The Role of a Universal Vascular Access System in Locoregional Chemotherapy for Solid Tumours

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Statement of Originality

This work has not previously been submitted for a degree or diploma in any university. To the best of my knowledge and belief, the thesis contains no material previously published or written by another person except where due reference is made in the thesis itself.

~ Nyan Y. Khin

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LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following original publications, which are referred to in the text by Roman numerals. Original publications are reproduced with permissions from their copyright holders.

I Khin NY*, Dijkstra ML, Huckson M, Phillips M, McMillan D, Itoh S, Roger G, Lane RJ*. Hypertensive extracorporeal limb perfusion for critical limb ischemia. Journal of Vascular Surgery. 58(5), 1244–1253 (2013). DOI: 10.1016/j.jvs.2013.05.004

II Lane RJ*, Khin NY*, Rogan CM, Magnussen J, Pavlakis N, Lane DM, Clarke S. Safety and Feasibility of Repeatable Hepatic Vascular Isolation Chemotherapy: A Pilot Study. Annals of Surgical Oncology. 23(11), 3699–3708 (2016). DOI: 10.1245/s10434-016-5198-z

III Lane RJ*, Khin NY*, Pavlakis N, Hugh TJ, Clarke SJ, Magnussen J, Rogan C, Flekser RL*. Challenges in chemotherapy delivery: comparison of standard chemotherapy delivery to locoregional vascular mass fluid transfer. Future Oncology. 14(7), 647–663 (2018). DOI: 10.2217/fon-2017-0546

* Equal contributors

CONFERENCE ABSTRACTS

Preliminary data or trial protocols were presented at conference proceedings listed below. They will not be referred to directly throughout the thesis but have been attached with their relevant original publications listed above in their corresponding chapters.

Khin N, Murphy S, Kyung C, et al. Emerging treatments using an implantable large bore vascular access system. *XLIII Annual ESAO Congress*; Warsaw, Poland, September 2016

Magnussen J, Clarke S, Khin NY, et al. Vascular organ isolation chemotherapy with extraction (VOICE). *Cardiovascular and Interventional Radiological Society of Europe*; Barcelona, Spain, September 2013

Lane RJ, Khin NY, Evtushenko M. et al. Superselective stop flow chemotherapy for solid neoplasma with chemoextraction. *Innovations in Cancer Treatment and Care NSW, Cancer Institute NSW*; Sydney, Australia, September 2012

Khin N, Lane R, Avolio AP. Development of Occlusion Devices for Hypertensive Extracorporeal Limb Perfusion. *Hypertension* 2011; 58(1): p. 124-124

OTHER PUBLICATIONS

Other original publications co-authored throughout the candidature but not relevant to the thesis topic are listed below and attached in Appendix I.

Dijkstra ML, Khin NY, Coroneos JC, Hazelton S, Lane RJ (2014) The effect of pregnancy on venous valve repair to the sapheno-femoral junction for varicose veins. *Obstetric Medicine;* 7(2): p. 87-89. DOI: 10.1177/1753495X14522617

Phillips MN, Dijkstra ML, Khin NY, Lane RJ (2013) Endovenous valve transfer for chronic deep venous insufficiency. *European Journal of Vascular and Endovascular Surgery;* 46(3): p. 360-365. DOI: 10.1016/j.ejvs.2013.05.013

Dijkstra ML, Khin NY, Thomas SD, Lane RJ (2013) Popliteal vein compression syndrome (PVCS) pathophysiology and correlation with popliteal compartment pressures. *Journal of Vascular Surgery: Venous and Lymphatic Disorders*; 1(2): p. 181-186. DOI: 10.1016/j.jvsv.2012.07.013

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Division of Labour in Co-Authored Articles

Contribution	Article		
	I	II	III
Conception & design	MP, NK, RL	NK, RL	NK, RF, RL
Planning & implementation	MP, NK, RL	NK, RL	NK, RF, RL
Data collection	MH, MP, NK, SI	NK, DL, RL	-
Analysis & interpretation	DM, MD, MP, NK, RL	NK, RL	NK, RL
Writing the article	NK, RL	CR, JM, NK, RL	NK, RF, RL
Critical revision of article	DM, GR, MD, MH, MP, NK, RL, SI	CR, DL, JM, NK, NP, RL, SC	CR, JM, NK, NP, RF, RL, SC, TH
Overall responsibility	NK, RL	NK, RL	NK, RL

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To my parents, I thank you for being my biggest believers and fans. Thank you, mum, for the hard decisions and sacrifices you have made just so I can have the opportunities that have been presented to me. Thank you for pushing me and equipping me with a thirst for knowledge. Thank you, dad, for passing onto me your patience and optimism which has allowed me to be impermeable to stress. While we may all stand on the shoulders of giants, I will always be thankful that I got to stand on the both of yours.

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Finally, I would like to share our love and wishes for our little Peanut. You would have been in our lives now as I approach the end of this chapter but, unfortunately, fate has dictated otherwise. I hope you know you would have been welcomed into a world of love and we will never truly forget you.

ABSTRACT

Background: Since the advent of chemotherapy, much of the progress gained in the treatment of solid tumours has primarily has been brought about by the advancement of drug designs and chemotherapy combinations. However, in advanced cancers the standard route of intravenous systemic delivery is unable to exploit the full potential of even third generation chemotherapeutic agents and as such, the prognosis for these patients remain grim. Alternatively, locoregional chemotherapy (LRC) techniques focused on delivering chemotherapy as close to the tumour as possible have been able to achieve responses where systemic therapy has failed in some cases. Nonetheless, such techniques are limited to specialised centres, associated with high morbidity and mortality, and are generally not repeatable due to limitations in vascular access technologies.

Aims: The aim of this thesis was to determine whether a universal vascular access device (UVAS) could be developed which could provide general vascular access and facilitate LRC treatments and if so, to assess the potential of the treatment it can facilitate.

Methods: A design for a UVAS was developed based on an existing transcutaneous access device as well as the clinical requirements deemed necessary to enable LRC treatments. A meta-analysis was carried out of devices with similar features to obtain an understanding of the risks that may accompany the use of such a device. The developed UVAS was then used in 5 patients with critical limb ischemia in a clinical trial as a general vascular access device. Additionally, a new LRC technique was developed with the UVAS and tested in another clinical trial of 10 patients with colorectal liver metastases.

Results: The device related outcomes in both studies demonstrated that the UVAS was able to perform its intended functions safely as a general vascular access device and in facilitating LRC treatments. The LRC technique developed demonstrated promising results (30% response rate) in patients that had previously exhausted all other therapies. The intra-arterial pressures measured and the minimal toxicity (grades I-II) reported is suggestive of the level of manipulation achieved within the liver which could potentially be applied to other organs.

Conclusions: A UVAS was successfully designed, developed, and proven to be fundamental in being able to administer a new LRC treatment in the form of minimally invasive, repeatable liver organ isolation chemotherapy. A system with such capabilities provides encouragement for further LRC techniques that were previously considered too burdensome to be properly investigated.

CHAPTER 1 – INTRODUCTION

The circulatory system serves as the primary transportation network within the human body; delivering oxygen, carbon dioxide, essential nutrients, hormones, red blood cells and plasma. In the same way irregularities within this transportation grid can cause malfunctions within tissues and organs, almost all drug-based regimens in modern-day medicine utilises the same transport grid in one way or another to treat adverse and or aberrant conditions within the body.

Historically, the most favoured route of administering a drug into a patient's bloodstream has been through the gastrointestinal tract, specifically via oral medication. The ease of administration and wide patient acceptance is unmatched by all other delivery routes. However, the efficacy of some drugs are limited by their accompanying systemic side effects and or the reduced bioavailability of the active ingredient being diluted as a result of the hepatic first pass effect [1]. While the latter can be partly addressed through increased dosage or drug design (e.g. drugs that control drug metabolising enzymes such as regulating cytochrome P-450 enzyme expression [2]), the issue of systemic side effects remains.

Parenteral drug administration such as intravenous (IV), intra-arterial, subcutaneous, and intramuscular injections is the most common drug delivery route second to the oral route. Drugs administered through the parenteral route are delivered directly into the patient's systemic circulation. Without the need to be processed through the gastrointestinal tract, the parenteral route sidesteps the issue of the hepatic first pass effect and the administered drug is considered to have "complete" bioavailability. In pharmacokinetics, bioavailability refers to the measure of the extent to which an administered drug is absorbed systemically [3] and is one of the critical parameters that determines the efficacy of a drug.

Bioavailability (*F*) is calculated using Equation 1.1 and is essentially a ratio of two ratios; the ratio of the measured area under the curve of the systemic concentration to time graph (*AUC*) versus the known dosage (*D*) of the drug administered against the same ratio but with the drug administered via the IV route [4]. The denominator is always 1 as the AUC in the venous circulation is equal to the dose administered via the IV route ($[AUC]_{0,IV}^{\infty} = D_{0,IV}$) immediately after the dose has been administered and prior to it reaching the arterial circulation. *F* is expressed as a percentage and "complete" bioavailability refers to an *F* value of 100%. In addition to the complete bioavailability the IV route offers, it also leads to rapid onset of effects from the medication, lower dose requirements compared to other non-IV routes, and sustaining prolonged doses by allowing direct control of the drug administration rate [5].

$$F = \frac{[AUC]_{0,\text{route}}^{\infty}/D_{0,\text{route}}}{[AUC]_{0,IV}^{\infty}/D_{0,IV}} = \frac{[AUC]_{0,\text{route}}^{\infty}}{D_{0,\text{route}}} \qquad \text{Equation 1.1}$$

These capabilities have cemented IV infusions/injections as a mainstay drug delivery route despite the inherent risks (albeit low) of infection, extravasation of the drug, and vascular trauma of the host vessel. However, even with the level of dose control the IV route provides the clinician, it still cannot fully exploit the drug's potential benefits in certain aggressive and or localised diseases. Bioavailability is only considered to be a secondary pharmacokinetic parameter compared to the distribution and elimination of the drug [6]. Distribution describes the rate of blood flow to and penetration into the membranes and tissues of the target organ(s). Elimination describes the process via which the drug escapes the central compartment (i.e. systemic circulation and highly vascular tissues/organs such as the liver, kidney, lungs etc.) as a result of drug metabolism and renal excretion. This is described below in Figure 1.1.

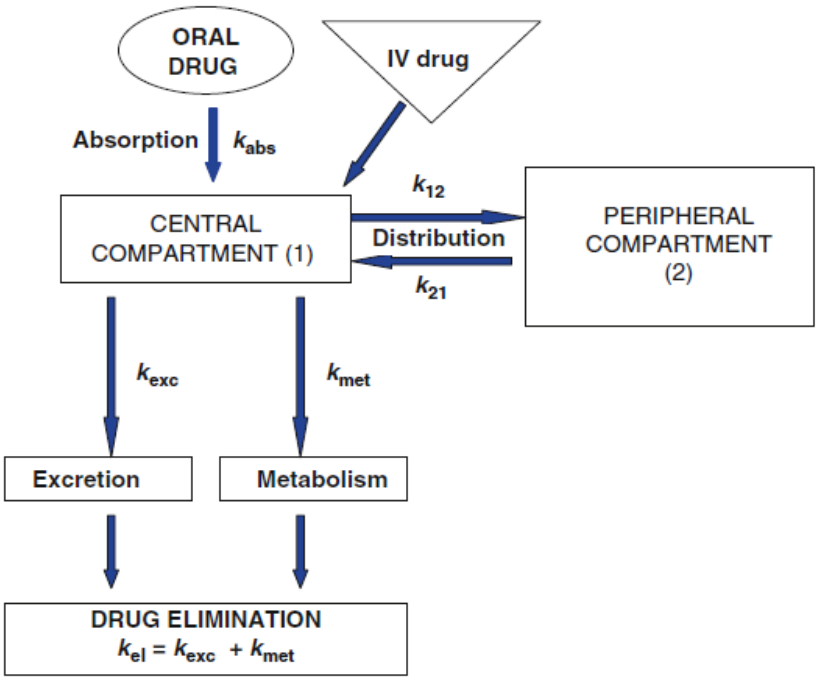

Figure 1.1 – Basic pharmacokinetics of drug movement and distribution as described by Tomlin [6].

