

# Regional Perfusion in the Treatment of Patients with a Locally Metastasized Malignant Melanoma of the Limbs

H. MARTIJN, J. OLDHOFF and H. SCHRAFFORDT KOOPS\*

*Division of Surgical Oncology, Department of Surgery, University Hospital, Groningen, The Netherlands*

**Abstract**—During the period 1964–1977, regional perfusion and wide local excision were used in the treatment of 104 patients with a locally metastasized malignant melanoma of the limbs. One hundred patients were considered in a study of 3-year and 5-year survival, which was 52% (52/100) and 38% (30/78), respectively. The 3-year and 5-year survival rates in 18 patients treated by normothermic perfusion prior to 1969 were 22% (4/18) and 17% (3/18), respectively; in 82 patients treated by hyperthermic perfusion after 1969, the 3-year survival was 58.5% (48/82) and the 5-year survival was 45% (27/60). The difference between the normothermic and hyperthermic group is significant at the 3-year and 5-year level ( $P < 0.005$  and  $P < 0.025$ , respectively). The 5-year survival in those treated by hyperthermic perfusion was 42% in stage II ( $n = 12$ ) and 46% in stage III ( $n = 48$ ), the difference not being significant. The male 5-year survival was 36% (8/22), while the female was 53% (20/38). The 5-year survival for tumours of the arm and those of the leg was 23% (3/13) and 51% (24/47), respectively. No significance could be demonstrated between these groups. Of the entire group of 100 patients, 35 developed a local recurrence after perfusion; in 11 there was simultaneous general metastasization as well. The recurrence developed within 2 years after perfusion in 27 (77%) patients and 16 (76%) died within 2 years of recurrence.

## INTRODUCTION

SINCE 1964, in the department of surgery of the Groningen University Hospital, regional perfusion has been used in the treatment of patients with a malignant melanoma of the limbs.

The first publications on regional perfusion of the limbs appeared around 1960 [1, 2]. Most of these perfusions were performed in patients with a malignant melanoma. In most cases, regional perfusion was combined with wide excision of the tumour area, the defect being usually closed with the aid of a free skin graft.

Not only primary tumours but particularly also malignant melanomas which have already locally metastasized are so treated. The department has already published reports on both groups of patients [3–7]. The present

study is to be regarded as a continuation and extension of the earlier studies [6].

## PATIENTS

During the period 1964–1977, 104 patients with a locally metastasized melanoma of the limbs were treated exclusively by a combination of regional perfusion and wide excision. No general prophylactic medication in the form of chemotherapy or immunotherapy was given. The study of these patients was completed on 31st December 1979. The patients were staged in accordance with the classification of M.D. Anderson Hospital, Houston, Texas, U.S.A. (Table 1). The study was confined to patients in stages II, IIIA, IIIB and IIIB.

Of these 104 patients, four were excluded from further consideration: three did not complete therapy (two refused further therapy and one had vascular problems), and one patient died from pulmonary embolism shortly after operation. None of the remaining 100 patients died from intercurrent disease; all remained available for follow-up, which co-

Accepted 6 October 1980.

\*Address for reprints: H. Schraffordt Koops, M.D.,  
Division of Surgical Oncology, A.Z.G., Oostersingel 59,  
9713 EZ Groningen, The Netherlands.

Table 1. Staging of malignant melanoma (M.D. Anderson Hospital, Houston, Texas, U.S.A.)

Stage		Number of patients treated
Stage 0	: Superficial melanoma	
Stage I	: Primary melanoma only	
	A: Intact primary melanomas	
	B: Primary melanoma, locally excised	
	C: Multiple primary melanoma	
Stage II	: Local recurrence or metastases	19
	All disease within 3 cm of primary site	
Stage III	: Regional metastases	81
	A: Tissues excluding nodes (in-transit metastases)	22
	B: Lymph node(s)	45
	AB: Skin, etc., plus node(s)	14
Stage IV	: Distant metastases	

vered a period from a minimum of 3 to a maximum of 15 years.

The total group ( $N=100$ ) included 62 females and 38 males. In 81 patients the tumour was localized in the leg, while 19 had a tumour of the arm.

