

The Treatment of Stage I Melanoma of the Extremities with Regional Hyperthermic Isolation Perfusion

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One hundred twenty-two clinically Stage I malignant melanoma patients were treated prospectively in a nonrandomized trial by hyperthermic isolation perfusion with l-phenylalanine mustard (l-Pam), regional lymphadenectomy (RL), and wide local excision (WLE) between April 1965 and July 1980. There were 31 males and 91 females. All primary lesions were retrospectively microstaged by Clark's levels and Breslow's thickness criteria by one of the senior authors. Morphologically, 71% were superficial spreading melanomas (SSM), 16.5% were nodular melanomas (NM), and 11.9% were acral lentiginous melanomas. Survival by microstaging and morphology are reported in Table 1. Eighty-one per cent of all patients were disease-free at five years. Twenty-three patients (18.8%) recurred and of these, 15 died of their disease. This included six of the seven patients with histologically positive lymph nodes. Complications were not only acceptable but preventable and will be discussed. Microstaging provides a valid basis by which to compare treatment regimens and, more importantly, a valid criteria by which to select treatment for a given patient. These data compare favorably with other reported series. At the time these studies were initiated, five-year survivals for clinically Stage I and II melanoma were roughly 55% and 15%, respectively. Existing data clearly indicate that hyperthermic isolation perfusion with RL is superior to WLE and warrants further study in selected patients.

THE OPTIMAL TREATMENT of Stage I malignant melanoma of the extremities remains a controversial subject. The development of microstaging techniques by Clark,¹ McGovern,² and Breslow^{3,4} has allowed the authors' to identify groups of patients who are at high

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risk for developing recurrent disease and who, in turn, would benefit from more aggressive therapy. Two reports of prospective randomized studies to assess the benefit of prophylactic regional lymphadenectomy (RL) have revealed no benefit of RL although reports to the contrary continue to be published.⁴⁻⁷

In 1958 Creech⁸ first reported the use of regional perfusion (RP) with l-phenylalanine mustard (l-PAM) in a 76-year-old male with regional cutaneous metastatic melanoma of his left leg. This new procedure resulted in total regression of tumor, and the patient lived the remaining 14 years of his life free of disease. Since this first published report, several medical centers in the world have reported a 10 to 20% improved survival and recurrence rate over conventional surgical therapy.⁹⁻¹³ In 1967 Stehlin began adding heat to the perfusion and reported improved results over his non-heated perfusion results.^{14,15}

McBride, et al.¹⁶ recently compared survival and recurrence rates in patients with melanomas of the extremities who had wide local excision (WLE) alone, WLE with RL, or WLE with RP. He discovered that patients with lesions level III or greater and thicker than 1 mm had significant improvement in survival, rates of recurrence, and disease-free interval if they had been treated by WLE and RP.

Method and Materials

One hundred and twenty-two patients with clinical Stage I malignant melanoma of the extremities were treated prospectively in a nonrandomized trial with regional hyperthermic isolated perfusion at the Oregon Health Sciences University (OHSU) between April 1965 and July 1980. The results are reported according to micro-staging, sex, morphology, and primary site.

All patients in the study were treated with regional hyperthermic perfusion with l-phenylalanine mustard

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followed by wide local excision and regional lymphadenectomy at the same operation. Most local excisions required a split thickness skin graft, although many were closed primarily. Two subungual lesions were treated by amputation of the digit. Follow-up for all patients was at least one year and ranged from one to 17 years with a mean of 6.1 years.

Perfusions were performed using the Sarns perfusion pump along with the Bentley Q130 infant oxygenator and a heat exchanger. The pump was primed with one unit of fresh whole blood, and the l-PAM was circulated for one hour at a temperature of 40 to 41 C carefully monitored throughout the procedure. The extremity was not otherwise heated and tissue temperatures of 35 to 36 C were obtained. L-PAM was administered in a dose of 0.75 to 1.0 mg/kg for upper extremity perfusions and 1.0 to 1.5 mg/kg for lower extremities. Following termination of the perfusion, the extremity was washed with one liter of 6% dextran.

