Regional aspects of melanoma diagnosis and treatment
Huismans, Annemarleen

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
2015

Link to publication in University of Groningen/UMCG research database

Citation for published version (APA):
Chapter 5

Isolated Limb Infusion of the Extremity

Anna M. Huismans,1 Hidde M. Kroon,2 Peter C.A. Kam,2,3,4 John F. Thompson1,5,6

1 Melanoma Institute Australia, Sydney, NSW, Australia
2 Sydney Medical School, The University of Sydney, Sydney, NSW, Australia
3 Discipline of Anaesthetics, The University of Sydney, Sydney, NSW, Australia
4 Department of Anaesthetics, Royal Prince Alfred Hospital, Camperdown, NSW, Australia
5 Discipline of Surgery, The University of Sydney, Sydney, NSW, Australia
6 Department of Melanoma and Surgical Oncology, Royal Prince Alfred Hospital, Camperdown, NSW, Australia

Introduction
The treatment of patients with advanced or recurrent malignancies in a limb is often challenging due to the size and number of the satellite and/or in-transit metastasis in those who have melanomas, or the invasion of tumor into adjacent structures in those who have sarcomas. Before the mid-1950s amputation of the affected limb was usually recommended, but following the introduction of the isolated limb perfusion (ILP) technique this mutilating procedure has been avoided in the majority of patients.\(^1\) Using this technique high-dose cytotoxic drugs are administered into the affected limb after it has been isolated from the systemic circulation, resulting in complete response (CR) rates of 46% (7% to 90%) in melanoma and 29% (8% to 40%) in sarcoma.\(^2,3\) Leakage of cytotoxic drugs from the isolated circuit causing systemic toxicity is low as a result of vascular isolation of the affected limb with a tourniquet.\(^3,4\)

The ILP technique, however, is a technically complex procedure and involves an invasive surgical approach. In the past, attempts were made to design a simplified and less invasive alternative to ILP. Procedures such as intra-arterial infusion\(^5\) and tourniquet infusion with partial venous outflow occlusion\(^6,7\) were used for this purpose, but these techniques failed to achieve response rates comparable to those obtained by ILP. In the early 1990s Thompson and colleagues at Melanoma Institute Australia (MIA; former the Sydney Melanoma Unit) developed a simplified, minimally invasive procedure that they called isolated limb infusion (ILI). Using the ILI technique, they sought to obtain the benefits of ILP without incurring its major disadvantages.\(^8,9\) ILI is essentially a low-flow ILP, performed under hypoxic conditions (i.e. without oxygenation of the perfusate) via percutaneously-placed catheters. This simplified technique, now in use at many centers around the world, produces response rates similar to those achieved by ILP for both melanoma and sarcoma.\(^10-13\)

Until now, ILI with cytotoxic drugs has been used predominantly as a therapeutic procedure, but its simplicity and low morbidity suggest that it has great potential as induction therapy for advanced limb tumors. Limited clinical experience with ILI as induction therapy (described later in this chapter) indicates that it is indeed useful in reducing the size of large limb tumors and rendering operable many tumors that were previously considered inoperable.
Isolated limb infusion

