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Technical considerations for isolated limb perfusion: A consensus paper☆

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A B S T R A C T

Background: Isolated limb perfusion (ILP) is a well-established surgical procedure for the administration of high dose chemotherapy to a limb for the treatment of advanced extremity malignancy. Although the technique of ILP was first described over 60 years ago, ILP is utilised in relatively few specialist centres, co-located with tertiary or quaternary cancer centres. The combination of high dose cytotoxic chemotherapy and the cytokine tumour necrosis factor alpha (TNFα), mandates leakage monitoring to prevent potentially serious systemic toxicity. Since the procedure is performed at relatively few specialist centres, an ILP working group was formed with the aim of producing technical consensus guidelines for the procedure to streamline practice and to provide guidance for new centres commencing the technique.

Methods: Between October 2021 and October 2023 a series of face to face online and hybrid meetings were held in which a modified Delphi process was used to develop a unified consensus document. After each meeting the document was modified and recirculated and then rediscussed at subsequent meeting until a greater than 90% consensus was achieved in all recommendations.

Results: The completed consensus document comprised 23 topics in which greater than 90% consensus was achieved, with 83% of recommendations having 100% consensus across all members of the working group. The consensus recommendations covered all areas of the surgical procedure including pre-operative assessment, drug dosing and administration, perfusion parameters, hyperthermia, leakage monitoring and theatre logistics, practical surgical strategies and also post-operative care, response evaluation and staff training.

Conclusion: We present the first joint expert-based consensus statement with respect to the technical aspects of ILP that can serve as a reference point for both existing and new centres in providing ILP.

1. Introduction

Isolated limb perfusion (ILP) is a well-established surgical procedure for the administration of high dose chemotherapy to a limb for the treatment of advanced extremity malignancy, usually not amenable to surgical resection. Although the technique of ILP was first described over 60 years ago [1]; ILP is utilised in relatively few specialist centres, co-located with tertiary or quaternary cancer centres. The combination of high dose cytotoxic chemotherapy, with the vasoactive cytokine tumour necrosis factor alpha (TNFα), requires leakage monitoring to ensure effective isolation of these drugs within the limb to prevent potentially serious systemic toxicity. Because the procedure is limited to relatively few specialist centres, the ILP Working Group decided to construct a consensus statement with respect to the technical aspects of ILP, that can serve as a reference point for both existing and new centres in providing ILP (see Table 1).

There are two principle pathological indications for ILP. The first is in advanced extremity sarcoma that is unresectable by standard limb conserving surgery. Amputation confers no overall survival benefit when compared with limb conserving surgery [2]. ILP therefore has a role in the palliative context, to either abrogate or delay the need for amputation and its associated significant morbidity. This may be in a patient with an advanced sarcoma who has synchronous metastatic disease, or where a patient with an advanced primary tumour in the absence of metastatic disease but still wishes to avoid amputation. This is often the case with elderly patients were an amputation can have a significant negative effect on quality of life. ILP can also be used as a neoadjuvant strategy, for a locally advanced non-metastatic primary sarcoma that is at the limits of limb conserving because of factors such as size, fixation to bone, or involvement of neurovascular structures [3]. ILP may effectively downstage the tumour, to allow an oncologically satisfactory limb sparing resection. Radiotherapy may be used in conjunction with this neoadjuvant approach.

The second indication for ILP is advanced (multiple, bulky and/or recurrent) melanoma in-transit metastases (ITM) that are not amenable to simple surgical excisions. In the years prior to effective systemic therapy for melanoma, regional chemotherapy treatments including ILP represented first-line treatment for advanced ITM [4]. The overall response rates (ORR) for ILP were 90%, with complete response (CR) rates of 58% [5]. Local response rates have been shown to be durable, though there are no proven benefits with respect to distant dissemination [6–9]. ILP is also effective in the context of patients that have failed previous immunotherapy with an ORR between 59 and 75% [4,10]. ILP has also proven safe and effective in the treatment of ITM in elderly patients, and as a repeat treatment following previous ILP [11–14].

ILP can also have a role in the treatment of other regionally-based malignancies in the extremities including: squamous cell carcinoma, Merkel cell carcinoma and cutaneous lymphomas [15].

This consensus document is a joint effort giving recommendations on how to perform ILP in a safe and efficacious way, but also to harmonize routines and methods to allow for easier comparisons and future development within the field.

2. Methods: terms of reference

This consensus statement was established utilising a modified Delphi methodology. A steering group established statements which were first presented in a hybrid (face-to-face and online) meeting at the 41st Congress of the European Society of Surgical Oncology in Bordeaux to the ILP working group. The ILP working group being made up of representatives from thirty-three units around the world performing TNFα ILP.

Following this initial meeting, a structured communication process utilising online questionnaires, led by the steering committee was conducted to establish the recommendations. The ILP working group then formally convened again at the 42nd Congress of the European Society of Surgical Oncology in Florence, Italy to ratify the recommendations and discuss any suggested modifications. The level of consensus, presented as a percentage of the thirty-three participating units is presented for each of the recommendations. This document represents the final consensus statement from the ILP working group.

[1] These authors contributed equally.

3. Preoperative assessment

3.1. Recommendation 1.1: general assessment

Given the complexity in decision making with respect to advanced melanoma and sarcoma, the authors would advocate that all patients go through an appropriate multidisciplinary team (MDT) meeting prior to ILP. The assessment of patient suitability for ILP is not different from the assessment of a patient for any significant, peripheral vascular surgery. In general, ILP is well tolerated even in elderly patients [11,12], as the surgical insult is not great, and toxicities are limited to the limb, unless there is a significant systemic leak, which in the majority of patients should be identified prior to the administration of chemotherapeutic agents.

Level of consensus: 100% (n=33), No 0% (n=0).

3.2. Recommendation 1.2: vascular assessment

With respect to the peripheral vasculature there are a number of crucial considerations prior to ILP, and the creation of an adequate perfusion circuit. Significant peripheral arterial disease, particularly superficial femoral and popliteal disease, should be considered an absolute contraindication. In these circumstances, it is very unlikely that a viable perfusion circuit can be established, and furthermore, the risks associated with cannulation of the artery and subsequent closure has to be taken into consideration. Similarly, serious small vessel arterial disease could be considered a relative contraindication. In both cases, it is important that this is identified prior to attempted cannulation, where associated morbidity may then result for no therapeutic benefit.

In addition to adequate arterial flow, it is essential to have adequate venous return. Where there is venous occlusion, either intrinsic such as deep vein thrombosis (DVT), or extrinsic such as in the case of a large bulky tumour, cannulation may not be possible, and therefore there will be no establishment of a perfusion circuit. Small calibre vessels, particular in the arm, may require cannulation of multiple veins and connection with a Y-connector to establish adequate venous returns (see Recommendation 3.6 below).

Where the patient has no history of vascular disease, diabetes, or smoking; and where the patient has readily palpable peripheral pulses in the affected limb, then specific vascular imaging is not required. Where there is concern on history or examination of peripheral arterial disease or venous insufficiency, then appropriate vascular imaging should be undertaken in the form of CT angiogram with three vessel run-off in the leg for arterial assessment, and Doppler ultrasound for assessment of the venous system.

Level of consensus: 100% (n=33), No 0% (0).

3.3. Recommendation 1.3: pre-existing lymphedema

In addition to assessing peripheral vasculature, many patients undergoing ILP will have pre-existing lymphoedema that may or may not be related to their disease, classic examples being angiosarcoma developing in a chronic lymphoedematous limb (Stewart-Treves syndrome), or melanoma patients with ITM, and a prior lymph node dissection in the ipsilateral nodal field. It has been suggested that for patients with lymphoedema, a period of strict leg elevation for 24 hours prior to

Table 1
Centres performing TNF based ILP worldwide.

