,33,35–45]

Individual patient survival data could be extracted from 14 studies for 99 patients treated with Rx for MLMs and are shown in **Fig. 3**.

ABLATION AND STEREOTACTIC RADIATION THERAPY

The study details, treatment specifics, and outcomes of 6 studies investigating ablation and stereotactic radiation therapy (SRTx) as treatment of MLMs are reported in

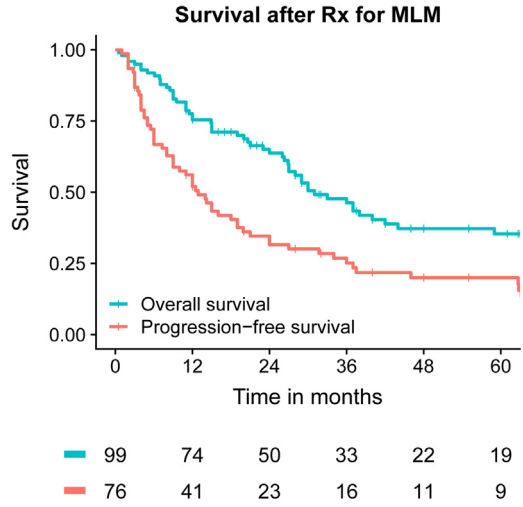

Fig. 3. Kaplan-Meier survival curves for OS and PFS after Rx of MLMs based on individual patient data of 99 patients extracted from 14 studies. PFS data were available for 76 patients.

Supplementary Data [Table 3].[38,46–50] There were 5 retrospective cohort studies and 1 prospective phase Ib/II trial.[50] One study investigated SRTx[49]; the other 5 reported on ablation, all of which treated patients using radiofrequency ablation (RFA)[38,46–48,50]; 2studies also treated patients using cryoablation,[38,48] and 1 study also used microwave ablation.[38] In all the retrospective series, complete treatment of all known (liver) lesions was performed using ablation, SRTx, or Rx (2 patients),[38,46–49] whereas in the prospective phase Ib/II trial by Rozeman and colleagues[50] only 1 liver lesion was treated by RFA and patients subsequently received 4 courses of systemic ipilimumab at varying dosages (0.3 mg/kg, 3 mg/kg, or 10 mg/kg). In this trial it was hypothesized that through an abscopal effect of treating a single MLM with RFA the efficacy of systemic ipilimumab therapy could increase. A total of 134 patients treated with ablation or SRTx are described, 55 (41%) of whom had MLMs from cutaneous and 79 (59%) uveal origin. No treatment-related mortality was reported. Treatment-related morbidity was approximately 20% (range 0%–42%), with the highest morbidity rate of 42% reported in the prospective phase Ib/II trial of RFA plus systemic ipilimumab.[50] Median PFS and OS were 7 (range 3–11) months and 19 (range 11–46) months, respectively. Reported survival was higher in the retrospective studies compared with the prospective phase Ib/II trial of RFA plus systemic ipilimumab. The trial correspondingly concluded that "Combining RFA with ipilimumab 3 mg/kg was well tolerated, but showed very limited clinical activity in uveal melanoma."[50] Akyuz and colleagues[46] directly compared ablation (and laparoscopic Rx in 2 patients) to systemic chemotherapy and found OS to be significantly improved in the patients treated with ablation. Doussot and colleagues[38] directly compared ablation with Rx (see results in Supplementary Data [Table 2] and demonstrated comparable survival outcomes.

TRANSARTERIAL CHEMOEMBOLIZATION

The study details, treatment specifics, and outcomes of 19 studies investigating TACE as treatment of MLMs are reported in Supplementary Data [Table 4].[51–69] There were