Based on Figure 1.1, it is obvious that the key advantage the IV route offers in relations to drug distribution is that the issue of drug absorption (k_{abs}) into the systemic circulation can be overlooked as it offers complete bioavailability. However, once in the venous circulation, the drug's distribution to the target tissue or organ is in direct competition with its distribution to the liver and kidney where it may be eliminated through metabolism and excretion of the drug respectively. Therefore, the distribution of blood flow within the circulatory system [7] to the target organ must be considered as shown in Figure 1.2. By definition, IV administered drugs must travel from the vein from which the drug is administered to the right heart, through the pulmonary network, before it is pumped into the systemic arterial network by the left ventricle of the heart. From here on, regardless of bioavailability, the drug solution will be split up to be distributed throughout all the organs along with the rest of the arterial supply. Effectively, the potency of the IV drug is diminished since the actual dose of the drug the target organ or tissue is exposed is the total IV dose administered minus the portion of the drug distributed to the

non-target orangs and tissues. As the drug is distributed throughout the body, the drug will generally illicit either a desired response, an unwanted response, or no response depending on whether the drug is processed at the targeted or non-targeted organs/tissues. If the drug is not processed at all, it is recirculated into the systemic venous circulation to undergo this cycle again.

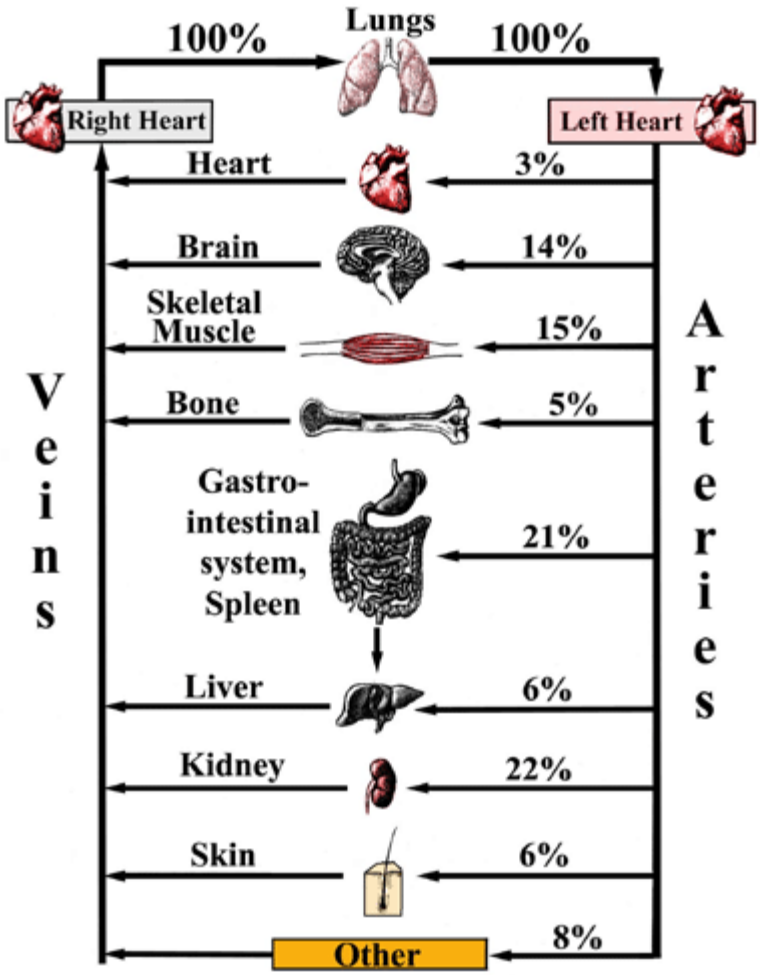

Figure 1.2 - Relative percentages of the total blood flow that is delivered to the major organ systems within the body [7].

The effect of clearance must also be considered. A significant portion of the arterial blood supply, carrying with it a portion of the IV drug at any given time, is distributed to the liver and kidneys (6% and 22% respectively) as shown in Figure 1.2 [7]. When distributed to these two organs, the drug can only be recirculated into the systemic circulation if it is not metabolised by the liver or excreted by the kidneys. For any drug to be useful, the rate of distribution of the drug to the target site must be greater than the elimination rate of the drug from the body so that the drug can accumulate to the required therapeutic concentration at the target site [6]. Therefore, the drug concentration the interstitum of the targeted tissues or organ is exposed to cannot be assumed to be equivalent to that of the IV dose.

This is particularly relevant in aggressive mutations such as a cancerous neoplasms where the dose of the antineoplastic drug (i.e. chemotherapy) that is delivered to and accumulates within the tumour has a significant effect on mortality outcomes [8,9]. It is generally well accepted that for chemotherapy to be effective in targeting tumours, it must [10]:

a) localise its pharmacological activities within the tumour;
b) achieve intratumoral concentrations high enough to induce a therapeutic response, and
c) be able to recognise and interact with the target cells of the tumour.

Since the dawn of chemotherapy in the 1940's [11-13], the effects of higher concentrations have been well investigated. It is well established that higher concentrations are generally associated with longer term survival and higher curative rates [9]. However, the systemic cytotoxic effects accompanying chemotherapy such as myelosuppression, severe neutropenia, and neuropathy amongst many others have deterred patients and clinicians from maintaining higher dose regimens [14,15]. This is a direct result of IV chemotherapy not being able hone in on the first two principles of tumour targeting.

Although this dilemma is not isolated to cancerous neoplasms, the enormity of this specific population warrants focus. Considering that a global estimate of 14.1 million new cases of cancers were diagnosed and 8.2 million deaths occurred in 2012 alone [16], new developments in tumour targeting techniques with a potential to improve mortality outcomes are worth exploring.

1.1 The Micro: Chemotherapy & the Magic Bullet

Since Ehrlich's concept of a "magic bullet" drug was first coined in 1906 to describe a drug that could be selectively delivered to the required site of action [17,18], significant strides have been made in targeted drug delivery methods and technologies. Over the last 50 years this has come in the form of being able to achieve better control of drug release, maintaining a certain concentration of a drug in the blood, and better targeting of tumour proliferating contributors.

The Spansule technology in 1952 was the first revolutionary advancement in drug delivery technology and in oral drug formulations which allowed for a 12 hour drug delivery as opposed to previous formulations which were required to be taken three to four times daily [19,20]. This was improved upon with several extended release and sustained release formulations, and while ground-breaking, these advancements were limited primarily to oral formulations [21]. The key advantages brought into clinical practise were patient compliance and convenience.

However, as discussed previously, the oral formulations have practical limitations in targeting tumours due to their accompanying systemic dose limiting toxicities.

Between this advancement and prior to the exploration of polymeric and nanotech drug delivery concepts, oncologists were equipped with the oral and IV chemotherapy drugs made available to them. With no significant breakthroughs in drug delivery technologies, progress was primarily made in the discovery and development of new chemotherapy agents and the effects of various chemotherapy combinations.

The development of chemotherapy drugs in colorectal cancer is an appropriate case in point. The first effective chemotherapy agent for colorectal cancer, the enzyme inhibitor 5-flurouracil (5-FU), was discovered in 1957 [22] and its therapeutic benefit in humans via inhibition of the enzyme thymidylate synthase was confirmed several decades later [23,24]. Since then, 5-FU has been combined with many other chemotherapy drugs even in non-colorectal cancers.

This was improved upon by Ullman *et al* in 1978 when they discovered that the biomodulation of 5-FU cytotoxicity could be achieved using leucovorin to potentiate its effects [25]. Soon after, human studies confirmed that the combination of 5-FU and leucovorin translated into improved clinical outcomes [26-28] and became the new gold standard.

Concurrently, two new chemotherapy agents, irinotecan and oxaliplatin, were discovered in 1983 and 1976 respectively [29,30]. Irinotecan is a prodrug analogue that is converted to the active metabolite SN38 which acts as an indirect inhibitor of DNA replication in tumour cells [31]. In the year 2000, its combination with 5-FU and leucovorin (IFL) was shown to improve outcomes compared to 5-FU/leucovorin alone [32]. Alternatively, oxaliplatin was shown to act through non-targeted cytotoxic effects that prevented DNA replication and cell death in the tumour [33]. Its improved clinical outcomes when used in combination with 5-FU/leucovorin (FOLFOX) compared to 5-FU/leucovorin alone was confirmed in 2004 [34]. FOLFOX was initially observed to have a better toxicity profile compared to IFL [34] but when the irinotecan was changed from a bolus injection to a continuous infusion over two hours (FOLFIRI), the toxicity profile was comparable to that of FOLFOX [35,36] and both regimens became standard treatment regimens for oncologist.

The most recent improvement has come from the combination of biological agents with FOLFOX or FOLFIRI. In 1971 it was proposed that targeting angiogenesis within the tumour by inhibiting the vascular endothelial growth factor (VEGF) could have anticancer benefits [37]. This was confirmed in 2007 when the monoclonal antibody and VEGF inhibitor bevacizumab was able to achieve this to improve patient outcomes when combined with FOLFOX [38]. Similarly, after the idea of targeting the epidermal growth factor receptor (EGFR) to inhibit

cancer cell growth was proposed in 1983-84 [39,40], the monoclonal antibody cetuximab was developed to specifically target EGFR. Its benefit in a genetic subset of patients when combined with FOLFIRI was confirmed in 2011 [41]. The FOLFOX/bevacizumab and FOLFIRI/cetuximab regimens are the current gold standards of therapy for colorectal cancers.

Overall, these advancements have accounted for a moderate improvement in overall survival (OS) for patients. Since the use of 5-FU, the survival outcomes have been improved from 11 months to 12 months when combined with leucovorin [27,28]. The addition of oxaliplatin and irinotecan lead to OS outcomes of 19.5 months [34,42]. Combinations with bevacizumab and cetuximab led to further improvements in OS of 20.3-23.5 months [41,43,44]. While this overall improvement in median OS from 11 months to 23.5 months is significant, this is still a rather grim prognosis.

This improvement in OS data should also be contextualised. The general precept behind this progress relies on adding a newly discovered agent to a pre-existing treatment regimen. This can be partly attributed to the regulatory framework in which new drugs must be introduced in tandem with existing treatment regimens so as not to deny patients the established standard of care. Regardless, the result is an OS improvement model which describes a directly proportional relationship between the number of drugs in a chemotherapy regimen to OS outcomes. This can be seen in the OS outcomes (21.5 - 22.6 months) in trials combining 5-FU, leucovorin, irinotecan, and oxaliplatin (FOLFOXIRI) which is an improvement upon what could be achieved with FOLFOX and FOLFIRI [42,45]. However, with the addition of each agent, there are additional cytotoxic side effects introduced and the patient's tolerance for this will always be the limiting factor as confirmed in those studies which demonstrated significantly increased level of side effects in the FOLFOXIRI regimen compared to the standard FOLFIRI regimen [45].