Country	Name	Address
Australia	Peter Mc Callum	305 Grattan Street, Melbourne VIC 3000, Australia
Belgium	UZ Leuven	Campus Gasthuisberg, Herestraat 49, 3000 Leuven, Belgium
Colombia	The Instituto Nacional de Cancerología de Colombia in Bogota	Calle 1 No.9-85 Bogotá - Colombia
Czechia	General University Hospital in Prague	2nd Department of Surgery - Department of Cardiovascular Surgery, First Faculty of Medicine, Charles University in Prague, miroslav.spacek@vfn.c (Delete email address)
France	Hopital Pellegrin (CHU) - Institut Bergonié	Institut Bergonié Sarcoma Unit, '229 cours de l'Argonne, 33,000 Bordeaux
France	Institut Gustave Roussy	Institut Gustave Roussy, 39, Rue Camille Desmoulins, 94,805 Villejuif Cedex, France
France	Institut Curie	Institut Curie, 26, Rue d'Ulm, 75,248 Paris Cedex 05, France
Germany	Helios Klinikum Berlin	Helios Klinikum Berlin-Buch, Schwanebecker Chaussee 50, 13,125 Berlin, Deutschland
Germany	Universitätsklinikum Erlangen	Universitätsklinikum Erlangen, Maximiliansplatz 2, 91,054 Erlangen, Deutschland
Germany	Universitätsklinikum Essen	Universitätsklinikum Essen, Hufelandstr. 55, 45,147 Essen, Deutschland
Germany	Universitätsklinikum Frankfurt	Klinikum Frankfurt Höchst GmbH, Gotenstraβe 6–8, 65,929 Frankfurt am Main, Deutschland
Germany	UMM Universitätsmedizin Mannheim	UMM Universitätsmedizin Mannheim, Theodor-Kutzer-Ufer 1–3, 68,167 Mannheim, Deutschland
Greece	Metropolitan Hospital Athens	264 Mesogion Avenue, GR-15562 Holargos, Athens, Greece
Israel	Tel Aviv Sourasky Medical Center	Tel Aviv Sourasky Medical Center, 6 Weizman Street, 64,234 Tel Aviv, Israel
Italy	Ospedale San Martino	Ospedale San Martino, Largo Rosanna Benzi 10, 16,132 Genova, Italy
Italy	Fondazione IRCCS Istituto Nazionale dei Tumori	Fondazione IRCCS Istituto Nazionale dei Tumori, Sarcoma Service, via Venezian 1, 20,133 Milano, Italy
Italy	Istituto Europea die Oncologia	Istituto Europea die Oncologia, Via Ripamonti 435, 20,141 Milano, Italy
Italy	Azienda Ospedaliera di Padova	Azienda Ospedaliera di Padova Clinica Chriurgica II, Via Giustiniani 23, 35,128 Padova, Italy
Mexico	Instituto Nacional de Cancerologia (INCAN) Main contact for Mexico	Instituto Nacional de Cancerologia (INCAN), Av. San Fernando 22, Col. Seccion XVI, Mexico, DF 14080, Mexico
Norway	The Norwegian Radium Hospital	Sykehusapoteket Oslo, Radiumhospitalet Avd. Tilvirkning i OCCI bygget, Ullernschaussen 64, 7 etg.
Portugal	Instituto Português de oncologia de Lisboa	Rua professor Lima Basto, 1099-023 Lisboa, Portugal
Slovenia	Onkološki Inštitut Ljubljana	Onkološki Inštitut Ljubljana, Zaloška 2, 1000 Ljubljana, Slovenia
Spain	Clinica Universitaria de Navarra	Clinica Universitaria de Navarra, Avenida de Pio XII 36, 31008 Pamplona, Spain
Spain	Hospital Universitario Virgen Macarena	Calle Dr. Fedriani, 3, 41,009 Sevilla, Spain
Sweden	Sahlgrenska University Hospital	Sahlgrenska University Hospital, 41345 Gothenburg, Sweden
Switzerland	Clarunis University Basel	Clarunis, University Center for Gastrointestinal and Liver Disease Basel, Basel, Switzerland
Switzerland	Lausanne University Hospital and University of Lausanne	Center Hospitalier Universitaire Vaudois, Rue du Bugnon 46, 1011 Lausanne CHUV
The Netherlands	Netherlands Cancer Institute	Netherlands Cancer Institute, Antoni van Leeuwenhoek Hospital, Plesmanlaan 121, 1066 CX Amsterdam, The Netherlands
The Netherlands	University Hospital Groningen	University Hospital, The Universal Medical Center, Hanzeplein 1, PO Box 30.001, 9700 R B Groningen, The Netherlands
The Netherlands	Erasmus MC	Erasmus MC - Daniel Den Hoed Cancer Center, Department of Surgical Oncology, 301 Groene Hilledijk, 3075 EA Rotterdam, The Netherlands
United Kingdom	The Royal Marsden Hospital	The Royal Marsden Hospital, Fulham Road, SW3 6 J J London, United Kingdom

surgery can considerably reduce the degree of oedema in the limb. Decreasing the amount of swelling in the leg makes dissection and vascular isolation easier and may potentially also assist in minimizing the degree of post-operative exacerbation of swelling as a result of ILP.

Level of consensus: *91%* (n=30)*Yes*, *No 9%* (n=3)

3.4. Recommendation 1.4: volumetric assessment

The dose of cytotoxic drug utilised depends upon the volume of the leg below the tourniquet, and the volumes depend on a multitude of factors including age, weight, nutritional status and tumour burden. The most accurate method of assessing limb volume is via perometry, either using a water displacement system or laser perometry. The most common is however to estimate the limb volume via measuring length circumference, where limb volume is calculated through dividing the limb into cylinders and summing the total. Despite the relative simplicity of the limb circumference technique, it has been demonstrated to be reproducibly accurate as compared to other methodologies [16,17]. There are even simpler methods for estimating limb volume particularly in the lower limb such as using a proportion of bodyweight as a surrogate calculation for limb volume (see section 2).

The whole limb will generally be perfused below the tourniquet; however, it may be possible to exclude distal elements of the limb such as the hand and foot, through wrapping an Esmarch bandage to reduce toxicity. Indeed, it is often the distal extremities that suffer the most troublesome side effects post-operatively, and where this can be avoided it should be. This is particularly the case for primary sarcomas in the lower limb which do not affect the foot, whereas with in-transit melanoma when there is a risk of disease developing within the foot exclusion of the foot is not advised. Any excluded regions of the limb should be deducted from limb volume calculations, and the calculation should start at the level of the tourniquet. In patients with severe lymphedema, it is possible to calculate the volume based on the contralateral extremity, in essence using this as an unaffected control.

Level of consensus: *91%* (n=30) *Yes*, *No 9%*(n=3)

4. Drugs, perfusion and nuclear medicine utilised during ILP

4.1. Recommendation 2.1: melphalan

ILP involves the delivery of high dose cytotoxic chemotherapy, often in combination with TNFα. The high dose is predicated upon the ability of ILP to avoid systemic exposure, while the bypass of hepatic and renal clearance maintaining high concentration in the perfused limb. Initial ILP regimens utilised doxorubicin as the chemotherapeutic agent. However, it has subsequently been established that melphalan provided better efficacy and less toxicity as compared to doxorubicin and other agents [18–20].

Melphalan has a number of characteristics that make it suited to ILP including: a short half-life, low relative toxicity to the vasculature and soft tissue, and a linear cytotoxic dose-response relationship [21]. The dose of melphalan is calculated based on volume as described above, highlighting again the need to use the contralateral leg for limb volume assessment in the context of significant lymphoedema (see Recommendation 1.4). A dose of 10mg/L is used in the lower limb, and 10–13mg/L used in the upper limb [22]. Higher doses used in the upper limb reflect lower concentrations in the perfusate of small volume perfusions [23]. A dose of 1mg/kg of body weight approximates to 10mg/L of limb volume for a leg perfusion performed with an upper thigh pneumatic tourniquet.

Level of consensus: 100% (n=33)*, No 0% (n=0)*.