## METHODS

The perfusion technique used in our department has already been described in previous publications [8–10]. Melphalan (L-phenylalanine mustard) was used as cytostatic. Since 1974, actinomycin-D as well as melphalan has been added to the perfusion fluid for all patients in stages II, IIIA and IIIAB. The amount of cytostatic was calculated on the basis of the body weight, level of perfusion, skin complexion and leakage to the systemic circulation. The amount of melphalan added ranged from 1.0 to 1.5 mg/kg body wt for leg perfusion, and from 0.5 to 0.7 mg/kg body wt for arm perfusion. The amount of actinomycin-D ranged from 0.014 mg/kg body wt for leg perfusion to 0.006 mg/kg body wt for arm perfusion.

After perfusion, the limb involved was washed out with an indifferent fluid. Next, the tumour site was widely excised ( $5 \times 5$  cm); since 1970, leg perfusions have been followed by prophylactic fasciotomy of the lateral compartment of the lower leg. This was done in order to prevent compression of nerves as a result of oedema in the compartments of the lower leg [7].

From 1964 until September 1969, normo-thermic perfusions were performed. The temperature of the perfusion fluid was  $37.5^\circ\text{C}$ ,

Table 2. Stage and type of perfusion

Stage	Normo-thermic	Hyper-thermic	Total per stage
II	4	15	19
III A	2	20	22
III B	9	36	45
III AB	3	11	14

and the duration of perfusion was 45 min. From September 1969 onwards, 82 patients were treated by hyperthermic perfusion at a skin/muscle temperature of  $39.5\text{--}40^\circ\text{C}$ ; the duration of perfusion was increased to 60 min (Table 2). Survival after perfusion was calculated by determining the number of patients still alive after 1, 2, 3, 4 and 5 years. In this study the so-called determinate survival was calculated; that is, all deceased patients were considered to have died as a result of general metastasization; no correction was made for death per age group as compared with mortality in a normal population.

Significance between the differences in several 3-year and 5-year survival rates were tested by means of the chi-square test, for a  $2 \times 2$  table, at a one-sided level of  $P \leq 0.025$ . This was only done when the number of patients per group was more than 10.

## RESULTS

### Survival after perfusion

For the entire group of patients ( $N=100$ ), the 3-year survival was 52% (52/100) and the 5-year survival was 38% (30/78).

*Survival after normothermic versus that after hyperthermic perfusion.* Of the 100 patients, 18 were treated by normothermic perfusion. The 3-year and 5-year survival in this group was 22% (4/18) and 17% (3/18), respectively. The corresponding figures for the 82 patients treated by hyperthermic perfusion were 58.5% (48/82) and 45% (27/60), respectively. The differences between the normothermic and the hyperthermic group are significant at the 3-year and the 5-year level as well ( $P < 0.005$  and  $P < 0.025$ , respectively). The number of patients treated by normothermic perfusion is too small to calculate separate 3-year and 5-year survival figures for the various clinical stages. This was done for the patients treated by hyperthermic perfusion, even though their number was likewise rather small (Figs. 1 and 2). The differences between the stages failed to show significantly at the 3-year and the 5-year level as well.

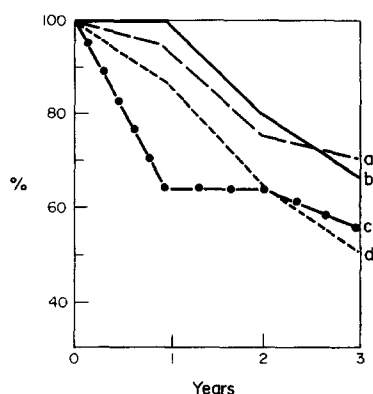


Fig. 1. 3-year survival after hyperthermic perfusion in 82 patients. (a) 14/20 (70%)—stage III<sup>A</sup>, 20 patients. (b) 10/15 (67%)—stage II, 15 patients. (c) 6/11 (55%)—stage III<sup>AB</sup>, 11 patients. (d) 18/36 (50%)—stage III<sup>B</sup>, 36 patients.

