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Improved durable responses regardless of age following cytoreduction and "no-tourniquet" hyperthermic isolated limb chemotherapy for in transit melanoma of the extremity

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ABSTRACT

Background: In-transit metastatic melanoma of the extremity is a clinically aggressive disease. For patients with disease confined to the limb, regional chemotherapy remains an effective option. However, no studies thus far have included cytoreduction or perfusion/infusion without using a limb tourniquet as part of the operative procedure. We hypothesize that combining cytoreduction with no-tourniquet HILP/HILI is safe in patients of all ages and results in durable responses.

Methods: A retrospective analysis was performed of a prospectively collected database of patients with in-transit malignant melanoma who underwent cytoreduction and HILP/HILI between 2013 and 2017. The primary endpoint was RECIST response at 3–12 months. Secondary endpoints included length of hospital stay, adverse effects, overall survival, and time to recurrence. A subgroup analysis was performed in patients ≥80 years old.

Results: HILP patients had significantly higher disease burdens than HILI patients. Complete response rates for HILP and HILI were 95% and 75%, respectively at 3 months and 47% and 50%, respectively at 1 year (50% for patients >80) with 100% 1-year survival rates for both HILP and HILI patients. Three-year survival rates were 57% (HILP), 52% (HILI) and 68% (patients >80 years old). The average length of stay for all patients was 3.6 ± 1.4 days.

Conclusion: Combining cytoreduction with no-tourniquet HILP/HILI for in-transit metastatic melanoma of the extremity resulted in 100% survival regardless of age at 1 year and 68% 3-year survival in patients over 80 without any increase in adverse events.

Introduction

In the United States, melanoma is the 5th most common cancer with an estimated 7,200 deaths and 96,000 new cases in 2019.[1] Despite an overall excellent prognosis for early stage melanoma, the 5-year survival rate for stage III disease is between 40 and 78% and only 15–20% for stage IV disease.[2] A subset of patients with advanced stage melanoma develop in-transit disease, which is defined as skin or subcutaneous metastases that are more than 2 cm from the primary lesion but not past the regional nodal basin3. In-transit disease is part of a larger classification group known as locoregional metastases, which includes local recurrences, in-transit metastases, and satellite metastases. According to the most recent AJCC staging system, the presence of in-transit disease upstages patients to clinical stage III and pathologic stage IIIB/IIIC.[3] The best estimates of the incidence of locoregional disease suggest that up to 10% of patients develop in-transit metastases after initial wide local excision of their primary melanoma.[4] The 5-year survival rate after the diagnosis of in-transit melanoma ranges from 19 to 47%, depending on disease burden and involvement of regional lymph nodes.[5] Thus, the optimization of currently existing therapies and the investigation of novel methods for the treatment of in-transit melanoma is urgently needed.

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Currently, there are many possible options for the treatment of in-transit melanoma, including wide local excision of easily resectable single or multiple lesions with or without systemic therapy, regional therapies, and intralesional therapies such as oncolytic viruses (T-VEC).[6] To date, regional therapy has been critically important in the treatment of in-transit melanoma that is confined to one limb due to the ability to deliver much higher than systemic doses of chemotherapy to an isolated limb. The two widely accepted techniques for administration of regional chemotherapy are hyperthermic isolated limb perfusion (HILP) with melphalan (with or without TNF- α) and hyperthermic isolated limb infusion (HILI) with melphalan (with or without actinomycin-D).[6] HILP is an invasive surgical technique that involves direct cannulation of the main vascular inflow and outflow to a limb (femoral or iliac vessels for the lower extremities or axillary vessels for the upper extremities) and connecting them to a bypass circuit. By comparison, HILI is a more minimally invasive technique in which balloon catheters are percutaneously placed within the vessels for chemotherapy infusion. Despite evidence demonstrating that a significant number of patients experience a partial or complete response after HILP or HILI, the vast majority of patients will still experience disease recurrence over time; in one series as many as 65% of HILP and 85% of HILI patients who achieved an initial complete response experienced recurrence within 3 years.[7]

In this manuscript, we describe a novel operative approach of performing cytoreduction of visible and resectable disease with wide local or en-bloc excision at the time of HILP and HILI using a "no-tourniquet" technique for HILP and HILI. Traditionally, administration of regional chemotherapy requires placement of a tourniquet at the root of the upper or lower extremity in order to prevent systemic distribution of the chemotherapeutic agent.[8] However, tourniquet use can result in rare complications such as ischemia, pain, and neuropathy.[9] Additionally, the need for a tourniquet limits high perfusion of chemotherapy, as the infusion catheter is placed below the level of the tourniquet. Therefore, a "no-tourniquet" technique may be beneficial to patients with disease in the upper arm or thigh, as the infusion catheter can be placed in the more proximal femoral or axillary vessels. Currently, there are no data on the effect of surgical cytoreduction on postoperative outcomes, complications, and durability of response. We hypothesize that combining cytoreduction with regional chemotherapy may enhance results with this procedure. Additionally, we feel that outcomes in an elderly cohort will be comparable to that of the general population without any increased risks of complications.