The microscope slides of the primary lesion and lymph nodes were all reviewed by one pathologist who had no knowledge of the patients' clinical course. All lesions were microstaged according to both Clark's¹ and Breslow's² classifications. Histologic type was recorded as well as a systematic evaluation for other histologic features.

All but one patient were available for follow-up and complete survival data was obtained. A Berkson-Gage life table analysis was performed for all patient subgroups as well as the entire population. A disease-free interval rate was also calculated by this method. A student t-test was used to assess statistical significance of all data curves at five and ten years.

Results

There were 31 males and 91 females entered into the study. Seventy-eight (71.6%) of the patients were found to have superficial spreading melanoma (SSM). Eighteen (16.5%) of the patients had nodular melanoma (NM) and 13 (11.9%) had acral lentiginous melanoma (ALM). No patient had a lentigo melanoma. Eighty-five (69.7%) patients had lower extremity primary lesions, and 35 (28.7%) had upper extremity primary lesions. The remaining two (1.6%) patients had subungual lesions. Seven patients (5.7%) had microscopic lymph node metastases, all of whom went on to have recurrent disease.

The breakdown of the population into Clark's levels is as follows: eight level II (7.1%), 53 level III (46.9%), 46 level IV (40.7%), and six level V (5.3%) (Fig. 1). Microstaging according to Breslow's depth of invasion reveals 20 patients (16.4%) ≤ 0.76 mm, 42 patients (34.4%) 0.77 to 1.49 mm, 45 patients (36.9%) 1.50 to

TABLE 1. Survival by Microstaging and Morphology

Microstage	% of Patients	Five-yr. Survival	Ten-yr. Survival
All patients	100	90%	76%
SSM	71.6	91%	91%
NM	16.5	78%	35%
AL	11.9	71%	71%
Clark's level II	7.1	100%	100%
Clark's level III	46.9	100%	81.8%
Clark's level IV	40.7	80.3%	56.7%
Clark's level V	5.3	47.6%	47.6%
Breslow's thickness:			
Less than 1.49 mm.	50.8	100%	100%
1.5 mm-2.99 mm.	36.9	84.5%	58.8%
3.0 mm-3.99 mm.	5.7	75%	75%
More than 4.0 mm.	6.6	50%	25%
Female	74.6	91.6%	77.7%
Male	25.4	84.1%	70.1%

2.99 mm, seven patients (5.7%) 3.00 to 3.99 mm and eight patients (6.6%) ≥ 4.00 mm (Fig. 2).

Twenty-three patients (18.8%) developed recurrent disease during the study, of whom 16 (13.1%) were found to have disease in the perfused extremity, six local (4.9%), eight intransit (6.6%), and two regional nodes (1.6%). It is notable that five of six patients with local recurrence had required a skin graft for the initial wide excision. Of the males, 22.6% had recurrences while only 17.6% of all females recurred. Only 16 (13.1%) of the patients whose tumor recurred had histologically

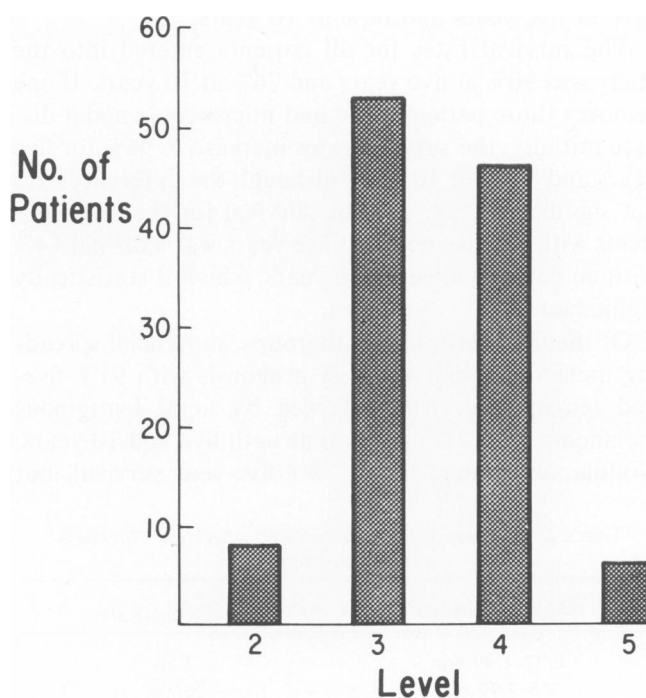


FIG. 1. Number of patients in each Clark's level.