In addition, such progress is underwhelming considering these new drugs are the best of what this current era of nontechnology has to offer. With drug-protein conjugates, dendrimers, polymer micelles, liposomes and many other nanoparticles available since the 1960s [46], one of the smartest drugs developed has been bevacizumab which prolongs patient OS by several months. It is evident that much of the progress has been brought about by a focus on a nano/microscopic level such as the targeting of enzymes, growth factors, and metabolites. On a macro level, the only tweaks that have occurred with respect to colorectal cancer chemotherapy were the change in the administration of irinotecan from an IV bolus (IFL) to an IV infusion (FOLFIRI) and the discovery of capecitabine as an oral prodrug which metabolised to 5–FU [47]. Otherwise, all these newly developed chemotherapy agents have been administered through the IV route.

Even in the age of matured nanotechnology, it is well understood that between about 90-95% of nanoparticle-based drugs end up in non-target organs [48-50]. The majority of the drugs either leak out of the nanoparticles or extravasate in other non-target organs prior to reaching the target tumour (Figure 1.3) [49]. The small portion of the drug that does reach the target tumour tissue is then faced with the biological, mechanical and chemical barriers within the tumour microenvironment as well. It is worth questioning the current research paradigm which focuses on drug design and drug carrying molecules/particles with little attention paid to other possible solutions.

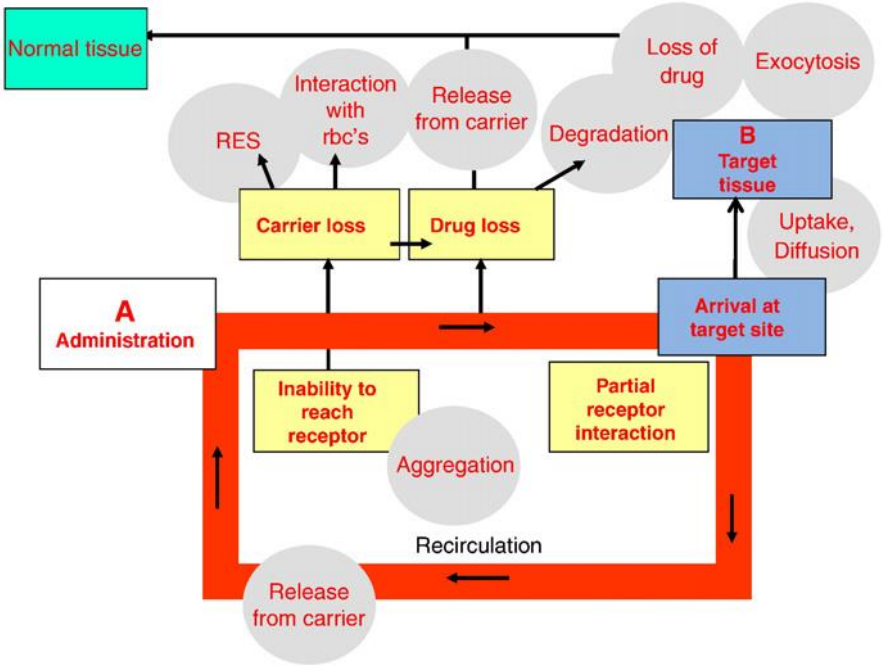

Figure 1.3 – A schematic showing the pathway of systemic chemotherapy injected at A to target tumour tissue B and the pathways via which the chemotherapy exit, degrade, or prematurely react prior to reaching the target tumour. Even in advanced drug designs with nanocarriers, the chemotherapy is usually lost from the carrier. Reproduced from Ruenraroengsak *et al* [51].

It could be thought that Ehrlich's idea of a "magic bullet" is still yet to be realised. However, another very real possibility is that such a bullet is already available, but more focus is required on improving the guns that can deliver such a bullet.

1.2 The Macro: Locoregional Chemotherapy

Over the last several decades various locoregional chemotherapy (LRC) techniques has been explored by select research groups. LRC is a broad term to describe various treatment modalities that are aimed at delivering the chemotherapy directly to the feeding artery of the tumour via a single or multiple vascular access devices [52]. Most LRC treatments involve the administration of chemotherapy intra-arterially whereby a catheter is guided to an artery directly feeding the tumour or the organ containing the tumour. For example, in LRC treatments of the pancreas, a catheter may be guided to the gastroduodenal artery to treat the head of the pancreas or the distal pancreatic arteries to treat the tail of the pancreas. Differences

between various LRC therapies are typically defined by the proximity of the catheter to the target tumour, the drug or drug combination used, the drug administration rate (i.e. bolus vs infusion), frequency of administration, and the presence/absence of drug removal systems and recirculation loops. These differences typically manifest in the form of the difference in hardware between the various LRC treatments. A conceptual schematic of the variations in the LRC treatments is shown below in Figure 1.4. As can be seen, it is significantly more mechanically involved than the standard route of IV administration.

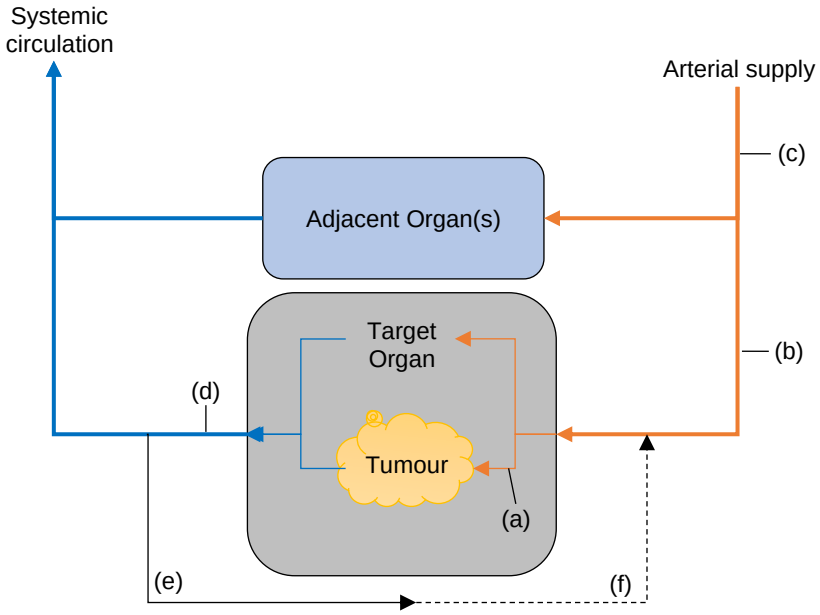

Figure 1.4 – A schematic of the various LRC techniques; chemotherapy is administered at either points (a), (b), or (c). Point (a) is used to selectively treat the tumour, point (b) to treat the tumour cells as well as the normal cells in the entire target organ, or at point (c) to treat the tumour, target organ, as well as the adjacent organs. The chemotherapy can be contained by obstructing the venous outflow at point (d), or removed entirely by extracting the venous outflow with an externalised circuit at point (e), or filtered and recirculated into the arterial flow (f).

Theoretically, the advantage of delivering chemotherapy directly via the feeding vessel of the cancerous organ is that the total dose delivered can be assumed to be equivalent to the AUC of the drug unlike in the IV setting where the AUC is a systemic measure and thus the total dose delivered to the target organ or site generally ranges between 5-10% [48-50]. This relative advantage of LRC to IV chemotherapy is quantified by Equation 1.2 where R_d, Cl_{TB}, Q, and E are the relative advantage, total body clearance of the drug, regional blood flow, and the fraction of the drug extracted during a single pass through the target tissue [53].

$$R_d = 1 + \frac{Cl_{TB}}{Q(1-E)} \qquad \text{Equation 1.2}$$

The conversion of this theoretical advantage to a practical improvement in patient outcomes has been challenging. While some LRC treatments such as transarterial chemoembolization for the treatment of hepatocellular carcinomas has been widely adapted to become a routine procedure [54], some other therapies such as intraperitoneal chemotherapy for ovarian cancer [55,56] and peritoneal carcinomatosis of colorectal cancer [57] have yet to be incorporated into

a standardised treatment regimen despite promising patient outcomes. There is also the issue of the general scarcity of randomised controlled trials comparing LRC to systemic IV chemotherapy regimens in carcinomas with poor prognoses such as in the pancreas [58] and the liver [54].

This significant discrepancy between the theoretical advantage and clinical outcomes is worth exploring and troubleshooting. The sections below will provide a summary of the LRC techniques that have been used for various solid organ tumours to achieve mixed results.

1.2.1 Solid Tumours in the Limbs – Isolated Limb Perfusion/Infusion

Treating solid tumours in the limb is one area where LRC has been successful. Histologically, solid tumours in limbs typically manifest as melanomas or soft tissue sarcomas (STSs). Melanomas account for approximately 91,270 estimated new cases and 9,380 deaths annually within the US alone while STSs account for 13,040 estimated new cases and 5,150 deaths [59]. Isolated limb perfusion (ILP) and isolated limb infusion (ILI) are two similar techniques that have been developed over the last several decades to treat these two solid tumours.

ILP was first pioneered by Creech *et al*. in the late 1950's who treated a patient with recurring melanoma in his leg to achieve a complete response [60]. As shown in Figure 1.5, The technique comprised of a surgical cut down at the patient's groin to access the common femoral artery and vein under anaesthetic, catheterisation of the artery and vein, applying a tourniquet around the limb superior to the cut down, and connecting the catheters to an extracorporeal pump which oxygenated the blood and pumped chemotherapy from the arterial side [60]. The catheters are removed after the procedure and the access wound closed.

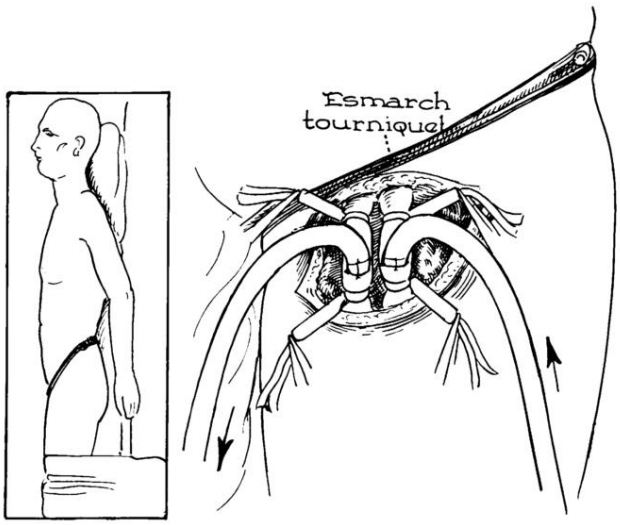

Figure 1.5 – ILP technique developed by Creech *et al*. to isolate and perfuse the extremities with chemotherapy agents. Reproduced from Creech *et al* [60].

ILI is similar technique that was developed in the 1990's by Thompson *et al* [61,62] with the aim of simplifying and reducing the invasiveness of ILP. The key difference in ILI is the use of

hyperthermia and a syringe to manually infuse the chemotherapy in intervals instead of an extracorporeal pump. Otherwise, the technique is relatively similar as can be seen in Figure 1.6. An arterial and venous catheter are introduced percutaneously using the Seldinger technique via the common femoral artery and vein and advanced up to the popliteal artery and vein. Tourniquets are applied around the proximal region of the limb and around the foot and the chemotherapy infused through the arterial catheter [61]. Due to the absence of an oxygenation process throughout the circuit, ILI also has a progressively hypoxic effect upon the limb and tumour.