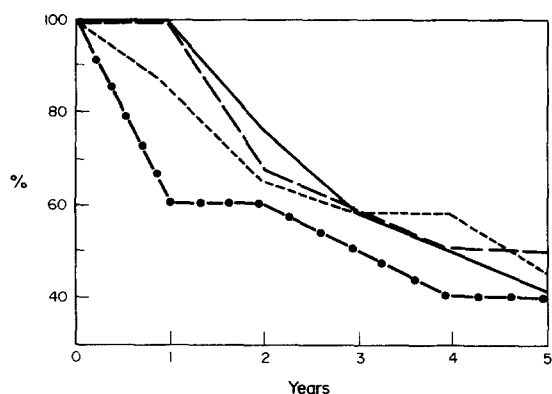


Fig. 2. 5-year survival after hyperthermic perfusion in 60 patients. (a) 6/12 (50%)—stage III<sup>A</sup>, 12 patients. (b) 12/26 (46%)—stage III<sup>B</sup>, 26 patients. (c) 5/12 (42%)—stage II, 12 patients. (d) 4/10 (40%)—stage III<sup>AB</sup>, 10 patients.

*Survival according to sex.* The group of patients ( $N=100$ ) included 38 males and 62 females. The overall male 3-year survival was 34% (13/38), while the overall 3-year female survival was 63% (39/62). The corresponding figures for the overall 5-year survival were 27% (8/30) and 44% (21/48), respectively. The group treated by hyperthermic perfusion consisted of 30 males and 52 females. The 3-year survival was 40% (12/30) and 67% (35/52), respectively, while the 5-year survival was 36% (8/22) and 53% (20/38), respectively. The differences in this group are significant at the 3-year level ( $P < 0.01$ ), but not at the 5-year level.

*Survival according to limb involved.* Of the 100 patients, 19 had an arm tumour while 81 had a leg tumour. The overall 3-year and 5-year survival in the arm tumour group was 37% (7/19) and 17% (3/18), respectively, the corresponding figures for the leg tumour group being 56% (45/81) and 43% (26/60), respectively.

The group treated by hyperthermic perfusion included 14 patients with an arm tumour and 68 with a tumour of the leg. The 3-year and 5-year survival in the arm group was 50% (7/14) and 23% (3/13), respectively, the corresponding figures for the leg tumour group being 60% (41/68) and 51% (24/47), respectively. The differences in this group were not significant at 3-year and 5-year level.

*Survival according to sex and limb involved.* The 100 tumours can be divided as follows to sex and limb involved: 62 females included 10 with an arm tumour and 52 with a leg tumour, while of 38 males 9 had an arm tumour and 29 had a leg tumour.

The overall 3-year survival was 50% (5/10) in females with an arm tumour and 65% (35/52) in females with a leg tumour. The corresponding figures for males were 22% (2/9) and 38% (11/29), respectively. The 5-year survival was 33% (3/9) in females with an arm tumour and 46% (18/39) in females with a leg tumour; the corresponding figures for the males being 0% (0/9) and 38% (8/21), respectively.

The 3-year and 5-year survival figures for the 82 patients treated by hyperthermic perfusion are represented in Figs. 3 and 4. A striking finding is that the marked difference in survival between males and females with leg tumours after 3 years is not reflected in the 5-year survival figures. Significance was only tested for these two groups and the differences showed to be significant only at the 3-year level ( $P < 0.025$ ).

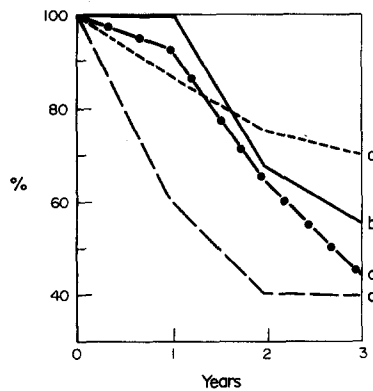


Fig. 3. 3-year survival after hyperthermic perfusion, related to sex and location, in 82 patients. (a) 30/43 (70%)—female—leg. (b) 5/9 (56%)—female—arm. (c) 11/25 (44%)—male—leg. (d) 2/5 (40%)—male—arm.