Methods

Patients

We performed a retrospective analysis of patients with in-transit malignant melanoma of the extremities who underwent first time HILP or HILI at our institution between 2013 and 2017 from a prospectively collected database of HILP/HILI patients (including melanoma, merkel cell carcinoma, and sarcoma patients). All patients included in our study had in-transit melanoma without distant disease by whole body imaging (AJCC stage IIIB/IIIC). Patients were selected for HILP or HILI at the discretion of the treatment team. Patients were not excluded from the study based on receiving any prior treatment for in-transit disease, including immunotherapy, radiation, surgery, or interferon therapy. Demographic and clinical data, including age, gender, N stage at the time of treatment, burden of disease, response to treatment, survival, and toxicity were collected for analysis. Burden of disease was classified as high versus low based on the number of lesions resected during cytoreduction (high $\geq$5) and whether a lymph node dissection was included during the procedure (no lymph nodes removed from patients with low burden of disease). After discharge home, patients were contacted by clinic nursing staff within 72 h to assess their recovery and all patients were tested as an outpatient for neutropenia during their first week at home. Patients were evaluated post-operatively by the surgical team at 2 weeks, at least every 3 months for a year, and additionally followed long-term by our colleagues in medical oncology and dermatology. Patients without response to regional chemotherapy or evidence of recurrent/progressing disease were evaluated and treated with adjuvant therapy per the judgement of the multidisciplinary care team. Patients with a complete response to HILP or HILI did not receive any adjuvant therapy unless there was evidence of disease recurrence. All research was performed after review board approval and per institutional ethical guidelines.

Hyperthermic isolated limb perfusion (HILP)

The patient's axillary artery and vein for upper extremity cases or external iliac or common femoral artery and vein for lower extremity cases were accessed by open surgical dissection, controlled with vessel loops, and cannulated after heparinization. The perfusion circuit was tested and evaluated for any volume losses, confirming an isolated circuit without any external tourniquet. The limb was warmed to 41–42° Celsius through a combination of a heating blanket encircling the limb and the heat exchanger pump in the bypass circuit. Melphalan (dose 1 mg/kg of ideal body weight) was injected in the arterial line and circulated for 90 min. Prior to cannula removal, the chemotherapy was flushed from the limb by saline and blood through the arterial line.

Hyperthermic isolated limb infusion (HILI)

For lower extremity cases, ultrasound-guided access of the contralateral common femoral artery and vein were performed to establish "up and over" access to the affected limb. Specialized balloon occlusion catheters were then positioned above the level of the inguinal ligament in the external iliac vessels. For upper extremity cases, the axillary vessels proximal to the circumflex vessels were accessed via the femoral artery and vein. Following systemic heparinization, the occlusion catheter balloons were inflated, and sufficient isolation of the limb vasculature was confirmed by fluoroscopy and injection of contrast, again without any external tourniquet on the limb. The limb infusion circuits were established through connection of the catheters to the Belmont® Rapid Infuser and Cellsaver™ autotransfusion system, and the limb was warmed to 38.5° Celsius through a combination of a heating blanket encircling the limb and warming of the circuit fluid. Melphalan (dose 1 mg/kg of ideal body weight) was injected in the arterial line and circulated for 30 min. Prior to cannula removal, the chemotherapy was flushed from the limb by saline and blood through the arterial line.

Cytoreduction

At the time of operation, patients underwent wide local excision of single lesions or en-bloc excisions of multiple lesions grouped together. This cytoreduction was performed on all palpable and resectable disease either prior to or following HILP or HILI. Patients who had wide-spread or miliary in-transit disease were not candidates for cytoreduction. Patients' wounds were closed primarily, through second intention via wound vac, or through complex reconstruction including delayed skin grafting. In select patients, resection of bulky lymphadenopathy or formal regional lymph

node dissection was performed at the same time as HILP/HILI.

