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Original Paper

A Single Centre's 10 Year Experience With Isolated Limb Perfusion in the Treatment of Recurrent Malignant Melanoma of the Limb

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The aim of this study was to assess whether isolated limb perfusion can be performed safely and whether it offers improved disease-free survival for patients with limb malignant melanoma. Between August 1983 and July 1993, 103 patients (78 female, 25 male) with recurrent limb melanoma were treated by isolated limb perfusion (ILP) in Glasgow, U.K. The mean age of the patients was 62 years; 95 had leg recurrence, 8 had arm recurrence. The mean time from original diagnosis to ILP was 48 months (range 1–290). 102 iliac, 5 femoral, 7 popliteal and 8 axillary perfusions were performed. All patients had stage II (local recurrence within 3 cm of primary site) or stage III (regional metastases; tissues excluding nodes, nodes or combination) disease according to the MD Anderson Cancer Centre Staging System. At a mean follow-up of 30.7 months, 68 patients had died of recurrent disease (mean time to death 22.5 months). The 2 and 5 year survival of the group was 50 and 26%, respectively and disease-free survival was 23 and 12%, respectively. At first perfusion, 76% of patients showed complete response and 23% showed partial response. With repeat perfusion, 47% showed complete response and 53% had partial response. In conclusion, ILP is safe and has an acceptable morbidity. It achieves highly satisfactory local disease control but long-term survival is the exception.

Key words: isolated limb perfusion, therapeutic, melanoma
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INTRODUCTION

MALIGNANT MELANOMA of an extremity can give rise to cutaneous or subcutaneous recurrences which may be solitary or multiple and located around the scar or proximally along the limb. Traditionally these have been described as satellite and in-transit metastases. Such recurrences are often difficult to treat and in the past surgeons have felt obliged to carry out amputation as a palliative measure. Since the introduction of regional isolated limb perfusion (ILP) in 1958 by Creech and coworkers [1], isolated limb perfusion has become the treatment of choice in many centres which manage large numbers of patients with recurrent malignant melanoma of the extremities. ILP has been shown to offer a high likelihood of achieving regional disease control with an overall objective tumour response of 80% [2–4].

ILP was first made available in Scotland in 1983. We present our experience in the treatment of the first 103 patients treated with stage II and stage III malignant melanoma of the extremities using mild hyperthermic (ILP).

PATIENTS AND METHODS

Between August 1983 and July 1993, 103 patients with stage II and stage III (according to the MD Anderson Cancer Staging) malignant melanoma underwent therapeutic limb perfusion for recurrent melanoma of upper or lower limb, the disease being left *in situ*. Patients were mainly referred from hospitals within the West of Scotland but also from the North of England and Ireland. Serious medical frailty prevented ILP from being undertaken in 5 other patients. The small number of patients precluded a prospective randomised trial. All patients with recurrent melanoma confined to a single limb,

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vascular suitability for catheterisation and adequate medical status for general anaesthesia were offered ILP. Disseminated disease was generally considered to be a contraindication, unless the local disease was so gross that ILP was considered justifiable to achieve local disease control.

The clinical details of the patients are summarised in Table 1. The number of tumours on the limb varied from 1 to 257 nodules with the size of the nodules ranging from 0.5 to 4.2 cm. Response rate to perfusion was assessed at a dedicated perfusion clinic at 3 month intervals.

All the treatments were carried out under general anaesthesia. Since this technique uses hyperthemia, the operating room was kept at 21°C and the patient was placed on a heated water blanket (Hawksley Ripple Heat System with custom blanket, Hawksley & Son Ltd, Lancing, Sussex, U.K.) at 40°C. The temperature was monitored by placing between four and six thermistor probes (Yellow Springs, YSI Ltd, Farnborough, Hampshire, U.K.) on the skin surface and the temperature readings were displayed continuously on a monitor screen (Siemann Sirecrust, Siemann, Sunbury-on-Thames, Middlesex, U.K.). Transcutaneous oxygen tension in the skin was measured using the TCM2 System (radiometer) at several points in the treated and untreated limb. The limb was placed in a cotton stockingette and a water heated blanket was wrapped closely around the limb.

The external iliac vessels were approached retroperitoneally via an oblique incision in the iliac fossa. Iliac lymph nodes along the vessels were removed. All the minor branches of the external iliac artery and all tributaries of the external iliac vein were ligated and divided. The inferior epigastric vessels and most veins were ligated. The internal iliac artery and vein were temporarily occluded throughout the perfusion.