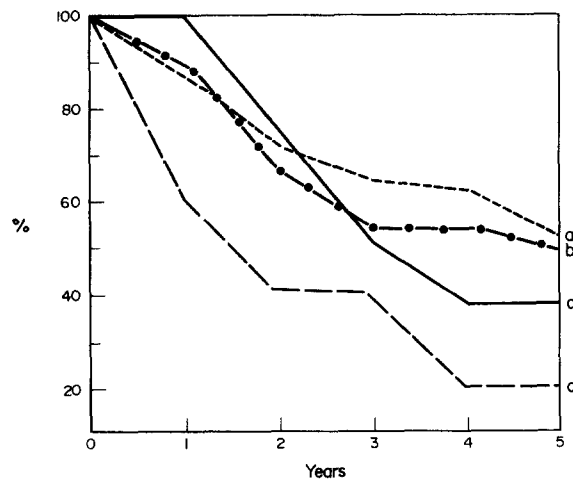


Fig. 4. 5-year survival after hyperthermic perfusion, related to sex and location, in 60 patients. (a) 15/30 (50%)—female—leg. (b) 8/17 (47%)—male—leg. (c) 3/8 (38%)—female—arm. (d) 1/5 (20%)—male—arm.

#### Local recurrence after perfusion

In this study, two types of local recurrence after perfusion are distinguished:

(A) Regional skin recurrence (RSR): recurrence in or around the scar of the local excision, and in-transit metastases.

(B) Regional lymph node recurrence (RLR).

Of the 100 patients, 35 developed a local

recurrence after perfusion. Of these 35 patients, 28 showed RSR and 8 showed RLR. One patient who was in stage IIIA at the time of perfusion subsequently showed both RSR and RLR.

RLR developed only in patients who had been in stage II or IIIA when treated by perfusion (Table 3), as patients in stage IIIB or IIIAB were always treated by lymph node dissection as well. The rate of RLR in stages II and IIIA was 16% (3/19) and 23% (5/22), respectively. The rate of RSR for all stages ( $N = 100$ ) was 28%.

In 11 of the 35 patients, local recurrence developed after or at the same time as general metastasization.

*Interval between perfusion and local recurrence.* The interval between perfusion and local recurrence ranged from 3 to 60 months. Of the 35 patients, 27 developed local recurrence within 24 months of perfusion (77%).

*Survival after local recurrence.* The survival of the 35 patients was calculated from the first local recurrence, regardless of whether recurrences followed and regardless of whether therapy was given. If given, therapy consisted of excision, cryosurgery, BCG therapy or general chemotherapy, dependent on the extent of the local process and the presence or absence of general metastases.

At completion of the study, 21 of 35 patients (60%) had died after a survival period ranging from 0 to 48 months; 16 (76%) of these 21 patients died within the first 24 months of perfusion. In the patients still alive at completion of the study, survival ranged from 2 to 97 months after the first recurrence.

Of the 11 patients who developed local recurrence with or after general metastasization, two were still alive at completion of the study. One patient survived 18 months after general metastasization. She was treated with DTIC and has been free of disease symptoms for about a year—a situation which can be regarded as exceptional.

*Local recurrence according to sex and limb involved.* The sex distribution of the 35 local

Table 3. Local recurrence according to regional lymph-node recurrence (RLR) and regional skin recurrence (RSR) per stage

Stage	Normothermic		Hyperthermic		Total	
	RSR	RLR	RSR	RLR	RSR	RLR
II	1/4	—/4	2/15	3/15	3/19	3/19
III A	—/2	1/2	9/20	4/20	9/22	5/22
III B	2/9	—/9	8/36	—/36	10/45	—/45
III AB	—/3	—/3	6/11	—/11	6/14	—/14
Total	3/18	1/6	25/82	7/35	28/100	8/41

Table 4. Local recurrence according to sex and limb involved

	Arm	Leg	Total
Male	2/9 (22%)	13/29 (45%)	15/38 (39%)
Female	3/10 (30%)	17/52 (33%)	20/62 (32%)
Total	5/19 (26%)	30/81 (37%)	35/100 (35%)

recurrences was 20 females vs 15 males. As compared with the total numbers of males and females, the rate of recurrence was 32% (20/62) in females and 39% (15/38) in males. The recurrence group included 5 arm tumours and 30 leg tumours. As compared with the total numbers of arm and leg tumours, the rate of recurrence was 26% (5/19) for the arm tumours and 37% (30/81) for the leg tumours (Table 4).