Evaluation of response and toxicity

Patients were evaluated post-operatively, and the primary endpoint was response at 3 months, 6 months, and 1 year classified using RECIST 1.1 as having either a complete response, partial response, no response, or recurrent disease. Patients were evaluated for recurrence every 3 months with a physical exam and systemic imaging (alternating PET scan with CT of the chest/abdomen/pelvis through the mid-thigh). Recurrences were biopsy-proven based on suspicious findings detected on physical exam or imaging. Secondary endpoints included overall survival at 1 and 3 years post-operatively and time to disease recurrence. Limb toxicity was determined by Wieberdink classification and recorded if greater than Grade 3. Other side effects that were noted were neutropenia requiring filgrastim subcutaneous injection treatment, wound complications including wound breakdown and infection, and elevation in creatine phosphokinase (CPK) level graded per Common Terminology Criteria for Adverse Events.

Statistical analysis

Patient characteristics are reported as number of observations and percent for categorical variables and mean and standard deviation for continuous variables. Characteristics and outcomes were compared by operation type and age cohort using Fisher's exact tests, χ^2 tests and/or the Mann-Whitney U tests as appropriate. Kaplan-Meier survival curves along with log rank tests were used to assess and compare time to death by operation type and age cohort. A subgroup descriptive analysis was performed on elderly patients, defined as age greater than or equal to 80 years old. The age cut off was chosen to correspond with the eldest third of our patient cohort. All statistical analyses were conducted with STATA 15 and $p < 0.05$ was set as the level of significance.

Results

Patient demographic data

Between 2013 and 2017, a total of 44 patients underwent hyperthermic isolated limb perfusion or isolated limb infusion. Eleven patients were treated for merkel cell carcinoma, squamous cell carcinoma, or sarcoma and were excluded from our analysis. A total of 33 patients underwent HILP or HILI at our institution for treatment of malignant melanoma with in-transit disease confined to a single extremity. Nineteen patients underwent HILP and 14 patients underwent HILI. Of the patients who underwent HILI, one patient was lost to follow up immediately post-operatively and one patient died from unrelated circumstances after discharge home; these patients were excluded from subsequent analysis due to lack of follow up data.

In Table 1, the demographic and clinical characteristics are compared by group for HILP and HILI. There was a significant difference in age and gender, with more elderly patients ($p = 0.05$) and more female patients undergoing HILI ($p = 0.02$). The majority of cases for both HILP and HILI involved in the lower extremity. There is no difference in the clinical stage of patients based on their nodal status. Patients who underwent HILI were significantly more likely to have a low burden of disease (<5 lesions), although overall most patients undergoing both HILI and HILP had high burden of disease ($p = 0.05$). Cytoreduction was performed at the time of surgery on 18/19 patients undergoing HILP and 11/12 patients undergoing HILI.

A cohort of elderly patients, defined as age greater than 80 years was separately analyzed. There were a total of 10 patients in this group (about 30% of the cohort); 6 patients underwent HILI and 4 patients underwent HILP. In Table 2, the demographic and clinical characteristics are summarized comparing the subset of elderly patients to the younger cohort. There is a statistical difference in age; however, the remaining characteristics including the N stage and burden of disease are equivalent between the older and younger cohorts.

Table 1
Demographic and clinical characteristics of patients by treatment type.

	HILP (n = 19)	HILI (n = 12)	p-value
Age, mean ± SD (years)	66.5 ± 15.6	76.3 ± 13.1	**0.05**
Male, n (%)	12 (63)	2 (17)	**0.02**
Extremity, n (%)			1.00
Upper extremity	4 (21)	3 (25)	
Lower extremity	15 (79)	9 (75)	
N stage at the time of HILI/HILP, n (%)			1.00
N1c	2 (11)	2 (17)	
N2c	9 (47)	5 (42)	
N3c	7 (37)	5 (42)	
Nx	1 (5)	0 (0)	
Burden of disease, n (%)			**0.05**
Low	0 (0)	3 (25)	
High	19 (100)	9 (75)	
Cytoreduction performed, n (%)	18 (95)	11 (92)	1.00

SD– standard deviation, N- nodal.