ILI technique

A schematic overview of the procedure is shown in Figure 1.\textsuperscript{14} In the radiology department, standard radiological catheters with additional side-holes near their tips are inserted percutaneously into the axial artery and vein of the disease-bearing limb via the contralateral groin using the Seldinger technique. For lower limb ILIs, the catheter tips are positioned in the popliteal artery and vein just above the knee; for upper limb ILIs, the catheter tips are positioned in the brachial artery and basilic vein, just above the elbow. Tissues located more proximally in the limb but distal to the level of the tourniquet are perfused in a retrograde fashion via collateral vascular channels. As soon as the catheters are inserted a warm air blanket is placed over the patient, to prevent a decrease in the patient’s body temperature both during transport to the operating theatre and while waiting in the anesthetic room. The patient is given a general anesthetic, and heparin (3 mg/kg) is administered to achieve full systemic heparinization. Intra-arterial papaverine (30 to 60 mg) is then injected directly into the popliteal or brachial artery via the arterial catheter and a pneumatic tourniquet is inflated around the root of the disease-bearing limb. If the foot or hand is not involved in the tumor process, it is excluded by applying an Esmarch rubber bandage tightly around it to decrease local toxicity.\textsuperscript{15,13} When there is no tumor distal to the knee or elbow, a second pneumatic tourniquet can be applied around the calf or forearm to exclude a larger volume of the limb that does not require drug exposure. The volume of limb tissue distal to the thigh or arm tourniquet and proximal to the distal tourniquet or Esmarch bandage (if either has been used) is then estimated, based on volume measurements made pre-operatively and marked on the limb. Limb volume can be determined using several techniques; the simplest is the water-displacement method, first described by Wieberdink et al.\textsuperscript{16} Another method is to perform calculations based on measurements of the patient’s leg or arm circumference at 1.5-cm intervals up to the level of the tourniquet, encompassing the entire area to be infused.\textsuperscript{10} Both methods are subject to a certain margin of error, however, a more precise method suitable for everyday clinical use has not yet been reported.

The cytotoxic agents are infused into the isolated limb via the arterial catheter. For the duration of the ILI procedure (usually 30 minutes), the cytotoxic infusate is
continually circulated by repeated aspiration from the venous catheter and reinjection into the arterial catheter using a syringe attached to a three-way tap in the external circuit. Figure 2 shows an overview picture of the operating theatre during an ILI. Subcutaneous and intramuscular limb temperatures are monitored and recorded continuously during the ILI procedure, and blood samples are taken at regular intervals to measure the melphalan concentrations and blood gases in limb blood. Limb temperature is increased by incorporating a blood-warming coil in the extracorporeal circuit and by encasing the limb in a hot-air blanket, with a radiant heater placed over it. After 30 minutes, the limb is flushed with one liter of Hartmann’s solution via the arterial catheter, and the venous effluent is discarded. The limb tourniquet is then deflated to restore normal limb circulation, the effect of heparin is reversed with protamine, and the catheters are removed. For patients with metastatic disease in the groin or axilla requiring a regional lymph node dissection as well as an ILI, this is undertaken directly after completion of the ILI procedure (and after reversal of the heparin) while the patient is still under general anesthesia.
The drug leakage rate from the isolated limb into the systemic circulation is evaluated retrospectively in all patients using melphalan concentrations in the systemic blood that are measured routinely during the procedure. Intra-operative systemic leakage monitoring, as performed routinely during ILP, is not performed in ILI since early studies demonstrated that systemic leakage is invariably minimal. Postoperatively the serum creatine phosphokinase (CK) level is measured daily as an indicator of muscle and tissue damage. CK levels exceeding 1,000 IU/l after ILI correlate with increased and potentially serious limb toxicity.\textsuperscript{17,18} Therefore all patients whose CK levels exceed 1,000 IU/l and those who develop clinically severe limb toxicity are treated with systemic corticosteroids until CK levels have fallen below 1,000 IU/l and clinical evidence of toxicity has subsided. Limb toxicity and systemic toxicity are assessed daily and tumor response is assessed at regular intervals postoperatively.

The ILI technique as described above is the result of progressive modifications based on increased experience over time. Initially a dose of 5-7 mg/l melphalan and a circulation time of 15-20 minutes were used. Over time the melphalan dosage was gradually increased to the current 7.5 mg/l. In 1998 the drug circulation time was prolonged to 30 minutes, when it became apparent that drug uptake was not complete after 20 minutes and satisfactory limb temperatures had often not yet been reached.\textsuperscript{11} This prolonged drug circulation increased the total tourniquet time to over 60 minutes, resulting in a prolongation of limb ischemia.\textsuperscript{19} The increased limb ischemic times have not been a problem, however, and in orthopedic surgery even longer
tourniquet times are used routinely without adverse effects. Indeed, the greater hypoxia and acidosis resulting from prolonged tourniquet times are likely to be beneficial, since in vitro studies have shown that increased hypoxia and acidosis produce a threefold increase in the cytotoxic effects of melphalan on tumor deposits.²⁰-²³