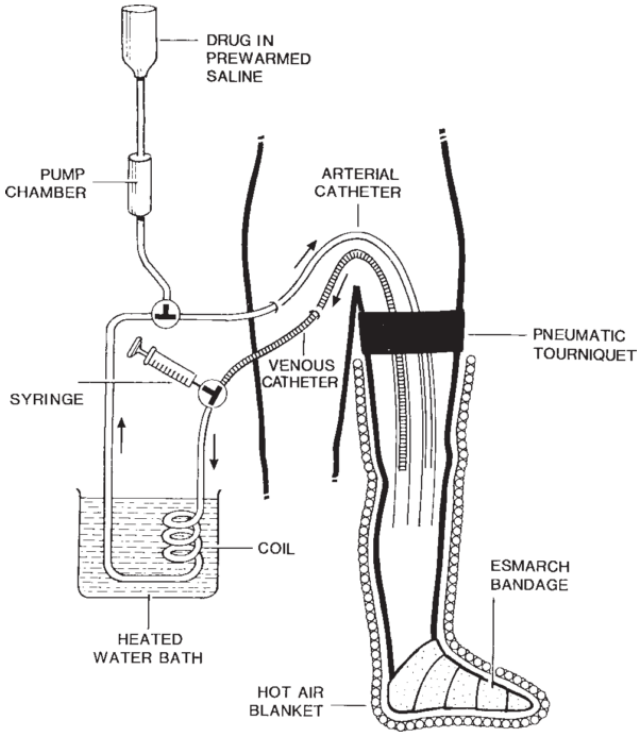

Figure 1.6 – ILI technique developed by Thompson *et al*. to isolate and infuse the extremities with chemotherapy agents. Reproduced from Thompson *et al* [61].

Over the course of their development, these two techniques have become more similar to one another with hyperthermia of the perfusate/infusate or the limb itself becoming common practise. However, the extracorporeal circuit in ILP allowed for continuous monitoring of toxicity levels from the venous line to gauge the level of systemic toxicity. As a result, the drug combinations made available for ILP and ILI vary as ILI is confined to using drugs with a lower toxicity profile.

A series of case studies by Liénard *et al* which reported highly promising results (89% and 11% complete and partial responses respectively; n = 30) [63] when combining melphalan with tumour necrosis factor alpha (TNFα) in ILP to treat locally advanced unresectable melanoma and STSs triggered a wave of studies using this drug combination. Since then, several pivotal randomized controlled melanoma trials [64-66] have confirmed this drug combination as being able to deliver complete response (CR) rates as high as 69% using ILP. Similarly, a pivotal

study in the late 1990's confirmed the success of ILP with melphalan and TNFα [67] showing a limb salvage rate and CR rate of 82% and 29% respectively for patients with STSs [67]. The CR rate for ILI has also seen an improvement over time with CR rates ranging between 30-57% for STSs [68,69].

Overall, the prognosis for patients with a CR via ILP/ILI is relatively optimistic with a ten year survival of 49% [70]; a vast improvement from a 3-year survival rate of only 56% [66] when it was first introduced. Even in the other half of the population who relapse after a CR, a repeat ILP/ILI procedure can still lead to remission [71]. Consequently, ILP and ILI have become established techniques for unresectable local advanced melanomas and STSs of the limbs albeit being confined to specialised centres with ILP/ILI resources. Even in the age of advanced drugs like vemurafenib and ipilimumab, the high CR rate and low morbidity associated with regional infusion/perfusion using ILI/ILP is a more attractive option for clinicians [72].

Even though melanomas and STSs only make up for approximately 6% [59] of all new estimated cases of cancer annually, the success of ILP/ILI in this cohort of patients is promising and, if translatable to other solid organ cancers, could be revolutionary.

1.2.2 Peritoneal Metastases and Carcinomas – Hyperthermic Intraperitoneal Chemotherapy

LRC has also been successful in treating cancers within the peritoneum. The peritoneum is the compartment containing the abdominal organs and primary carcinomas of the peritoneum are extremely rare with only about 6-7 cases per million of a give population [73]. Hence cancers in the peritoneum of the abdomen typically manifest as metastases that have spread from carcinomas of other abdominal organs. As a result, there are no real accurate statistics available on the prevalence of peritoneal cancers since this patient cohort is comprised of an amalgamation of the metastatic subset of several gastric (liver, colorectal, pancreas, stomach etc.) and non-gastric (ovarian, mesothelial) cancers. The peritoneum contains a visceral medium surrounding the abdominal organs which can also serve as a transport medium for malignant cancer cells to proliferate in the organs of the abdomen and if treated with systemic IV chemotherapy alone, has a prognosis worse than that of metastatic spread to the liver or lung [74]. Initially, for patients with symptomatic peritoneal disease 6-month survival was unlikely and even those with low-volume disease were unlikely to survive 1 or 2 years [75,76].

Up until the early 2000's, the standard treatment for peritoneal cancer patients was cytoreductive surgery (CS) followed by adjuvant systemic chemotherapy. CS is a surgical resection of the visible malignant tumour(s) within the peritoneum otherwise known as "tumour debulking". However, after the large scale EVOSCAPE 1 study in 2000 which investigated the outcomes of CS and adjuvant chemotherapy, it was shown that even in patients with complete resection of the disease, there were no 5-year survivors and 2-year survival was only 10%

[77]. In the same year, Loggie *et al* published a landmark study on the outcomes of CS plus hyperthermic intraperitoneal chemotherapy (HIPEC) leading to a 35% 5-year survival rate [78]. The outcomes of the latter study catalysed further investigations into the role of CS and HIPEC for various malignant tumours with peritoneal involvement.

The combination of CS with HIPEC was first investigated by Spratt in 1980 [79] and researched further by Sugarbaker [80-82]. The essential idea is to debulk the tumour during CS by specifically resecting all tumours rooted greater than 1mm where possible, then bathing the entire peritoneum with chemotherapy. This allows cancer cells rooted up to 2mm in depth within the at-risk lining surfaces of the peritoneum to physically come into contact with very high doses of chemotherapy that would otherwise be unreachable with IV chemotherapy [83]. Limiting the time and dose of the chemotherapy bath provided a means to control the overall toxicity. HIPEC followed CS immediately since it was shown in the EVOSCAPE 1 study that surgical resection of the disease alone is ineffective due to rapid postoperative tumour recurrence [77]. Like all LRC techniques, the process of HIPEC varies across institutions in their drug combinations, concentrations, composition and volume of the perfusion, duration, and temperature. However the two main techniques used are a closed-abdomen technique with mitomycin C over 60-90 minutes at 41°C or an open-abdomen technique with oxaliplatin (with or without irinotecan) over 30-40 minutes at 43°C as shown in Figure 1.7 [84]. Hyperthermia promotes greater diffusion of the chemotherapy to penetrate into the lining of the peritoneum to potentiate the effects of the chemotherapy within the time limits of the procedure [85].

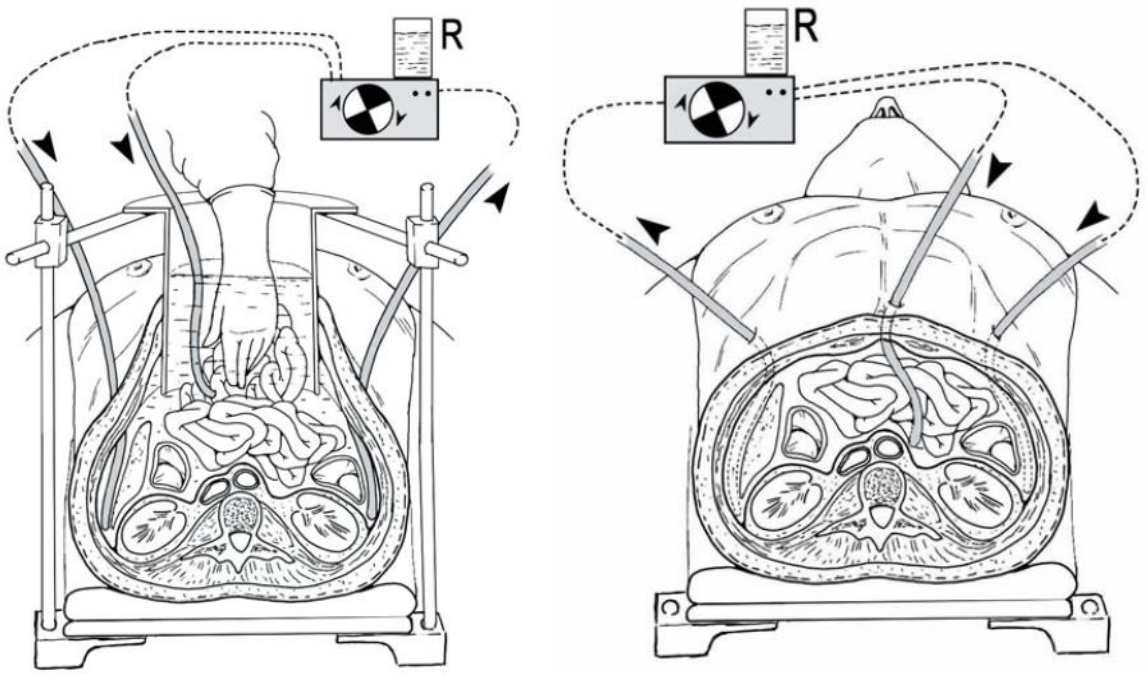

Figure 1.7 – Schematic of the open (left) and closed (right) HIPEC setup. The roller pump (R) heats and perfuses the chemotherapy into the peritoneum extracts it from the peritoneum with a drainage catheter. Reproduced from Virzì *et al* [84].

CS with HIPEC has now become the standard of care for patients with peritoneal mesotheliomas and epithelial ovarian cancers. In the former cohort, CS with HIPEC has median OS and 5-year survival rates of 53 months and 47% respectively [86]. In the latter cohort CS with HIPEC can achieve median OS and 5-year survival rates of 46.1 months and 51% respectively and 34.9 months and 46.3% for recurrent disease [87].

These benefits of CS with HIPEC must be taken into account with the reported perioperative mortality and morbidity rates of 3-4% and 34-43% respectively where morbidity constitutes a grade III/IV adverse event (National Cancer Institute Common Toxicity Criteria) [88,89]. However, the complications rates associated with HIPEC are considered to be outweighed by the benefits of HIPEC to warrant its place as the first line treatment for such patients.

1.2.3 Tumours of the Pancreas – Aortic Stop-Flow Infusion, Coeliac Axis Infusion, and Selective Arterial Infusion

Pancreatic tumours, unlike those of the limb or peritoneum, have had less success with LRC therapies but is generally a poor responder to all therapies available. There are approximately 55,440 new cases of pancreatic cancer diagnosed each year which accounts for only 3% of all cancers, yet it reports the third highest mortality rate after colorectal and lung cancer [59]. This is a direct reflection of the deadliness of the cancer which has a prognosis of an estimated OS of 3.0-4.6 months from diagnosis depending on resectability and the onset of metastatic disease [90,91]. This is all with the management options of radiotherapy, and various chemotherapy regimens such as gemcitabine, 5-FU, and other advanced cocktails like FOLFIRINOX (5-FU, leucovorin, irinotecan, oxaliplatin) [92].

