Intra-arterial perfusion-based therapies for regionally metastatic cutaneous and uveal melanoma

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Locoregional disease remains a challenging problem in cutaneous melanoma and uveal melanoma. Arterial-based chemoperfusion strategies enable regional therapy delivery with minimal systemic toxicity. Herein we discuss intra-arterial therapies for in-transit cutaneous melanoma of the extremity including hyperthermic-isolated limb perfusion and isolated limb infusion. We also discuss open (isolated hepatic perfusion) and percutaneous hepatic perfusion techniques for isolated liver metastases from uveal melanoma. We review the current state of knowledge with respect to indications, procedural techniques, outcomes and expected toxicities for intra-arterial chemoperfusion for locoregional melanoma metastases.

Despite dramatic advances in medical and surgical management of melanoma, locoregional disease remains a considerable problem. Approximately 4–10% of cutaneous melanoma recurrences present as in-transit disease [1–3]. Additionally, as survival improves for patients with widespread metastases, locoregional disease can become a source of significant symptoms. Regional delivery of chemotherapy represents one treatment option for unresectable and symptomatic locoregional cutaneous melanoma.

Uveal melanoma is distinct from cutaneous melanoma in that over 50% of all patients will develop metastases, which may occur several years after treatment of the primary tumor [4,5]. In 80% of cases, metastatic disease is confined to the liver [6–8]. Historically, median survival after diagnosis of metastatic uveal melanoma is 2–9 months [6–8]. Unlike cutaneous melanoma, systemic immunotherapy is minimally effective against uveal melanoma, producing short duration responses in 5–10% of patients [9]. Given its unique presentation and refractoriness to systemic treatment, liver-directed therapies including intra-arterial chemoperfusion offer a targeted approach.

The concept of regional delivery of chemotherapy was first described over six decades ago, propelled by the development of the extracorporeal bypass machine for cardiac surgery and the establishment of effective chemotherapy to treat cancer. A mechanism to deliver higher doses of chemotherapy directly at the metastatic disease while minimizing systemic toxicity, regional chemoperfusion remains an important therapeutic tool today.

Intra-arterial therapies for cutaneous melanoma of the extremity

The upper and lower extremities are well suited for arterial-based therapies given the relative ease of isolating blood flow to and from the affected site. Regional limb therapy is an option for patients with in-transit disease that is limited to the extremity and is too extensive or refractory to simple excision or intralesional therapy. It can also be used as a bridge to surgical resection to render a patient free of disease. When distant disease is present, it may be considered for palliative purposes to treat symptomatic locoregional disease, but does not impact distant foci.

Two intra-arterial infusion strategies exist, both of which isolate circulation to and from an involved extremity, creating a closed circuit with an extracorporeal pump for regional delivery of chemotherapy (Table 1). The mainstay chemotherapeutic agent is L-phenylalanine mustard (melphalan), a cytotoxic agent with unique responsiveness to hyperthermic and acidotic environments [10]. Dosing for extremity infusions is based on limb volume, which can be determined by water displacement or sequential circumferential measurements along the length of the limb [11,12].

Future Medicine

Table 1. Comparison of hyperthermic isolated limb perfusion and isolated limb infusion.

Technical aspect	Hyperthermic isolated limb perfusion	Isolated limb infusion
Technique	Open, surgical vessel cannulation	Minimally invasive, percutaneous vessel cannulation
Flow rate	400–600 cc/min	80–120 cc/min
Temperature	Hyperthermia (>38°C)	Normothermia to slight hyperthermia (37–40°C)
Limb environment during perfusion	Oxygenated, aerobic	Ischemic, anaerobic
Ability to repeat	Difficult to repeat	Easily repeatable

Table 2. Weiberdink grading system for measurement of melphalan-related toxic reactions.