Table 1. Details of patients undergoing ILP for stage II and III malignant melanoma of the limb

	Number of patients (unless otherwise stated) ($n = 103$)	
Mean age (years)	62 (21–92)	
Mean recurrence interval prior to ILP (months)	20 (1–129)	
Mean time from primary melanoma to ILP (months)	48 (1–290)	
Mean number of nodules	32 (1–257)	
Mean diameter of nodules (cm)	2.1 (0.5–4.2)	
Male	25	
Upper limb	3	
Lower limb	22	
Female	78	
Upper limb	5	
Lower limb	73	
Tumour site	First perfusion	Repeat perfusion
Iliac	95	7
Femoral		5
Popliteal		7
Axillary	8	
Number of recurrences prior to ILP		
1	45	
2	33	
3	12	
4	5	
5	4	
>5	4	

Prior to cannulating the vessels, systemic heparin (150 iu/kg) was given intravenously. Through a longitudinal arteriotomy and venotomy the largest possible French polyvinyl chloride cannula (Bard Ltd, Crawley, West Sussex, U.K.) was placed in the artery and vein. It was important that the tip of the cannula lay in the femoral triangle inferior to the inguinal ligament and distal to where the lower edge of the tourniquet was to lie. The cannulae were secured in place using two cotton snares per cannula. An Esmarch's bandage was used as a tourniquet and was secured at the root of the limb over a Steinmann pin which was driven into the iliac crest to hold the tourniquet in position.

Perfusion of the upper limb was carried out through the distal part of the axillary vein and artery. The vessels were exposed through an incision in the skin of the axilla. Lymph nodes on the first portion of the axillary vein were removed and thereafter the technique did not differ from the lower limb except that the Steinmann pin was placed in the head of the humerus.

The perfusion apparatus consisted of a simple roller pump (Stockert instrument, Sorin-Biomedical UK Ltd, Midhurst, West Sussex, U.K.) attached in series to a disposable hybrid oxygenator (Bard) which incorporated an integral heat exchanger. The pump oxygenator was primed with 500 ml lactated Ringer solution and 400 ml of matched packed cells to which was added 3000 units of heparin prior to connecting the arterial and venous cannulae to the circuit (Figure 1).

Once the circuit had been established, 5 ml of 20% fluorescein was injected into the arterial line and with the room darkened, a portable UV lamp was used to inspect the skin above and below the tourniquet. Any significant leak from the limb to the systemic circulation was corrected by tightening the tourniquet. In our early experience of ILP, we initially used radiolabelled isotope to quantify limb to systemic leak. That experience together with detailed pharmacokinetic studies [5] led us to be confident that significant leakage was extremely rare. Thereafter, we chose to use the UV fluorescein as our routine method for confirming isolation. The perfusate inflow temperature was maintained at 40–41°C resulting in a limb skin temperature of up to 40°C (mild hyperthermia). The limb pressure was maintained just below the systemic arterial pressure and flow rates ranged from 250 to 900 ml/min. Once the limb temperature reached 38°C, Melphalan was administered. The dosage used was 1.75 mg/kg body weight for the lower limb and 0.75 mg/kg body weight for the upper limb and was given as a bolus into the arterial port of the oxygenator. Calculating the optimal dose of melphalan is a controversial matter. Although many centres now use limb volume as the means of calculating drug dosage, studies performed at our unit showed that there was no significant difference in the dose calculated using limb volume or body weight [6]. In order to remain consistent throughout the study, we therefore retained body weight as our means of calculating dosage. The perfusate was oxygenated using 100% oxygen. Perfusion was carried our for 1 h during which flow rate, oxygen saturation, perfusion pressure and temperature was continuously monitored. At the completion of the perfusion, the circuit was washed out with 2 litres of Ringer lactate, after which the tourniquet was released, the cannulae