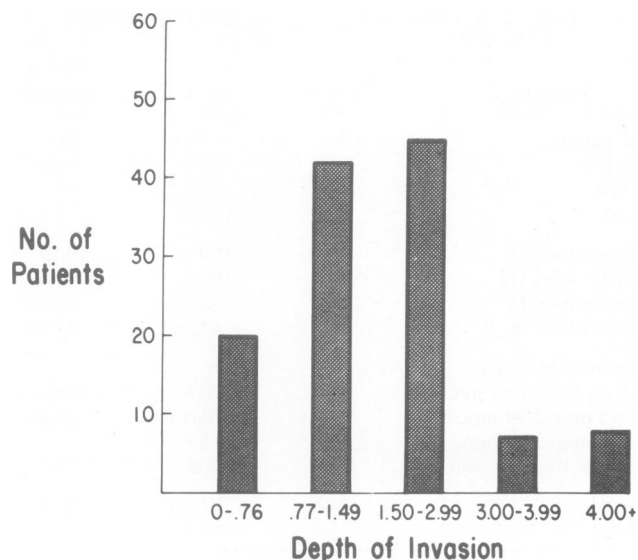


FIG. 2. Breakdown of patient population into Breslow thickness categories.

confirmed negative lymph nodes at the original surgery. Fifteen of the patients who developed recurrent disease eventually died of their disease, six of them had microscopically positive nodes at surgery.

Sixty-seven % of the patients who had level V disease developed recurrence; 30.4% of the patients with level IV disease and 7.5% of patients with level III primary lesions had recurrent disease. None of the patients with a level II lesion experienced recurrence. Similarly, increase in recurrence rate is seen as depth of invasion increases (Table 2). The overall disease-free interval is 81% at five years and 66% at 10 years.

The survival rates for all patients entered into the study was 90% at five years and 76% at 10 years. If one removes those patients who had microscopic nodal disease initially, the survival rates increase to 95% for five years and 82% for 10 years although the differences are not significant (Fig. 3). The survival for the seven patients with positive nodes at five years was a dismal 14% with no patients alive at ten years, which is statistically significant.

Of the three histologic subgroups, superficial spreading melanomas had the best prognosis with 91% five- and ten-year survival, followed by acral lentiginous melanoma with 71% survival at both five and 10 years. Nodular melanoma had a 78% five-year survival, but

TABLE 2. Recurrence Rate According to Breslow Thickness Classifications

Depth of Invasion	Recurrence Rate
0.77-1.49mm	3.2%
1.5-2.99 mm	26.7%
3.0-3.99 mm	42.9%
≥4.00 mm	75.0%

only 35% lived ten years. These differences were not significant however (Fig. 4).

Females fared better than males with 92% five-year and 78% ten-year survival. The male population had an 84% five-year and 74% ten-year survival ($p = 0.3$) (Fig. 5).

Study of survival rates of the various Breslow groupings shows that none of the patients with a lesion less than 2.00 mm died. For the group between 1.50 and 2.99 mm, survival was 85% at five years and 59% at ten years. Seventy-five per cent of those with lesions 3.00 to 3.99 were alive at five and ten years. As expected the thicker lesions (≥ 4.00 mm) had the worst five- and ten-year survival: 50% and 25%, respectively ($p = 0.01$) (Fig. 6).