Grade	Clinical signs and symptoms
I	No reaction
II	Slight erythema and/or edema
III	Considerable erythema and/or edema with some blistering; slightly disturbed motility permissible
IV	Extensive epidermolysis and/or obvious damage to the deep tissues, causing definite functional disturbances; threatening or manifest compartment syndrome
V	Reaction which may necessitate amputation

Hyperthermic isolated limb perfusion

Hyperthermic isolated limb perfusion (HILP) was initially described by Creech in 1959 and involves open dissection of the extremity inflow and outflow vessels and isolation using collateral vessel ligation. Large bore cannulas are placed under direct visualization and the limb is occluded by a pneumatic tourniquet above the level of cannula insertion [13]. Regional lymphadenectomy, if indicated, can be performed at the time of vascular dissection. The chemotherapy perfusate is heated, oxygenated and circulated at a high flow rate. The hyperthermic environment increases the cytotoxicity of melphalan, dosed at 10 mg/l, with or without the addition of TNF-α or other experimental agents [10]. TNF-α is not available for use in the USA but is used widely in Europe, Australia and other countries.

The patient is systemically heparinized prior to cannula placement and inflow/outflow occlusion. Chemotherapy is administered with flow of 30–60 ml/l/min for 45–90 min, while continuously monitoring temperature and venous pressures. Systemic leakage is measured using a precordial scintillation probe. After chemoperfusion, the limb is flushed with isotonic solution before releasing the tourniquet and removing access cannulas [13].

Isolated limb infusion

Isolated limb infusion (ILI) was initially described by Professor John Thompson in 1998 as a less invasive alternative to HILP. Vascular access is achieved percutaneously, bypass cannulas are smaller than in HILP, and an anaerobic, acidotic, normothermic environment is maintained [10]. Percutaneous catheters are placed above the most proximal disease but distal to planned tourniquet placement, and the patient is systemically heparinized. The infusion circuit includes a low flow roller pump or three-way stopcock with syringe (hand pump) and a heater. The extremities are also externally heated, routinely achieving 40°C. The synergistic effect of hyperthermia, hypoxia and acidosis increases melphalan cytotoxicity 2.5–3.5-fold [10] Additionally, the low flow rate may provide more uniform drug distribution in target tissues. Drug doses are melphalan 7.5 mg/l for lower and 10 mg/l for upper extremity and actinomycin-D (Dactinomycin) at 75–100 mcg/l [14]. As in HILP, the limb is flushed with isotonic solution prior to tourniquet release.

Peri-procedural complications & adverse events

Safety considerations with both HILP and ILI include complications of vascular access, limb toxicity and systemic chemotherapy delivery [15]. Vascular access problems can include bleeding, hematoma formation, pseudoaneurysm, thrombosis or embolization or vascular stenosis. Acute arterial thrombosis can occur in the immediate postoperative period, and necessitates return to the operating room for thrombectomy. Open groin access with HILP also entails risk of infection, seroma formation and lymphedema. Systemic toxicity should be rare with effective isolation of the extremity during either procedure. Bone marrow suppression can occur, but is especially rare with ILI.

Limb toxicities are graded using the Wieberdink extremity toxicity scale [12] (Table 2). Some limb erythema and edema are expected (categorized as grade 2 toxicity) and absence of these changes indicates underdosage of

Table 3. Outcomes of hyperthermic isolated limb perfusion and isolated limb infusion.

Proc	Study setting	Study type	N	ORR (%)	CR (%)	Grade ≥3 AE	PFS (mo)	OS (mo)	5-year surv (%)	Ref
HILP	ACOSOG Z0020, USA, 1999–2004									[18]
	Melphalan	RCT	58	64.0	25.0	3.0	NR	NR	NR	
	Melphalan/TNF-α		58	69.0	26.0	37.0				
HILP	Europe, multi-center									[19]
	Melphalan (historic control)	RCT	103	78.0	52.0	NR	NR	NR	NR	
	Melphalan/TNF-α		32	91.0	69.0		10.9	27.3		
	Melphalan/TNF-α/IFN-γ		32	100.0	78.0		16.6	23.5		
HILP	Germany, 1992–2003									[20]
	Melphalan/Dactinomycin	PC	101	90.8	66.7	NR	21.0	42.0	38.0	
HILP	Netherlands, 1991–2003									[21]
	Melphalan/TNF-α	RC	87	95.0	69.0	31.0	NR	25.0	32.0	
HILP	Netherlands, two centers									[22]
	Melphalan	RC	40	45.0	45.0	29.0	30.0	25.0	29.0	
	Melphalan/TNF-α		90	59.0	59.0	25.0	16.0			
ILI	Australia, five institutions, 1992–2008	RC	316	75.0	33.0	30.0	NR	44.0	46.0	[16]
ILI	Moffitt Cancer Center, USA 2007–2016	PC	148	59.0	25.7	11.9[†]	NR	22.1	NR	[23]
ILI	Duke University, USA, 1995–2007	PC	61	44.0	30.0	18.0	NR	NR	NR	[11]
ILI	Memorial Sloan Kettering, USA, 1999–2011	PC/RC	58	45.0	25.0	NR	NR	36.0	46.0	[24,25]
ILI	International, nine institutions 1992–2018	RC	687	64.1	28.9	27.9	10.1	38.2	NR	[26]

