A Prospective Randomized Study of Regional Extremity Perfusion in Patients with Malignant Melanoma

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One hundred seven patients presenting with malignant melanoma of the extremities were included in a prospective randomized study, which was conducted to evaluate the effectiveness of adjuvant hyperthermic regional cytostatic perfusion. In a control group (A, N = 54) the tumors were excised widely and the regional lymph nodes were dissected. The patients in the second group (B, N = 53) received additional hyperthermic (42 C) perfusion with melphalan. The mean follow-up observation period was 554 days. We chose the disease-free survival time as the criterion for success. The study could be discontinued prematurely, since the intermediate evaluation revealed a highly significant difference between the groups (p = 0.0001). We observed 21 local recurrences in the control group and four recurrences in the perfusion group. The retrospective breakdown by clinical stages also showed significant differences. The recurrence rate in the control group was 27.8% in Stage I, 31.6% in Stage II, and 58.8% in Stage III. In the perfusion group we observed recurrences equaling 5.6% in Stage I, 5.5% in Stage II, and 12.5% in Stage III. The differences between the groups based on the target-criterion of disease-free survival represent significance levels of p = 0.09 in Stage I, p = 0.03 in Stage II, and p = 0.003 in Stage III. We feel that on the evidence provided by our study, shown in the above results, the adjuvant application of regional hyperthermic cytostatic perfusion has proven itself to be superior to conventional procedures alone.

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WITH SIGNIFICANT PROGRESS in our understanding of the biologic behavior of cutaneous malignant melanoma, it becomes more obvious that local surgical removal of the tumor, when utilized as sole therapy, has only a chance of success in patients presenting with a primary of minor invasion depth.[1,2] In more extensive tumor invasion or in local or regional metastases, even additional, often aggressive regimen of therapy, such as systemic chemotherapy and immunotherapy or combinations of both, have in the past not resulted in any substantial improvement of results.[3-6]

Regional cytostatic perfusion, supplemented by hyperthermia,[7] has been used as adjuvant procedure in the treatment of malignant melanoma of the extremities since 1958.[8] Improvements in the rate of recurrence or survival of up to 25%, as compared to conventional surgical therapy, have been reported by several authors.[9-13] Owing to the fact that a controlled evaluation has not hitherto been conducted, the results achieved by these authors are of rather limited value. We therefore planned a prospective randomized study in which the additional use of regional hyperthermic cytostatic perfusion of the extremity in patients with malignant melanoma was examined.

Method

We carried out a prospective comparative study with a fixed number of patients.[14] All patients who were admitted to the surgical or dermatological departments of the University of Cologne from October 1, 1980 onwards were scheduled to participate in the study provided that the following criteria were met: age below 70; no clinical evidence of distant metastases, localization of the primary other than in the proximal third of the extremity, and written consent to take part in a randomized study.

Patients with minor invasion depth (Clark's level < IV and tumor thickness of <1.5 mm) of the primary were excluded from the study. Pathologic materials of all patients admitted to this study, including lymph nodes and resection specimens, were reviewed by our resident pathologist.

Patients were randomly assigned to two groups. Those in the control group (group A) had their tumors widely excised and regional (inguinal or axillary) lymph nodes dissected. The patients in the perfusion group (group B) were treated as in group A, but also received regional hyperthermic cytostatic perfusion. To achieve this on the upper extremity, the first portions of the axillary artery and vein were catheterized. For the lower limb,

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the external iliac vessels were used. After heparinization (100 units/kg), the perfusion catheters were connected to an extracorporeal circuit consisting of a disposable Bentley pediatric-size heater/bubble oxygenator and a low-flow rotary pump. The perfusate consisted of 750 ml heparinized whole blood (2000 units/500 ml). The arterial line tempeature was maintained at 42.5 C. Flow rates ranged from 350 to 600 ml/min for the lower extremity and 250 to 400 ml/min for the upper extremity. The tourniquet consisted of two loops of Esmarch bandage placed around the root of the extremity and held in place by Steinmann pins placed through the skin and subcutaneous tissue. Limb temperatures were elevated to 42 C and monitored by thermistor probes placed into both intramuscular and subcutaneous tissue. The drug was added in divided doses as soon as the limb reached a temperature of at least 40 C; the perfusion was then continued for a further 60 minutes. Melphalan was used in dosages of 1.5 mg/kg of body weight (BW) for perfusing the lower extremities, and 1 mg/kg BW for perfusing the upper extremities. The leakage from regional to whole body circulation was measured by means of a modified dye-dilution method.[15] To achieve this, 0.1 ml/kg BW of 0.5% Evans blue solution was systemically applied at the onset of anesthesia and after 10, 20, and 30 minutes we measured the dye concentration in plasma by means of a spectral photometer at 620 nm. Through extrapolation to zero, the plasma volume and the elimination rate of the dye were calculated. After isolation of the extremity, 0.1 ml/kg BW of the dye solution was again injected in the isolated circuit and plasma dye concentration in the whole body circulation was measured at 10-minute intervals.