4.2. Recommendation 2.2: TNFα and sarcoma

TNFα was first introduced in 1988 as a combination treatment with melphalan [24]. It is a natural mediator of the systemic inflammatory response and has both direct and indirect anti-tumour effects, in part mediated by its effect on tumour vasculature. TNFα causes destruction of tumour neo-vasculature, thereby increasing the permeability resulting in a better diffusion of melphalan into the tumour tissue. When administered in combination with melphalan it mediates a 4-6-fold increase in the uptake of melphalan in the tumour [25]. The dose according to European Medicines Agency, summaries of product characteristics (SmPC), is 3mg total dose for 4mg for the lower limb and 3mg for upper limb [26,27]. However, a clinical trial showed similar efficacy using a dose of 0.5mg, 1mg, 2mg or 3–4mg, but with less toxicity, specifically lower rates of post-operative vasopressor requirement and therefore intensive care admission [28,29]. Based on this, for patients with sarcoma, most centres advocate for a lower dose of either 1 or 2mg (up to 4mg) to be used in combination with melphalan for a lower limb perfusion and 0.5 or 1mg (up to 2mg) for an upper limb perfusion.

Level of consensus: 100%(n=33)*, No 0% (n=0)*.

4.3. Recommendation 2.3: TNFα and melanoma

The evidence for the benefit of TNFα in the treatment of ITM in melanoma is less clear, due to the findings of the only randomised control trial of melphalan alone versus melphalan in combination with TNFα [30]. This study failed to demonstrate increased response rates at the primary endpoint of 3 months. This study was however limited in that there was no stratification of patients with bulky ITM and the primary endpoint for this trial was assessed at 3 months which was considered very early as many responses in melanoma are seen at a later time point after the perfusion. Higher response rates were seen in the TNF arm at later time point in this study. Notwithstanding these caveats, TNFα is not routinely recommended for patients with melanoma ITM, but can be considered in a dose of 1mg–2mg for bulky melanoma (largest metastasis >3cm) and repeat ILPs [7,31].

Level of consensus: 100% (n=33)*, No 0% (n=0)*.

4.4. Recommendation 2.4: drug preparation and administration

TNFα is supplied as an anhydrous compound that is reconstituted with sterile saline, which can be easily done by either the surgical or anaesthetic team. Once the perfusion circuit is established, as outlined below, it is delivered as a bolus injection 10 minutes prior to the administration of melphalan. The rationale being that this time period allows for vasodilation of the tumour vasculature, prior to the administration of the cytotoxic drug to maximise uptake, and thereby increase the concentration of melphalan in the tumour.

Ordinarily cytotoxic agents such as melphalan that are prepared for intravenous delivery will be prepared under strict regulated conditions within an aseptic unit in the hospital pharmacy. Melphalan, once reconstituted under conditions suitable for cytotoxic agents, is recommended to be administered within a limited time period (1–4 h) as it is suggested that its efficacy diminishes over time after reconstitution, although the precise duration of that time limit varies between differing pharmacy recommendations between units. The delivery of melphalan into the perfusion circuit is either as a bolus or by a 10-min infusion directly into the perfusion circuit.

Level of consensus: 100%(n=33)*, No 0% (n=0)*.

4.5. Recommendation 2.5 perfusion

The perfusion circuit is a standard cardiac perfusion circuit, preferably a paediatric circuit to minimize dilution, especially important in upper limb ILP due to the considerably smaller volumes utilised in the arm (Fig. 1). In the leg, the volume of the perfusion reservoir is small in comparison to the intravascular volume of the lower limb, whereas even with the paediatric circuit, the volume of the reservoir is large compared to the intravascular volume of the upper limb. This is important in the priming of the perfusion circuits, where in the upper limb the circuit is

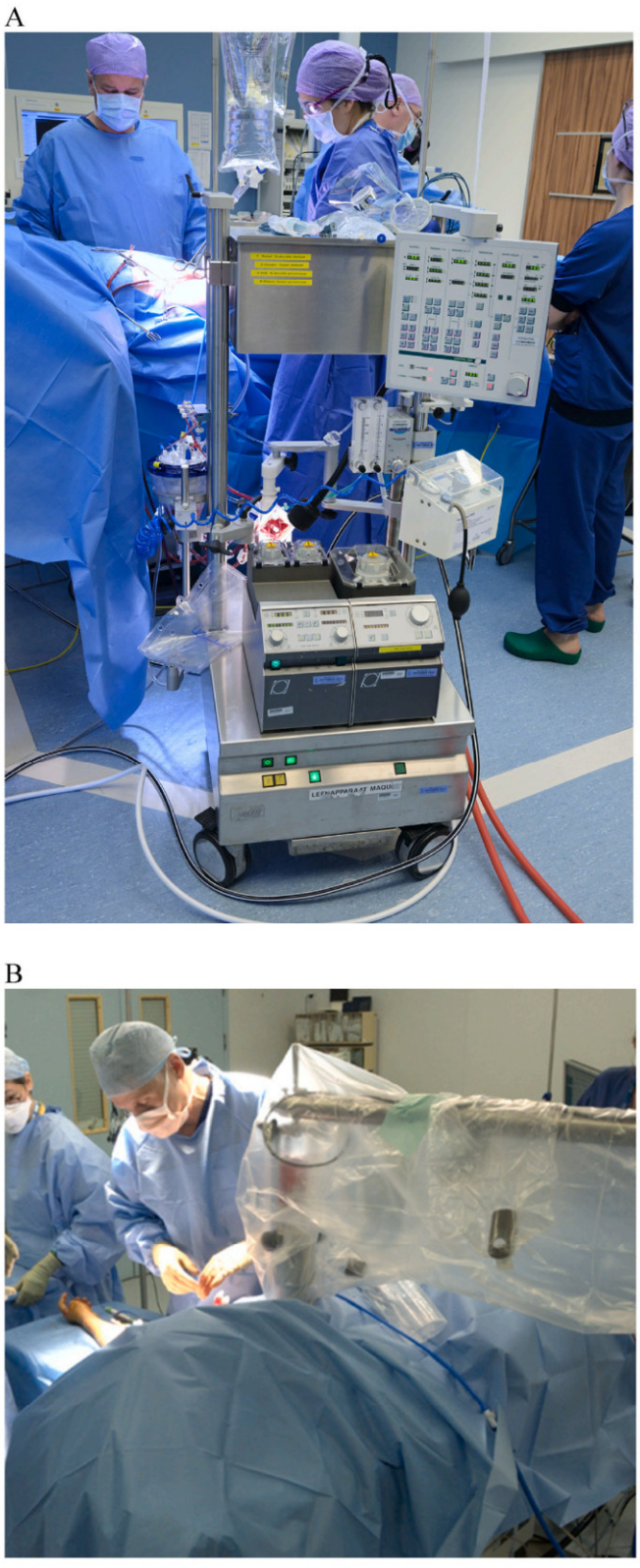


Fig. 1. Theatre logistics. *Panel A*: Extra corporeal bypass circuit using a modified cardiac bypass machine. *Panel B:* A scintillation counter secured over the patients praecordium.

primed with blood to ensure that there is an adequate haematocrit for tissue oxygenation during the ILP, in the leg, where the relative volumes are inverse, priming with a crystalloid solution is adequate [32].

The priming of the perfusion circuit, and the monitoring of haemodynamic parameters of the limb perfusion and the final washout will be undertaken by a perfusionist who should be suitably trained in the technique of isolated limb perfusion. During the perfusion it is vital to maintain excellent communication with the whole team, especially the perfusionist, as changes seen in the perfusion circuit including flow rates and volumes returned, may reflect critical surgical issues such as an increasing systemic leak, either to or from the patient, or even haemorrhage at the cannulation site. In satisfactory ILP circuits flow rates of between 200 and 500mL/min should be achievable in a lower limb perfusion, and 80–200mL/min in an arm which is sufficient to ensure oxygenation and hyperthermia without recourse to any external radiant heating system (as compared with isolated limb infusion (ILI)) [33].

There has historically been some variability concerning the duration of the perfusion, though most units initially perfuse with TNFα for 10–15min, followed by 45–50min in combination with melphalan [3]. This has been demonstrated to have equivalent outcomes to initial protocols which saw longer perfusion times [34]. Melphalan has been demonstrated to have maximal uptake in the tissues during the first 30min of perfusion [35]; whilst TNFα retains stability for a longer period throughout perfusion.