Regional toxicity

In Table 3, regional toxicity is summarized by group. The average length of hospital stay for all patients was 3.6 (±1.4) days with a slightly shorter length of stay for HILI patients (3.4 ± 2.0) compared to HILP patients (3.7 ± 0.9). There were no patients undergoing HILP who experienced a grade 3 or higher limb toxicity per Wieberdink classification. One patient undergoing HILI had a grade 3 reaction and one patient had a grade 5 reaction, requiring a mid-humeral amputation. Forty-two percent of HILP patients experienced some wound breakdown compared to 33% of HILI patients, and 53% and 42% of HILP and HILI patients, respectively, experienced a wound infection requiring antibiotics. The majority of complications were managed on an outpatient basis; however 7 patients (23%) required inpatient interventions, including reoperation (4 patients) and IV antibiotics (7 patients). There was no difference in the mean creatine phosphokinase level for HILP compared to HILI patients, and only 4 patients (13%) experienced a grade 3 or 4 serum elevation in CPK during their initial postop hospitalization (per Common Terminology Criteria for Adverse Events); all patients recovered appropriately with IV hydration prior to discharge home. Thirty-seven percent of patients undergoing HILP and 67% of patients undergoing HILI experienced neutropenia; all were treated successfully with subcutaneous filgastrim injections. Overall, the rate of 30-day readmission was 16% with no difference between the patients undergoing HILP compared to HILI.

In Table 4, the regional toxicity is summarized comparing the elderly to the younger cohort. Notably, the elderly patients had a shorter average length of hospital stay (3.3 ± 1.2 days vs. 3.8 ± 1.5 days for the non-elderly cohort), experienced no significant wound complications (one patient had minor wound erythema that improved with oral antibiotics), and had lower CPK values with no patients experiencing a grade 3 or 4 elevation in CPK. There was a slightly higher rate (60% vs 43%) of neutropenia in the elderly cohort compared to the younger cohort. Of note, in addition to having a shorter length of hospital stay, no patients age 80 or greater were readmitted within 30 days of discharge.

Table 2
Demographic and clinical characteristics of patients by age group.

	Age ≥80 (n = 10)	Age <80 (n = 21)	p-value
Age, mean ± SD (years)	85.5 ± 3.4	63.0 ± 13.1	**<0.01**
Male, n (%)	4 (40)	10 (48)	1.00
Extremity, n (%)			0.65
Upper extremity	3 (30)	4 (19)	
Lower extremity	7 (70)	17 (81)	
N stage at the time of HILI/HILP, n (%)			0.77
N1c	2 (20)	2 (10)	
N2c	5 (50)	9 (43)	
N3c	3 (30)	9 (43)	
Nx	0 (0)	1 (5)	
Burden of disease, n (%)			0.24
Low	2 (20)	1 (5)	
High	8 (80)	20 (95)	
Cytoreduction performed, n (%)	8 (80)	21 (100)	0.10

SD– standard deviation, N- nodal.

Table 3
Regional toxicity by treatment group.

	HILP (n = 19)	HILI (n = 12)	p-value
Hospital length of stay, mean ± SD (days)	3.7 ± 0.9	3.4 ± 2.0	0.08
Wieberdink >3, n (%)	0 (0)	2 (17)	0.14
Wound breakdown, n (%)	8 (42)	4 (33)	0.72
Wound infection, n (%)	10 (53)	5 (42)	0.72
Required reoperation, n (%)	2 (11)	2 (17)	0.63
Required IV antibiotics, n (%)	4 (21)	3 (25)	1.00
Neutropenia, n (%)	7 (37)	8 (67)	0.15
CPK, mean/median (IU/L)	546/388	573/146	0.09
Grade 3–4 elevation, n (%)	3 (16)	1 (8)	
30 day readmission, n (%)	2 (11)	3 (25)	0.35

SD– standard deviation.

Table 4
Regional toxicity by age group.

	Age ≥80 (n = 10)	Age <80 (n = 21)	p-value
Hospital length of stay, mean ± SD (days)	3.3 ± 1.2	3.8 ± 1.5	0.44
Wieberdink >3, n (%)	0 (0)	2 (10)	1.00
Wound breakdown, n (%)	0 (0)	12 (57)	**<0.01**
Wound infection, n (%)	1 (10)	14 (67)	**<0.01**
Required reoperation, n (%)	0 (0)	4 (19)	0.28
Required IV antibiotics, n (%)	0 (0)	7 (33)	0.07
Neutropenia, n (%)	6 (60)	9 (43)	0.46
CPK, mean/median (IU/L)	204/153	725/388	0.24
Grade 3–4 elevation, n (%)	0 (0)	4 (19)	
30 day readmission, n (%)	0 (0)	5 (24)	0.15

SD– standard deviation.