*Survival after local recurrence according to limb involved.* The five patients with local recurrence of an arm tumour had all died at completion of the study, survival ranging from 0 to 32 months. Of the 30 patients with a leg tumour recurrence, 14 were still alive at completion of the study, survival ranging from 2 to 97 months after recurrence. The survival of the 16 deceased patients had ranged from 2 to 48 months; 14 of these patients died within 2 years of recurrence.

*Interval until and survival after local recurrence, according to sex.* In the 20 females with local recurrence after perfusion, the median interval between perfusion and local recurrence was 11 months (range 3–53 months). General metastasization developed in five of these women. The corresponding figure for the 15 males with local recurrence after perfusion was 12 months (range 4–60 months); six men developed general metastasization.

At completion of the study, 10 of the 20 females (50%) were still alive, the survival after recurrence ranging from 11 to 97 months. The 10 deceased females had survived 4–48 months after recurrence; 6 of the 10 (60%) had died within 2 years. Of the 15 males, 4 (27%) were still alive. The deceased had survived 0–32 months after recurrence; 10 of these 11 males (91%) had died within 2 years.

## DISCUSSION

All operations on these patients were performed by two surgeons (J.O. and H.S.K.) This ensured uniformity of operative and per-

fusion technique. The study concerned 38 males and 62 females. With the exception of stage IIIB, all stages showed a female predominance. The male:female ratio in stage IIIB was 28:17, the ratio in the other stages being the reverse.

None of the patients died from complications caused by perfusion. Complications did occur, especially during the early perfusion years (more specifically: transient or permanent dysfunction of the peroneal nerve—a complication prevented since 1970 by prophylactic fasciotomy of the lateral compartment of the lower leg [3]).

The literature comprises numerous reports on patients with locally metastasized malignant melanoma of the limbs. Therapy is variously described as ranging from local excision to amputation. The survival rates reported vary widely; for amputation, as the most rigorous therapy, up to a maximum of 34% [8, 9, 10, 11]. With the introduction of regional perfusion, indications for amputation have been substantially reduced [6, 12–14]. It is difficult to compare our survival figures with those in the literature. With regard to survival rates after regional perfusion for recurrent malignant melanoma, it can be concluded that in our series patients treated by hyperthermic perfusion produced better survival figures than those treated by normothermic perfusion: 59% versus 22% after 3 years, and 45% versus 17% after 5 years. The difference between the two groups is statistically significant at 3-year and 5-year survival level. In our study, only a few patients were treated by normothermic perfusion, but this difference is also apparent in the literature [15, 16].

Our study revealed no significant differences in survival between stages II, IIIA, IIIB and IIIB. The literature does describe such differences, particularly between the stages II and III [7, 13, 15, 16]. Another striking finding is that survival rates of stages II and IIIB in the literature do not differ markedly when only one abnormal lymph node was found [5]. Comparison of our 5-year survival rates with those reported by other authors using regional perfusion fails to reveal any marked differences [13–17].

Female patients had a significantly better chance of survival than the males—a finding repeatedly also reported in the literature. There was no significant difference in the survival between location of the tumour on a leg and on an arm. However, although 3-year survival in females with a leg tumour significantly exceeded that in males with a leg

tumour, no significant difference was demonstrable 5 years after perfusion.

Of the 100 patients studied, 35 developed a local recurrence after perfusion: RSR in 28 and RLR in 8 patients (one patient developed both RSR and RLR).

In 11 of the 35 cases, local recurrence was associated with general metastasization. Local

recurrence developed within 2 years of perfusion (77%) of the cases—an observation corroborated by several other authors [14, 19]. The majority (76%) of the patients with a local recurrence died within 2 years of this recurrence. With the recurrences, too, localization in the leg and occurrence in females meant a better prognosis.