Lesions staged according to Clark's levels showed a progressive decrease in survival as the level increased. Level III lesions were associated with 100% five-year and 82% ten-year survival. The patients with level IV lesions had an 80% five-year survival and 57% ten-year survival. Forty-eight per cent of those with level V lesions were alive at five and ten years ($p = 0.02$) (Fig. 7).

The morbidity of this procedure was both acceptable and in many cases preventable. No patient died from

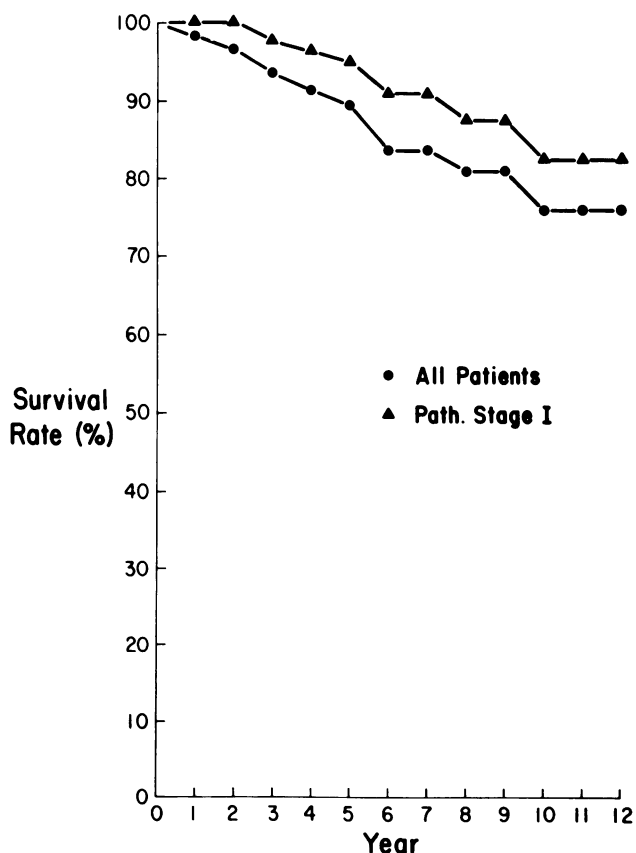


FIG. 3. Overall group survival rate and overall survival rate of all patients.

the procedure and one patient had a nonfatal pulmonary embolus. Two patients required lower extremity amputation, and one patient developed severe arm contractures secondary to a compartment syndrome. These three complications occurred early in the study and were all caused by a faulty heat exchanger that allowed the perfusate to become too hot. Once discovered, the heat exchanger was replaced and no such morbidity has occurred since.

Mild edema occurred in 18% of upper extremities perfused and 41% of lower extremities but was easily controlled with elevation or elastic stockings. Most cases of edema occurred in obese patients or those who had delayed flap healing. Only two patients developed massive lymphedema. Fifteen patients developed wound complications. The average hospital stay was 16.2 days.

Discussion

The theoretical advantage of regional perfusion is that it enables one to deliver 6 to 10 times the usual systemic dose of a given agent without the systemic