15 retrospective cohort studies,[51–53,56,57,59–66,68,69] 2 prospective cohort studies,[55,67] 1 pilot study[58] and 1 prospective phase II trial.[54] The most common chemotherapeutic agent used was cisplatin, which was used in 10 studies,[51–53,56–60,68,69] 2 of which combined cisplatin with doxorubicin and mitomycin C,[56,69] another combined cisplatin with dacarbazine,[53] and 1 study used either fotemustine or cisplatin.[59] Of the other 9 studies, 3 used mitomycin C,[55,62,63] 1 of which combined mitomycin C with doxorubicine[63]; 2 used 1,3-bis(2-chloroethyl)-1-nitrosourea (BCNU)[54,65]; and either fotemustine,[61] drug-eluting beads loaded with irinotecan (DEBIRI),[64] CPT-11,[66] or drug-eluting beads loaded with doxorubicin (DEBDOX)[67] was used in the remaining 4 studies. TACE was combined with SYS in 2 studies,[52,66] and 1 study combined TACE with HAI in 10 patients.[60] In total, 591 patients are described who underwent treatment with TACE for MLMs, a great majority of whom had MLMs of uveal origin (n = 539 [91%]), with only 52 patients (9%) with MLMs from cutaneous origin. Treatment-related mortality and morbidity were approximately 2% (range 0%–7%) and 28% (range 0%–67%), respectively. Response was seen in approximately 28% of patients (range 0%–67%). The 3 studies that reported a response rate of greater than 50% all treated 20 patients or fewer.[53,58,67] Two of these studies used cisplatin,[53,58] and 1 study treated patients with DEBDOX.[67] One study described 14 patients treated with DEBIRI and reported a response rate of 0%.[64] Median PFS and OS were 4 (range 2–9) months and 9 (range 5–28) months, respectively. Two studies directly compared TACE with SYS and reported no discernible survival difference between treatments.[52,64] Valpione and colleagues[66] retrospectively compared TACE with CPT-11 combined with SYS to "other first line regimens" and found a marginally improved OS for TACE ($P = .050$).

HEPATIC ARTERIAL INFUSION CHEMOTHERAPY

The study details, treatment specifics, and outcomes of 17 studies investigating HAI as treatment of MLMs are reported in Supplementary Data [Table 5].[27,70–85] There were 9 retrospective cohort studies,[27,71,76,77,79–81,83,84] 2 prospective pilot studies,[70,73] 5 prospective phase (I and) II trials,[72,74,75,78,85] and 1 randomized controlled trial (RCT).[82] Fotemustine was the most common drug and was used in 8 studies,[73,74,76–78,80,82,83] including the RCT.[82] One phase II trial combined fotemustine with systemic interferon alfa (IFN-α) and interleukin-2 (IL-2).[74] Another phase II trial combined fotemustine with dacarbazine followed by sequential adoptive cell therapy (ACT), systemic IL-2, and granulocyte-macrophage colony-stimulating factor (GM-CSF).[78] Three studies treated patients intra-arterially with cisplatin,[72,75,79] 1 combined with bland embolization[75] and another with vinblastine and dacarbazine.[79] Melphalan was used in 2 studies,[81,84] dacarbazine alone in 1,[70] and there was 1 phase I/II trial that used nab-paclitaxel.[85] For 2 studies, the drugs were not specified (including 1 conference abstract).[27,71] A proportion of the patients treated with HAI also underwent debulking in 2 studies.[27,76] In total, 483 patients treated with HAI for MLMs are described. Primary melanoma origin was cutaneous for 39 patients (8%), uveal for 415 patients (86%), mucosal for 5 patients (1%), and unknown for 7 patients (1%). For 17 patients (4%), primary melanoma origin was not reported. Treatment-related mortality and morbidity were 2% (range 0%–21%) and 25% (range 13%–38%), respectively. The study with the highest mortality (21%) reported no procedure-related morbidity within the 14 patients treated; however, 3 patients died within 30 days.[84] The response rate for HAI was 21% (range 7%–38%). The study with the highest response rate (38%) treated 8 patients with intra-arterial cisplatin, of which 3 responded.[72] Contrastingly, only 9 of the 86 patients (11%) randomized to HAI

with fotemustine responded in the RCT (11%).[82] Median PFS and OS were 6 (range 3–9) months and 13 (range 3–21) months, respectively. One prospective phase II trial directly compared HAI with fotemustine and systemic IFN-α and IL-2 to SYS with fotemustine, IFN-α, and IL-2 and found no survival difference between treatments.[74] The only RCT randomized 171 patients to either HAI with fotemustine (n = 86) or SYS with fotemustine (n = 85) and did not find an improvement in OS, despite a better response rate and PFS observed in the patients treated with HAI.[82] Accrual was stopped prematurely based on a futility OS analysis.[82]