## REFERENCES

1. O. CREECH JR., E. T. KREMENTZ, R. F. RYAN and J. N. WINBLAD, Chemotherapy of cancer: regional perfusion utilizing an extra-corporeal circuit. *Ann. Surg.* **148**, 616 (1958).
2. J. S. STEHLIN JR., R. L. CLARK JR., E. C. WHITE, J. L. SMITH, A. C. GRIFFIN, R. H. JESSE and J. E. HEALY JR., Regional chemotherapy for cancer: experiences with 116 perfusions. *Ann. Surg.* **151**, 605 (1960).
3. H. SCHRAFFORDT KOOPS, Prevention of neural and muscular lesions during hyperthermic perfusion. *Surg. Gyn. Obst.* **135**, 401 (1972).
4. H. SCHRAFFORDT KOOPS, Melanoblastoma malignum cutis van de extremiteten, regionale perfusie en recidief. Thesis, van Gorcum, Assen (1973).
5. H. SCHRAFFORDT KOOPS, J. OLDHOFF, E. VAN DE PLOEG, A. VERMEY, R. EIBERGEN and H. BEEKHUIS, Some aspects of the treatment of primary malignant melanoma of the extremities by isolated perfusion. *Cancer (Philad.)* **39**, 27 (1977).
6. H. SCHRAFFORDT KOOPS, J. OLDHOFF, E. VAN DE PLOEG, A. VERMEY and R. EIBERGEN, Regional perfusion for recurrent melanoma of the extremities. *Amer. J. Surg.* **133**, 221 (1977).
7. K. WELVAART and H. SCHRAFFORDT KOOPS, Sub-ungual malignant melanoma: A nail in the coffin. *Clin. Onc.* **4**, 309 (1978).
8. K. R. COX, Survival after amputation for recurrent melanoma. *Surg. Gyn. Obst.* **139**, 720 (1974).
9. C. J. McPEAK, G. P. McNEER, H. W. WHITELEY and R. J. BOOHER, Amputation for melanoma of the extremity. *Surgery* **54**, 426 (1963).
10. J. S. STEHLIN JR. and R. L. CLARK JR., Melanoma of the extremities. Experiences with conventional treatment and perfusion in 399 cases. *Amer. J. Surg.* **110**, 366 (1965).
11. A. TURNBULL, J. SHAH and J. FORTNER, Recurrent melanoma of the extremity treated by major amputation. *Arch. Surg.* **106**, 496 (1973).
12. T. C. AU and L. I. GOLDMAN, Isolated perfusion in limb melanoma: a critical assessment and literature review. In *Human Malignant Melanoma*. (Edited by W. H. Clark, L. I. Goldman and M. J. Mastrangelo) p. 295. Grunewald & Stratton, New York (1978).
13. E. T. KREMENTZ, E. D. CARTER, C. M. SUTHERLAND and M. CAMPBELL, The use of regional chemotherapy in the management of malignant melanoma. *World J. Surg.* **3**, 289 (1979).
14. E. D. WAGNER, A retrospective study of regional perfusion for melanoma. *Arch. Surg.* **111**, 410 (1976).
15. J. S. STEHLIN JR., B. C. GIOVANELLA, P. D. DE IPOLYI, R. L. MUENZ and R. F. ANDERSON, Results of hyperthermic perfusion for melanoma of the extremities. *Surg. Gyn. Obst.* **140**, 339 (1975).
16. J. S. STEHLIN JR., B. C. GIOVANELLA, P. D. DE IPOLYI and R. F. ANDERSON, Eleven years experience with hyperthermic perfusion for melanoma of the extremities. *World J. Surg.* **3**, 305 (1979).
17. W. W. SHINGLETON, Perfusion chemotherapy for recurrent melanoma of the extremities: a progress report. *Ann. Surg.* **169**, 969 (1969).
18. W. W. SHINGLETON, H. F. SEIGLER, L. H. STOCKS and R. W. DOWNS JR., Management of recurrent melanoma of the extremity. *Cancer (Philad.)* **35**, 574 (1975).
19. C. M. McBRIDE, Advanced melanoma of the extremities, Treatment by isolation perfusion with triple drug combination. *Arch. Surg.* **101**, 122 (1970).