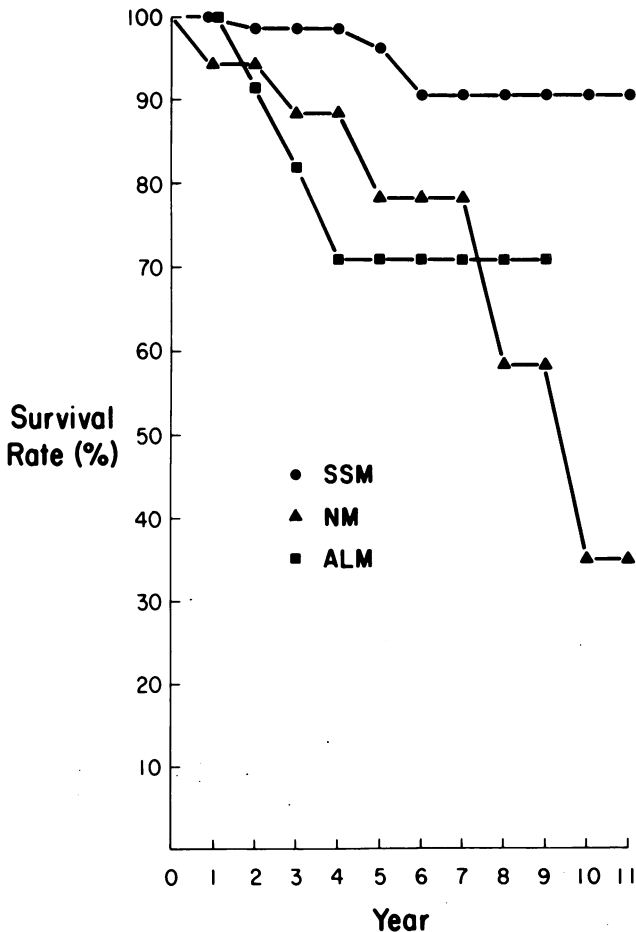


FIG. 4. Survival rate according to histology.

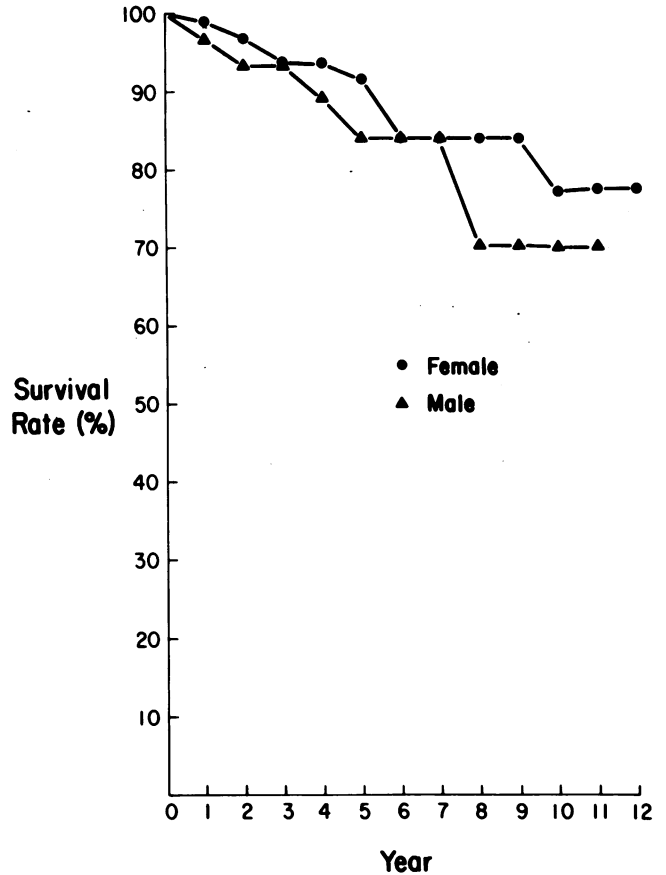


FIG. 5. Survival rate by sex.

toxicity. Kremenz,¹⁷ and others,^{18,19} have shown that increasing tissue oxygen tension potentiates the effect of alkylating agents. The infant oxygenator used during perfusion enables one to achieve increased tissue oxygen tension in an extremity while perfusing that extremity.

Cavaliere,²⁰ in 1967, showed that perfusing heated blood without drugs caused tumor regression in certain tumors while others have reported synergism between heat and chemotherapeutic agents.^{21,22} Stehlin^{14,15} found that heating the blood during perfusion of l-PAM improved the survival rate of melanoma patients when compared with his previous patient population who underwent normothermic perfusion. Stehlin also reported an increased plasma cell and lymphocyte activity after hyperthermic perfusion¹⁴ although Hersh²³ reported an inhibitory effect on lymphocyte blastogenic response in the perfused extremity, even though no systemic effects were seen. Kremenz has suggested that perfusion may produce autoimmunization by local tumor destruction which stimulates a host immune response.⁸