LRC for the pancreas was first explored in 1980 but due to discouraging results and a treatment related death, it failed to gain any traction [93,94]. The concept was revisited in the 1990's by Aigner, Fiorentini, and Muchmore in the form of aortic stop-flow infusion (ASFI) and coeliac axis infusion (CAI) [95-97]. During ASFI balloon catheters were guided from the femoral artery and vein up to the aorta and inferior vena cava (IVC). Typically, the aortic catheter was positioned retrograde to the bifurcation of the coeliac trunk or the superior mesenteric artery and the caval catheter was positioned in the IVC immediately antegrade to the hepatic veins. Tourniquets were also placed around the thighs before chemotherapy was infused through the aortic catheter. The chemotherapy would reach the pancreas after traversing from the coeliac axis and the splenic artery to the superior pancreaticoduodenal arteries and the dorsal/greater pancreatic arteries respectively. Alternatively, if the aortic catheter tip was placed retrograde to the superior mesenteric artery, the chemotherapy would reach the pancreas via the inferior pancreaticoduodenal arteries. The caval catheter was used to remove/reduce the amount of unbound chemotherapy exiting the pancreas that would otherwise end up in the patient's

systemic circulation. CAI differed slightly in that the aortic catheter was advanced further to be positioned directly in the coeliac axis and thus the tourniquets were not required [97].

As both techniques evolved, the technique varied from study to study with the inclusion of hemofiltration, perfusion, and or recirculation units between the aortic and caval catheters [98]. While some studies introduced the infusion catheters percutaneously under angiographic guidance, others did so laparoscopically or via open surgery. The presence/absence of a caval catheter was also an inconsistency between techniques. A general setup of ASFI and CAI are shown below in Figure 1.8.

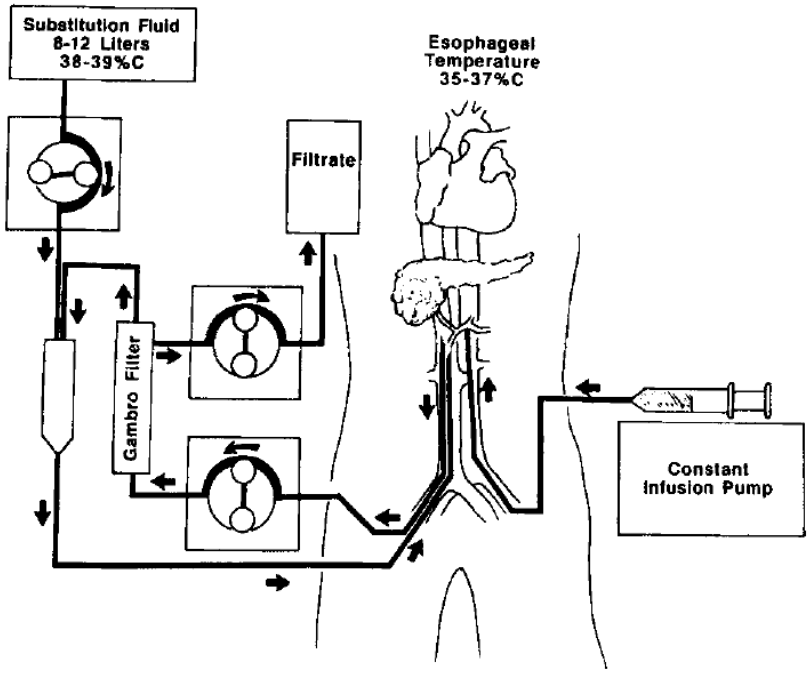

Figure 1.8 – Schematic of setup for ASFI/CAI with a haemofiltration recirculation unit. Reproduced from Muchmore *et al* [97].

The two largest ASFI and CAI studies to date were carried out in 2005 and 2006 by Aigner and Mambrini respectively (n = 476 between the two studies) to treat patients with locally advanced or metastatic unreserctable pancreatic cancer [99,100]. Each patient was treated 3-4 times to achieve a partial response (PR) and 1-year survival rate of 7.3% and 30% respectively from which 39% of those who survived past the one-year mark were resectable. However, the OS remains bleak with a median OS of 6.5 months and 10.5 months for those with and without metastatic disease respectively. Nevertheless, this is promising given that the OS data reported with current standard of care is 3.0-4.6 months [90,91].

Direct comparison of LRC of the pancreas to standard systemic chemotherapy is difficult though with most randomised studies being unable to enrol enough patients (n < 10 each arm) to warrant credibility [101,102]. However, once another level of targeting was achieved with the introduction of selective arterial infusion (SAI) by Homma in 2000 [103], there has been a few more randomised trials. The SAI setup is identical to CAI except that the infusion catheter

is guided even further than the coeliac axis and into the gastroduodenal artery or sometimes the splenic artery. SAI is typically more surgically involved as vascular redistribution is carried out prior to chemotherapy infusion to maximise the flow to the chemotherapy and minimise the flow to the non-target organs (i.e. spleen, stomach, liver, and bowels). Redistribution is typically done by coil embolization of the gastric or splenic arteries [103-107].

The randomised trials using SAI have shown the most encouraging signs for LRC of the pancreas to date. 1-year survival rates of 48% versus 14.6% and a median OS of 10-21 versus 4.8-14 months have been reported for SAI versus systemic chemotherapy by three studies that treated a total of 51 and 53 patients respectively in the two arms [108,109]. The largest randomised study (n = 140) reported a median OS of 13.5 months versus 6.2 months in the SAI and systemic chemotherapy arms respectively [110]. However, LRC of the pancreas is still not a part of the disease management algorithm. This is likely a consequence of the scarcity of the disease (3% of all cancers) which, when coupled with its short OS prognosis, poses a logistical challenge for clinicians as the treatment window in which to assess the patient's suitability, find an appropriately resourced specialised LRC centre, and to administer the treatment is significantly narrow [92]. Nonetheless, the pseudo-capsule of pancreatic cancers present a morphological barrier for standard IV chemotherapy and hence justifies further investigation into LRC techniques that could potentially manipulate interstitial pressures and diffusion gradients.

1.2.4 Tumours of the Liver – Transarterial Chemoembolisation, Isolated Hepatic Perfusion/Infusion, and Radioembolization

Tumours in the liver have had a mixed response to LRC therapies. Cancers of the liver can occur in several histologies with primary cancers typically manifesting as hepatocellular carcinomas (HCC) while metastatic tumours in the liver are typically a result of colorectal adenocarcinomas or ocular melanomas. Liver cancer is the fifth most commonly diagnosed cancer in men worldwide and the ninth most common for women. Yet it registers the second highest and fifth highest number of cancer deaths of any organ in men and women respectively [16]. The majority of primary and metastatic liver cancers are HCCs and colorectal liver metastases (CRCLM) respectively.

Transarterial chemoembolization (TACE) is a LRC procedure for HCCs whereby chemotherapy is injected into the vessels supplying the hepatic tumour followed by the injection of embolic agents to cause blockages within the tumour. However, the concept of blocking the blood supply to the liver was assumed to have fatal consequences up until the 1970's when it was shown that occlusion of the hepatic artery for up to 10 months was shown to be safe [111,112]. It is now well known that hepatic infarction is highly unlikely from embolization of the hepatic artery as there is plentiful blood supply to the liver via the portal vein and neighbouring collateral arteries.

Around the same time the therapeutic effects of hepatic arterial embolization were being investigated [113,114], the use of intra-arterial chemotherapy with agents were also being investigated [115,116]. Naturally, the techniques of embolization and intra-arterial chemotherapy were combined to create what is now TACE [117]. A landmark study by Llovet in 2002 reporting a 2-year survival rate of 63% versus 27% for TACE versus conventional treatment [118] made TACE a standard of care for patients with HCC. It is currently the first-line therapy for patients with intermediate-stage HCC [119-120]. One of the key advantages of TACE is its repeatability made possible by the use of standard angiographic catheters to administer the drug-embolic agents which allows for minimally invasive transfemoral access. TACE can be repeated until either the best possible response has been achieved after two procedures (stable disease or complete response), disease progression, or technical infeasibility such as not being able to achieve near static flow in the feeding artery to the tumour [121]. In some cases, this allows patient to be treated with TACE for up to 5-6 times although on average, most patients are treated just twice [121].

Like all other LRC modalities, there is heterogeneity in the procedure for TACE in terms of the chemotherapy, dosage, embolic agent, and treatment schedule. In general, this is split into conventional TACE (cTACE) or TACE using drug-eluting beads (DEB-TACE). Typically, in cTACE, chemotherapy (doxorubicin) and an embolic agent (lipiodol) are injected in succession [122] whereas in DEB-TACE the doxorubicin is loaded into the same vial as the drug coated beads and injected altogether [123]. Although there is some evidence of DEB-TACE having a superior safety profile in regards to liver-related adverse events, the 4 randomised studies carried out since 2010 have not shown any significant difference in survival outcomes to be able to set cTACE and DEB-TACE apart [124-127].

The use of embolic agents is not without risks and post embolization syndrome is the most common procedure related adverse event. While manageable [128], in severe cases where the embolic agents are lodged within the arteries supplying healthy hepatic tissue or reflux to non-target arteries feeding adjacent organs can lead to death through liver failure and pancreatitis [121,129]. However, the incidence rates for such procedure related deaths are low (< 2%) and its ability to impart a median OS of 39 and 32 months for cTACE and DEB-TACE respectively [121] have made TACE the current standard of care for patients with inoperable intermediate HCC.

TACE has not had the same level of success in the treatment of metastatic liver diseases though. While it has been shown to be superior to some chemotherapy systemic regimens [130], the lone randomised controlled trial comparing TACE combined with FOLFOX against the standard of care (FOLFOX combined with bevacizumab) did not assess for any OS benefit

in patients with CRCLMs [131]. While promising results have been observed in patients with liver metastases from the breast with the largest study to date reporting a median OS of 18.5 months using cTACE [132] and the most recent study to date reporting a median OS of 17 months using DEB-TACE [133], they have all been confined to single-arm settings. Thus, further assessment of TACE is required in randomised controlled trails to determine its suitability as a first-line treatment in the metastatic setting.

A similar LRC technique known as selective internal radioembolization therapy (SIRT) is probably the most well studied LRC technique for treating CRCLMs but has also been loosely investigated in patients with metastatic ocular/cutaneous melanomas in the liver (MOML). The technique is identical to TACE with the exception of substituting the drug eluting beads with the resin/glass microsphere containing yttrium-90 to emit β radiation. The radioactive embolic microspheres are injected through the patient's hepatic artery and, similarly to TACE, relies on the fact that the hepatic tumour blood supply is primarily through the hepatic artery while the healthy hepatic tissue derives its supply from the portal vein [134,135]. Consequently, the metastatic tissue is treated through the induced ischemia as well as the radiation. A large meta-analysis of 18 trials with SIRT in chemotherapy refractory patients with CRCLMs showed response rates up to 80% and 90% when used as a salvage therapy or as a first line therapy respectively [136]. Consequently, large phase III randomised controlled trials comparing the OS benefit from the combination of SIRT with systemic chemotherapy against chemotherapy alone were commenced [137,138]. The results from these trials showed that, while systemic chemotherapy combined with SIRT led to improved hepatic progression-free survival (hPFS) compared to systemic chemotherapy alone, it did not translate into any significant OS benefit (22.6 vs 23.3 months respectively) [139]. Considering such a result, the scale of this analysis, the procedure related mortalities from radiation induced liver disease, drug-induced pneumonitis, off-target delivery of microspheres [139], it is unlikely that SIRT will become a first line therapy option for inoperable CRCLM patients. It will most likely remain a treatment option as a salvage therapy although evidence from randomised trials is still required in terms of OS benefit.

SIRT has also been trialled in MOML patients although only in non-randomised studies. A meta-analysis of SIRT in 207 MOML patients have shown response rates up to 19.3% and a median OS of 10 months [140]. While complications were not as pronounced as of those in the CRCLM studies, this is likely due to the smaller scale of the studies. Given the SIRT procedure is identical for both MOML and CRCLM patients, it would be reasonable to anticipate the same types and rates of complications. Additionally, randomised controlled trial data is still required and the benefits must be weighed against the benefits offered by other LRC therapies for MOML patients discussed later in this section.