To test the sufficiency of perfusion, the perfusion pressure was continuously registered and samples of arterial and venous blood were taken at 10-minute intervals from the extracorporeal circulation and blood gas analysis carried out.

During perfusion, the lesions were widely excised and the defect closed either with a split-thickness skin graft or by mobilization of flaps. The deep fascia was left intact unless involved by tumor. On completion of the perfusion a washout of the circuit was performed using 1000 ml whole blood. After the catheters were withdrawn and the vessels repaired, protamine sulfate in doses equal to that of heparin was administered.

Following perfusion, lymphadenectomy was done in the same manner as in group A.

A precondition for the design of the study was the definition of the target criterion, the therapeutic difference between the groups, the errors type 1 and 2, and number of patients fulfilling the above criteria. As target criterion we established a disease-free survival period for each group. We assumed the therapeutic difference between the control group (A) and the perfusion group (B) to be 25%. This assumption was based on results reported in literature, achieved with or without perfusion.[10,12,13] Rating errors type 1 and type 2 at five per cent and 10%, respectively, we calculated the number of cases, *i.e.*, 67 patients per group for a one-sided test.[16] Since Stehlin and co-workers[12] estimated that the efficacy of regional hyperthermic cytostatic perfusion was substantially greater than assumed when starting the study, we intended to perform an intermediate evaluation after one-half or three-quarters of the patient population had been admitted to the study. In the event of a higher level of significance ($p = 0.005$ or 0.0001) being observed, it was planned to discontinue the study prematurely.[17]

The cumulative disease-free survival rate was calculated according to the product-related method given by Kaplan and Meier.[18] The baseline for each observation period was taken as the day of the operation, and the end point as any clinically detectable recurrence or death. The observation periods, thus defined, can then be regarded as having been randomly established. Based on complete follow-up data ending July 31, 1983, significant difference between groups A and B could be detected. No new patients were admitted to the study after March 1983. No correction for survival rates in the various age groups was made. We compared the survival rates using a nonparametric rank test, according to Mantel.[19,20]

In order to gain further evidence of the effectiveness of regional hyperthermic cytostatic perfusion in different clinical stages, the patient population was retrospectively broken down into its separate clinical stages. Our patients were classified according to the staging system of M. D. Anderson.[21]

Stage I tumors have no clinical signs of metastasis or any microscopic evidence of melanoma in the node removed on regional lymphadenectomy.

In Stage II, local metastasis or local recurrence occurs within 3 cm from the scar of a primary lesion. In Stage IIIa, regional in-transit metastasis develops without clinical or microscopic evidence of metastasis in the regional lymph nodes. Stage IIIb consists of proven metastasis to the regional lymph nodes with no evidence of in-transit disease. In Stage IIIc, in-transit metastasis occurs as well as regional lymph node metastases.

Stage IV tumors are those with distant metastasis. The disease-free survival rate and the difference between the two groups was calculated using the methods mentioned above.

All patients have been followed up at 3-month intervals by physical examination, chest x-rays, and sonography of the abdomen.

In the presence of any recurrence detected by the patients themselves, the follow-up net was refined.

TABLE 1. *Characteristics of 107 Patients with Malignant Melanoma of the Extremities Separated into Therapeutic Groups (A: No Perfusion, B: Perfusion)*

	Group A (N = 54)	Group B (N = 53)	Total (N = 107) (100%)
Sex			
Male	12	11	23 (21.5%)
Female	42	42	84 (78.5%)
Tumor site			
Upper extremity	4	12	16 (15.0%)
Lower extremity	50	41	91 (85.0%)
Age (years)	48.0	46.5	47.25
±	8.1	12.9	10.5
Previous surgery	21	21	42 (39.2%)
Recurrence	21	4	25

Results

The study was discontinued before the planned number of cases was reached. The current evaluation results in highly significant differences between the groups.

Up to March 1983, 115 patients were primarily admitted to the study, randomized, and operated on. Eight patients had to be excluded after surgery because the final examination of the surgically removed specimens revealed a tumor thickness of less than 1.5 mm or an invasion depth of less than Clark's level IV. Of the 107 patients evaluated (Table 1), 84 were female and 23 male. The average age was 47.2 years. The tumor was located on the upper extremity in 16 cases and on the lower extremity in 91 cases. Forty-two patients had undergone at least one previous surgical procedure.