Hyperthermic isolated limb perfusion

For patients undergoing HILP, 100% of patients demonstrated a response to therapy. At 3 months post-operatively, 18/19 (95%) patients had a complete response (CR) and 1/19 (5%) patients had a partial response (PR). At 6 months post-operatively, 9/17 (53%) patients had a CR, 1/17 (6%) patients had a PR, and 7/17 (41%) patients had progressing/recurrent disease; 2 patients were lost to follow up. At 1 year follow-up post-operatively, 8/17 (47%) patients had a CR and 9/17 (53%) patients had progressing/recurrent disease (Table 5). Overall, 14/19 (74%) patients experienced a recurrence of their disease with a mean time to recurrence of 10.7 months. Of the 8 patients who had a CR at 1 year, 5/8 (63%) experienced recurrence of their disease with a mean time to recurrence of 21.0 months (Table 6). The remaining 3 patients (38%) were still disease free at the end of the study period.

Hyperthermic isolated limb infusion

For patients undergoing HILI, 10/12 (83%) of patients demonstrated a response to therapy. At 3 months post-operatively, 9/12 (75%) patients had a CR, 1/12 (8%) patients had a PR, and 2/12 (17%) patients had no response (NR). At 6 months, 8/12 (67%) patients had a CR, 1/12 (8%) patients had a PR, and 1/12 (8%) patients had progressing/recurrent disease (Table 5). At 1 year, 6/12 (50%) patients had a durable CR and 4/12 (33%) patients had progressing/recurrent disease. Overall, 6/10 (60%) patients who demonstrated a response to therapy had a recurrence of their disease with a mean time to recurrence of 10.7 months. However, of the 6 patients who had a CR at 1 year, only 2 patients experienced a recurrence of their disease; the remaining 4 patients were disease free until the end of the study period or until their time of death due to medical causes (Table 6).

Table 5
Clinical outcomes by treatment group.

	HILP (n = 19)	HILI (n = 12)	p-value
3 month response, n (%)			0.27[b]
Complete	18 (95)	9 (75)	
Partial	1 (5)	1 (8)	
None	0 (0)	2 (17)	
6 month response, n (%)[a]			0.70[b]
Complete	9 (53)	8 (67)	
Partial	1 (6)	1 (8)	
None	0 (0)	2 (17)	
Recurrent disease	7 (41)	1 (8)	
12 month response, n (%)			1.00[b]
Complete	8 (47)	6 (50)	
Partial	0 (0)	0 (0)	
None	0 (0)	2 (17)	
Recurrent disease	9 (53)	4 (33)	
Overall recurrence rate, n (%)	14 (74)	6 (60)	0.28
Time to recurrence, mean/median (days)	322/202	320/258	0.65

[a] Two patients in HILP group lost to follow up at 6 months.
[b] Comparison between patients with a complete response versus all other responses.

Table 6
Clinical outcomes by age group.

	Age ≥80 (n = 10)	Age <80 (n = 21)	p-value
3 month response, n (%)			0.09[b]
Complete	7 (70)	20 (95)	
Partial	2 (20)	0 (0)	
None	1 (10)	1 (5)	
6 month response, n (%)[a]			0.69[b]
Complete	5 (50)	12 (63)	
Partial	2 (20)	0 (0)	
None	1 (10)	1 (5)	
Recurrent disease	2 (20)	6 (32)	
12 month response, n (%)			1.00[b]
Complete	5 (50)	9 (47)	
Partial	0 (0)	0 (0)	
None	1 (10)	1 (5)	
Recurrent disease	4 (40)	9 (47)	
Overall recurrence rate, n (%)	7 (78)	13 (65)	0.84
Time to recurrence, mean/median (days)	333/240	315/224	0.53

[a] Two patients in age<80 group lost to follow up at 6 months.
[b] Comparison between patients with a complete response versus all other responses.

Subgroup analysis of patients over 80 years of age

For the cohort of patients over 80 years old, at 3 months post-operatively, 7/10 (70%) of patients had a CR, 2/10 (20%) patients had a PR, and 1/10 (10%) patients had NR. At 6 months, 5/10 (50%) patients had a CR, 2/10 (20%) patients had a PR, and 2/10 (20%) patients had progressing/recurrent disease. At 1 year, 5/10 (50%) patients had a CR and 4/10 (40%) patients had progressing/recurrent disease. Overall, the rate of recurrence was 7/9 (78%) for patients who demonstrated a response to therapy with a mean time to recurrence of 11.1 months.