[†]Included patients with melanoma, squamous cell carcinoma, sarcoma and Merkel cell carcinoma.
AE: Adverse event; CR: Complete response; HILP: Hyperthermicisolated limb perfusion; ILI: Isolated limb infusion; mo: Month; NR: Not reported; ORR: Overall response rate; OS: Overall survival; PC: Prospective cohort; PFS: Progression-free survival; Proc: Procedure; RC: Retrospective cohort; RCT: Randomized controlled trial; surv: Survival.

chemotherapy. The range of acceptable toxicity includes grades 1–3 reactions, while extensive epidermolysis, deep tissue damage, profound functional disturbances and compartment syndrome (grade 4) indicate an unacceptable level of toxicity. Compartment syndrome mandates return to the operating room to prevent limb loss. Grade 5 toxicity (may necessitate amputation) is a rare but devastating event which defeats the purpose of intra-arterial therapy for limb salvage [12].

Muscle ischemia can cause rhabdomyolysis, resulting in myoglobin-induced renal failure. CPK levels should be monitored post-procedure and are expected to peak 4 days post-procedure. In addition to ongoing observation and aggressive hydration, systemic steroids may be considered when CPK levels exceed 1000 µ/l. Regional limb symptoms usually subside within 2–3 weeks [10,15].

Some patients are at higher risk for limb toxicity, including females and patients with larger limb volumes. Melphalan uptake is lower in fatty tissue, so patients with lower muscle to fat ratios can be inadvertently overdosed, resulting in increased limb toxicity [16]. Dose correction for ideal bodyweight decreases variability in mean drug concentration in perfused tissues and decreases regional limb toxicity without impacting response rates [11,17].

Outcomes of extremity intra-arterial therapies

With unique technical expertise and equipment required to perform intra-arterial therapies, few centers routinely perform these procedures and have sufficient patient cohorts to publish their outcomes. Randomized controlled studies are scarce. Contemporary reports from these centers have established a fairly wide range of potential response rates but report uniformly low and predictable toxicities (Table 3).

Efficacy of HILP

Reported response rates for HILP vary widely. A systematic review included outcomes for over 2000 patients undergoing isolated limb perfusion for melanoma from 1990 to 2008 [27]. The majority (91%) were observational studies, with only two randomized controlled trials identified. The collective median overall response rate (ORR) was 90%, with 58% of patients having a complete response (CR). Responses were better with addition of TNF-α (69 vs 47%). Eighteen percent of patients experienced grade ≥3 toxicity, including compartment syndrome in 25 (2%) and toxicity-related amputation in 8 (0.65%) [27].

The two available randomized controlled trials yielded lower overall and CR rates. One Netherlands-based study randomized 64 patients to HILP with melphalan plus TNF-α or melphalan, TNF-α and IFN-γ [19]. Compared with a melphalan-only historic control, ORRs were 78, 91 and 100% for melphalan, melphalan/TNF-α, and melphalan/TNF-α/IFN-γ, respectively [19].

Response rates were lower from the US-based ACOSOG Z0020 randomized trial, which found no difference between melphalan alone (ORR: 64%; CR: 25%) and melphalan plus TNF-α (ORR: 69%, CR: 26%; p = 0.890) [18]. Toxicity was greater with the addition of TNF-α, including two toxicity-related amputations among 68 patients [18].