ISOLATED HEPATIC PERFUSION AND PERCUTANEOUS HEPATIC PERFUSION

The study details, treatment specifics, and outcomes of 14 studies investigating hepatic perfusion as treatment of MLMs are reported in Supplementary Data [Table 6].[69,86–98] There were 11 retrospective cohort studies,[69,88–94,96–98] 1 prospective phase I trial,[86] 1 prospective phase II trial,[87] and 1 phase III RCT.[95] All studies used melphalan as active drug in their perfusate.[69,86–98] One phase I trial combined melphalan with cisplatin[86] and there was a phase II trial that combined melphalan with tumor necrosis factor alfa (TNF-α).[87] In 1 retrospective series, either cisplatin or TNF-α also was added in a small number of patients.[93] Hepatic perfusion was performed operatively (ie, isolated hepatic perfusion [IHP]) in 7 studies[86–91,94] and percutaneously in the other 7,[69,92,93,95–98] including the phase III RCT.[95] In total, 364 patients treated with IHP/percutaneous hepatic perfusion (PHP) for MLMs are described. Origin of MLM was cutaneous in 20 patients (5%), uveal in 331 patients (91%), mucosal in 2 patients (<1%), and unknown in 1 patient (<1%). Primary melanoma origin was not reported for 10 patients (3%). Treatment-related mortality and morbidity were 6% (range 0%–30%) and 33% (9%–68%), respectively. The highest treatment-related mortality was observed in a small phase I trial of 10 patients published in 1994, of whom 3 died (30%).[86] Another retrospective cohort study of 27 patients reported a mortality rate of 22% (6 patients).[89] The response rate for IHP/PHP was 53% (range 10%–60%). Apart from 1 phase I trial with a response rate of 10%,[86] all other 11 studies that reported response had a response rate greater or equal to 33%.[87–93,95–98] Median PFS and OS were 8 (range 5–11) months and 11 (range 5–27) months, respectively. All 3 studies that reported a median OS of 20 months or longer were retrospective cohort studies.[69,93,98] One phase II trial directly compared IHP with melphalan to IHP with melphalan and TNF-α and reported a longer duration of response in the TNF-α group.[87] The randomized phase III trial included 93 patients, which were randomized to either PHP with melphalan (n = 44) or best alternative care (n = 49).[95] Despite a longer (hepatic) PFS and higher response rate in patients treated with PHP, no difference in OS was observed.[95] The investigators contribute this lack in OS difference to the 57% of patients in the best alternative care group that crossed over to PHP with melphalan after progression after their initial treatment.[95]

SELECTIVE INTERNAL RADIATION THERAPY

The study details, treatment specifics, and outcomes of 13 studies investigating selective internal radiation therapy (SIRT) as treatment of MLMs are reported in Supplementary Data [Table 7].[69,99–110] There were 12 retrospective cohort studies[69,99–107,109,110] and 1 prospective phase II trial.[108] All studies performed SIRT with yttrium 90 (Y90)-labeled microspheres. Two studies combined SIRT Y90 with systemic immunotherapy.[107,109] In total, 287 patients treated with SIRT Y90 for MLMs are described, which were of cutaneous origin in 23 patients (8%), of uveal origin in 259 patients (90%), of mucosal origin in 3 patients (1%), and the origin was unknown for

2 (<1%). Treatment-related mortality and morbidity were 2% (range 0%–13%) and 13% (range 0%–32%), respectively. The study that reported the highest mortality rate of 13% was a small retrospective cohort study with only 8 patients, of whom 1 died.[103] The response rate to SIRT Y90 was 26% (range 0%–77%). The 2 studies that reported exceptionally high response rates of 62%[101] and 77%[99] were both small retrospective series with 13 or fewer patients. Contrastingly, the largest retrospective series of 71 patients reported a response rate of 8%.[104] Median PFS and OS were 5 (range 1–15) months and 11 (range 4–26) months, respectively. The longest median OS of 26 months was observed in a small retrospective series of 12 patients treated with SIRT Y90 and systemic immunotherapy.[109] That same study also analyzed 12 patients who received only SIRT Y90 and reported an improved survival in the patients treated with SIRT Y90 plus systemic immunotherapy.[109] Two retrospective studies directly compared SIRT Y90 to SYS[106] or BSC.[105] Although both reported improved survival for SIRT Y90, the patients receiving SYS or BSC were treated in the same centers during the same period and, therefore, by default were not considered for or refused SIRT Y90.[105,106] Furthermore the patients treated with SIRT Y90 or BSC all were patients with progressive disease after prior SYS.[105] The prospective phase II trial compared SIRT Y90 in treatment-naïve patients (n = 23) to SIRT Y90 in patients with progressive disease after immunoembolization.[108] A difference in neither response rate nor survival was observed between the 2 groups. The trial, therefore, concluded that SIRT Y90 is safe and effective as either first-line or second-line treatment of MLMs of uveal origin.[108]