The data presented in this report support the claims of other centers currently using regional perfusion of Stage I melanoma of the extremities. An overall five-year survival rate of 90% and 76% 10-year survival is

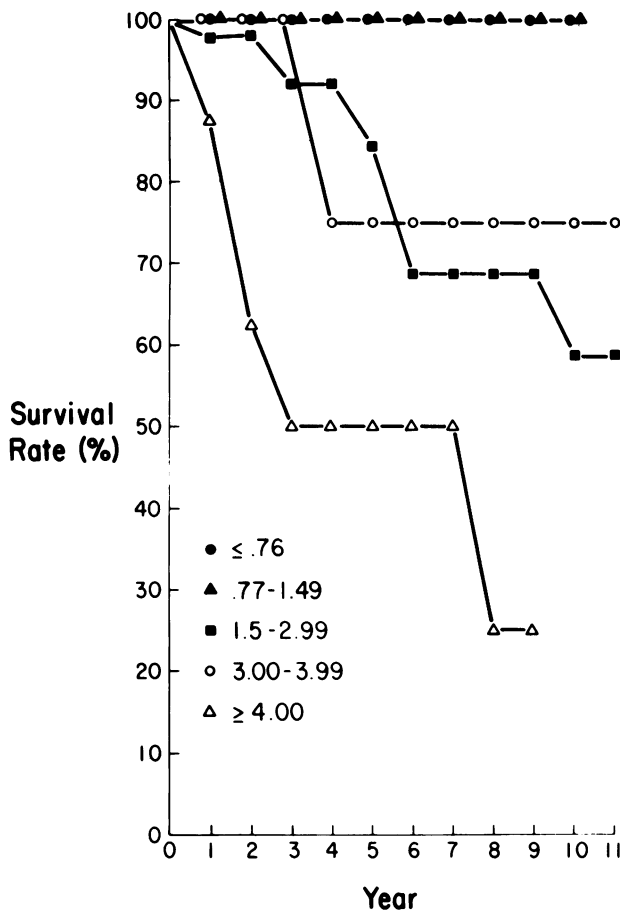


FIG. 6. Survival rate according to Breslow thickness classification.

similar to that reported by others using perfusion.⁸⁻¹² If the patients with microscopic nodal metastases are removed, survival is 95% at five years and 82% at 10 years. These figures represent a 10 to 20% improvement over reported series of wide excision with or without lymphadenectomy.^{4,6,24-27} Similar comparisons are seen when the data is considered by sex, location, histologic type, and Clark's and Breslow's classifications. The inconsistency seen in the Breslow group 3.00 to 3.99 mm was most likely because of small sample size. The five-year survival was probably more representative of the group. It is notable that no patient with a lesion less than 2.00 mm died through the entire study, and only two have had recurrence in this group. Both of these patients are alive without disease following further treatment, one six and one-half years and the other four years. This is remarkably better than other reported series for patients with lesions up to 2.00 mm.

In the total population of 122 patients, 23 developed recurrence of disease for a total recurrence rate of 18.8% while only 16 (13.1%) developed recurrence within the treated extremity. The local recurrence rate of 4.9% is consistent with Sugarbaker's rate of 2%, al-

though the nodal recurrence rate of 1.6% is lower than Sugarbaker's 13% without node dissection.²⁸ Fifteen of the 23 patients who developed recurrence ultimately died of their disease. The intransit metastasis rate of 6.6% is lower than McCarthy's 22%,²⁹ Moore's 20%,³⁰ and Fortner's 18%.³¹ These figures are quite favorable when one considers nearly 50% of the population had level IV or V lesions or lesions greater than 1.5 mm. Sugarbaker et al. reported a 25% overall recurrence rate in Stage I patients.²⁸