Because of the synergistic anti-tumor effects of hyperthermia and melphalan, and the fact that melphalan is ineffective when administered to a hypothermic limb, strenuous efforts are made to maintain limb temperatures pre-operatively and increase limb temperatures intra-operatively.²⁴ To achieve mild limb hyperthermia (ideally 38°C-39°C) special precautions are necessary to avoid body and limb cooling in the immediate pre-operative period. These include the placement of a hot-air blanket over the patient as soon as the vascular catheters have been inserted. This measure is very effective because the patient’s body temperature decreases rapidly after the insertion of the catheters in the radiology department, during the transportation to the operating theatre and while awaiting the ILI procedure in the anesthetic room. Intra-operatively special precautions to maintain limb temperature are used, including use of an overhead radiant heater, and placement of a hot-air blanket around the disease-bearing limb to form a cocoon around it.⁸,¹¹

Intra-arterial administration of papaverine prior to drug infusion is an important part of the protocol, to enhance early blood flow through the capillary vessels into cutaneous and subcutaneous tumor deposits. This results in exposure of the tumor deposits to higher concentrations of melphalan early in the circulation. This is important since there is a rapid decline in melphalan concentration early in the drug-exposure period because of to the short half-life of melphalan.²⁵,²⁶

As a result of these modifications and increased experience with the procedure, the response rates remain similar to those following conventional ILP, despite the increased tumor load in patients treated with ILI, and the fact that many more of them have systemic disease also.¹⁹

**Similarities and differences between ILI and ILP**
Both ILP and ILI involve vascular isolation and perfusion of an extremity with high doses of cytotoxic agents. The major differences between the procedures are the low-
er blood flow and shorter circulation time in the isolated extremity during ILI (150-1000 ml/min for 60 minutes during ILP versus 50-100 ml/min for 30 minutes during ILI). Furthermore the ILI procedure is a hypoxic procedure, which leads to marked acidosis in the isolated circuit in contrast to ILP where an oxygenator maintains full oxygenation in the limb. Obtaining vascular access in ILP to perform a repeat procedure or after groin or axillary lymph node dissection can be technically difficult due to the presence of scar tissue, resulting in a considerably increased risk of morbidity. A repeat ILI, on the other hand, is normally straightforward because the catheters are inserted via the contralateral groin. Also, blood transfusion, or more recently, the use of autologous blood is required for ILP to prime the perfusion circuit but is unnecessary during ILI. A 400 ml infusion of normal saline into the limb is sufficient for ILI, due to the small volume of the circuit. Finally, ILP is a technically demanding procedure that requires complex and expensive equipment, occupies many hours of operating theatre time and involves numerous surgical, anesthetic and nursing personnel plus ancillary technical staff. Compared to this ILI is a much simpler procedure, which requires more modest equipment, considerably less time in the operating theatre and fewer personnel. Figure 1 gives a schematic overview of the ILI technique. The main differences between ILI and conventional ILP are listed in Table 1.

**Drugs used in Isolated Limb Infusion**

Melphalan remains the gold standard to treat patients by either ILP or ILI. In some centers actinomycin D is used in addition to melphalan in ILI procedures because of the good response rates (CR 73%) without any apparent increase in toxicity when it is administered with melphalan during ILP. The melphalan dose that is usually administered for an ILI procedure is 7.5 mg per liter of infused tissue, with a maximum dose of 100 mg for large tissue volumes and a minimum dose of 15-20 mg for very small tissue volumes. Melphalan is infused in a warmed, heparinized, normal saline solution. Infusion fluids containing albumin should be avoided because albumin binds melphalan and reduces melphalan uptake into the tissues by a factor of three. The dosage of actinomycin D is usually 75 µg per liter of infused tissue, with a minimum of 200 µg for smaller limb volumes and a maximum of 500 µg for larger limb volumes.
Table 1: Differences between isolated limb perfusion and isolated limb infusion.  