OTHER LOCOREGIONAL THERAPIES

The study details, treatment specifics, and outcomes of 4 studies investigating other locoregional treatments for MLMs are reported in Supplementary Data [Table 8].[111–114] There are no series about liver transplantation for unresectable MLMs, although an open nonrandomized clinical trial investigating liver transplantation for uveal MLMs has been registered (NCT01311466, clinicaltrials.gov) and reportedly recruited 2 patients from 2011 to 2017.

SYSTEMIC THERAPY

Systemic Therapy in Metastatic Cutaneous Melanoma

Until recently, dacarbazine was the chemotherapeutic agent used most often. Large clinical trials investigating dacarbazine monotherapy reported response rates of approximately 7%, with median survival times of just 6 months.[115,116] Combining dacarbazine with other agents did not improve clinical response or survival.[117–119] In 2010, ipilimumab, a CTLA-4 inhibitor, was proved to prolong survival in previously treated patients with metastatic cutaneous melanoma, with a response rate of 11% and a median survival of 10 months.[120] Besides prolonging survival, treatment with ipilimumab also produced durable responses with long-term survivors; pooled analysis of 1861 patients treated with ipilimumab showed overall survival plateauing at 20% from 3 years on, all the way up to 10 years.[121] In 2014, nivolumab and pembrolizumab, 2 anti–PD-1 antibodies, were approved for the treatment of metastatic melanoma. In a randomized phase III study of 834 advanced cutaneous melanoma patients, pembrolizumab proved superior to ipilimumab in terms of PFS and OS, with less toxicity.[122] Combining CTLA-4 and PD-1 checkpoint inhibitors has proved even more effective. In a randomized phase III trial, 945 patients with unresectable or metastatic cutaneous melanoma were randomized 1:1:1 to either first-line nivolumab, nivolumab plus ipilimumab, or ipilimumab.[123,124] Recent 5-year results demonstrated a striking 5-year PFS and OS for combination therapy of

36% and 52%, respectively, compared with 29% and 44%, respectively, for nivolumab and 8% and 26%, respectively, for ipilimumab.[125] Importantly, reported results are best in the BRAF-mutant patients, with 5-year OS rates of 60% for combination therapy, 46% for nivolumab, and 30% for ipilimumab.[125] Preliminary results for the combination of pembrolizumab and ipilimumab report similar efficacy.[126] Immune checkpoint inhibitors also have proved efficacy in the adjuvant setting, with adjuvant nivolumab demonstrating better performance than ipilimumab in resected stage III or stage IV cutaneous melanoma.[127] Combination therapy, however, again proves superior with recent results reporting a significantly improved 2-year recurrence-free survival of 70% for adjuvant nivolumab with ipilimumab in resected stage IV cutaneous melanoma versus 42% for nivolumab monotherapy and 14% for placebo.[128] In parallel, BRAF inhibitors (dabrafenib, encorafenib, and vemurafenib) and MEK inhibitors (trametinib, binimetinib, and cobimetinib) also have demonstrated considerable efficacy in BRAF-mutated patients with metastatic cutaneous melanoma, which are present in approximately 50%. Similarly to checkpoint inhibitors, BRAF and MEK inhibitors demonstrated superior survival compared with dacarbazine[129] and proved most effective when combined.[130–133] Results may be inferior (cave selection bias) compared with combination immune checkpoint inhibitor therapy, with reported 5-year PFS and OS rates of combined BRAF and MEK inhibitors of 19% and 34%, respectively.[134]

