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Functional Morbidity of Hyperthermic Isolated Regional Perfusion of the Extremities

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Background: Isolated regional perfusion (IRP) of an extremity is a major operation. The therapeutic value for stage I melanoma is still controversial and is presently being investigated in a prospective, randomized study by the European Organization for Research and Treatment of Cancer. So far there are no reliable data available concerning the morbidity of IRP. Therefore, we performed a prospective, randomized study on this topic.

Methods: In a prospective study, a group of 97 patients with a stage I melanoma localized on an arm or leg were randomized for IRP with melphalan followed by wide excision (WE) and fasciotomy *or* for WE only. Morbidity was evaluated on the basis of the following parameters: duration of hospitalization, postoperative pain, postoperative performance, and grade of perfusion toxicity. At 12-month follow-up, a physical diagnostic examination was performed to measure the mobility of the joints, and the circumference and volume of the treated and untreated extremities.

Results: All the parameters, including the physical diagnostic examination, could be evaluated in 83 of the 97 patients (8 patients died of metastatic disease and 1 patient died of another disease before they could be investigated; 2 patients were in too poor physical condition due to metastases to be examined, and 3 patients were unable to participate for nonmedical reasons). Age and sex distribution were comparable in the various patient groups. Treatment mortality was 0%. There were no complications except for urine retention (one patient) and wound dehiscence (one patient). After IRP + WE of the lower limb, the period of hospitalization was an average of 1.9 days longer ($p = 0.01$) than for WE on the limb only. This difference was absent for the arm. Naturally after perfusion, there was a significant difference in toxic reactions (edema and pain) between the IRP + WE patients and the WE-only patients. However, at 12-month follow-up, the difference in morbidity between IRP + WE and WE-only patients was no longer present: Morbidity of joints and circumference of the limb were the same. A number of subjective complaints were encountered fairly often after IRP + WE (e.g., pricking sensations or pain during changes in the weather), which can possibly be explained by fibrosis caused by perfusion. These complaints were not quantified further because they did not hinder the patients' functioning.

Conclusions: In the long term, IRP with fasciotomy does not cause any additional morbidity. Immediately after the operation, there was more morbidity as a result of the perfusion, which caused a 2-day- longer period of hospitalization in the patients with lower-limb perfusion compared with those who underwent WE only. These findings are in contrast to those in the literature, in which 25% limitation of motion in the ankle joint after perfusion is mentioned. One explanation may be that we always performed fasciotomy after perfusion to prevent (sub)clinical compression syndrome and avoid late fibrosis.

Key Words: Regional perfusion—Morbidity—Melanoma.

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In 1957, Creech et al. introduced a technique to perfuse the extremities with high doses of cytotoxic agents using extracorporeal circulation (1). The underlying idea was to administer high doses of chemotherapeutic agents locally, with a maximum tumoricidal effect, without giving rise to general toxic side effects. Melphalan has become the most widely used cytotoxic agent for isolated regional perfusion (IRP) of an extremity for the treatment of a melanoma.

This therapeutic approach has also proved to be useful for patients with melanoma recurrence, satellites, and in transit metastases of an extremity. For patients with clinical stage I melanoma of an extremity (i.e., the melanoma is limited to the primary lesion), controversy still exists as to whether regional perfusion has a favorable effect (2–7). Nearly all the studies on this subject were retrospective (2,3). One prospective study by Ghussen et al. only evaluated a very small number of patients with a stage I melanoma, so no definitive conclusions can be drawn (4).

In 1984, the previously mentioned controversy prompted the European Organization for Research and Treatment of Cancer (EORTC) to start a prospective, randomized study on the value of adjuvant, IRP for primary melanoma of an extremity. In this ongoing study, the therapeutic effect of hyperthermic, IRP with high doses of melphalan followed by wide local excision (WE) is being compared with that of WE only (8). Patients with a melanoma localized on an arm or leg, with a Breslow thickness of 1.5 mm or more in clinical stage I, are eligible for randomization in this trial. The University Hospital Groningen has been participating in this study since June 1986.