Metastatic disease of the liver has instigated the most exploration in LRC treatments more so than any other cancer. The liver is an attractive organ for LRC therapies due to its vascular anatomy and simplicity of access. It has a dual blood supply from the hepatic arteries and portal vein (approximately 30% vs 70% respectively) with most tumour lesions being supplied by the hepatic arteries [141]. Such anatomy and the ease of access to the hepatic artery present little to no challenge in being able to achieve complete control of the arterial flow (i.e. infusion, perfusion, or obstruction) and deliver therapeutic agents directly to the hepatic tumour's feeding arteries. Considering the bleak 5-year survival prognosis of less than 19% for those with inoperable CRCLMs [142] and an even worse situation of a 1-year survival rate of 15% for those with MOML [143] with the current standard of care/systemic chemotherapy, the accessibility and anatomy of the liver presents an opportunity where LRC could be a major game changer.

Hepatic arterial infusion (HAI) is a LRC technique developed specifically to treat CRCLMs. HAI was first explored by Kemeny *et al* in the mid 1980's by infusing 5-fluorodeoxyuridine (FUDR) continuously through the hepatic artery over 14 days in 45 patients with CRCLMs to achieve impressive results [144]. The technique relies on implanting a subdermal access port connected to an infusion catheter that is advanced to the segmental hepatic arteries or into the common hepatic artery with the gastroduodenal artery embolised (Figure 1.9). The infusion catheter is typically introduced through the peripheral artery (i.e. femoral or brachial arteries) and chemotherapy infused via an extracorporeal infusion pump connected to the access port as needed. Alternatively, a 'pump' could be built into the access port itself where the access port served as chemotherapy reservoir and automated dispenser [144-147].

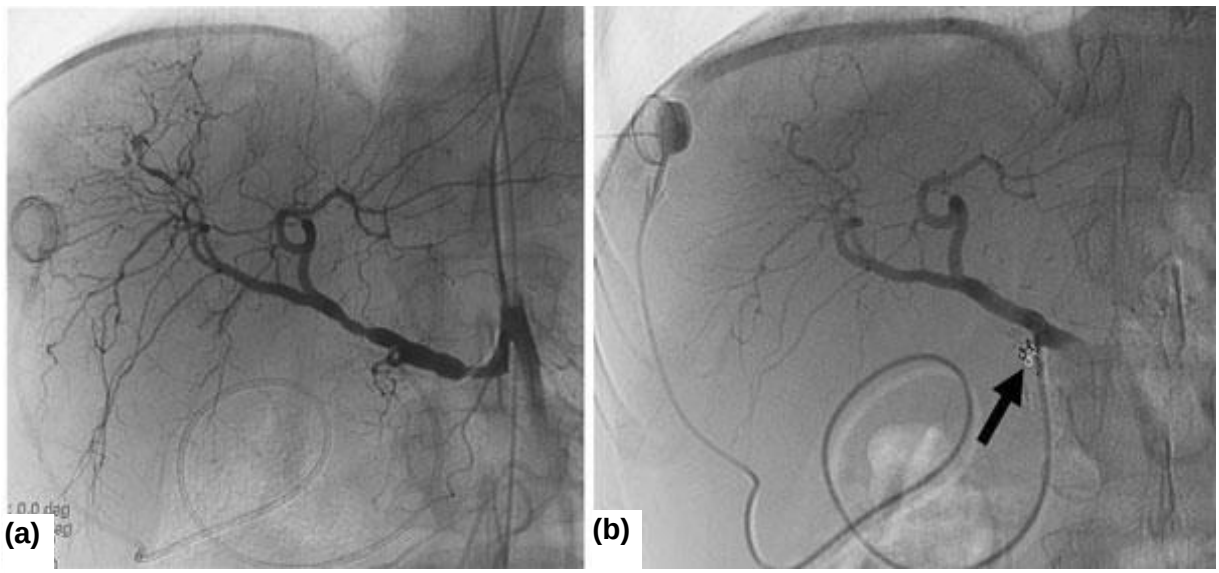

Figure 1.9 – Schematic of one of the setups for HAI as used by Lévi *et al* [148]; the infusion catheter is introduced via a peripheral artery such as the femoral or brachial arteries with the access port implanted subcutaneously near the introduction site. The infusion catheter is sutured onto the in the common hepatic arteries near the gastroduodenal artery (a) which is embolised with a coil to prevent extrahepatic toxicity as shown by the arrow in (b). Angiograms from Deschamps *et al* [149].

The early data of HAI with FUDR demonstrated response rates as high as 41% in CRCLM patients which were significantly higher than that of standard IV therapies but showed no significant improvements in OS when compared to IV FUDR or 5-FU [150]. Soon after, a randomised controlled trial reported results on outcomes from CRCLM patients treated with either 5-FU/LV via HAI, FUDR via HAI, and 5-FU/LV via the IV route. The minor OS benefit of the 5-FU/LV via HAI arm compared to the IV arm (18.7 vs 17.6 months), the poor OS of the FUDR via HAI arm (12.7 months), and HAI related adverse events such as biliary sclerosis and chemical hepatitis [151] resulted in the abandonment of solely relying on HAI in a neoadjuvant setting for inoperable CRCLMs and clinicians to shy away from FUDR in an intra-arterial setting. This was later confirmed in a phase III randomised study which showed an OS benefit for HAI with FUDR combined with IV 5-FU/LV compared to HAI alone (20 vs 14 months) [152].

Since then, oxaliplatin based HAI paired with various combinations of IV chemotherapies have been investigated in Europe [148,153-156] whereas FUDR based HAI combinations have remained largely in the US [145-147,157]. A recent study showed 33% of all chemorefractory patients with inoperable CRCLMs when treated with irinotecan, oxaliplatin, and 5-FU given via HAI combined with IV cetuximab up to 6 times were successfully down-staged to be suitable for liver resection [148] while another study using oxaliplatin via HAI combined with IV chemotherapy reported a down-stage rate of 16.4% [155]. Alternatively, FUDR-HAI with IV irinotecan and oxaliplatin have reported downstaging resection rates as high as 47% when used in a mix of pre-treated and chemotherapy-naïve patients [147]. In such patient populations who have received several lines of therapies, the conversion to resection rate is a more accurate measure of the efficacy of the therapy since OS data is confounded by the inestimable combinations of previous treatments. It is well established that the OS associated with resection is more than double that of patients who cannot be resected (medians of 49.8 vs 22.2 months) [142]. This is reflected in two HAI studies where the 4-year and 3-year survival rates for those successfully down-staged for liver resections were 45% [148] and 80% [155] respectively compared to zero for those who remained inoperable. Thus, the reported outcomes of HAI combined with systemic chemotherapy in tumour down-staging are promising enough to suggest earlier adaptation (i.e. as a first or second line therapy) but still require assessment through a large randomised controlled trial.

The lack of mainstream uptake of HAI with systemic chemotherapy could be due to several factors. The procedure is multidisciplinary by nature and requires close collaboration between surgeons, interventional radiologists, and oncologists which limits its use to institutions equipped with all skillsets. There is probably still a prevailing perception of its non-superiority to systemic therapy from the large randomised controlled trail from 2000 [151] when HAI was still being investigated as a lone treatment. Additionally, adverse events such as hepatic

arterial thrombosis, extrahepatic perfusion, catheter migration related to the procedure are regularly reported in every HAI study [148,155,158,159]. Such adverse events are expected given the more surgically involved nature of the procedure and the long-term indwelling nature of the catheter within the hepatic artery. Furthermore, such events only require minor intervention and at most, lead to treatment interruption. Nevertheless, the combination of all these factors most likely explain the lack of mainstream uptake of HAI plus IV chemotherapy.

Unlike CRCLM patients for whom novel treatments through clinical trials are generally only considered upon lack of response to establish chemotherapy regimens (e.g. FOLFOX with bevacizumab/cetuximab), there is no consensus on the first line therapy for patients with MOML and thus most patients are immediately considered for clinical trials [160]. As such, trials directly comparing LRC therapies against IV chemotherapy are possible in patients with MOML even though the cohort is smaller than CRCLM patients. A recent large multicentric randomised controlled trial treating MOML patients with HAI or IV chemotherapy demonstrated that while HAI results in higher response rates and progression-free survival, it did not translate to any OS benefit [161].

Where HAI has been unsuccessful, other LRC techniques known as isolated hepatic perfusion (IHP) and percutaneous hepatic perfusion (PHP) have shown potential in treating MOML. IHP was developed in the early 1960's [162] and extensively investigated in the 1990's and 2000's [163-167]. IHP is very similar to ILP (see Section 1.2.1, Figure 1.5) but is a more surgically intensive procedure performed under general anaesthetic and laparotomy (Figure 1.10) whereby the patient's liver is extensively mobilised. On the venous side, the IVC is then exposed between the renal veins and the diaphragm and ligated antegrade to the hepatic and renal veins. The portal vein is also ligated antegrade to the superior mesenteric vein. A cannula is then used to shunt the regions retrograde to the IVC and portal vein ligations to the axillary vein thereby establishing a veno-venous bypass circuit. On the arterial side, the common hepatic artery is ligated retrograde to the origin of the gastroduodenal artery which is also ligated. Finally, the isolated region of IVC is connected to the common hepatic artery antegrade to the ligation to create a perfusion circuit to administer the chemotheraptic agents through. Theoretically, this provides near complete isolation and control of the hepatic inflow (portal vein and hepatic artery) and outflow (hepatic vein) to achieve extremely high dose chemotherapy delivery to the whole or segment of the liver with minimal or no systemic side effects. However, due to the invasiveness nature of it, IHP is considered to be a one-shot treatment.

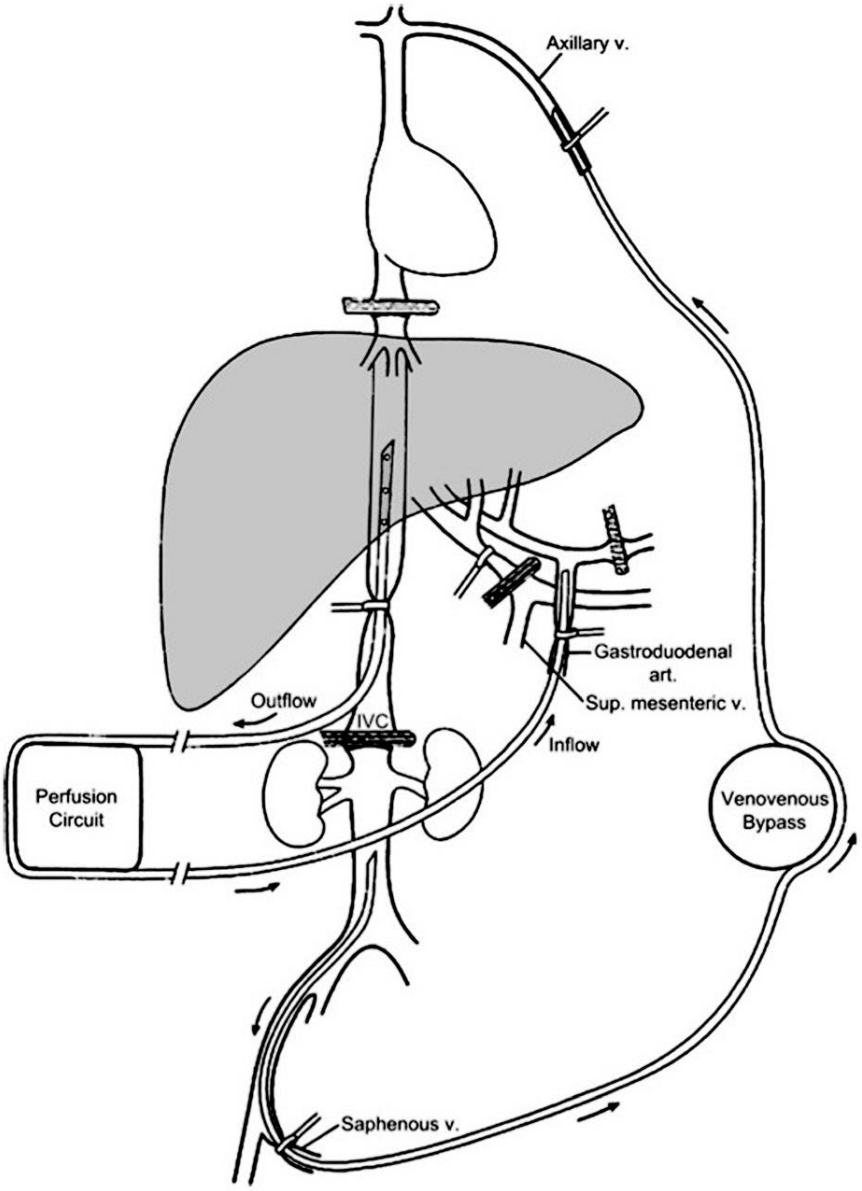

Figure 1.10 – Schematic of a typical IHP setup [168].