Overall survival

For patients undergoing HILP, the overall mortality was 7/19 (37%) patients; the rate of death due to melanoma was 5/19 (26%) patients and the cause of death was unknown in 2/19 (11%) patients. The median survival was 22.6 months (mean 23.2 ± 5.5 months). The 1 year survival for HILP was 100% with a 3 year survival of 57%. For patients undergoing HILI, the overall mortality was 5/12 (42%) patients; the rate of death due to melanoma was 2/12 (17%) and the cause of death was medical in 3/12 (25%) patients. The median survival was 21.0 months (mean 21.2 ± 3.3 months). The 1 year survival for HILI was 100% with a 3 year survival of 52%. For elderly patients, the overall mortality was 30%; the median survival was 24.1 months (mean 21.6 ± 4.7 months). The 1 year survival for elderly patients was 100% with a 3 year survival of 68%. The Kaplan-Meier survival curves are shown in Figs. 1 and 2.

Subgroup analysis of patients experiencing complications

For patients who experienced a wound infection, the complete response rate at 1 year, rate of recurrence, overall mortality, and 1 and 3 year survival rates were similar to patients who did not experience a wound infection. For patients who did not experience a wound breakdown, the overall complete response rate at 1 year was slightly higher compared to those who did experience wound breakdown. The overall mortality was higher in patients with a wound breakdown compared to those without a wound breakdown (50% versus 32%), with a 3 year survival of 34% compared to 67%, respectively. These findings were not statistically significant and are summarized in Table 7.

Discussion

Since isolated limb perfusion was first introduced in 1958, regional chemotherapy has been a mainstay of treatment for melanoma patients with in-transit metastases.[10] Since the introduction

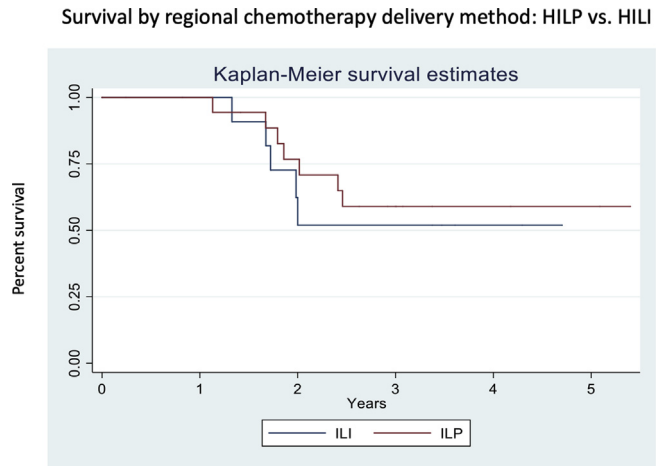

Fig. 1. Kaplan-Meier curve comparing survival in years by treatment (HILP versus HILI).

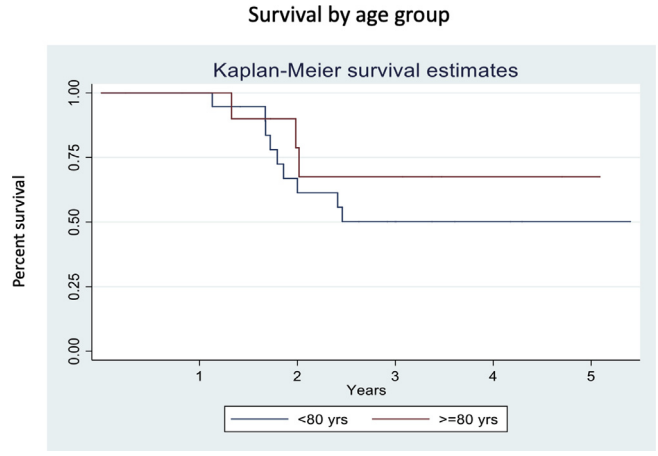

Fig. 2. Kaplan-Meier curve comparing survival in years by patient age (≥80 years old versus less than 80 years old).

Table 7
Clinical outcomes by complication.

	Yes	No	p-value
Wound infection (n = 15)			
Complete response at 1 year, n (%)	7 (47)	7 (44)	1.00
Rate of recurrence, n (%)	10 (67)	10 (71)	0.87
Overall mortality, n (%)	6 (40)	6 (38)	0.85
1-year survival, %	100	100	
3-year survival, %	52	58	
Wound breakdown (n = 12)			
Complete response at 1 year, n (%)	4 (33)	10 (53)	0.46
Rate of recurrence, n (%)	7 (58)	13 (76)	0.65
Overall mortality, n (%)	6 (50)	6 (32)	0.27
1-year survival, %	100	100	
3-year survival, %	34	67	