IRP is a much more serious operation for a patient than is WE only. This is reflected by, for example, the duration of the operation, which takes an average of ~4 h in the former case as opposed to 30 min in the latter case.

In IRP, the extremity is perfused by means of extracorporeal circulation with a cytotoxic agent that causes a local toxic effect in the perfused extremity.

In view of the existing controversy concerning the therapeutic effect of perfusion in this group of patients and the difference in the "severity" of the treatment options in the EORTC study, we decided to further analyze the postoperative and long-term morbidity of the patients treated at our department.

TABLE 1. *Surgical techniques*

Upper extremity/arm	
Isolated regional perfusion + local excision and fasciotomy	Local excision only
Isolated regional perfusion with melphalan (13mg/L extremity volume) for 60 min under mild hyperthermia (39–40°C) Wide local excision (margin 3 cm normal skin) Axillary node dissection Fasciotomy	Wide local excision (margin 3 cm normal skin) Axillary node dissection
No. of patients: 14	No. of patients: 15
Lower extremity/leg	
Isolated regional perfusion plus local excision	Local excision only
Isolated regional perfusion with melphalan (10 mg/L extremity volume) for 60 min under mild hyperthermia (39–40°C) Wide local excision (margin 3 cm normal skin)	Wide local excision (margin 3 cm normal skin)
No. of patients: 36	No. of patients: 32

MATERIALS AND METHODS

In the period from June 1986 to January 1992, 97 patients were treated at the University Hospital Groningen for stage I melanoma of >1.5-mm Breslow thickness localized on one of the extremities. All of the patients were assigned at random to one of two treatment modalities. The treatment techniques, which were applied according to a protocol, are described in Table 1. The technique used for fasciotomy is the blind one as described by Reneman (9) for the lateral (peroneal) compartment of the lower leg, and we used the same technique for decompression of the anterior (flexor) and the posterior (extensor) compartment of the forearm. The postoperative treatment of a lower extremity consisted of elevation and immobilization for at least 1 week. During this period, the joints were exercised without weight bearing. A free skin graft was used in 83% of the patients to close the wound, whereas in 17% primary closure was possible. Patients with a free skin graft on their leg were advised to keep it elevated for a total of 6 weeks. All the patients who were treated for a melanoma on an upper extremity underwent axillary lymph node dissection and were mobilized directly after the operation.

Until the moment of full mobilization, all the patients received anticoagulant therapy.

The median follow-up period was 36 months (range 12–76 months). During this period, 14 patients were excluded from the morbidity study for the following reasons: 8 died as a result of metastases (5 IRP + WE and 3 WE only); sudden death *e causa ignota* (e.c.i.) (1 patient, 10 months after perfusion of the leg); very poor physical condition as a result of metastases (2 patients after WE only of a melanoma of the leg); and unable to participate for nonmedical reasons (3 patients, all after WE only).

Therefore, 83 patients took part in the morbidity study. These patients and the various treatment groups are described in Table 2.

To study the extent of morbidity in the postoperative phase, the following parameters were evaluated: (a) duration of hospitalization; (b) the performance state preoperatively and postoperatively after 7 and 30 days (8). A score of 0 = normal activity; 1 = some complaints but nearly full ambulatory capacity; 2 = spends <50% of the day in bed; 3 = spends >50% of the day in bed; 4 = unable to get out of bed; (c) pain in the first month after the operation; and (d) the grade of the toxic reaction after perfusion (Table 3) (10).

At long-term follow-up, after a median of 36 months (range 12–76 months), the following physical measurements were obtained to evaluate functional morbidity: (a) the circumference of the extremity (in cm for the upper extremity 15 cm proximal and 15 cm distal from the olecranon; for the lower extremity 20 cm proximal and 20 cm distal from the patella); (b) the volume of the extremity, by placing the arm or leg in a cylinder filled with water up to the axilla or groin and calculating the displacement of the water; and (c) the mobility of the joints (in degrees).

All these measurements were performed on the treated and untreated extremities, so that the patients could act as their own controls and to establish their comparability.

The results were compared between treatment groups and per extremity: upper extremity group I versus group III and lower extremity group II versus group IV (Tables 4 and 5). Student's *t* test and the Mann–Whitney test were used in the analyses.