Efficacy of ILI

A contemporary series including 316 procedures performed over a 15-year period at five Australian institutions demonstrated an ORR of 75% [16]. Patients with CR had longer overall survival (OS) than those with PR (80 vs 36 months, HR: 2.56; 95% CI: 1.67–3.09) [16]. In the USA, 148 ILI procedures for melanoma performed at Moffitt Cancer Center over a 10-year period demonstrated a slightly lower ORR of 59% [23]. Again, responders had better outcomes, including longer in-field progression free survival (PFS) (14.1 vs 3.2 months, p < 0.001), distant metastatic-free survival (not reached vs 25.8 months, p = 0.006) and OS (56 vs 26.7 months, p < 0.001). After ILI, 26% of the population was resected to no evidence of disease [23].

A prospective series from Duke University included 61 consecutive ILI treatments performed from 1995 to 2007, demonstrating an ORR of 44% with a longer median response duration of 24 months [11]. A smaller cohort from Memorial Sloan Kettering demonstrated a 52% ORR among 31 patients with melanoma (26% CR; 26% PR) [24]. Median response durations were 12 and 11 months after CR and PR. An updated cohort including 27 additional patients demonstrated a lower ORR of 45% [25]. The five-year survival for after CR was 91 versus 34% with PR, stable disease or progression [25].

In the largest report in the literature to date, an international, multi-institutional study recently examined the collective experience of first-time ILI for stage IIIB/C melanoma over a 27-year period. Among 687 cases, ORR was 64.1% and median OS was 38.2 months. Findings confirmed superior outcomes for responders compared with nonresponders, with longer in-field PFS (21.9 vs 3.0 months), distant PFS (53.6 vs 12.7 months) and OS (46.5 vs 24.4 months) [26].

Comparison of outcomes for HILP versus ILI

There have been no randomized comparisons of ILI and HILP, though efforts have been made to compare the procedures during different time periods within the same institution [11,28] and between institutions [29]. At Duke University, 59 HILPs performed from 1995 to 2003 were compared with 61 ILIs from 2003 to 2007. ORRs were better for HILP than ILI (ORR: 88 vs 44%, p < 0.001; CR: 57 vs 30%), but more patients experienced a grade ≥3 toxicity (32 vs 18%, p = 0.037) including nine fasciotomies for suspected compartment syndrome and one amputation after HILP group versus none after ILI [11]. Updated results through 2010 including 72 HILPs and 144 ILIs demonstrated similar ORRs (81 vs 43%; CR: 55 vs 30%) but no difference in OS (32 vs 33 months, p = 0.647) [28]. Grade ≥3 toxicity was reported in 27% after HILP and 22% after ILI, including two post HILP amputations. There were more wound infections (13 vs 0%) and venous thromboembolic events (11 vs 4%) with HILP [28].

A comparison of 94 ILIs performed at Moffitt Cancer Center (USA) and 109 HILPs at Sahlgrenska University Hospital (Sweden) from 2007 to 2015 also found higher ORR for HILP than ILI (80 vs 53%) but similar OS (40 vs 46 months) [29]. The incremental improvement in OS in this more recent cohort might be attributable to more effective systemic therapies [29].

After intra-arterial therapy, approximately 20–50% of patients recur locoregionally [21,30,31]. Repeat HILPs have produced response rates of 72–96% (62–76% CR; 10–20% PR) with similar toxicity profiles to index procedures [30,32]. A benefit of ILI is that it can be repeated without the potential morbidity of re-operative open vessel cannulation. Repeat ILIs performed at a median of 11–14 months after the index procedure have response rates of 71–83% with fewer complete responders [31,33]. Some series report more grade ≥3 toxicities after repeat ILI. In one study, 10.4% of patients experienced threatened or actual compartment syndrome (vs 2% with the initial ILI), but none required amputation [33]. A planned double ILI protocol (4 weeks after the initial infusion) did not improve ORR or response duration (88 vs 82%, 18 vs 17 months), but toxicity was higher after second ILI (grade ≥3; 76 vs 52%) [31].

Table 4. Comparison of isolated hepatic perfusion and percutaneous hepatic perfusion.

