# Current Trends in Regional Therapy for Melanoma: Lessons Learned from 225 Regional Chemotherapy Treatments between 1995 and 2010 at a Single Institution

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**BACKGROUND:** Hyperthermic isolated limb perfusion (HILP) and isolated limb infusion (ILI) are used to manage advanced extremity melanoma, but no consensus exists as to which treatment is preferable and how to monitor patients post-treatment.

**STUDY DESIGN:** Using a prospectively maintained database, we reviewed our experience with melphalan-based HILP (which included 62 first-time and 10 second-time) and ILI (which included 126 first-time and 18 second-time) procedures performed in 188 patients. PET/CT was obtained 3 months postregional treatment for 1 year and then every 6 months thereafter.

**RESULTS:** Overall response rate (complete response [CR] + partial response) of HILP was 81% (80% CI, 73−87%), and overall response rate from ILI was 43% (80% CI, 37−49%) for first-time procedures only. HILP had a CR rate of 55% with a median duration of 32 months, and ILI had a CR rate of 30% with median duration of 24 months. Patients who experienced a regional recurrence after initial regional treatment were more likely to achieve a CR after repeat HILP (50%, n = 10) compared with repeat ILI (28%, n = 18). Although the spectrum of toxicity was similar for ILI and HILP, the likelihood of rare catastrophic complication of limb loss was greater with HILP (2 of 62) than ILI (0 of 122). PET/CT was effective for surveillance after regional therapy to identify regional nodal and pulmonary disease that was not clinically evident, but often amenable to surgical resection (25 of 49; 51% of cases). In contrast, PET/CT was not effective at predicting complete response to treatment with an accuracy of only 50%.

**CONCLUSIONS:** In the largest single-institution regional therapy series reported to date, we found that although ILI is effective and well-tolerated, HILP is a more definitive way to control advanced disease.
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After initial appropriate therapy, approximately 2% to 10% of extremity melanoma lesions recur in the extremity as in-transit metastases.[1,2] This pattern of recurrence represents multifocal involvement of the extremity's lymphatic system and local excision of these lesions is frequently followed by rapid recurrence. Treatment of recurrent regional melanoma is important because at least half of these patients survive for longer than 2 years without evidence of distant disease.[1] Surgical isolation of an extremity and treatment with regional chemotherapy can deliver cytotoxic agents (usually melphalan) at dosages 10 to 20 times higher than can be achieved systemically. This form of therapy has been a relatively effective limb-sparing treatment modality for in-transit disease since the 1950s.[3] Currently, there are 2 ways drugs are regionally delivered: hyperthermic isolated limb perfusion (HILP) and isolated limb in-

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**Abbreviations and Acronyms**

CPK = creatine phosphokinase
CR = complete response
CTCAE = Common Terminology Criteria for Adverse Events
HILP = hyperthermic isolated limb perfusion
IBW = ideal body weight
ILI = isolated limb perfusion
NE = not evaluable
PD = progressive disease
PR = partial response
SD = stable disease
TTiP = time to in-field progression

fusion (ILI). HILP, which involves a surgical incision and open cannulation of the extremity's artery and vein, has been associated with single-institution complete response (CR) rates of 40% to 80%.[4-11] ILI is a less-invasive alternative to HILP, whereby percutaneous catheters are placed in the artery and vein of the involved extremity and no surgical incision is required. CR rates to ILI have been reported to be between 30% and 38%.[12,13] Although response rates to ILI are considered to be less than HILP, ILI remains popular because of the disappointing results of HILP in the multicenter randomized American College of Surgeons Oncology Group's Z0020 trial, where substantial toxicity and CR rates of only 25% were reported.[8,12]

The major technical differences between HILP and ILI are that higher doses of melphalan per liter of treated limb volume are used in HILP, along with a flow rate that is much higher for HILP (150 to 1,000 mL/min) as compared with ILI (50 to 100 mL/min).[14] In addition, HILP uses a higher degree of hyperthermia than ILI and the chemotherapy is circulated for 60 minutes for HILP compared with 30 minutes for ILI. These differences could explain, in part, why HILP is associated with higher overall response rates. However, HILP often requires blood transfusions (to prime circuit), poses short and long-term risk to vessel patency, and is associated with increased limb loss and morbidity.[15] Given our large practice involving patients with in-transit disease, we realized that both ILI and HILP, each with their benefits and shortcomings, had potential use in managing the spectrum of patients with advanced extremity melanoma. We proposed an algorithm in 2008 based on a review of our experience and that of several other institutions that had the goal of optimizing regional response and minimizing toxicity.[9] This algorithm tried to identify the appropriate clinical and patient situations for use of either ILI, HILP, or protocol-based regional therapies in the management of these patients. Since the review on which the algorithm is based, we have expanded our regional therapy experience by >40% and wanted to re-evaluate some of the assumptions on which the treatment algorithm was based to determine if modifications should be constructed. This article summarizes our global experience in managing in-transit extremity melanoma using regional therapy at a single institution during the last 15 years.

## METHODS

A prospective melanoma surgical database at Duke University Medical Center identified 188 patients who underwent 225 regional procedures for metastatic melanoma (ILI and/ or HILP) from 1995 to 2010. There were a total of 62 first-time HILPs and 126 first-time ILIs performed. Several patients underwent a second regional treatment: ILI after ILI in 16 cases, HILP after ILI in 7 cases, ILI after HILP in 2 cases, and HILP after HILP in 3 cases. Nine other procedures were performed as a third or fourth regional treatment in 5 patients. All patients had advanced extremity melanoma; American Joint Committee on Cancer stage IIIB, IIIC, or IV disease.[16] Response was determined at 3 months post-treatment according to Response Evaluation Criteria in Solid Tumors modified for cutaneous lesions.[9,12] Overall toxicity was measured using both the Wieberdink limb toxicity scale and the Common Terminology Criteria for Adverse Events (CTCAE, version 3) grading scheme. The Wieberdink limb toxicity scale focuses on regional toxicity only and is more commonly used in reports of regional therapy currently present in the literature.[17] With this scale, toxicity ranges from grade 1, which is no visible effect on the extremity, to grade 5, which consists of toxicity resulting in limb amputation. The CTCAE scoring system allowed for documentation and grading of systemic complications in addition to regional skin and soft tissue problems. Serologic toxicity, most notably an elevation of creatine phosphokinase (CPK), could also be assessed according to CTCAE. A CPK of 100 to 250 U/L is considered a grade 1 toxicity, 250 to 500 U/L is a grade 2 toxicity, 500 to 1,000 U/L is a grade 3 toxicity, and CPK >1,000 U/L is a grade 4 toxicity. Postoperative complications, including rate of deep venous thrombosis, wound infection, and limb loss, were also examined. Presence of a deep venous thrombosis was defined as evidence and treatment for deep venous thrombosis and/or pulmonary embolus shown by ultrasound, ventilation-perfusion scan, or spiral CT; wound infection was defined as evidence and treatment for wound infection during the initial postoperative hospitalization or requiring readmission for incision and drainage or intravenous antibiotics. Patients who had a partial response (PR) or stable disease (SD) that could not be surgically resected, or developed progressive disease (PD) after their first