of effective systemic therapies such as BRAF/MEK inhibitors and immunotherapy, it has been challenging to directly compare the efficacies of these treatment regimens to that of regional chemotherapy because patients with in-transit melanoma are a heterogenous population who typically represent only a small subset of patients enrolled in clinical trials for systemic therapies.[11] In a trial of over 1,000 patients with unresectable stage III and IV melanoma, treatment with immunotherapy was variably effective; the rate of overall survival at 3 years was 58% in the nivolumab-plus-ipilimumab group, 52% in the nivolumab group, and 34% in the ipilimumab group.[12] However, 59% of the patients in the treatment group with the best response (nivolumab plus ipilimumab) experienced grade 3 or 4 adverse events with many requiring treatment termination.[12] Therefore, it is clear that an important role still remains for regional chemotherapy by HILP and HILI for these patients who have disease confirmed to a single extremity.[13] Through the years, many different techniques for performing HILP and HILI successfully have been described in the literature. Our operative technique is unique because we perform HILP and HILI without a limb tourniquet. In HILP, flow is isolated to the involved extremity by proximal clamps and leakage is determined by evaluating for losses through the perfusion circuit; in HILI, specialized occlusion catheters are used to isolate flow to an extremity. We feel the occlusion balloon catheters we place proximal to the limb in HILI cases, with on-table angiography to demonstrate limb occlusion of contrast flow, allow for a more efficient chemotherapy circuit than a limb tourniquet. Notably, our protocol for all regional chemotherapy cases utilizes Melphalan only; we do not add TNF-a to HILP cases nor actinomycin-D to HILI cases based on drug availability through our institution and lack of clear data that shows any superiority to outcomes with multiple chemotherapy agents.[14] In the past, one of the biggest concerns with regional chemotherapy has been drug leakage into the systemic circulation leading to significant renal and bone marrow toxicity. In our cohort, none of the patients experienced any life-threating toxicity from drug leakage outside the circuit. While a few patients experienced an increase in serum CPK levels in the immediate 24 h post-operatively, all were managed effectively with intravenous saline hydration during their initial hospitalization.

At the time of surgery, we perform an aggressive cytoreduction of all resectable disease, which can often require in some cases 10 or more separate wide local excisions as well as a formal lymph node dissection if this has not been done previously. Newer investigations suggest that the process of treating an isolated limb with high doses of melphalan followed by restoration of normal circulation can lead to the release of immunostimulatory antigens.[15] A 2018 report demonstrated that HILP with melphalan triggers immune activation, which lends further support to exciting clinical trials that are currently underway to determine whether there is a potential for synergism between regional chemotherapy and immunotherapy[15,16]. Therefore, we feel that performing a cytoreduction at the time of HILP/HILI adds to the inflammatory and immunogenic response in the limb and may enhance antigen presentation that can amplify the immune-inflammatory response.

Traditionally, HILP and HILI have been regarded as fairly morbid procedures with considerable concerns for vascular complications, local toxicity, and systemic toxicity, which has been reported in up to 27% of patients in early series.[17] Overall, regional chemotherapy has been shown to be safe with a low rate of limb compromise and minimal systemic leakage of chemotherapy.[18] Therefore, our postoperative protocol is to discharge patients home early when they have met appropriate standards for safety and perform monitoring for complications that may arise later on an outpatient basis. Our patients have an average length of stay of 3.6 days (3.7 days for HILP patients and 3.4 days for HILI patients). By comparison, a 2004 study of 130 patients in the Netherlands showed that the average hospital length of stay for patients undergoing HILP was between 19 and 23 days and a more recent report in 2016 examining administrative claims data of 113 patients found an average hospital length of stay of 5.6 (±3.5 days), which is nearly double our average length of stay[8,19]. Despite our accelerated protocol for discharge home, our patients experience a low rate of serious complications; only one person experienced a significant limb

complication and no patients developed elevations in creatine phosphokinase or neutropenia refractory to saline hydration or subcutaneous filgastrim treatment. In this series, the rate of patients experiencing true neutropenia after regional chemotherapy is difficult to assess; in our practice, to prevent any serious complications, we prophylactically treat patients in the outpatient setting with 300 mcg filgrastim subcutaneously when their WBC drifted below 3000/μL. We therefore classified all patients who were prophylactically treated with filgastrim injections as leukopenic, (37% of HILP and 67% of HILI patients in this series). The higher rate of mild leukopenia in the HILI group is likely due to the inability to control all the collateral venous outflow channels that open up during high flow perfusion and hyperthermia which can be better (but not completely) controlled with an open dissection technique as seen in the HILP group. Minor wound complications such as wound breakdown or infections were relatively common; however, the majority were managed successfully on an outpatient basis and most of these patients had 4 or more incisions to heal in the setting of a post-chemotherapy immune-modulated limb. For the entire cohort, including 10 patients over age 80, only 5 patients (16%) were readmitted within a 30-day time period. Therefore, we feel that compared to regional therapy alone, the addition of cytoreduction is safe to perform and can be done for any aged patient and may lead to a more durable response.