Controversy prevails as to whether "prophylactic" regional lymphadenectomy (RL) is beneficial when compared to wide local excision (WLE) alone. Contrary to the WHO and Mayo series as cited above, Balch showed significant benefit of RL in patients with lesions 0.76 to 3.00 and found the benefit did not become apparent until the fifth to eighth years.⁷ Neither prospective study followed their patients that far from initial treatment. Breslow reported benefit in patients with lesions greater than 1.50 mm although he reported 6% recurrence in lesions 0.76 to 1.50 mm.⁴ Wanebo³² and MDAH¹⁶ have both reported marked increase in survival (19% and 26%, respectively) in patients with level

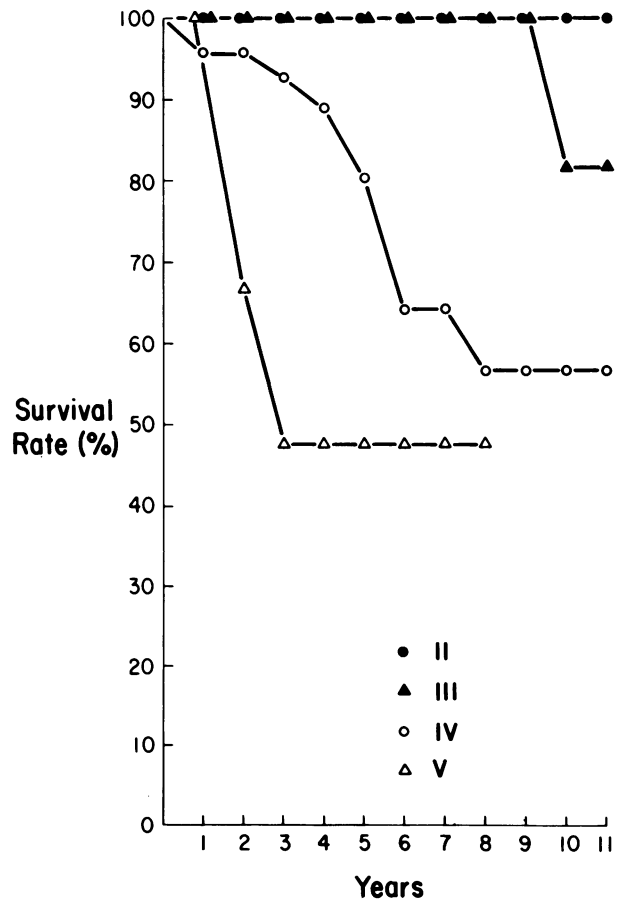


FIG. 7. Survival rate by Clark's levels.

III lesions who receive WLE and RL compared with WLE alone. Neither of these differences was significant, but probably because the numbers were too small. The authors' regional node recurrence rate of 1.6 per cent is superior to those who do perfuse but do not perform RL.²⁸ The authors believe this supports the use of prophylactic RL.

Conclusions

The authors are of the opinion that the prognosis of Stage I melanoma of the extremities can be favorable and can be improved with an aggressive approach to the disease initially. Microstaging techniques have allowed the authors to identify patients at high risk for recurrence of disease. It is recommended that all patients with level III to V lesions greater than 0.76 mm undergo wide local excision with regional lymphadenectomy and regional hyperthermic perfusion and that with this regimen 90%, or better, five-year survival can be achieved.

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DISCUSSION

DR. WATTS R. WEBB (New Orleans, Louisiana): Dr. Krementz, who could not be here, asked me to present a few of the relevant data from the Tulane series, which started with the pioneering work of Dr. Oscar Creech in June of 1957, when he perfused the extremity (slide) of the man shown here, who had satellitosis (slide) of the extremity on the medial aspect of the thigh.

(slide) Nine years later there was total absence of any recurrent

melanoma, and this man lived for a total of 16 years, dying at the age of 92 without any evidence of recurrence.

(slide) To pick a couple of pertinent points from this, you will notice that over the 20-year survival curve of all patients with Stage I having perfusion therapy, you notice that at five years the survival is 87.7%, very similar to that presented today; at ten years, 78%; and then at 15 and 20 years very little drop-off. Essentially, there is a plateauing at eight years, and essentially nothing except a very rare, dramatic recurrence after ten years.