<table>
<thead>
<tr>
<th>Isolated Limb Perfusion</th>
<th>Isolated Limb Infusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Technically complex</td>
<td>Technically simple</td>
</tr>
<tr>
<td>Open surgical exposure of vessels for catheter insertion</td>
<td>Percutaneous vascular catheter insertion in radiology department</td>
</tr>
<tr>
<td>4 to 6 hours duration</td>
<td>Approximately 1 hour</td>
</tr>
<tr>
<td>Perfusionist and ancillary staff required</td>
<td>No perfusionist required and fewer total staff</td>
</tr>
<tr>
<td>Complex and expensive equipment needed</td>
<td>Equipment requirements modest</td>
</tr>
<tr>
<td>Magnitude of procedure excludes patients</td>
<td>Well tolerated by medically compromised, frail and elderly patients</td>
</tr>
<tr>
<td>Not possible in occlusive vascular disease</td>
<td>Can be performed in occlusive vascular disease</td>
</tr>
<tr>
<td>Technically challenging to perform a repeat procedure</td>
<td>Not difficult to perform a repeat procedure</td>
</tr>
<tr>
<td>Systemic metastases normally a contraindication</td>
<td>Systemic metastases not a contraindication</td>
</tr>
<tr>
<td>Higher perfusion pressures predispose to systemic leakage</td>
<td>Low pressure system, effective vascular isolation with tourniquet</td>
</tr>
<tr>
<td>High flow blood circulation</td>
<td>Low-flow circulation system</td>
</tr>
<tr>
<td>Limb tissues oxygenated, with normal blood gases maintained</td>
<td>Progressive hypoxia and acidosis</td>
</tr>
<tr>
<td>Hyperthermia (&gt;41 °C can be achieved)</td>
<td>Usually not possible to raise limb temperature above 40 °C</td>
</tr>
<tr>
<td>General anesthesia required</td>
<td>Possible with regional anesthesia</td>
</tr>
</tbody>
</table>
The relationship between infused melphalan dose in mg/l and outcome remains unclear. Roberts et al. demonstrated in a dose-response study that increasing the melphalan tissue concentration above a threshold of 25 µg/ml does not further improve the response rates, whereas higher melphalan concentrations cause more severe toxicity.

Increasing melphalan dose above a certain threshold will only increase toxicity without improving outcome. However, melphalan concentration levels are quite variable in individual patients and the factors that determine melphalan concentration levels are not yet fully understood.

In an attempt to decrease toxicity without compromising outcome, clinicians at Duke University Medical Centre adjusted the melphalan dose according to ideal body weight (IBW). This adjustment was based primarily on the observation that the strongest predictor of toxicity in patients undergoing conventional ILP is the ratio of estimated limb volume (Vesti) to steady-state limb drug volume of distribution (Vss).

Hypothetically, patients with a weight greater than their IBW are likely to have a high Vesti/Vss since melphalan uptake is lower in fatty tissue compared to muscle. The Duke University group reported that dose adjustment according to IBW decreased toxicity, but at the expense of a lower partial response (PR) rate, while the CR rate remained unchanged. Although it might be argued that the achievement of a CR is clinically most important, any reduction in the PR rate due to administration of a lower melphalan dose is clinically relevant since a PR and even stable disease following an ILI greatly improve the quality of life in most patients. Moreover, in many cases a PR can be followed by resection of the remaining lesions, thus using ILI as an induction therapy, often resulting in a CR in the limb after this palliative surgery. A retrospective study at MIA showed a correlation between larger limb volume and total melphalan dose, but BMI was not correlated with toxicity. This seeming contradiction was described 30 years ago by Wieberdink et al, who pointed out that regional volumes as a percentage of body weight showed a +/- 30% variability about the mean. It is clear that to further lower toxicity following ILI without compromising outcome, more research is required, focusing on optimizing melphalan concentrations in the individual patient.