The current consensus is that after the establishment of the perfusion circuit, the perfusion of drugs starts after ensuring there is no, or minimal leakage. If TNFα is used, then this is given as a bolus, and after 10 min, a 10 min infusion of melphalan is started, whereafter the perfusion is continued for another 45min (55min total perfusion time with melphalan). Thereafter the extremity is typically rinsed with 2000 mL of crystalloids for upper limb and 3000 mL of crystalloids for lower limb, most often using the same flow rate as during the perfusion. Wash out may be manually assisted through physical manipulation of the limb, compression from distal to proximal will help ensure adequate washout of the capacitance vessels within the calf or forearm. Wash out is considered complete when the venous line is mostly clear. Any Esmarch bandage on the distal limb should also be released. Once washout is complete, with sufficient time and adequately clear character of the venous outflow cannula, the tourniquet can be released, and the arterial and venous catheters can be removed, and vascular repair is then undertaken using the principles described below.

Level of consensus: 100%(n=33)*, No 0% (n=0).*

4.6. *Recommendation 2.6: hyperthermia*

Hyperthermia increases the efficacy of alkylating agents such as melphalan [36], though also leads to increased toxicity in the limb, thus a balance must be struck in the degree to which the limb is warmed. Most centres target a temperature of between 38 and 40°C in an effort to balance increased efficacy with increased rates of toxicity [3], where temperatures greater than 40°C are associated with disproportionate limb toxicity for limited to no additional clinical benefit. Historically, the temperature has been measured both in the arterial and the venous line of the perfusion circuit, and also subcutaneously and intramuscular at different levels in the limbs. For the purpose of standardisation, it is recommended to measure the temperature in the arterial cannula (incoming blood) and subcutaneously 15cm above and below the knee/elbow joint. The temperature of the ingoing blood is then typically set to 39°C. By the end of the procedure the temperature recorded by the venous temperature probe in the efferent blood returning to the perfusion machine will approximate to the arterial inflow temperature unless the flow rate is very low. Skin surface temperature probes will record temperatures at least 1°C below venous blood temperatures and may be considerably lower if the flow rate is low and the starting limb temperature is hypothermic, as can be the case if the surgical dissection to cannulate the limb is prolonged. Therefore, skin surface temperature probes should not be considered accurate measures of limb temperature. Intramuscular temperature probes are much more accurate measures of actual limb temperature but have been increasingly difficult to access from manufacturers in recent years.

Level of consensus: 100%(n=33), *No 0% (n=0)*.

4.7. Recommendation 2.7: leakage monitoring

It is asserted that best practice in ILP necessitates the use of continuous leakage monitoring for all ILPs, whether or not TNFα is used, but is mandatory for any perfusion utilising TNFα given the profound systemic toxicity that may be induced with systemic administration. The principle of continuous leakage monitoring is that a low dose of radioactive tracer, most commonly Technetium-99 m labelled to a carrier molecule such as human serum albumin or sodium pyrophosphate [37], is administered to the systemic circulation at the beginning of the procedure. A scintillation detector is placed over the praecordium for detection of this baseline level of radioactivity prior to commencement of perfusion. After vascular isolation of the limb has been achieved and confirmed by the perfusionist, a 10-fold higher dose of the radioactive tracer is added to the perfusion circuit, the principle being that during the ILP, the higher dose of radioactivity should not register on the scintillation detector which measures only the radioactivity in the systemic circulation as the distance from the higher dose in the isolated limb is too great to register on a scintillation counter positioned over the praecordium. If there is a leak from the limb circuit into the systemic circulation, this will register via the scintillation detector, and furthermore given the relative concentrations a relatively precise percentage of leak can be calculated, allowing for minute-by-minute calculation of the leakage from the limb to the systemic circulation. It is important in arm perfusions to try and position the venous and arterial cannulas so that they do not lie too close to the scintillation counter otherwise a reading from the perfusion circuit may be registered in the scintillation counter and could be incorrectly interpreted as a leak.

The signal detection from the systemic circulation is performed using a detector unit which comprises a collimator, scintillation crystal, photomultiplier tube and signal analyser connected to a computer with appropriate software. The detector is mounted on a mechanical support and suspended securely over the praecordium (Fig. 1 Panel B). A lateral collimation of the detector significantly reduces signal that arises from the perfusion circuit. The analysis software should be capable of a live display of continuous short interval readings (30s or 1min) and decay correction should be performed [37]. The use of radionuclides in the operation room requires additional procedures for the involved personal, and the collection of all radioactive waste created during the procedure and protocols for this should be defined according to the standard operating procedures of the nuclear medicine department.

An ILP in a patient with normal body habitus and a good flow rate in the isolated limb, should see a systemic leak rate of less than 5%, and indeed in many cases the leak rate should be entirely negligible. A multitude of factors may contribute to increased leak rates in an ILP, including large leg circumference (ie. obesity), use of an elastic tourniquet as opposed to a pneumatic tourniquet, high perfusion pressures secondary to intrinsic elevated vascular resistance (ie. atherosclerosis), technical problems resulting in low venous return, and also anatomical variations with e.g. collateral veins inside of the bones causing the leakage. Extensive proximal limb lymphoedema is likely to result in a higher rate of leak, and should be noted clinically, and discussed with the patient preoperatively.

In circumstances where there is an increased likelihood of leak, it is important to undertake any possible manoeuvres to minimize leak rate prior to the administration of TNFα, such as meticulous tourniquet placement and surgical control of all possible venous collaterals running in parallel to the canulated vessels in the surgical field. High leak at the commencement of vascular isolation should be communicated between the medical physics team, the perfusion team and the surgeon. If there are high leak rates recorded at the beginning of the procedure before drug administration that cannot be redressed, this should be considered an absolute contraindication to proceeding with the perfusion and drugs should not be administered. Low to moderate leak rates at the commencement of the procedure, or leak rates that develop during the perfusion should be considered a relative contraindication to commencing, or continuing with the ILP. Any decision to discontinue the procedure, should be taken within the context of the individual patient circumstances including clinical need for the procedure and comorbidities of the patient, particularly cardiovascular and renal comorbidities. The goal should be to have a total leak below 5% [38].

Level of consensus: *97%*(n=32), *No 3%*(n=1)

4.8. Recommendation 2.8: theatre logistics

ILP can be performed in any normal operating theatre environment, though the addition of a nuclear medicine team, perfusionists, and pharmacy teams, along with accompanying equipment do necessitate a theatre with plenty of physical space. In practical terms, a large theatre, the positioning of the perfusion machine, scintillation counter, tourniquet machine and scrub trolley around the operating table should be carefully coordinated to allow optimal access for all team members. Like any major operation, it is also useful to limit the numbers of unnecessary personnel within the theatre such that the surgeon has efficient and effective support during the ILP. No particular special skillset is required of the anaesthetic team, though as with any vascular procedure there is the possibility of significant and rapid blood loss as well as potential systemic toxicity related to leak of TNFα. It is strongly recommended that a clear team briefing, involving all of the relevant teams involved in ILP and led by the surgeon, occurs at the beginning of the procedure.

Level of consensus: 100%(n=33), *No 0% (n=0)*.

5. Surgical approaches for ILP

The surgical approach in ILP is dictated fundamentally by the anatomical location of the tumour(s) within the limb, combined with surgical expediency and the familiarity of the operating surgeon. The levels of surgical approaches within the upper and lower limb are described below in further detail, but the principles defining the decision making are described here. In both the upper and lower limb, the incision and exposure of the vessels can occur either proximal or distal to tourniquet providing limb isolation. Generally, cannulation proximal to the tourniquet can be more difficult because running cannulas underneath a wide pneumatic tourniquet can be unsuccessful either because of a change in calibre of the vein, arterial stenosis, or a bifurcation of the vein, which will result in a failure to create a perfusion circuit. Sometimes using modified suction cannulas rather than formal armoured arterial and cannulas helps with running a cannula underneath a wide pneumatic tourniquet although the flow rate may be diminished as the radius of these cannulas can be small and flow rate is a function of the 4th power of radius of the cannula. The advantages of cannulating vessels above a tourniquet are particularly of note in an external iliac approach (see below), where an Esmarch bandage is used, sometimes also in conjunction with a Steinmann pin, to create a tourniquet in the proximal thigh (groin crease) and facilitate the largest possible perfusion field in the thigh, allowing treatment of proximal disease. However, it is also possible and technically easier to place the Esmarch bandage as high as possible, and then cannulate the femoral artery below the tourniquet.