During the surgical procedure itself, none of the patients in either group developed any complications. In the perfusion group we measured flow rates of 300.83 ± 53.28 ml/min in the upper and 507.74 ± 66.67 ml/min in the lower extremity. At these flow rates the perfusion pressure was 84.23 ± 9.89 mmHg. The blood gas analysis gave the following results. In the arterial line of the extracorporeal circuit the partial pressure was 506.86 ± 55.27 mmHg for O_2, 27.74 ± 4.88 mmHg for CO_2, and the pH was 7.475 ± 0.057. In the venous line the partial pressure was 54.05 ± 8.52 mmHg for O_2, 30.63 ± 3.62 mmHg for CO_2, and the pH was 7.390 ± 0.039.

The plasma volume was on average 55 ml/kg BW. The elimination rate of the dye was between 7.5% and 13.2%/hour. Leakage was found to be 5% ± 0.3% of the volume of the extracorporeal circuit.

We observed postoperative complications in the wound healing process and lymphatic fistulae in both groups. In the perfusion group we found systemic and local disorders in addition to the above (Table 2). Any disorders, however, were reversible over a maximum period of 12 weeks, and in none of the cases was the patient's life endangered, nor was the function of the extremities permanently impaired.

After a mean follow-up period of about 550 days, 21 local recurrences occurred in the control group and four recurrences in the group having received adjuvant regional hyperthermic cytostatic perfusion. The differences between the groups (Fig. 1) are based on the target criterion of highly significant "disease-free survival" ($p = 0.0001$). The retrospective breakdown showed an even distribution of the patient population in the individual tumor stages (Table 3). In the control group, the recurrence rate was 27.8% in Stage I, 31.6% in Stage II, and 58.8% in Stage III. In the perfusion group, we observed a recurrence rate of 5.6% in Stage I, 5.5% in Stage II, and 12.5% in Stage III. The differences between the groups were significant: $p = 0.09$ in Stage I, $p = 0.03$ in Stage II, and $p = 0.003$ in Stage III.

Of interest is the difference in time of onset of local recurrence between the two groups. In the control group we observed on average local recurrence in Stage I after 174 days, Stage II after 115 days, and Stage III 195 days. In the perfusion group local recurrence occurred in patients from Stage I after 540 days, Stage II after 488 days, and Stage III 708 days.

Four patients from the the control group died (after 15, 16, 19, and 20 months, respectively) after local recurrence as result of systemic metastases. In the perfusion group only one patient with local recurrence died after 33 months of systemic metastases. This difference between the two groups is significant ($p = 0.0207$).

TABLE 2. *Major Complications Following Wide Excision and Node Dissection (Group A) with Adjuvant Regional Perfusion (Group B) in 107 Patients with Malignant Melanoma of the Extremities*

	Group A (No Perfusion) (N = 54)	Group B (Perfusion) (N = 53)
Local complications		
Wound infection	3 (5.5%)	3 (5.7%)
Edema	2 (3.7%)	4 (7.5%)
Lymph fistula	4 (7.4%)	4 (7.5%)
Pain	—	4 (7.5%)
Erythema	—	4 (7.5%)
Systemic complications		
Fever	—	22 (41.5%)

Discussion

Although regional cytostatic perfusion of the extremities in the treatment of malignant melanomas has, over the past 2 decades, become routine practice in many oncological centers, its administration continues to be disputed. Critics of the method maintain that as yet no statistically reliable proof of its benefit has been provided. Experience gained from experiments both with cell