The simplicity of ILI makes it an ideal model to test other drugs. For example, the alkylating agent fotemustine was tested in a pilot study in patients with advanced
melanoma confined to a limb. In this study a high response rate was achieved after ILI, with a CR rate of 31% and a PR rate of 61%. Unexpectedly, however, the procedure was associated with severe local toxicity: 4 of 13 patients (31%) experiencing Wieberdink grade V toxicity requiring amputation of the infused limb.16,38

Recently, the alkylating agent temozolomide (TMZ) has been studied as a new regional cytotoxic agent to treat melanoma. ILI with TMZ is a potentially promising approach because of the ability to predict response more accurately. The effect of this agent is dependent on the activity of the DNA repair enzyme O6-alkylguanine-DNA alkyltransferase (AGT) in tumor cells. In an animal model, regional therapy with TMZ was more effective than melphalan for a xenograft tumor with low AGT activity, whereas melphalan was more effective than temozolomide in another xenograft tumor with high AGT activity.39 The results of a formal phase I clinical study using TMZ are awaited with great interest.

Another approach to increase tumor response is by using systemic modulators of drug resistance proteins to overcome regional chemotherapy resistance. TMZ chemomodulation with O6-benzylguanine (O6BG), an inhibitor of the DNA repair enzyme AGT, significantly improved the tumor response in a melanoma xenograft model using TMZ in ILI.40 Tumor resistance to melphalan was associated with elevated intracellular GSH levels. In an animal model short-term systemic therapy with butathione sulfoximine (BSO), an inhibitor of the rate-limiting enzyme in GSH-synthesis, enhanced the effects of regional melphalan without increasing toxicity.41 Phase I trials of these agents have not yet been completed. More drug modulators are currently under development and others are already being tested pre-clinically or in phase I studies.42

**Toxicity and Side Effects following ILI**

Following ILI with melphalan and actinomycin D, regional toxicity is normally low.9,10,35,43 The toxic reaction normally reaches its peak after 3 to 5 days and then begins to subside. In most cases conservative treatment involving bed rest, limb elevation and sometimes administering systemic steroids is sufficient. Toxicity is most often described using the Wieberdink toxicity scale (Table 2).16 Slight erythema and oedema is seen in 41-57% of patients and in 39-53% this is accompanied by the
formation of blisters, corresponding to Wieberdink toxicity grades II and III, respectively. In 3% of patients the muscle and other deeper tissues are involved and in order to prevent a compartment syndrome from occurring a prophylactic fasciotomy is performed in these cases. To date, except for the toxicity after fotemustine in an experimental setting, described previously, it has not been necessary to amputate a limb due to severe toxicity following ILI.\textsuperscript{44}

**Table 2**: Wieberdink toxicity grading.\textsuperscript{16}

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>No visible effect</td>
</tr>
<tr>
<td>II</td>
<td>Slight erythema and/or oedema</td>
</tr>
<tr>
<td>III</td>
<td>Considerable erythema and/or oedema with blistering</td>
</tr>
<tr>
<td>IV</td>
<td>Extensive epidermolysis and/or obvious damage to deep tissues with a threatened or actual compartment syndrome</td>
</tr>
<tr>
<td>V</td>
<td>Severe tissue damage necessitating amputation</td>
</tr>
</tbody>
</table>

**Table 3**: Isolated limb infusion studies using melphalan and actinomycin D.\textsuperscript{10,12,43,44,52,53}

<table>
<thead>
<tr>
<th>Author, year</th>
<th>No. of patiënts</th>
<th>Response criteria</th>
<th>CR</th>
<th>PR</th>
<th>SD</th>
<th>PD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mian, 2001</td>
<td>9*</td>
<td>best response</td>
<td>44%</td>
<td>56%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Lindnér, 2002</td>
<td>128</td>
<td>best response</td>
<td>41%</td>
<td>43%</td>
<td>12%</td>
<td>4%</td>
</tr>
<tr>
<td>Kroon, 2008</td>
<td>185</td>
<td>best response</td>
<td>38%</td>
<td>46%</td>
<td>10%</td>
<td>6%</td>
</tr>
<tr>
<td>Brady, 2009</td>
<td>32**</td>
<td>3 months</td>
<td>25%</td>
<td>28%</td>
<td>6%</td>
<td>41%</td>
</tr>
<tr>
<td>Barbour, 2009</td>
<td>74</td>
<td>best response</td>
<td>24%</td>
<td>30%</td>
<td>37%</td>
<td>7%</td>
</tr>
<tr>
<td>Beasley, 2009</td>
<td>128</td>
<td>3 months</td>
<td>31%</td>
<td>33%</td>
<td>7%</td>
<td>29%</td>
</tr>
<tr>
<td>Raymond, 2011</td>
<td>126</td>
<td>3 months</td>
<td>30%</td>
<td>13%</td>
<td>11%</td>
<td>29%</td>
</tr>
</tbody>
</table>

CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.
* 3 patients had >1 ILI.
** 1 patient had advanced sarcoma
Minor side effects include superficial desquamation of the skin, which often occurs after 2-3 weeks. Hair growth in drug-exposed sites of the treated limb normally ceases for up to 3 months after an ILI and residual pigmentation of the limb is common. If the foot or hand is not excluded by an Esmarch bandage or pneumatic tourniquet during ILI, loss of the superficial layers of the epidermis of the sole or palm may occur, leaving a delicate and sensitive new skin surface exposed. If this occurs, it takes many weeks until the area is again covered by normal plantar or palmar skin. Additional loss of toenails or fingernails can occur 3 to 4 months after the treatment.¹⁸ These side effects are identical to those observed after conventional ILP.²⁸

**Indications and results**

As for ILP, the primary indications for ILI are the presence of inoperable in-transit melanoma of an extremity, and advanced, inoperable extremity sarcoma.¹¹,¹³,⁴⁵ ILI has also been used successfully in patients with refractory warts of the hands,⁴⁶ refractory chromomycosis,⁴⁷ localized cutaneous T-cell lymphoma,⁴⁸ squamous cell carcinoma and Merkel cell carcinoma.⁴⁹

**Melanoma**

In a multi-center retrospective study conducted in the USA,¹⁰ 31% of patients experienced a CR following ILI, 33% had a PR and 36% showed no response to the treatment. In a single-centre experience a CR rate of 38% and a PR of 46% were achieved in patients suffering from melanoma following ILI.¹¹ Figure 3 shows a large melanoma tumor before and after ILI. The median limb recurrence-free interval (LRFI) in patients with a PR was 13 months and for those experiencing a CR it was 22 months (range 5 to > 72: p = 0.012). The median survival following a CR was 53 months (range 28 to > 120), following a PR 26 months (range 14 to > 120), and only 6 months for those who had stable or progressive disease following the procedure (p = 0.004). At the Duke University Medical Centre 126 first-time ILI’s were performed with a CR of 30% and a PR of 14%. In 88% of these procedures chemotherapy doses were corrected for IBW. The patients with a CR had a median survival of 31 months, those with a PR, SD or PD had a combined median survival of 28 months. These results and survival data are similar to those following ILP with melphalan.⁴⁴,⁵⁰,⁵¹ As well as these studies, a number of other institutions around the world have now reported their initial experiences with ILI; these are listed in Table 3.¹⁰-¹²,⁴³,⁴⁴,⁵²,⁵³ The wide range of
results in these studies is likely to be due to the low number of patients in some of them and possibly by a variable early experience with the technique in the institutions performing ILIs. Furthermore, some institutions have used protocols that differ in small but potentially important ways from the protocols used by others. The impact of protocol variations and the effect of increased experience have recently been investigated at MIA. In this study it was shown that increased experience and small modifications that were made to the ILI protocol over a 14 year period resulted in a positive effect on outcome. Another explanation for the range in results that have been reported could be the point in time at which the response to the procedure was assessed. Beasley et al., for instance, reported the response exactly 3 months following ILI, while others have reported the best response at any time after the procedure.