Good vascular surgical techniques are essential in performing ILP. While placement of the venous cannula in a sufficient capacitance vessel, that will allow for sufficient venous return for perfusion is often demanding technically, it is the arterial cannulation that carries the risk of complications. Arterial cannulation needs to be undertaken with great care, in particular vigilance must be exercised in avoiding raising an intimal flap. Whilst arteriotomies are often oriented longitudinally in many vascular surgical procedures, many surgeons favour a transverse incision in the vessels in ILP due to it being easier to perform arterial cannulation. This will very much be a matter of personal preference and experience. Once cannulation is achieved, they should be secured in

place with some form of vascular snugger, and then secondarily secured to the skin or the snugger with a suture to avoid inadvertent displacement of the cannulas and potentially catastrophic bleeding.

Similarly, vascular repair needs to be performed meticulously, to avoid raising an intimal flap. The method of precise closure will again be one of preference and experience, but generally will involve a continuous closure with 5–0 or 6–0 Prolene suture. Often following ILP, the distal pulses may be difficult to palpate, in this circumstance the use of Doppler ultrasound to assess the artery distal to the repair, or to assess the peripheral pulses provides reassurance as to the adequacy of the repair.

5.1. Recommendation 3.1: surgical access

In all ILPs, dissection is performed to expose and circumferentially characterise an adequate length (usually 5–10 cm) of the target artery and vein. Any collateral vessels should be meticulously ligated to mitigate against both bleeding and systemic leak. At least 3 min prior to applying vascular clamps heparin is administered systemically to the patient by the anaesthetic team. The decision regarding whether complete or partial systemic heparinisation is undertaken is a surgical and anaesthetic decision. Partial heparinisation will obviate the need for reversal with protamine at the end of the procedure and is quite sufficient to ensure intravascular thrombosis associated with cannulation or clamping of the vessels will not occur as the perfusion circuit itself is fully heparinised. Incisions are made in the recipient vessels with cannulas inserted (Fig. 2) and secured within the vessel using a 'snugger', as well sutured to the skin or the snugger, to prevent against accidental displacement during the procedure. It is also possible to cannulate the artery and vein percutaneously, similar to isolated limb infusion, but with large bore catheters allowing for a limb perfusion [39].

There are three principal approaches to access the lower limb for an ILP, where cannulation can occur.

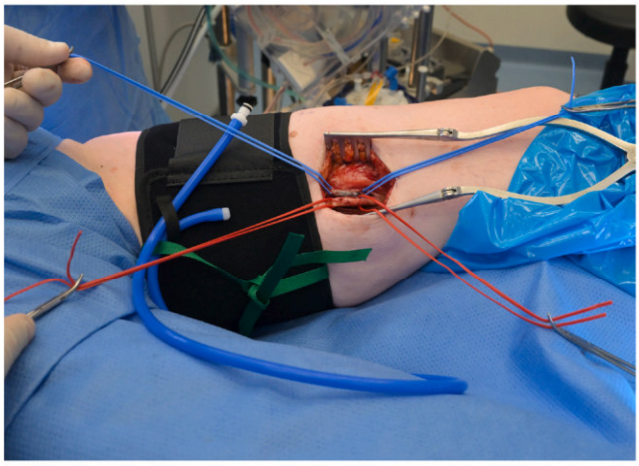
1 External Iliac (Intra-pelvic): In this approach, a retroperitoneal approach is utilised to expose the external iliac vessels within the pelvis. The cannulae are then passed underneath a high groin tourniquet, most commonly an Esmarch bandage secured with a Steinmann pin placed in the ilium at the anterior superior iliac spine. This creates a thin elastic tourniquet in the proximal thigh (groin crease) and facilitates the largest possible perfusion field in the thigh, allowing treatment of proximal disease which would be untreated with a more distal cannulation.
2 Inguinal: In this approach cannulation is undertaken in the inguinal triangle at the origin of the superficial artery and vein and then cannulas are run beneath a distally placed pneumatic tourniquet, such that tips of the cannulas lie in the mid-thigh. A significant advantage of this approach is that it can be combined with a synchronous inguinal node dissection and is therefore well suited to melanoma patients with synchronous nodal and ITM.
3 Superficial Femoral (Thigh): The final, and perhaps most common surgical approach is to place a pneumatic tourniquet across the proximal thigh, and access the superficial femoral artery and vein, as they run beneath sartorius. (Fig. 2). This approach is readily accessible and is ideal for all tumours from the middle third of the thigh distally unless the tumour is preventing surgical access to the vessels when another approach will be necessary. This approach can also be combined with the placement of a proximal Esmarch bandage instead of a pneumatic tourniquet to expand the treatment field (mimicking the external iliac approach).

There are analogous approaches to the vasculature of the upper limb, where there are two principal approaches.

1 Axillary: The axillary approach is somewhat analogous to the external iliac, and high femoral approach, in that it is a technique where cannulation occurs proximal to the tourniquet. Cannulation can be performed at the level of the axillary artery and vein lateral to pectoralis minor by a standard axillary incision especially if the operation is combined with a synchronous axillary dissection. Alternatively, it is also possible to access the axillary vessels more proximally by a muscle splitting pectoral approach. The cannulas are advanced under either an elastic or pneumatic tourniquet at the very top of the upper arm, again secured with a Steinman pin in the proximal humerus for an elastic tourniquet.
2 Brachial: This approach is anatomically analogous to the superficial femoral approach in the leg although the vessels are very much smaller. The brachial vessels are approached in the mid-arm as they lie medial and posterior to the biceps brachii, the median nerve runs in the same neurovascular bundle and must be identified and preserved (Fig. 3). The tourniquet is placed proximally.

Level of consensus: 100% (n=33), *No 0% (n=0)*.

A



B

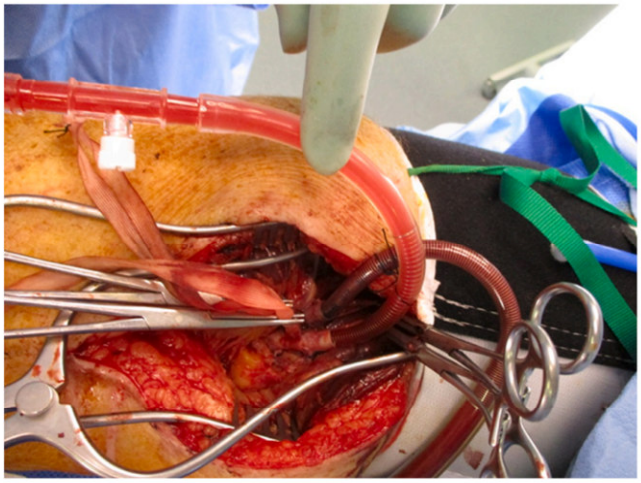


Fig. 2. Superficial femoral access for a lower limb ILP; *Panel A* Surgical access to the superficial femoral artery (red sling) and vein (blue sling) beneath the retracted sartorius muscle. *Panel B* Cannulation of the superficial femoral artery and vein with wide bore armoured cannulae, secured with vascular snuggers, and subsequent placement of a large pneumatic tourniquet proximal to the surgical access.