Technical aspect	Isolated hepatic perfusion	Percutaneous hepatic perfusion
Technique	Open, surgical vessel cannulation, IVC clamps above/below liver	Minimally invasive, percutaneous vessel cannulation, fenestrated catheter in IVC with double balloons above/below liver
Flow	High (>400 cc/min)	Low
Temperature	Hyperthermic	Normothermic to slightly hyperthermic
Perfusate environment	Aerobic, oxygenated	Anaerobic, ischemic
Perfusion duration	60 min	30 min
Melphalan dose	1–2.5 mg/kg	3 mg/kg
Ability to repeat	More difficult	Less difficult
IVC: Inferior vena cava.		

Choice of ILI versus HILP should consider the patient's overall treatment plans and potential need for repeat procedures for recurrent unresectable regional disease. Based on a series of 44 patients undergoing repeat ILI or HILP at three institutions, a practical algorithm proposed initial ILI in most cases because it is less complex and more replicable. Exceptions might include high volume disease, for which HILP could improve ORR. For repeat procedures, patients with prior HILP or ILI can undergo repeat ILI or HILP, although HILP after HILP is difficult to perform [34].

Predictors of response to intra-arterial therapy

Lower burden of disease, measured by number and size of lesions, is associated with a higher response rates to both ILI and HILP [25]. Low disease burden also portends more CRs, longer PFS (6.9 vs 3.8 months) [35,36], and longer OS after ILI [29]. Other tumor factors associated with response to intra-arterial therapy include lower stage and thinner Breslow depth of the primary tumor [16]. Patients with lower mean limb volumes appear to respond better to intra-arterial therapies [23]. Response rates appear to be similar for upper and lower extremity ILI, though toxicity may be higher for lower extremity procedures [37].

Intra-arterial hepatic perfusion

Two strategies exist for hepatic perfusion of cytotoxic chemotherapy, which are options for patients with metastatic melanoma limited to the liver (Table 4). Metastases should comprise less than 50% of the liver parenchyma to mitigate risk of post-perfusion hepatic failure. For both, melphalan is perfused using an extracorporeal circuit with the patient on veno-venous bypass.

Isolated hepatic perfusion (IHP) is an open surgical technique that involves mobilization of the liver, arterial infusion via a cannula in the hepatic artery, venous drainage via a cannula in the retrohepatic vena cava and clamping of the inferior vena cava (IVC) above and below the liver. The patient is placed on veno-venous bypass using cannulas in the saphenous, portal and axillary veins [38]. Like HILP, the perfusion circuit includes a roller pump, membrane oxygenator and heat exchanger which enables a high flow (>400 ml/min), hyperthermic, aerobic perfusion environment [38].

Percutaneous hepatic perfusion (PHP) is a minimally invasive alternative involving hepatic arterial access via a femoral artery, with embolization of aberrant, accessory and proximate nonhepatic arterial branches to mitigate systemic chemoperfusion. Hepatic venous isolation is accomplished using a double balloon catheter inserted through a femoral vein, with the cephalad balloon positioned at the atrio-caval junction and the caudal balloon in the infrahepatic IVC above the level of the renal veins. The patient is systemically heparinized prior to balloon inflation and an activated clotting time of >400 is maintained throughout the procedure. Fenestrations in the double balloon catheter provide hepatic venous outflow to the extracorporeal circuit, which comprises a centrifugal pump and two activated charcoal filters. A separate post-filter venous return cannula is placed in an internal jugular or subclavian vein [38]. Typically, the left and right lobes are independently perfused via advancement of the arterial catheter into either arterial branch. After a 30-min infusion, a 30-min washout is performed prior to re-establishing systemic flow to and from the liver. Due to the minimally invasive approach and limited peri-procedural morbidity, PHP can be repeated.

IHP is associated with response rates of 37.5–66%, with CRs seen in 0–10% [39–42] (Table 5). In available series, mortality can be as high as 27%, mostly from post-procedure hepatic failure and sequelae of major ab-

Table 5. Outcomes isolated hepatic perfusion and percutaneous hepatic perfusion for uveal melanoma liver metastases.