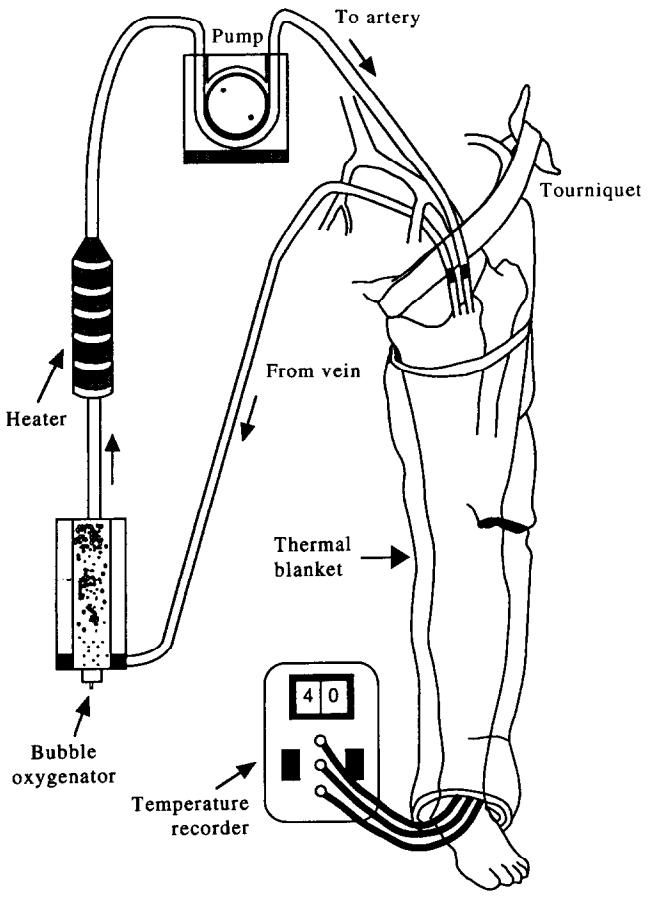


Figure 1. Illustration of the ILP circuit.

withdrawn and the vessels repaired with 5/0′ non-absorbable sutures.

The effect of heparin was reversed with the appropriate dosage of Protamine Sulphate. The approximate length of the operation was 120–180 min.

Postoperatively, the patient was nursed with the leg elevated in a high dependency area of the ward. Patients were followed up at a special perfusion clinic 4 weeks postoperatively and at 3 month intervals thereafter for 5 years. Repeat perfusions were performed for further recurrences or when inadequate disease control was achieved by a single ILP. For repeat perfusions, the ILP was performed at varying arterial levels.

RESULTS

Complications

There were no significant intra-operative complications. 1 patient, who was taking a long-term non-steroidal anti-inflammatory drug died a month following discharge from an upper gastrointestinal bleed. No amputations were carried out either as a result of complications from the perfusion or from the disease. There was significant morbidity associated with this treatment. Skin blistering (especially on the sole or palm) was a fairly common occurrence. Swollen and painful limbs were the norm after this procedure but these rapidly subside over the course of 4–6 weeks and in our experience limbs do return to normal in almost all patients. Before undertaking the procedure, the likely morbidity was carefully explained to all patients. A small but important minority can be left with chronic stiffness of the ankle, knee or elbow joints. Immediate complications are summarised in Table 2.

Follow-up after ILP

Of the 103 patients treated, 78 patients showed complete initial response, i.e. disappearance of all recurrent nodules from the limb [7]. In these 78 patients, at a mean follow-up of 18 months, 21 patients had local recurrence; 34 patients developed systemic disease; 18 patients were disease free, and 5 were disease-free at their time of death from a different cause. Of the 21 patients with local recurrence, 6 had local skin recurrence, 7 had lymph node recurrence and 8 had both skin and lymph node recurrences. These patients were treated with repeat ILP in 5 and laser ablation in 5 with combination of lymph node dissection in the others. In this group of patients at long-term follow-up of 30 months, 17 patients had developed systemic disease and died. 4 patients are currently alive, but, despite having had repeat ILP, still have local disease. The 34 patients who developed systemic disease following ILP were all dead at a mean follow-up of 30 months. The mean time to recurrence was 12 months.

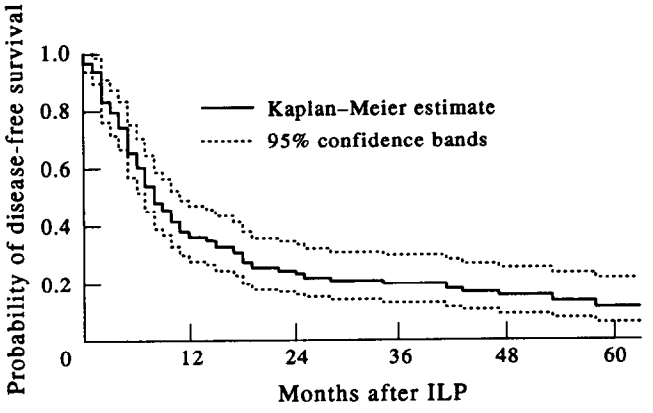
In the 25 patients who did not show complete response to the first ILP, 1 had no response, developed systemic disease and died, 24 patients had a partial response but only 10 patients underwent further ILP, with complete response (i.e. total eradication of local disease) in 7 patients and partial responses in 3 patients. 8 others developed systemic disease and died and 2 are alive with disease being controlled with laser therapy. In the other 14 patients, 10 patients had laser therapy and 4 had systemic chemotherapy in an attempt to control the disease. In this group, 8 developed systemic disease and died and 6 are alive with disease. The 2 and 5 years disease-free survival was 23 and 12%, respectively (Figure 1).