TABLE 2. *Patient characteristics*

	Isolated regional perfusion plus local excision		Local excision only	
Extremity	Arm	Leg	Arm	Leg
No. of patients	13	33	13	24
Average age, yrs (range)	52.1 (32–71)	47.9 (24–65)	50.5 (22–68)	47.5 (19–69)
Male:female	4:9	7:26	5:8	9:15
Group	I	II	III	IV

TABLE 3. *Grading system of skin and muscle toxicity (10)*

Grade	Description
I	No subjective or objective evidence of a reaction
II	Slight erythema and/or edema
III	Considerable erythema and/or edema with some blistering; slightly disturbed mobility permissible
IV	Extensive epidermolysis and/or obvious damage to the deep tissues, causing definite functional disturbances; threatened or manifest compartmental syndromes
V	Reaction that may necessitate amputation

RESULTS

Preoperative functioning was normal in all the cases. None of the patients died in the preoperative phase or directly after the operation.

Except for urine retention (one patient) and wound dehiscence (one patient), there were no general postoperative complications. Age and sex distribution of the patients who underwent IRP + WE was comparable to that in the group who underwent WE only (Student's *t* test, $\alpha = 0.05$).

The difference in the duration of hospitalization between patients treated for a melanoma on the upper extremity and those treated for a melanoma on the lower extremity was due the fact that the former group underwent axillary dissection and a vacuum drain was left in situ for ~10 days. The patients remained hospitalized during this period.

The results are presented separately for the patients treated for a melanoma of the upper extremity and for those treated on the lower extremity.

Upper extremity

Table 2 shows that the group treated with IRP + WE and fasciotomy (group 1) and the group treated with WE only (group III) comprised 13 patients each and that the groups were comparable regarding age and male:female ratio ($p = 0.78$). The duration of hospitalization, the postoperative performance state, postoperative pain, and the grade of the toxic reaction are described in Table 4. Table 5 shows the results of the physical examination in which the circumference, volume, and mobility of the extremities were measured. This examination was performed after an average of 29.8 months (range 14–61 months) in group I and after an average of 34.7 months (range 15–69 months) in group III. Table 4 shows that there was no significant dif-

TABLE 4. *Postoperative morbidity*

	Arm			Leg		
	I: isolated regional perfusion plus wide local excision	III: local excision only	p, two-tailed test	II: isolated regional perfusion plus wide local excision	IV: local excision only	p, two-tailed test
Days in hospital						
Average	11.4	10.0	0.092	8.0	6.1	0.01
Range	(9–18)	(7–14)	(n.s.)	(3–17)	(3–14)	
Performance status 7th day						
Average	1.2	1.1	0.76	2.9	2.7	0.05
Range	(1–3)	(0–2)	(n.s.)	(2–3)	(1–3)	(n.s.)
30th day						
Average	0.8	0.7	0.51	1.6	1.5	0.43
Range	(0–1)	(0–1)	(n.s.)	(0–3)	(0–3)	(n.s.)
Pain %	62	8	0.02	7	0	0.00
Toxic reaction						
Average	2.0	1.0	0.00	2.1	1.0	0.00
Range	(all)	(all)		(2–3)	(all)	

ference in the duration of hospitalization and the postoperative performance status between groups I and III, but that there was a significant difference in the grade of the toxic reactions and the occurrence of postoperative pain.

Physical diagnostic examination of the arm (Table 5) revealed a significant better mobility of the elbow joint in the perfused patients (group I) than in the patients after WE only (group III). The same difference, however, was found in the contralateral, untreated elbow joint of both groups. There was no significant difference in the mobility of other joints and the circumference and volume of the arm between the two groups.

Lower extremity

The group who underwent IRP + WE and fasciotomy (group II) comprised 33 patients, while the group who underwent WE only comprised 24 patients (group IV) (Table 2). Age and sex distribution was comparable in the two groups ($p = 0.9$). Table 4 shows the duration of hospitalization, postoperative performance state, pain, and the grade of the toxic reaction.