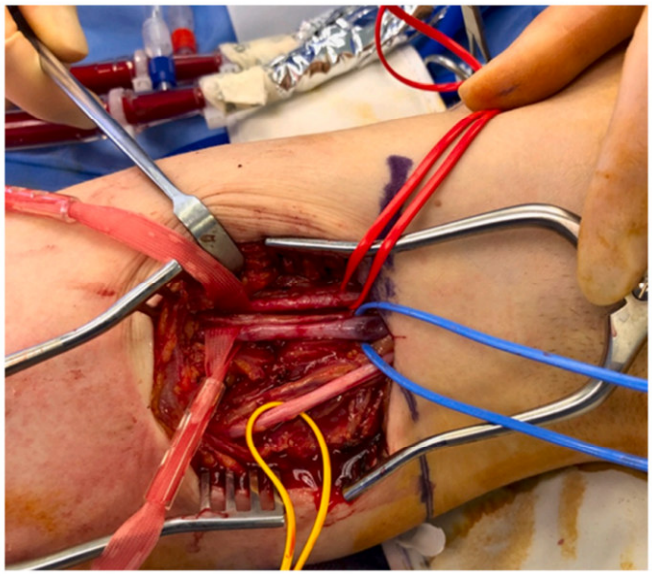


Fig. 3. Surgical access for an arm ILP using a brachial approach showing dissection of relatively small calibre brachial artery (red sling) and vein (blue sling), with the accompanying median nerve identified and protected (yellow sling).

5.2. Recommendation 3.2: specific technical considerations - external iliac approach

It is essential to the successful undertaking of this approach that excellent retroperitoneal exposure through a generous oblique incision over the relevant iliac fossa. The entirety of the external iliac vessels, including the distal common iliac vessels and therefore the origin of the internal iliac vessels should be exposed. To avoid significant systemic leak because of collateral venous return through the internal iliac system, both the internal iliac artery and vein need to be clamped during ILP, and any significant branches of the external iliac vasculature need to be either clamped or formally ligated, notably the inferior epigastric vessels. This is a technically challenging approach, where there are major risks for significant and difficult to control haemorrhage, as well as systemic leak via collateral vessels.

Once vascular control is sufficiently secured, cannulation should be undertaken at the distal aspect of the external iliac vessels, just deep to the inguinal ligament, and cannulas advanced beneath a proximal tourniquet as is described above. Long vascular cannulas may be necessary to traverse a pneumatic tourniquet. Cannulation can also be problematic because of the division of the superficial and deep (profunda femoris artery) systems, where successful perfusion requires that the cannula moves into the superficial femoral artery, rather than the deep system via the profunda femoris vessels.

Level of consensus: 100%(n=33)*, No 0% (n=0)*.

5.3. Recommendation 3.3: specific technical considerations - inguinal approach

The inguinal approach is a technically more straight-forward operation as compared to the external iliac approach. It does, however, necessitate careful dissection and ligation of the multiple venous branches within the groin. Where this approach is used in conjunction with an inguinal node dissection, the great saphenous vein will have been dissected and it is therefore possible to cannulate through the saphenofemoral junction directly into the superficial femoral vein if needed prior to ligation of the sapheno-femoral junction following perfusion.

Analogous to the external iliac approach, it is important to ensure that there is vascular control of the profunda femoris artery and vein. Once this is achieved, the superficial system can be cannulated, and the cannulas advanced under the tourniquet. The tips of the cannulas will lie in the mid-thigh. As in the external iliac approach selection of cannulas is important as they must be of sufficient length to traverse the width of the distally placed pneumatic tourniquet.

Level of consensus: 100%(n=33)*, No 0% (n=0)*.

5.4. Recommendation 3.4: specific technical considerations – superficial femoral approach

As stated above, this is considered the most straight-forward and indeed the lowest risk approach from a technical point of view and will readily treat tumours from the mid-thigh distally. A pneumatic tourniquet is placed as proximally as possible, and an incision made immediately distal to this. This approach is ordinarily undertaken using a pneumatic tourniquet placed at the upper thigh but if there is disease in the upper thigh it is possible to apply an Esmarch bandage in the groin crease so that, it is actually possible to achieve the same extent of the perfusion as for the external iliac approach without need for cannulation in the pelvis.

Sartorius is identified and retracted posteriorly to reveal the superficial femoral artery and vein, before they pass posteriorly through the adductor hiatus (Fig. 2). Both vessels have relatively few branches here, making vascular control relatively straightforward. The arterial and venous cannulas are then inserted under direct vision. It is common to encounter venous valves, which can be passed with slight twisting of the cannulas and judicious pressure. If this does not work, a trick is to attach a 50 mL syringe to the catheter, and while quickly drawing blood into the syringe (thereby opening the valves), push the catheter forward. This approach is associated with high flow rates and minimal leakage and it is therefore favoured where anatomically and oncologically appropriate.

Level of consensus: 100%(n=33)*, No 0% (n=0)*.

5.5. Recommendation 3.5: specific technical considerations - axillary approach

As above, this approach is analogous to the iliac and inguinal approach in that it involved cannulating proximally to the tourniquet, which can be either elastic or pneumatic. The relatively small circumference of the arm makes compression with an elastic tourniquet somewhat easier. The major technical issue with this approach is that there is very often a considerable calibre change in the axillary vein in the upper arm, as it becomes the much smaller brachial vein. Thus, what appears to be simple cannulation proximally in the axillary vein, may not progress beneath the tourniquet. Another important factor in the exposure, and control of the axillary artery is in the identification and preservation of the cords of the brachial plexus which will be intimately related to the medial, lateral and posterior aspect of the artery.

Level of consensus: 100% [33]*, No 0% (0)*.

5.6. Recommendation 3.6: specific technical considerations - brachial approach

Whilst this approach is somewhat analogous to the superficial femoral artery approach in the leg, it is more challenging due to the relatively small size of the brachial vessels, the venous anatomy of the arm, and the sizes of the cannulas that will perfuse the limbs. Even though a flow rate of 100 mL per minute is adequate to successfully run a perfusion of the arm, the venous return from the brachial vein may not allow this. Useful technical adjuncts include cannulating the large veins of the superficial arm, either the brachial or cephalic in addition to the brachial vein and connecting the venous lines using 'Y' connectors. Cannulation and subsequent vascular repair of a small brachial artery can also be much more technically demanding than cannulation and repair of larger vessels in the leg.

Level of consensus: 100%(n=33), *No 0% (n=0)*.

6. Post-operative care

6.1. Recommendation 4.1: postoperative monitoring, anticoagulants and antibiotic prophylaxis

There are three main generic post-operative risks after ILP that should be monitored. The first is arterial occlusion/dissection as a complication to the cannulation, and the routine should be that after the ILP procedure distal pulses are checked and verified. Vascular observations should be performed post-operatively, where the pulse is checked hourly for the first 24hours, either through palpation or using a Doppler ultrasound. The second is the development of deep vein thrombosis and it is recommended to commence venous thromboembolism prophylaxis post-operatively with low-molecular-weight heparin (LMWH) eg. Dalteparin 5000IU or direct oral anticoagulants (DOAC) eg. Rivaroxaban 10mg. Some surgeons continue this in the post-operative period for 30 days. The third is post-operative infections, and it is recommended to give pre-operative antibiotic prophylaxis as a routine component of the surgery.

Level of consensus: 100% (n=33), *No 0% (n=0)*.

6.2. Recommendation 4.2: compartment syndrome

A specific complication is the development of a compartment syndrome, which occurs when the pressure within a muscle compartment increases above venous pressure initially and then subsequently above end arteriole pressure, leading to ischaemia in muscle and nerves. The most commonly affected compartment is the anterior compartment of the distal leg. The classical hallmarks are "The five P's": pain, pulselessness, paraesthesia, paralysis and pallor. It should be noted, that almost all patients will develop a swollen and red limb 1–2 weeks after ILP, a normal reaction to the treatment.