Survival

The average time to ILP from first diagnosis was 48 months (range 1–290). A total of 122 therapeutic perfusions were performed on 103 patients. At a mean follow-up of 30.7 months, 68 patients had died of recurrent disease (mean time to death 22.5 months) and 30 patients are alive; 12 with known recurrence and 18 disease-free. 5 patients died from other causes including myocardial infarction, uterine carci-

Table 2. Postoperative complications following ILP

	Number of patients
Grade of toxicity [4]	
Grade I	22
Grade II	57
Grade III	23
Grade IV	1
Regional	
Nerve symptoms	6
Muscle symptoms	4
Systemic	
Leucopenia	16
Thrombocytopenia	3
Pancytopenia	18
General	
Deep vein thrombosis	3
Pulmonary thromboembolism	4
Wound infection	4
Haemorrhage	1
Haematoma	1



No. of patients at risk	103	34	21	15	10	6
No. dying in previous year	0	63	12	3	3	2

Figure 2. Probability of disease-free survival for stage II–III patients following ILP.

noma, ovarian carcinoma and pneumonia but were disease-free at the time of death (statistically, these patients are alive and disease-free). The overall 2 and 5 year survival was 50 and 26%, respectively (Figure 2).

Survival according to limb. The overall 2 and 5 year survival for upper limb was 38 and 18% whilst in the lower limb the survival was 52 and 27%.

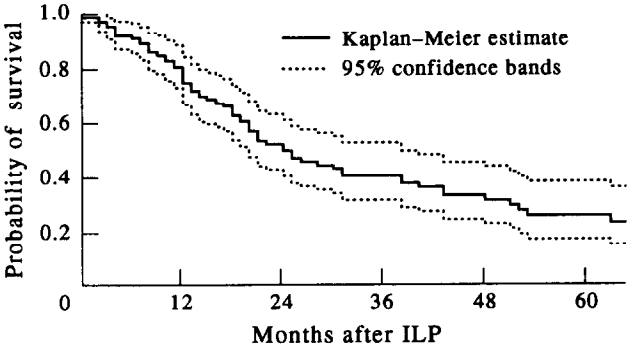
Survival according to sex. The overall 2 and 5 year survival in females were 60 and 35%, respectively, and in males, 18 and 4%, respectively.

Survival according to sex and limb involved. There were no male survivors with upper limb lesions at 2 years, while in females with upper limb lesions the 2 year survival was 75%. In those with lower limb lesions, the 2 and 5 year survival was 18 and 6% in males compared with 61 and 34% in females.

Statistical analysis of these results show that females have a better overall prognosis than males ($P < 0.0001$) and females also have a better disease-free survival ($P < 0.01$). The site of the primary lesion (arm or leg) does not appear to carry prognostic significance either for survival ($P = 0.49$) or disease-free survival ($P = 0.52$).

DISCUSSION

Cutaneous recurrence from malignant melanoma carries a poor prognosis even when the recurrence appears to be confined to a single anatomical site such as a limb. The use of ILP for such patients is theoretically attractive but numerous



No. of patients at risk	103	68	40	28	17	10
No. dying in previous year	0	24	22	7	6	3

Figure 3. Probability of survival for stage II–III patients following ILP.

studies have reported 5 year survival figures of 29–71% [8–14] after ILP. When we made ILP available to patients in Scotland (1983), there was no alternative therapy available and, at the request of the Scottish Melanoma Group, we attempted to assess prospectively whether this technique offered good short-term palliation and any prospect of long-term disease control.

Inevitably, when this facility was first made available, we were referred patients who had already undergone several other modes of therapy. 68 patients were only referred at the time of their second, third or subsequent recurrences. Colleagues initially referred patients who had no other prospect of disease control other than amputation, but with the passage of time, we are increasingly treating patients at the time of their first recurrence. Given that ILP is a significant surgical undertaking for both patient and surgeon, and knowing that the technique has been reported for many years, specialists not working directly with malignant melanoma clearly need to know the answers to several questions in relation to ILP. From our 10 year experience we feel we are in a position to answer some of the key questions:

1. Can ILP be performed safely?
2. What tumour response rate can be expected?
3. For how long will this response be sustained?