Systemic Therapy in Metastatic Uveal Melanoma

Similarly to metastatic cutaneous melanoma, dacarbazine long has been considered the standard and still is used as comparative treatment in contemporary clinical trials[135,136] Results of dacarbazine in the treatment of metastatic uveal melanoma are poor, with objective response seldom to never observed and a median OS of 9 months in clinical trial populations.[135,136] Several combinations with dacarbazine have been investigated, as well as other (combinations of) conventional chemotherapeutics, and several kinase inhibitors, but none definetively improved efficacy.[135–142] The CTLA-4 checkpoint inhibitors ipilumumab and tremelimumab both have been studied in metastatic uveal melanoma but both did not considerably improve survival; median OS was 7 months for ipilimumab[143,144] and 13 months for tremelimumab.[145] Concerning the combined treatment of nivolumab and ipilimumab, preliminary results report a median OS of 13 months, but final results from phase II studies have yet to be published.[146] A recent meta-analysis has pooled the individual patient data of many of these phase II trials, including several trials investigating liver-directed therapies, in order to create benchmarks for PFS and OS for future trials.[147] In total, individual patient data of 29 trials were included, resulting in a total of 912 patients.[147] Median PFS and OS were 3 months and 10 months, respectively, with a 1-year OS rate of 43%. These outcomes represent the benchmark against which (future) therapies for metastatic uveal melanoma should be gauged.[147]

Systemic Therapy in Metastatic Mucosal Melanoma

There is a high paucity of evidence concerning the systemic treatment of metastatic mucosal melanoma. Only retrospective cohort series and pooled analyses have been published. Reported response rates with (a combination of) dacarbazine-based chemotherapy range from 8% to 26%, with a median OS of 10 months to 12 months.[148,149] In contrast to uveal melanoma, there is evidence to suggest efficacy of immune checkpoint inhibitors in metastatic mucosal melanoma, with a reported response rate of 23% and a median PFS of 3 months for nivolumab monotherapy and 37% and 6 months, respectively, for nivolumab and ipilimumab combination therapy.[150,151] There is as yet no report on OS in these patients.

CONSIDERATIONS

The current body of evidence of liver-directed locoregional therapies for MLMs consists of 106 studies each describing 5 or more patients (see Fig. 2).[9–50,51–71,72–100,101–114] Most were retrospective cohort studies with the majority performed prior to immune checkpoint inhibitor systemic therapy. There currently are 3 prospective RCTs published, which almost exclusively included metastatic uveal melanoma patients.[82,95,114] All 3 RCTs failed to definitively demonstrate a survival benefit of liver-directed regional therapies.[82,95,114] Objectively the best results for any liver-directed therapy were seen when all MLMs were treated using local therapies, either with complete surgical resection or using ablative techniques. Herein, complete removal or ablation of all metastatic disease remains key, because multiple studies showed no discernible clinical benefit after surgical reduction of tumor load and subsequent adjuvant therapy.[11,14,15,25,27,28,43,50] Although many of these patients have recurrence of disease after curative treatment, repeat local treatment has been described and, therefore, should be considered in eligible patients.[152] In the 37 studies investigating surgical treatment of MLMs, 5 reported patients underwent repeat resection or ablation.[12,28,30,36,42] The absence of randomized data comparing complete local therapy remains impeding. All specialized centers performing these complex liver-directed therapies most certainly also perform surgical treatment of MLMs. This makes it highly likely that all patients eligible for complete local therapy for MLMs are by default not included in any of the studies investigating other liver-directed therapies. This selection bias likely overstates results observed for complete local treatment. Malignant melanoma of cutaneous, uveal, and mucosal origin should be regarded as separate entities, each with distinct biology.

Cutaneous Melanoma Liver Metastases

Compared with uveal MLMs, there are few studies that specifically evaluated liver-directed therapies for cutaneous MLMs. Although there are several studies investigating the surgical management, ablation, and radiotherapy of cutaneous MLMs (see Supplementary Data [Tables 1–3]), only 3 studies of other liver-directed therapies either had a majority of patients with cutaneous MLM,[69] or specifically reported results for patients with primary cutaneous melanoma.[60,77] Of these, 1 studied TACE,[60] another studied HAI,[77] and the third evaluated both TACE and PHP.[69] Reported results of these liver-directed therapies are poor compared with combination treatment with ipilimumab and nivolumab.[123–125] Granted, not all patients had metastatic disease or even visceral metastases in the prospective studies investigating checkpoint inhibitors and targeted therapies.[120–126,128–134,153,154] The reported 5-year PFS and OS rates for ipilimumab and nivolumab combination therapy of 32% and 52%, respectively,[123–125] in part achieved in patients with visceral cutaneous melanoma metastases, are however unparalleled compared with previous systemic therapies, liver-directed therapies, and even complete surgical resection (see Supplementary Data [Table 2], Fig. 3). Isolated (resectable) hepatic metastases in cutaneous melanoma are exceedingly rare (see Fig. 1).[3] They are so rare that in principle other metastatic sites always are part of the problem and so in principle systemic therapy always is considered as first-line treatment. Patients with cutaneous MLMs, therefore, always should be referred to a medical oncologist. The most effective systemic treatment of metastatic cutaneous melanoma is combination therapy with ipilimumab and nivolumab and is the treatment of choice in the absence of contraindications for immune checkpoint inhibitor systemic therapy. In some patients, solitary progression may become the target of a surgical salvage approach. If patients with isolated cutaneous

MLMs are considered for surgical resection, adjuvant systemic treatment with immune checkpoint inhibition should be part of the treatment course.[127,128] Future studies are needed to investigate whether the combination of (aggressive) surgical treatment and immune checkpoint inhibition can improve survival further.