Proc type	Study setting	Study type	N	Number of proc	ORR (%)	CR (%)	Death (%)	HPFS (mo)	OS (mo)	Ref.
IHP	National Cancer Institute, USA, 1994–1999			1			4.5		11.0	[40]
	Melphalan	PC	11		70.0	0.0		6.0		
	Melphalan/TNF-α	Ph I/II	11		54.5	18.0		14.0		
IHP	National Cancer Institute, USA, 1997–2002	PC Ph I/II	29	1	62.0	10.0	0.0	8.0	12.1	[39]
IHP	Sahlgrenska University Hospital, Sweden, 1985–2007	RC/PC	27†	1	70.0	7.4	27.0	NR	7.5	[42]
IHP	Erasmus University, Netherlands, 2002–2006	PC	8	1	37.5	0.0	0.0	6.0	11.0	[41]
PHP	National Cancer Institute, USA, 2001–2004	PC Ph I	10	2.6‡	50.0	20.0	0.0	NR	NR	[44]
PHP	Moffitt Cancer Center, USA, 2008–2013	RC	5	3	NR	NR	0.0	7.6	12.6§	[45]
PHP	National Cancer Institute, USA, 2006–2009	RCT					3.2			[46]
	PHP	Ph III	44	3	34.0	0.0		7.0	10.6	
	Best alternative care		49	N/A	2.0	N/A		1.6	10.0¶	
PHP	Moffitt Cancer Center, USA & University of Southhampton, UK, 2008–2016	RC	51	2	49.0	5.9	0.0	9.1	15.3	[47]

† Collective results for metastatic melanoma from ocular (20), cutaneous (5) and anal (2) primaries.
‡ Collective results for ten patients with ocular melanoma liver metastases and 18 with other primary liver metastases.
§ Collective results for ten patients with liver metastases of varying primaries–five with ocular melanoma, one with cutaneous/unknown primary melanoma and one with leiomyosarcoma.
¶ 57% in best alternative care arm crossed over to PHP.
CR: Complete response; Death: Treatment-related mortality; HPFS: Hepatic progression-free survival; IHP: Isolated hepatic perfusion; mo: Month; N: Sample size; ORR: Overall response rate; OS: Overall survival; PC: Prospective cohort; Ph: Phase; PHP: Percutaneous hepatic perfusion; Proc: Procedure; Proc type: Procedure type; RC: Retrospective cohort; RCT: Randomized controlled trial./p>

dominal surgery [39–43]. Responses have fairly short duration, with median PFS of 8–9 months and OS of 11–12 months [39,40].

An initial Phase I trial of PHP at the USA National Cancer Institute demonstrated a 50% response rate in ten patients with ocular melanoma (CR: 20%) [44] (Table 5). A separate series of five patients, each undergoing a median of 3 PHPs at Moffitt Cancer Center, demonstrated a 48.6% median decrease in hepatic tumor volume [45]. A subsequent multicenter Phase III study compared PHP (up to 6 perfusions at 4- to 8-week intervals) to best alternative care in 93 patients with unresectable ocular or cutaneous melanoma liver metastases [46]. PHP improved overall response (34 vs 2%) and median hepatic PFS (7 vs 1.6 months) [46]. In a subsequent two-institution series of 51 patients undergoing PHP, 49.0% responded. An additional 33.3% had stable disease for at least 3 months [47]. Median OS was 15.3 months, 37.5% experienced a grade ≥3 adverse event, and there were no treatment-related deaths. A multi-center, single-arm, Phase III study is currently evaluating safety, efficacy and quality of life in 80 patients (NCT02678572).

There are limited data comparing PHP with other liver-directed therapies for ocular melanoma liver metastases. In a retrospective comparison with Yttrium-90 (Y90) and chemoembolization (CE), PHP demonstrated longer hepatic PFS and overall PFS than Y90 or CE. OS was also longer (PHP 608 days vs Y90 295 days and CE 265 days), but not statistically significant [9].