The results of the physical diagnostic examination to measure the circumference, volume, and mobility of the lower extremities are presented in Table 5 in the same style as those for the upper extremity. In group II this test was performed after an average of 38.5 months (range 12–76 months) and in group IV after an average of 36.6 months (range 15–65 months). When group II was compared with group IV (Table 4), we found a significant difference in the duration of hospitalization, the toxic perfusion reaction, and postoperative pain, but no significant difference in the postoperative performance state. The results of physical diagnostic examination presented in Table 5 show that there was no significant difference between the groups regarding the mobility of the joints, the circumference, and the volume of the extremities.

Untreated (control) extremities

Table 6 presents the results of the various physical diagnostic measurements performed on the untreated extremities, which acted as a control. By comparing these results we could determine whether there were any differences in the measurements taken from the untreated extremities between the treatment groups: for the upper extremity group I versus group III and for the lower extremity group II versus group IV. In the case of significant differences, no conclusions may be attributed to any possible differences in the measurement results obtained from the treated extremities.

For instance, the significant difference between groups I and III regarding the mobility of the elbow joint of the untreated arms mean that no conclusion may be drawn from the significantly better mobility of the elbow joint in perfused patients compared with those after WE only. All the other measurements taken from the untreated arms or legs during physical diagnostic examination were not significantly different.

DISCUSSION

The results of the various measurement parameters for postoperative morbidity, as described in Table 4 for the upper and lower extremities, show that

TABLE 5. *Physical diagnostic test results after treatment*

	Arm				
	I: Isolated regional perfusion with local excision		III: Wide local excision only		
	Average	(Range)	Average	(Range)	p: two-tailed test
Shoulder					
Horizontal flexion	132.3	(110–180)	124.2	(95–170)	0.31 (n.s.)
Abduction	162.3	(60–180)	174.2	(140–180)	0.23 (n.s.)
Adduction	60.0	(40–70)	50.0	(20–85)	0.40 (n.s.)
Anterior flexion	166.2	(130–190)	173.5	(160–180)	0.20 (n.s.)
Elbow					
Flexion	140.0	(130–150)	131.9	(120–140)	0.00
Wrist					
Palmar flexion	77.7	(40–90)	76.9	(50–90)	0.89 (n.s.)
Dorsal flexion	77.3	(55–90)	70.7	(35–90)	0.27 (n.s.)
Circumference					
Upper arm	30.3	(24–33)	29.9	(26–37)	0.891 (n.s.)
Lower arm	22.4	(19–27)	22.4	(18–27)	0.98 (n.s.)
Volume arm	3.02	(2.08–4.36)	3.21	(2.6–4.6)	0.51 (n.s.)
	Leg				
	II: Isolated regional perfusion with local excision		IV: Wide local excision only		
	Average	(Range)	Average	(Range)	p: two-tailed test
Hip					
Flexion	115.8	(65–150)	116.4	(95–150)	0.88 (n.s.)
Abduction	57.1	(20–90)	53.8	(20–90)	0.51 (n.s.)
Adduction	34.8	(15–65)	36.7	(20–60)	0.57 (n.s.)
Extension	15.8	(0–40)	16.9	(10–30)	0.58 (n.s.)
Knee					
Flexion	132.3	(115–155)	134.2	(120–155)	0.43 (n.s.)
Ankle					
Flexion	9.1	(5–40)	11.0	(0–20)	0.36 (n.s.)
Extension	50.2	(10–80)	54.0	(40–70)	0.27 (n.s.)
Circumference					
Upper leg	49.9	(41–58.5)	51.1	(39–61)	0.38 (n.s.)
Lower leg	32.2	(25–43)	32.1	(24–38)	0.93 (n.s.)
Volume leg	11.77	(7.65–17.80)	11.98	(8.9–16.5)	0.73 (n.s.)

there was a significant difference in the toxic perfusion reaction between the two treatment groups for both the arm and the leg. This is not surprising, because by definition local excision only will not cause a toxic perfusion reaction. In addition, there were significantly more complaints of pain in the groups treated with IRP + WE, which can also be attributed to the toxic perfusion reaction. In group II this prolonged the duration of hospitalization by an average of 1.9 days, which was significantly longer ($p = 0.01$) than in group IV.