The outcomes of IHP in patients with MOML have varied with median OS ranging from 7.5 months to 11 months and response rates up to 62% [163,165,167]. Mortality rates as high as 37.5% in the immediate post-operative period have been a major deterrent in the mainstream uptake of the procedure [163]. The initial hypothesis that such a high mortality rate could be reduced by contraindicating IHP for those with a hepatic tumour burden greater than 50% [163] has more or less been confirmed in a recent Swedish study that reported no mortalities using IHP [169]. Furthermore, the study showed a benefit in median OS with IHP compared to a sample of the longest MOML survivors from the national registry (26 vs 12 months) [169]. Such promising results have led to the development of a large scale randomised controlled study to investigate the potential OS benefits of IHP in MOML patients which is currently underway [170]. If the doubling of the median OS can be confirmed in such a study, it is quite likely IHP may become the standard of care for MOML patients. This is despite the various procedure related grade IV morbidities reported in the Swedish study; perforation of a duodenal ulcer,

respiratory failure, cardiovascular failure, renal failure, pulmonary effusion, and pneumonia [169].

PHP is a tweaked version of IHP that was developed by Pingpank *et al* to reduce the invasiveness and surgical complexity of IHP and to allow for repeat treatments [171,172]. As shown in Figure 1.11, a double balloon chemoisolation catheter with side-ports between the two balloons is introduced percutaneously via the common femoral vein and guided to the IVC such that the proximal and distal balloons are immediately superior to the hepatic and renal veins respectively. The extracorporeal end of the catheter is connected to a perfusion pump, saline column, chemotherapy filtration cartridges, and a return cannula into the patient's jugular vein. On the arterial side, an infusion catheter is introduced percutaneously via the common femoral artery and guided to the common hepatic artery. During treatment, the chemotherapy is infused through the arterial catheter, the two balloons in the IVC catheter are deployed, and the hepatic venous outflow is extracted through the side ports of the IVC catheter to be filtered and perfused back into the patient's systemic circulation via the extracorporeal loop. Similar to IHP, this allows near complete control of the hepatic inflow and outflow allowing chemotherapy saturation of the whole or segments of the liver with minimal systemic side effects. After the procedure, the arterial and IVC catheters are retracted and discarded. While general anaesthesia was still required, the percutaneous and minimally invasive nature of PHP did not require a laparotomy like in IHP and thus allows the treatment to be repeated.

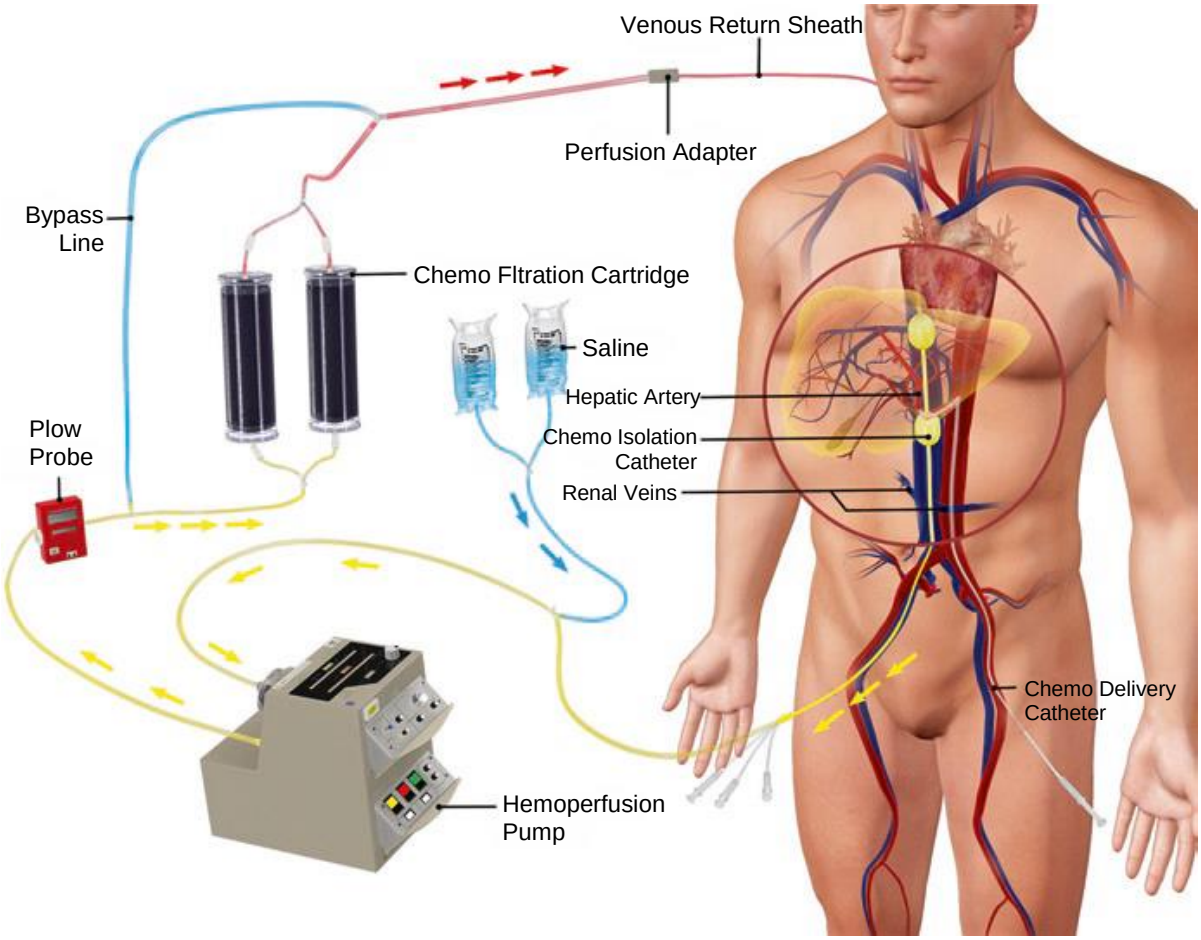

Figure 1.11 – Schematic of a typical PHP setup [173].

The initial studies of PHP in patients were feasibility studies and thus focused on procedure related complications and response rates. Unlike IHP, no perioperative mortalities were observed and a response rate of 29.6% was achieved but was as high as 50% for MOML patients [172]. The associated morbidities were also confined primarily to systemic and haematological toxicities [172] which is most likely due to chemotherapy leakage into the systemic circulation indicating that complete hepatic isolation was not achieved. Device related issues were a result of catheter placement (i.e. hepatic arterial dissection, haematoma). The most recent PHP study in MOML patients was a large phase III randomised controlled study that compared PHP against the best alternative care. The primary endpoint of the study of hPFS demonstrated a significantly increased hPFS for the PHP arm compared to the control arm (7.0 vs 1.6 months). Whether this translated into an improved OS could not be confirmed by the study due to the study design which allowed patients from the control arm to cross over to the PHP arm upon hepatic progression. Consequently, the OS reported for the PHP and control arms were 10.6 months and 10.0 months respectively which are inconclusive [174]. Nonetheless, it is reasonable to postulate that without the crossover, a survival benefit would have been observable given an increased hPFS would have delayed the point of severe and fatal tumour progression.

Alarmingly, it was reported that up to 90% and 91.4% of patients in the PHP arm experienced grade III/IV adverse events either almost immediately after the procedure or within the month after the procedure respectively [174]. Most events were chemotherapy related myelosuppression (e.g. thrombocytopenia, anaemia, neutropenia etc.) or hepatic dysfunction. The study dropout rate was as high as 34.3% directly as a result of such adverse events. Furthermore, three deaths were attributed to complications arising from these adverse events in the PHP arm [174]. Hence, while the hPFS results have implications for the potential of PHP to provide an OS benefit, it is unlikely to be integrated into mainstream treatments due to the high morbidity associated with the procedure. It is probable that the technical aspects of the procedure need to be improved upon to address the reported complications which indicate either inadequate isolation and or inadequate chemotherapy removal through the chemofiltration cartridges.

1.2.5 Summary & Current State of Locoregional Chemotherapy

A summary of the data from the review of existing LRC techniques for four different organs and various carcinomas is provided in Table 1.1 below. Apart from SAI and ASFI/CAI of the pancreas, all LRC techniques have been classified as either a first line therapy option, salvage therapy option (i.e. at best second line therapy), or as having insufficient evidence to date to warrant its use as a first line option.

Table 1.1 – Summary of LRC techniques, their current status amongst clinicians, and details of outcomes. *SYS = systemic chemotherapy; mo = months; RCT = randomised controlled trial*

Organ	Histology	LRC Technique	Status	Details
Limbs	Advanced melanoma & STS	ILI/ILP	1st line therapy	10-year survival of 49%
Peritoneum	Mesothelioma	HIPEC + CS	1st line therapy	Median OS = 53 mo; 5-year survival = 47%
	Epithelial ovarian	HIPEC + CS	1st line therapy	Median OS = 46 mo; 5-year survival = 51%
Pancreas	Advanced inoperable pancreatic cancer	ASFI, CAI	Abandoned	Median OS = 6.5 mo (no met) or 10.5 mo (met) Standard care median OS = 3.0 - 4.6 mo
		SAI	Specialised centres	Median OS = 13.5mo vs SYS OS = 6.2 mo
Liver	HCC (intermediate stage, inoperable)	TACE	1st line therapy	cTACE median OS = 39mo; DEB-TACE median OS = 32mo
	Metastases (carcinomas of the breast)	TACE	Insufficient evidence	cTACE median OS = 18.5 DEB-TACE median OS = 17mo but RCTs required
	CRCLM	TACE	Salvage setting only	No RCTs to show OS benefit
	CRCLM	SIRT + SYS	Salvage setting only	No OS benefit compared to SYS alone
	MOML	SIRT	Insufficient evidence	Median OS = 10 mo; OS data from RCTs needed
	CRCLM	HAI + SYS	Insufficient evidence	Down-staged to resection = 47%; 3-year survival = 80%; 4-year survival = 45%; OS data from RCTs needed
	MOML	IHP	Insufficient evidence	Median OS = 26 mo vs historical control OS = 12 mo; OS data from RCTs needed
		PHP	Insufficient evidence	Median OS = 10.6 mo vs control arm OS = 10.0 mo; inconclusive OS benefit

What is noteworthy is that of the 13 histological and LRC technique combinations, only two of them have been shown to offer no OS benefit (TACE and SIRT + systemic chemotherapy for CRCLMs). Two combinations that have shown promise but have not been adopted in standard practice are SAI and ASFI/CAI for advanced inoperable pancreatic carcinomas. The former likely due to the treatment not yet being scalable and thus being restricted to specialised centres while the latter showed too small an OS benefit to warrant its use given the accompanying surgical risks even though the OS benefit was almost double that of standard care. Five other combinations require further phase III OS data from randomised controlled trials to verify their potential benefits.