However, if the leg in the early post-operative period becomes severely swollen with increasing pain, out of proportion to that expected and not relieved by normal doses of opioids, then a compartment syndrome should be considered even when normal pulsations are found. It is then recommended to measure the intra-compartmental pressure, where a normal pressure is 0–8mmHg, and an intra-compartmental pressure greater than 30mmHg indicates compartment syndrome and a need for fasciotomy. To aid in diagnosis, creatine phosphokinase (CK) and myoglobin is often elevated as an effect of rhabdomyolysis. However, the routine evaluation of these lab tests is not recommended without a clinical suspicion of compartment syndrome [39]. It should be emphasized than in an uncomplicated isolated limb perfusion which is not complicated by excessive periods of limb ischaemia because of a prolonged time for cannulation, the limb will have been oxygenated throughout the whole operation so creatinine kinase should not rise in the post operative period and compartment syndrome should be a very rare complication.

Level of consensus: 100% (n=33), *No 0% (n=0)*.

6.3. Recommendation 4.3: post-operative care

Most commonly, a patient after ILP could be monitored within either a post-operative high dependency ward, or transferred to a surgical ward with experienced nursing staff, capable of monitoring distal pulsations and awake to the risk of compartment syndrome. Most patients can be discharged from hospital after 2–4 days. It is important that the patient is given written information as to what will happen in the weeks after surgery, specifically that the limb most likely will become swollen, red and painful, usually starting within a week, reaching a maximum after 3–5 weeks, and then slowly normalising over approximately 3 months.

Level of consensus: 100% (n=33), *No 0% (n=0)*.

6.4. Recommendation 4.4: response evaluation

Response evaluation after ILP is unfortunately not standardized, and the recommendations below are therefore strongly encouraged to follow, also in scientific reporting. The evaluation system is either based on radiology (RECIST 1.1. criteria) for tumours that are measurable on radiology, or a modified version of RECIST for non-measurable disease.

6.4.1. RECIST 1.1 criteria

In summary a baseline scan should be done within 4 weeks before ILP (either CT or MRI), target lesions are identified, and the sum of the longest diameters (SLD) are calculated. Also, non-target lesions can be identified, especially those that are not suited for exact measurements, but that can be followed. In lytic or mixed lytic-blastic bone lesions, only the identifiable soft tissue component is suitable for measurement, blastic lesions are considered non-measurable. Follow-up imaging is recommended at 3, 6 and 12 months, and then at least annually thereafter. These exams are then compared to the smallest SLD of the target lesions (nadir SLD), the presence or absence of the non-target lesions are defined. Based on these findings the response is determined as either complete response (CR; disappearance of all lesions), partial response (PR; $\geq$30% decrease in SLD, no new lesions, no progression of non-target lesions), stable disease (SD; neither PR or PD) or progressive disease (PD; $\geq$20% increase in SLD, new lesions, progression of non-target lesions). Of note is that the absolute increase of SLD should be $\geq$ 5 mm to be called progressive disease.

6.4.2. Modified RECIST 1.1 criteria

When the tumours are not visible on imaging, e.g., melanoma intransit metastasis, there is no defined system of response reporting, and previously many used WHO criteria with a 50% shrinkage in tumours as cut-off for PR. Our recommendation is instead to use a modified RECIST 1.1 criteria for cutaneous lesions, where both the number of tumours and the largest tumours diameter (measured with calliper) is recorded. A photograph of the affected limb should be taken before ILP, and is recommended at follow-up at 3, 6 and 12 months, and then yearly. The response is then defined as complete response (CR; disappearance of all lesions), partial response (PR; $\geq$30% decrease in number of tumours and $\geq$30% decrease in largest tumour diameter, no new lesions), stable disease (SD; neither PR or PD) or progressive disease (PD; $\geq$20% increase in number of tumours, or $\geq$20% increase in largest tumour diameter, or any new lesions). Of note is that pigmented melanoma ITMs often disappear but leaves a melanin stain in the skin (a tattoo) that will slowly disappear over time. These tattoos are to be considered as response, and in any uncertainty, a biopsy is recommended for verification.

Level of consensus: *97%* (n=32), *No 3%*(n=1)

6.5. Recommendation 4.5: staff training

ILP is a procedure that requires highly specialized training, and it is important that the medical staff involved in the ILP procedure have the necessary training and experience to ensure that the treatment is safe and effective. Patients should feel comfortable asking their healthcare providers about their experience and training before undergoing any medical procedure. It is strongly recommended that the responsible surgeon, perfusionist and medical physicist visit an experienced ILP center and learn how to perform the procedure before setting up an ILP service. All members of the team should be familiar with the specific protocol for the ILP procedure, and it is the surgeon that is responsible that all members of the team receive this information. The medical team should also receive proper and certified training concerning safety protocols to ensure that both chemotherapy and radioactive substances are handled properly, minimizing the risk for exposure. The medical team, especially the surgeon and the perfusionist, should also be trained in the use of the perfusion equipment and how to monitor the patient

during the procedure. Of vital importance is that the medical team communicate effectively with each other during the procedure, to ensure that the patient is safe, and the treatment is effective. The team should also receive proper training concerning the post-operative care, how to monitor the patient for potential complications, and how to best provide the necessary follow-up care, including response evaluation.

Level of consensus: 100%(n=1)*, No 0% (n=0*).

7. Conclusion

ILP is truly a multidisciplinary undertaking, involving not only the usual working relationships with surgeons, anaesthetists and nursing staff, but also pharmacy, medical physicians, nuclear medicine teams and perfusionists. Adhering to these guidelines will provide a safe and efficacious treatment and will also allow for a standardized ILP technique improving the possibilities to compare results and innovations. This along with further formalised collaborations will enable further studies in the future.

Declaration of competing interest

Angela Märten works as a consultant for Belpharma SA.

References

[1] Creech O, Krementz ET, Ryan RF, Winblad JN. Chemotherapy of cancer. Ann Surg 1958;148(4):616–32.

[2] Rosenberg SA, Tepper J, Glatstein E, Costa J, Baker A, Brennam M, et al. The treatment of soft-tissue sarcomas of the extremities. Ann Surg 1982;196(3):305–15.

[3] Martin-Tellez KS, Houdt WJ van, Coevorden F van, Colombo C, Fiore M. Isolated limb perfusion for soft tissue sarcoma: current practices and future directions. A survey of experts and a review of literature. Cancer Treat Rev 2020;88:102058.

[4] Davies EJ, Reijers SJM, Akkooi ACJV, Houdt WJV, Hayes AJ. Isolated limb perfusion for locally advanced melanoma in the immunotherapy era. Eur J Surg Oncol 2022;48(6):1288–92.

[5] Moreno-Ramirez D, Cruz-Merino L, Ferrandiz L, Villegas-Portero R, Nieto-Garcia A. Isolated limb perfusion for malignant melanoma: systematic review on effectiveness and safety. Oncol 2010;15(4):416–27.

[6] Rossi CR, Foletto M, Mocellin S, Pilati P, Lise M. Hyperthermic isolated limb perfusion with low-dose tumor necrosis factor-α and melphalan for bulky in-transit melanoma metastases. Ann Surg Oncol 2004;11(2):173–7.

[7] Deroose JP, Eggermont AMM, Geel AN van, Wilt JHW de, Burger JWA, Verhoef C. 20 Years experience of TNF-based isolated limb perfusion for in-transit melanoma metastases: TNF dose matters. Ann Surg Oncol 2012;19(2):627–35.

[8] Deroose JP, Eggermont AMM, Geel AN van, Burger JWA, Bakker MA den, Wilt JHW de, et al. Long-Term results of tumor necrosis factor α– and melphalan-based isolated limb perfusion in locally advanced extremity soft tissue sarcomas. J Clin Oncol 2011;29(30):4036–44.

[9] Liénard D, Eggermont AMM, Koops HS, Kroon B, Towse G, Hiemstra S, et al. Isolated limb perfusion with tumour necrosis factor-α and melphalan with or without interferon-γ; for the treatment of in-transit melanoma metastases. Melanoma Res 1999;9(5):491–502.

[10] Holmberg CJ, Mattsson J, Bagge RO. Effects of the introduction of modern immunotherapy on the outcome of isolated limb perfusion for melanoma in-transit metastases. Cancers 2023;15(2):472.

[11] Smith HG, Wilkinson MJ, Smith MJF, Strauss DC, Hayes AJ. The effect of age on outcomes after isolated limb perfusion for advanced extremity malignancies. Eur J Cancer 2018;100:46–54.