Uveal Melanoma Liver Metastases

Studies investigating liver-directed locoregional therapies for MLMs almost exclusively were performed in patients with primary uveal melanoma. This can be attributed to the unique hepatotropic metastatic behavior of uveal melanoma[5] (see **Fig. 1**), with the hepatic metastases a driver of survival and poor results obtained with systemic therapy,[147] which has prompted many liver-directed therapies to focus on this rare disease. Uveal MLMs are the only MLM type with data to support complete local/surgical intervention and might be considered for selective patients in which a complete resection/ablation can be achieved. Herein it is important to recognize that in approximately half of all surgically explored (uveal) MLM patients, complete local treatment proves impossible (see Supplementary Data [Table 1]), meaning large uncertainty lies in a percutaneous approach. Aggressive strategies with combined reduction of tumor load and subsequent adjuvant therapy have not been shown to improve survival.[11,14,15,25,27,28,43] Novel immune checkpoint inhibitors have shown little to no clinical activity in metastatic uveal melanoma, although results of combined ipilimumab and nivolumab still are expected.[146] Despite the consistently higher response rates observed for IHP or PHP,[95] no single liver-directed or systemic therapy has proved superior effectiveness.[147] Treatment decisions in patients with metastatic uveal melanoma not eligible for complete local treatment, therefore, should be based more on a center's own experience and patient preference.

Mucosal Melanoma Liver Metastases

Only 13 patients with MLMs from mucosal origin are described in all 106 studies combined with no single study reporting specific outcomes for these patients. Based on current evidence, no recommendations for any liver-directed regional therapy in the treatment of MLMs from mucosal origin can be made. Although evidence is limited, immune checkpoint inhibitions should be the treatment of choice in metastatic mucosal melanoma, either as first-line treatment or possibly in the adjuvant setting.[150,151]

THE MEDICAL ONCOLOGIST'S PERSPECTIVE

Because the introduction of immune checkpoint inhibition and targeted therapy has significantly improved the survival of patients with advanced cutaneous melanoma, surgical treatment of advanced cutaneous MLMs has become complementary, whereas surgical treatment still is the cornerstone of the treatment of uveal MLMs. In an era of novel systemic therapies, surgical treatment can complement systemic therapy for cutaneous MLMs. In particular, local treatment of cutaneous MLMs can be considered for oligoprogression, which is defined as progressive disease at a limited number of disease sites after an initial response to systemic therapy.[155] Local treatment of oligoprogressive MLMs may eliminate drug resistant clones, thereby achieving stable disease or even complete response. After treatment with immune checkpoint inhibitors, pseudoprogression also can mimic oligoprogression. Pseudoprogression is a phenomenon in which metastases show an increase in size on imaging due to T-cell infiltration, which can be confirmed by a surgical biopsy.[156] On the other hand, surgical treatment may support the efficacy of systemic therapy by

debulking large or symptomatic MLMs. Because low tumor burden, which is reflected by low serum lactate dehydrogenase, is associated with better outcome of patients with cutaneous melanoma during immune checkpoint inhibition,[157] surgical debulking may facilitate tumor response to these drugs.[158] Although the combination of surgical treatment of cutaneous MLMs and immune checkpoint inhibition has not yet been investigated prospectively, surgeons increasingly are consulted to complement systemic therapy with surgical treatment. Because immune checkpoint inhibitors have shown improved OS of greater than 10 years in patients with metastatic cutaneous melanoma,[121,125] treatment is shifting slightly from palliative toward more curative intent. This paradigm shift in the treatment of cutaneous metastatic melanoma requires a multidisciplinary approach, involving experienced radiologists, dermatologists, medical oncologists, radiotherapists, and surgeons.

DISCLOSURE

Authors have nothing to disclose.

SUPPLEMENTARY DATA

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