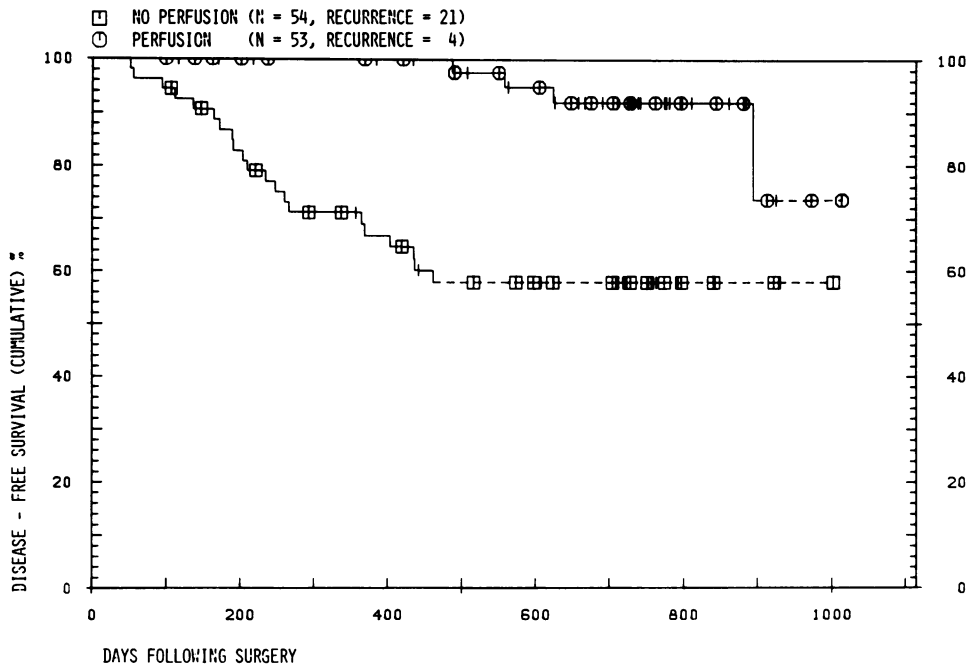

FIG. 1. Actuarial analysis of patients with malignant melanomas of the extremities randomized to receive either regional hyperthermic cytostatic perfusion or no perfusion following definitive local treatment. An advantage for the perfusion group is seen ($p = 0.0001$); symbols ⊞, ⊕, and + represent censored observations, a dashed line is plotted to designate the open end-interval of observation.

cultures and animals on the efficacy of hyperthermia and regional high-dose administration of cytostatics in malignant tumors,[22-25] and the improved results of perfusion therapy available from retrospective studies[9-13] does not, after all, prove the superiority of the method. An additional negative factor is that the individual study groups have applied the method in different ways. Without considering the other aspects of additional personnel, financial burden, and the lengthy operation time, many surgeons are still reluctant to apply the method.

In this study the tumors and lymph nodes were removed in accordance with the generally accepted rules of tumor surgery. Lymphadenectomy was performed in all patients, even in clinical Stage I patients. Although this procedure continues to be the subject of discussion,[26-28] in our opinion, considering the relatively high rate of occult metastasis in the lymph nodes and the inconsiderable strain the patients are subjected to, this procedure is justified and necessary for an accurate classification of the stages in the current study.

For perfusing the extremities, we used the cytostatic

TABLE 3. *Characteristics of 107 Patients with Malignant Melanoma of the Extremities Separated into Therapeutic Groups (A: No Perfusion, B: Perfusion) and Clinical Stages*

	Clinical Stages									
					III					
	I		II		III a		III b		III c	
	A	B	A	B	A	B	A	B	A	B
Total	18	19	19	18	3	1	5	4	9	11
Sex										
Male	2	4	5	1	1	—	1	3	3	3
Female	16	15	14	17	2	1	4	1	6	8
Tumor site										
Upper extremity	2	3	1	6	—	—	1	—	—	3
Lower extremity	16	16	18	12	4	2	5	3	7	8
Clark's level										
IV	11	13	10	8	1	—	—	1	5	5
V	7	6	9	10	2	1	5	3	4	6
Tumor thickness										
1.5–3.0 mm	12	10	8	9	—	1	2	2	3	3
3.1–4.5 mm	6	9	11	9	3	—	3	2	6	8
Recurrence	5	1	6	1	2	—	1	—	7	2

agent melphalan. This drug is used by nearly all study groups and is regarded as the most effective cytostatic agent under conditions of hyperthermic perfusion.[9-13,21]

Some authors perfuse at temperatures of 40.5 C, because they fear the increased incidence of further complications such as edema, tissue necrosis, and nerve damage at higher temperatures.[7,10,11] In animal studies, we performed the cytostatic perfusion with whole blood instead of physiologic solutions and did not observe any irreversible postoperative damage, not even at tissue temperatures of 42 C.[29] For this reason, *i.e.*, in order to make full use of the hyperthermic effect, we perfused the patient's extremities at this temperature. We found, compared to the other authors, substantially fewer postoperative complications.

The results of the study show the superiority of adjuvant hyperthermic perfusion in the treatment of malignant melanomas as compared to conventional methods. The results of hitherto retrospective studies are thus confirmed.[10-13]

Our criterion of success was disease-free survival time, since this represents the earliest parameter for a reliable evaluation of the further course of the disease in melanoma patients.[30,31] In view of the fact that the results of the two treatment groups show highly significant differences, we do not consider it tenable to conduct a study in which 5 to 10 years of survival are regarded as criteria for success; nevertheless, we continue observation and statistical analysis in order to fix any late effects.

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