Only a limited number of centres have the expertise to provide ILP. In these patients, whose prognosis is poor, it is important that the morbidity of limb perfusion should not seriously hamper the quality of life for a significant period of time if such a period is relatively short for these patients. Our experience has shown that, although the morbidity is significant, it is almost always relatively short and has led us to conclude that it is not a major concern in terms of quality of life.

While there were reports of severe morbidity in early studies of limb perfusion, in centres that are performing more than 25 perfusions per annum, the morbidity has been reduced to an acceptable level [15–17]. We have no operative mortality and an acceptable morbidity for an operation of this magnitude. Most patients will experience some heat and swelling in the limb for weeks or months after the surgery, but this is acceptable to them if disease control is achieved. Initially there is a gratifyingly high local tumour response to ILP. In our study, complete tumour response with respect to total eradication of macroscopic disease was achieved in 76% (78/103) of which 23% (18/78) also gained sustained long-term disease-free survival. This compares favourably with other published series [18, 19]. It was our somewhat surprising finding that remarkable responses can be achieved from subsequent perfusions even though the agent used was the same. In part, this might be explained by our increasing knowledge of the physiology of the circuit and its control [20].

ILP results are superior to those seen with systemic chemotherapy, immunotherapy and radiotherapy. Laser ablation can effectively destroy local disease, but offers no prospect of control for microscopic tumour which may be present in the tissues of the limb, and it seems more logical to offer regional chemotherapy in the first instance and reserve local ablation for subsequent recurrences. We also know that the great majority of patients with cutaneous recurrences will already have systemic disease to which they are likely to succumb. The vital question, therefore, relates to whether a major operation such as ILP should be offered to all these patients or whether a more minor procedure such as local laser therapy would not be more sensible [21, 22]. Our anxiety about a policy which starts with laser therapy is that such a policy assumes that long-term disease-free survival cannot be achieved. Even with our unusually poor prognostic group, we do have long-term survivors (18 patients, 13 females and 5 males).

Any therapy for patients with cutaneous recurrence of substantial proportion has to be a balance of efficacy of local control against morbidity. We do not have evidence that limb perfusion necessarily alters prognosis, but we know of no other treatment modality which can effectively control obvious local disease and offer some prospect of controlling microscopic disease.

Clearly, a major procedure of this type with a definite morbidity should not be used for minimal recurrence that would be amenable to local surgical removal. It would not be appropriate for the elderly and frail. The only alternative therapy which has been shown to give sustained local control would be laser ablation. We look on ILP and laser ablation as complementary rather than alternative treatments. It would be our contention that, at this point in time, limb perfusion should be the initial treatment of choice for most patients with significant limb recurrence and that laser ablation be reserved for those in whom limb perfusion is either unsuitable or has failed to achieve control.

Although our experience of second perfusion has been encouraging, we are hopeful that TNF-alpha will soon be made more available, and a second perfusion could be done with melphalan and TNF-alpha as this would appear to give better response rates than with melphalan alone [23]. We have performed 19 repeat perfusions in 13 patients and achieved almost 50% complete response in these patients. In 2 patients, a third perfusion was performed to control local recurrences which are not amenable to surgery or laser. Systemic chemotherapy is not an appropriate initial treatment for limb recurrence since objective response rates are unacceptably low [24]. We would reserve systemic chemotherapy for those patients in whom systemic disease has been demonstrated.

ILP should retain an important role in the management of patients with limb recurrence from melanoma. From our experience in the use of ILP in the adjuvant context [25], it is clear that conventional staging methods are inadequate. It may well be that, in the future, we will be more accurate in determining those patients in whom systemic disease has not developed. Such patients should logically be offered aggressive local therapy such as ILP. Indeed, with new therapeutic agents now being assessed [23], it is likely that disease control will improve. Conversely, laser therapy can clearly offer very acceptable local control without the need for major surgery. It can be offered under local anaesthetic and it can be repeated on many occasions. Such a treatment is desirable for those patients in whom long-term survival is not expected and for those patients in whom ILP fails to provide disease control.

With the present state of our knowledge, we believe it is not reasonable to withhold the offer of ILP to all other patients with limb recurrence for whom it appears to offer the only real prospect of long-term local disease control.

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