Sarcoma and other non-melanoma skin malignancies
Experience with the use of ILI for sarcoma is still limited. A study conducted at MIA involved the use of ILI in a cohort of 21 patients with soft tissue sarcoma. In 14 of these patients the ILI was performed as induction therapy and in the other 7 patients the ILI was used as a palliative measure. The OR was 90%, with a CR of 57% and a PR of 33%. The response rate in the induction therapy group was 100%, with a histologically confirmed CR rate of 65% (i.e. in 65% of the surgical resection specimens no tumor cells were found). After a median follow-up of 28 months the limb salvage rate was 76%. Turaga et al. describe a cohort of 22 patients; 14 with sarcoma, 7 with Merkel cell carcinoma and 1 with squamous cell carcinoma, all treated with ILI. The overall response rate in this report was 79%, with a CR rate of 21% and a PR rate of 58%. In 86% of the patients limb preservation was achieved. Interestingly, 4 of the 5 patients who underwent resection of residual disease after their ILI remained disease free after a median follow-up of 8.6 months.

In another study ILI using doxorubicin followed by external beam radiotherapy was used as an induction therapy to obtain local control and make limb-sparing surgery feasible. In this study 30% of the patients showed a PR and 55% a minimal response. At a median follow-up of 15 months, limb salvage was achieved in 82.5%.

Isolated Limb Infusion as induction therapy
Besides using the ILI technique to test new drugs and to find systemic modulators to overcome resistance to known cytotoxic agents, it can also be used to provide induction therapy. The goals of therapeutic ILI are to achieve satisfactory palliation
Figure 3a: Extensive in-transit melanoma metastases of the left lower leg before ILI.

Figure 3b: Remission 4 weeks post-ILI.

Figure 3c: Complete response 4 months post-ILI.
and limb salvage. Achieving a CR improves the quality of life markedly, but achieving a PR or even SD can substantially improve the patient’s quality of life also. After a PR or when recurrent lesions appear following ILI simple local treatments of the remaining or recurrent lesions by excision, laser ablation, electrodesiccation, injection with rose bengal or radiotherapy can be effective in controlling the disease.\(^5^4\) If recurrent disease is too extensive to be treated with simple local measures, a repeat ILI can be considered, and can usually be performed without difficulty due to the minimally invasive character of the procedure.\(^5^5\) Over a 15-year period only 14 of 235 patients treated with an ILI at the MIA eventually needed an amputation to control persistent or recurrent limb disease.\(^5^6\) In patients with inoperable sarcoma ILI can be used as neo-adjuvant therapy, prior to surgical excision or radiotherapy, similarly to ILP. Using this approach limb salvage rates of 76-86% have been reported.\(^1^3,^4^5,^4^9\) Another approach has been to combine pre-operative ILI with doxorubicin and pre-operative external beam radiotherapy to obtain local control and make limb-sparing surgery feasible.\(^4^5\) This led to a limb salvage rate of 82.5%.\(^4^5\)

An interesting induction strategy is the use of systemic modulators to augment the cytotoxic effects of regional chemotherapy administered by ILI. In a phase II study designed to test whether systemic ADH-1 enhanced the tumor response to ILI with melphalan, an overall response rate of 60% was achieved without increasing toxicity, compared with an overall response rate of 40% achieved previously with melphalan alone at the same institution.\(^5^7,^5^8\) Along similar lines, following the promising results of systemic sorafenib therapy combined with DTIC, the effect of systemic sorafenib in combination with regional melphalan or temozolomide on melanoma was studied in an animal model.\(^5^9-^6^1\) This pre-clinical study showed that systemic sorafenib in combination with regional melphalan or regional temozolomide was more effective in reducing the tumor growth than either treatment alone.\(^6^2\) The results of a phase I clinical study are awaited with great interest.

**Conclusions**

By using ILI with therapeutic intent or as induction therapy, amputation of the affected limb in patients with inoperable melanoma or sarcoma can be avoided in almost all patients. When used for palliation of extensive or recurrent limb disease, good control can be achieved in the majority of them. ILI is an excellent model to test new
drugs or new treatment regimens. A number of studies are currently investigating new strategies for treating melanoma and sarcoma using the ILI technique, and innovative methods of using ILI as induction therapy, not yet fully exploited, are being developed.
References


PART TWO

regional melanoma staging