Conclusion

Intra-arterial therapies enable regional delivery of chemotherapy while minimizing systemic toxicity. They are effective tools for treating regionally metastatic, in-transit cutaneous melanoma and uveal melanoma metastatic to the liver. For both extremity-based and liver-based therapies, minimally invasive techniques produce comparable oncologic outcomes while minimizing morbidity; further, they can be repeated with greater ease.

Future perspective

Intra-arterial therapy is a valuable tool in the comprehensive management of patients with locoregionally advanced cutaneous melanoma and liver metastases from uveal melanoma. For uveal melanoma metastases, liver-directed therapies including hepatic perfusions are the most effective treatment option, surpassing available systemic treatments. Future work is needed to establish the role of hepatic perfusion alongside other liver-directed therapies including radioembolization and chemoembolization.

For cutaneous melanoma, intra-arterial therapies produce significant and durable responses for a large proportion of patients. With the advent of multiple effective treatments for metastatic and locally unresectable cutaneous melanoma including immune therapy, BRAF/MEK pathway inhibition and intralesional therapy, there is a unique opportunity to refine the role of intra-arterial chemoperfusion in patients' comprehensive treatment plans. An improved understanding of which patients are likely to respond to intra-arterial therapies could be used to individualize treatment sequencing or potentially combine therapies. For example, an initial regional approach to regionally metastatic disease may be ideal for those patients who are most likely to respond, reserving systemic therapy for patients with distant progression.

For both cutaneous and ocular melanoma, treatment selection and sequencing should be determined in a multidisciplinary and patient-centric fashion, including medical and radiation oncologists, surgeons, interventional radiologists, perfusionists and patients. With appropriate selection and orchestration, intra-arterial therapy can be performed safely with excellent outcomes.

Executive summary

Background
- Intra-arterial perfusion-based therapies enable regional delivery of chemotherapeutic agents while minimizing systemic toxicity.
- Regionally metastatic, in transit, cutaneous melanoma is common (5–15%) and can be highly morbid. Extremity-based intra-arterial therapies are an important treatment option for unresectable and symptomatic locoregional disease.
- Metastatic uveal melanoma is unique in that it typically solely or predominantly involves the liver, making it an opportune target for regional therapy.
- The aim of this review was to summarize the techniques and outcomes of intra-arterial therapies for regionally metastatic cutaneous and uveal melanoma.

Intra-arterial therapies for recurrent cutaneous melanoma of the extremity
- Hyperthermic isolated limb perfusion (HILP – open and complex) and isolated limb infusion (ILI – minimally invasive, easily repeatable) are two strategies used to treat regionally metastatic melanoma in transit disease, confined to a limb.
- In both techniques, the circulation of the involved extremity is isolated and a chemotherapeutic agent (typically melphalan) is infused intra-arterially using an extracorporeal pump.
- The most common adverse events after extremity-based intra-arterial therapy are limb toxicities, which are characterized using the Weiberdink toxicity scale.
- Response rates reported in the literature for extremity-based therapies (HILP and ILI) range from 44 to 100%, with 25 to 78% achieving complete response.
- Patients who respond to extremity-based intra-arterial therapies have been demonstrated to benefit from improved progression-free and overall survival.
- Some patients with recurrent locoregional disease respond to repeat intra-arterial therapy, though rates of overall and complete response are slightly lower than with initial procedure.

Intra-arterial hepatic perfusion
- Intra-arterial hepatic perfusion is an effective treatment option for uveal melanoma liver metastases, and can be performed using open (isolated hepatic perfusion) and percutaneous (PHP) approaches.
- Isolated hepatic perfusion is an open surgical technique that carries increased morbidity and cannot be repeated.
- PHP is a minimally invasive technique using a double balloon fenestrated catheter to isolate hepatic venous flow that can be repeated.
- In both procedures, hepatic flow is isolated and melphalan is delivered to the liver via an extracorporeal pump with the patient on veno-venous bypass.
- Intra-arterial hepatic perfusion is appropriate for patients with a liver metastatic burden <50% of total liver parenchyma, which minimizes risk of post-perfusion hepatic failure.
- Percutaneous hepatic perfusion has been shown to produce longer hepatic progression-free survival than best alternative care in previous Phase III clinical trials.

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●●   **Landmark article describing the technique andinitial results of isolated limb infusion**

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