Historically, HILP has been regarded as superior to HILI, with more patients achieving a complete response.[20] In theory, the benefit of being on bypass with an oxygenated circuit in HILP allows for 90 min of chemotherapy circulation (compared to 30 min in HILI due to warm limb ischemia time), a better hyperthermia of the limb from the HILP circuit, and higher intravascular flow rates to open up capillary beds in the soft tissues where the drug-tumor interface could be enhanced. In our series, the patients were not randomized between HILP and HILI, and the HILI patients had a lower disease burden; therefore comparisons between these groups should be viewed with caution. However, we found no significant difference in the number of patients who obtained a complete response versus a partial or no response for HILP compared to HILI. Additionally, there was no statistically significant difference noted in survival rates or in the time to death between the HILI and HILP groups, which is reflected by equivalent N-staging between the HILP and HILI cohorts. The overall survival rate does not appear to be significantly affected by the presence of disease recurrence. We observed that the survival rate in patients who have recurrent disease is slightly lower at 60.0% compared to 66.7% in patients who do not experience a recurrence ($p = 1.00$).

The performance of cytoreduction at the time of regional chemotherapy is distinctive to our institution and therefore comparing definitions of complete response, partial response, and no response to reported outcomes in the literature becomes a bit challenging. Because cytoreduction at the time of surgery removes most readily visible disease, the primary determination of degree of response in our patients is based on whether there is any evidence of recurrence. However, our 6-month complete response rates for HILP of 53% and HILI of 67% are comparable, if not slightly higher than reported rates in the literature[14,21,,22] Additionally, we observed a 100% 1 year survival rate of patients undergoing both HILP and HILI, and our 3 year survival rates of 57% and 52% for HILP and HILI, respectively, are similar to historical response data.[22]

Uniquely, almost one third of our patients were over 80 years old, with a few patients even undergoing surgery in their 90s. Evidence in the literature supports the safety of performing HILP and HILI in an elderly cohort (typically defined as greater than 70–75 years of age).[23] In our study, we found no difference in the number of patients who obtain a CR versus a PR or no response when comparing our older cohort (80 years and up) to the non-elderly cohort. Additionally, there was no difference in the overall mortality or recurrence rate. Interestingly, despite increased frailty associated with an older population, our patients older than 80 years old did very well post-operatively, with a shorter average hospital length of stay (3.3 days vs. 3.8 days for the non-elderly cohort), and significantly lower rates of wound breakdown and infection. Additionally, none of the patients in the elderly cohort required readmission within 30 days of discharge. The 1 and 3 year survival rates in this older cohort were 100% and 68%, respectively, which is higher than reported in the literature, especially when many in the past have considered age a direct contraindication to the procedure.[23] This important response and survival data suggests that even very elderly patients diagnosed with in-transit metastatic melanoma can be considered for regional chemotherapy due to a lack of increased risk for complications and very durable long-term responses. Additionally, these elderly patients would not be considered suitable candidates by most medical oncologists for standard immunotherapy protocols. Therefore, in this population, regional chemotherapy may in fact be a superior treatment option given the observed improved survival rates, which have not been reported with immunotherapies in this age group. While patient selection in this group is always important, we feel our use of cytoreduction and a no-tourniquet technique may contribute to this observed response improvement.

There are several limitations to this study. The sample size of only 31 patients is small and reflects the relatively rare nature of this procedure. Additionally, this study is a retrospective analysis of a single institution's practice pattern, and therefore it is uncertain if these findings are generalizable to other centers. Because patients were not randomized to a certain treatment group, we are unable to directly compare outcomes of HILP versus HILI. Additionally, we are unable to adjust for the effects of systemic therapy on overall survival in patients who experienced disease recurrence after regional chemotherapy.

Conclusion

Cytoreduction with no tourniquet regional therapy for in-transit melanoma of the extremities results in durable response rates with 100% 1 year and up to 68% 3 year survival. Additionally, patients over 80 years of age tolerated both HILP or HILI without increased risk of complications; regional therapy may be a better option over systemic therapy in this age group. Validation in larger cohorts with longer follow-up will help support more utilization of this surgical therapy option.

Declaration of competing interest

The authors report no proprietary or commercial interest in any product mentioned or concept discussed in this article.

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