Physical diagnostic examination of the upper extremity (Table 5) revealed a significant difference only for the postoperative mobility of the elbow joint when the results of the patients after IRP + WE were compared with those after WE only. We could not find an explanation for this, even after analyzing each individual patient and taking the site of the excision into consideration. An interesting finding was that the same measurement performed on the untreated arm in the same patient groups also revealed a significant difference in the mobility of the elbow joint (Table 6). We do not believe that conclusions should be drawn from the differences in measurement results between the treated and untreated extremities.

Table 5 shows that for the lower extremity there was no significant difference in the physical diagnostic examination results between the group of patients after IRP + WE and those after WE only.

Before the physical diagnostic examination, a brief anamnesis was obtained from all the patients concerning any complaints that had arisen in the extremity treated for a melanoma. The patients who had undergone IRP + WE and fasciotomy frequently expressed subjective complaints, such as

TABLE 6. *p value for two-tailed tests of the results of the physical diagnostic examination of the untreated extremities in the two treatment groups*

Arm	p value	Leg	p value
Shoulder		Hip	
Horizontal flexion	0.35 (n.s.)	Flexion	0.98 (n.s.)
Abduction	0.17 (n.s.)	Abduction	0.36 (n.s.)
Adduction	0.35 (n.s.)	Adduction	0.69 (n.s.)
Anterior flexion	0.52 (n.s.)	Extension	0.44 (n.s.)
Elbow		Knee	
Flexion	0.00	Flexion	0.50 (n.s.)
Wrist		Ankle	
Palm. flexion	0.86 (n.s.)	Flexion	0.86 (n.s.)
Dors. flexion	0.29 (n.s.)	Extension	0.58 (n.s.)
Circumference		Circumference	
Upper arm	0.98 (n.s.)	Upper leg	0.63 (n.s.)
Lower arm	0.97 (n.s.)	Lower leg	0.97 (n.s.)
Volume	0.60 (n.s.)	Volume	0.23 (n.s.)

"pricking sensations," "pain during changes in the weather," "numbness," etc. This was in contrast to the patients who underwent WE only; some of them mentioned complaints similar to those listed above, but these were always limited to the excision area. Owing to the fact that these complaints were reported with considerable variation in their nature and severity and could not be evaluated objectively, they were not considered in the analyses. None of the patients experienced hindrance from any of the complaints in daily life. Such complaints might be the result of fibrosis caused by a regional toxic effect—with edema—of hyperthermic IRP with melphalan (11). However, mild hyperthermia can possibly potentiate the efficacy of treatment with melphalan (8,11–13), but melphalan can be damaged by heat. The protocol made a compromise between these observations. A persistent neurotoxicity with motor-sensory neuropathy, as described after hyperthermic IRP with cisplatin (14), cannot be concluded for melphalan from these subjective findings. The complication can for the most part be prevented by performing prophylactic fasciotomy (15).

The results of our study differed from those published by van Geel et al. in 1989 (16). The latter study is the only one in the literature that focused on functional morbidity after perfusion. van Geel et al. stated that limitation of movement in the ankle joint occurred in 25% of the patients after IRP of the lower extremity. However, these authors did not perform fasciotomy after IRP of an arm or leg, which may explain the difference in morbidity.

Although van Geel et al. only examined patients who underwent IRP + WE, our study group comprised patients after IRP + WE and patients after WE only. Owing to the fact that local excision is also likely to cause morbidity, in our opinion conclusions can only be drawn by performing measurements on both treatment groups to single out morbidity that can be attributed to treatment with IRP. Obviously the groups must be comparable, which we established by analyzing the untreated extremities in both groups.

CONCLUSION

IRP led to a significant (expected) difference in perfusion reaction with erythema and edema. For the upper and lower extremities, there were significantly more complaints of pain in the postoperative phase, which led to a slightly longer duration of hospitalization in the patients who underwent IRP + WE of the leg. Treatment with IRP also led to vague subjective complaints that did not hinder the patients in their daily functioning. In the long term, IRP did not cause any morbidity that could be evaluated objectively.

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