[12] Madu MF, Deken MM, Hage JA van der, Jozwiak K, Wouters M, Akkooi ACJ van. Isolated limb perfusion for melanoma is safe and effective in elderly patients. Ann Surg Oncol 2017;24(7):1997–2005.

[13] Belgrano V, Pettersson J, Nilsson JA, Mattsson J, Katsarelias D, Bagge RO. Response and toxicity of repeated isolated limb perfusion (re-ILP) for patients with in-transit metastases of malignant melanoma. Ann Surg Oncol 2019;26(4):1055–62.

[14] Deroose JP, Grunhagen DJ, Eggermont AM, Verhoef C. Repeated isolated limb perfusion in melanoma patients with recurrent in-transit metastases. Melanoma Res 2015;25(5):427–31.

[15] Belgrano V, Ben-Shabat I, Bergh P, Bagge RO. Isolated limb perfusion as a treatment option for rare types of tumours. Int J Hyperther 2016;32(6):595–9.

[16] Podleska LE, Poeppel T, Herbrik M, Dahlkamp L, Grabellus F, Taeger G. Drug dosage in isolated limb perfusion: evaluation of a limb volume model for extremity volume calculation. World J Surg Oncol 2014;12(1):81.

[17] Cecchin D, Negri A, Frigo AC, Bui F, Zucchetta P, Bodanza V, et al. Calculating regional tissue volume for hyperthermic isolated limb perfusion: four methods compared. European J Surg Oncol Ejso 2016;42(12):1898–905.

[18] Rastrelli M, Campana LG, Valpione S, Tropea S, Zanon A, Rossi CR. Hyperthermic isolated limb perfusion in locally advanced limb soft tissue sarcoma: a 24-year single-centre experience. Int J Hyperther 2016;32(2):165–72.

[19] Wray CJ, Benjamin RS, Hunt KK, Cormier JN, Ross MI, Feig BW. Isolated limb perfusion for unresectable extremity sarcoma. Cancer 2011;117(14):3235–41.

[20] Noorda EM, Vrouenraets BC, Nieweg OE, Coevorden F van, Kroon BBR. Isolated limb perfusion: what is the evidence for its use? Ann Surg Oncol 2004;11(9):837–45.

[21] Minor DR, Allen RE, Alberts D, Peng Y, Tardelli G, Hutchinson J. A clinical and pharmacokinetic study of isolated limb perfusion with heat and melphalan for melanoma. Cancer 1985;55(11):2638–44.

[22] Thompson JF, Gianoutsos MP. Isolated limb perfusion for melanoma: effectiveness and toxicity of cisplatin compared with that of melphalan and other drugs. World J Surg 1992;16(2):227–33.

[23] Eggermont AMM, Hagen TLM ten. Isolated limb perfusion for extremity soft-tissue sarcomas, in-transit metastases, and other unresectable tumors: credits, debits, and future perspectives. Curr Oncol Rep 2001;3(4):359–67.

[24] Lienard D, Ewalenko P, Delmotte JJ, Renard N, Lejeune FJ. High-dose recombinant tumor necrosis factor alpha in combination with interferon gamma and melphalan in isolation perfusion of the limbs for melanoma and sarcoma. J Clin Oncol 1992;10(1):52–60.

[25] Wilt JHW de, Hagen TLM ten, Boeck G de, Tiel ST van, Bruijn EA de, Eggermont AMM. Tumour necrosis factor alpha increases melphalan concentration in tumour tissue after isolated limb perfusion. Br J Cancer 2000;82(5):1000–3.

[26] Deroose JP, Grunhagen DJ, Wilt JH de, Eggermont AM, Verhoef C. Treatment modifications in tumour necrosis factor-alpha (TNF)-based isolated limb perfusion in patients with advanced extremity soft tissue sarcomas. Eur J Cancer 2015;51(3):367–73.

[27] Nachmany I, Subhi A, Meller I, Gutman M, Lahat G, Merimsky O, et al. Efficacy of high vs low dose TNF-isolated limb perfusion for locally advanced soft tissue sarcoma. European J Surg Oncol Ejso 2009;35(2):209–14.

[28] Bonvalot S, Laplanche A, Lejeune F, Stoeckle E, Péchoux CL, Vanel D, et al. Limb salvage with isolated perfusion for soft tissue sarcoma: could less TNF-α be better? Ann Oncol 2005;16(7):1061–8.

[29] Bonvalot S, Rimareix F, Causeret S, Péchoux CL, Boulet B, Terrier P, et al. Hyperthermic isolated limb perfusion in locally advanced soft tissue sarcoma and progressive desmoid-type fibromatosis with TNF 1 mg and melphalan (T1-M HILP) is safe and efficient. Ann Surg Oncol 2009;16(12):3350–7.

[30] Cornett WR, McCall LM, Petersen RP, Ross MI, Briele HA, Noyes RD, et al. Randomized multicenter trial of hyperthermic isolated limb perfusion with melphalan alone compared with melphalan plus tumor necrosis factor: American college of surgeons Oncology group trial Z0020. J Clin Oncol 2006;24(25):4196–201.

[31] Grünhagen DJ, Etten B van, Brunstein F, Graveland WJ, Geel AN van, Wilt JHW de, et al. Efficacy of repeat isolated limb perfusions with tumor necrosis factor α and melphalan for multiple in-transit metastases in patients with prior isolated limb perfusion failure. Ann Surg Oncol 2005;12(8):609–15.

[32] Corderfeldt A, Nielsen S, Katsarelias D, Hjärpe A, Mattsson J, Bagge RO. Is blood a necessary component of the perfusate during isolated limb perfusion – a randomized controlled trial. Int J Hyperther 2019;36(1):793–9.

[33] a Corderfeldt Keiller A, Holmén A, Hansson C, Ricksten SE, Bragadottir G, Olofsson Bagge R. Non-invasive and invasive measurement of skeletal muscular oxygenation during isolated limb perfusion. Perfusion 2023 Jul;38(5):1019–28. b Hoven-Gondrie ML, Bastiaannet E, Ginkel RJ van, Suurmeijer AJH, Hoekstra HJ. TNF dose reduction and shortening of duration of isolated limb perfusion for locally advanced soft tissue sarcoma of the extremities is safe and effective in terms of long-term patient outcome. J Surg Oncol 2011;103(7):648–55.

[34] Scott R, Kerr D, Blackie R, Hughes J, Burnside G, MacKie R, et al. The pharmacokinetic advantages of isolated limb perfusion with melphalan for malignant melanoma. Br J Cancer 1992;66(1):159–66.

[35] Wieberdink J, Benckhuysen C, Braat RP, Slooten EAV, Olthuis GAA. Dosimetry in isolation perfusion of the limbs by assessment of perfused tissue volume and grading of toxic tissue reactions. Eur J Cancer Clin Oncol 1982;18(10):905–10.

[36] Technescan™ PYP™ Kit for the Preparation of Technetium Tc 99m Pyrophosphate Injection [Internet]. [cited 2023 Mar 15]. Available from: PRESCRIBING INFORMATION, TECHNESCAN PYP, Injection, for intravenous use, Marketing Start Date: 14.10.2015, Reference NDC: 69945-094-20 https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/017538s019lbl.pdf Accessed 11/March/2023.

[37] Stam TC, Swaak AJG, Vries MR de, Hagen TLM ten, Eggermont AMM. Systemic toxicity and cytokine/acute phase protein levels in patients after isolated limb perfusion with tumor necrosis factor-a complicated by high leakage. Ann Surg Oncol 2000;7(4):268–75.

[38] Olofsson Bagge R, Carlson P, Razzazian R, Hansson C, Hjarpe A, Mattsson J, et al. Minimally invasive isolated limb perfusion - technical details and initial outcome of a new treatment method for limb malignancies. Int J Hyperther 2018;35(1):1–7.

[39] Wendt AN, Mattsson J, Bagge RO. Myoglobin does not predict local toxicity in isolated limb perfusion. Int J Hyperther 2017;33(6):679–83.