Overall, Table 1.1 demonstrates the potential value of LRC techniques in the role of treating advanced and or inoperable cancers and thus its potential role as a neoadjuvant therapy. Of particular significance is that in patients with inoperable tumours initially non-responsive to systemic IV oxaliplatin, when the oxaliplatin has been administered via HAI, they have been able to achieve a response great enough to down-stage the tumour to qualify for resection [155]. Further to this, the review in Table 1.1 has been confined to the neoadjuvant setting. When used in an adjuvant setting after tumour resection, HAI combined with systemic IV chemotherapy has been shown to be superior to IV chemotherapy alone with 2-year and 10-year survival rates of 86% and 41% versus 72% and 27% respectively [175,176].

Ultimately, it is very likely that the full potential of LCR has not yet been realised. This could be a result of having to wait a long time for evidence of the longitudinal OS data from large scale randomised controlled studies. Additionally, recruitment times are lengthy due to the limited histological cohorts each study group may have access to. Of equal contribution could be the fact that apart from TACE which has become a first line treatment option for HCCs, most LRC techniques are not considered to be as “simple”. In the case of PHP and IHP, not only are they considered complex procedures, but the associated complication/mortality rates are a major deterrent for mainstream uptake regardless of the incremental OS benefit they may impart. This is reflected by the lack of uptake of SAI in pancreatic cancers for which the OS has been almost doubled compared to that of standard therapy. Yet, the OS from standard care is so remarkably low that even a twofold increase in OS is still considered “low” and not worthy enough to outweigh the complexity and surgical risks associated with the procedure.

Clinically, what is most probable is that if the risks and or complexity of a LRC technique cannot be improved upon, then the OS benefit must be substantial rather than just incremental. Such is the case for HIPEC and ILI/ILP for treating cancers in the peritoneum and limbs. These techniques are just as difficult and surgically complex as that of PHP and SAI yet have become first line therapeutic options. Alternatively, if only an incremental benefit can be achieved, the LRC technique must be made less surgically complex with a reduction in the rates and grades of procedure related adverse events.

To return to the running metaphor, it could very well be that the magic bullet for annihilating cancers already exist but is being misfired through the ancient gun of IV therapy. Better firearms have been designed through various LRC techniques which, when fired appropriately, can achieve phenomenal success. Different targets (i.e. tumours) require different guns and at this point in time, the target-specific guns are not yet deigned well enough and thus are accompanied with some risks to those around the target.

1.3 A New Need: A Universal Vascular Access System

As discussed in Section 1.1, all therapeutic agents must be delivered to a tumour via the circulatory network and all LRC techniques all rely on at least one form of vascular access. More specifically, regardless of the cancerous organ or histology, the one common denominator between all LRC techniques is the cannulation of the tumour’s feeding artery using a transcutaneous catheter. Where the LRC techniques vary is in the level of isolation achieved and the repeatability of the procedure. IHP can achieve a very high level of organ isolation through a highly surgically involved process which limits it as a “one-shot” treatment. Conversely, SIRT, TACE, and HAI have confined themselves to the platform of minimally invasiveness surgery to opt for user friendliness and organ selectivity rather than isolation

which has reduced resource requirements and allowed for repeat treatments. PHP and SAI fall in the middle of the spectrum as organ isolation and repeatability are both sought after but in doing so adds technical complexity and resources into the equation.

Being the mother of all inventions, it seems that necessity has long been demanding a solution for a vascular access system that:

a) facilitates adjustable organ isolation with
b) repeatable vascular access while
c) being scalable with the current clinical skillsets/specialities available

Such a solution, of a universal vascular access system (UVAS) that can be used to facilitate various LRC therapies could fast-track the assessment of various types of LRC modalities for different organs and histologies in the same way a simple IV cannula has been the platform for generations of chemotherapeutic agents and combinations to have been delivered through to assess their efficacy. In such a process, it would be inevitable that some LRC therapies will be realised as inferior while others prove to be the best option available and become first line treatment options. Either way, it may provide a pathway to equip clinicians in the field of oncology with an armamentarium of new treatment modalities and thus the development of such a UVAS is worth exploring.

1.4 Aims of Thesis

Given the potential benefits and breakthrough that may arise from the development of a UVAS specifically in the field of oncology, the aims of this thesis are three-fold:

1) to design and develop a prototype UVAS, and
2) to test its safety and feasibility:
    a) as a general vascular access, and
    b) in facilitating an LRC treatment
3) to assess the potential of the LRC technique developed with the UVAS

1.5 Thesis Structure & Method

Each chapter following this, apart from the discussion and conclusion, have been constructed to address each of the aims described above. The method used to generate the data for each of the chapters as well as a brief description of the data presented is provided in Table 1.2.

Table 1.2 – Methods used for each chapter/publication and the data generated.

Chapter	Publication	Method	Data/Content
2	None	Part 1: design review + system design Part 2: meta-analysis	Part 1: brief review of clinical requirements followed by the design and development of a UVAS to meet those requirements Part 2: identification of clinical critical risk through a meta-analysis of similar features/devices to that of the UVAS developed and risks to anticipate in its use.
3	I	Human clinical trial	Primary data generated from the use of the new UVAS in 5 patients for general vascular access form a 20 patient study.
4	II	Human clinical trial	Primary data generated from the use of the new UVAS in facilitating a new LRC technique for 10 patients with CRCLMs.
Discussion Part 1	None	Analysis of trial data	Analysis and discussion of trial outcomes, other relevant unpublished data, and future direction.
Discussion Part 2	III	Qualitative review	Discussion on the mechanisms behind the new LRC technique developed using the UVAS.
Conclusions	None	Conclusion	Conclusions from thesis

CHAPTER 2 – DESIGN & DEVELOPMENT OF A UVAS

The aim of the first part of this thesis was to design and develop a new UVAS that could be used as a platform for developing new LRC techniques or facilitating existing ones. Furthermore, a quantitative analysis of the most clinically significant risks of this newly developed UVAS was carried out so that such risks, their likelihoods, and mitigations procedures can be explored prior to its first-in-human studies and the clinicians and patients can be made aware of them.

2.1 Design Requirements of a UVAS

The clinical requirements of a UVAS for LRC treatments, as identified in Chapter 1, Section 1.3, can be deconstructed into the following design requirements:

a) Allows catheter access for the chemotherapy infusion, and
b) Can control inflow/outflow of the target organ/tumour to achieve "adjustable organ isolation", and
c) Above two functions are repeatable

These clinical requirements are shown diagrammatically in Figure 2.1a. Additionally, the existing technologies and solutions that satisfy these clinical requirements are shown in Figure 2.1b.

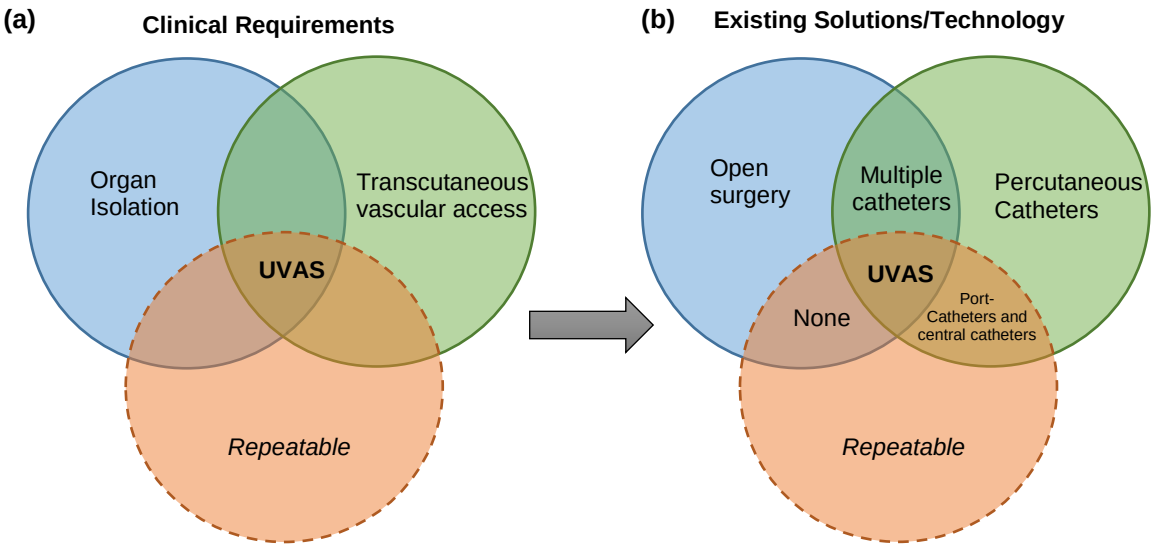

Figure 2.1 – Clinical requirements of LRC techniques (a) and the corresponding exiting technologies for each requirement (b). No solutions are shown for "repeatability" alone as it was too broad a requirement.

As shown in Figure 2.1, organ isolation alone can be achieved through open surgery such as that in IHP (see Chapter 1, Section 1.2.4). However, this is not a repeatable procedure and thus no existing repeatable organ isolation procedure currently exists. Alternatively, transcutaneous vascular access can be achieved through percutaneous catheters.

Technically, patients can be cannulated repeatedly with percutaneous catheters but the risk of repeated punctures accumulates with the frequency of access. Subdermally implanted port-catheters exist to fulfil this need for repeatable catheter access since they provide constant vascular access via a long-term indwelling catheter attached to a reservoir with a synthetic septum just beneath the skin for needle infusions (e.g. HAI). Alternatively, central catheters such as peripherally inserted central catheters (PICCs) and central venous catheters (CVCs) can remain in-situ for an extended period to provide longer term vascular access without the need for re-puncturing of the vessel. Finally, multiple catheters can be used to achieve organ isolation as well since balloon catheters can be used to obstruct blood flow and infusion catheters can be used to provide positive or negative flows within the vessels. This approach is most similar to the PHP technique except that PHP did not control the hepatic venous flow via the portal vein and thus the organ isolation achieved was very crude.

Most importantly, what is evident from Figure 2.1 is that a UVAS can be developed by combining the capabilities of a port-catheter and percutaneous catheters. Thus, the specific features of percutaneous catheters and port-catheters that allowed for the capabilities being sought after in a UVAS were identified as discussed in the following sections.

2.1.1 Percutaneous Catheters

Percutaneous catheters are flexible polymer tubes inserted directly into the lumen of the selected vessel (usually a vein) in order to gain access to the vascular system. They are frequently made from either polyurethane or silicone. They are typically introduced into the patient's vasculature via a process known as the Seldinger technique using a needle, guidewire, and introducer sheath as shown below in Figure 2.2.

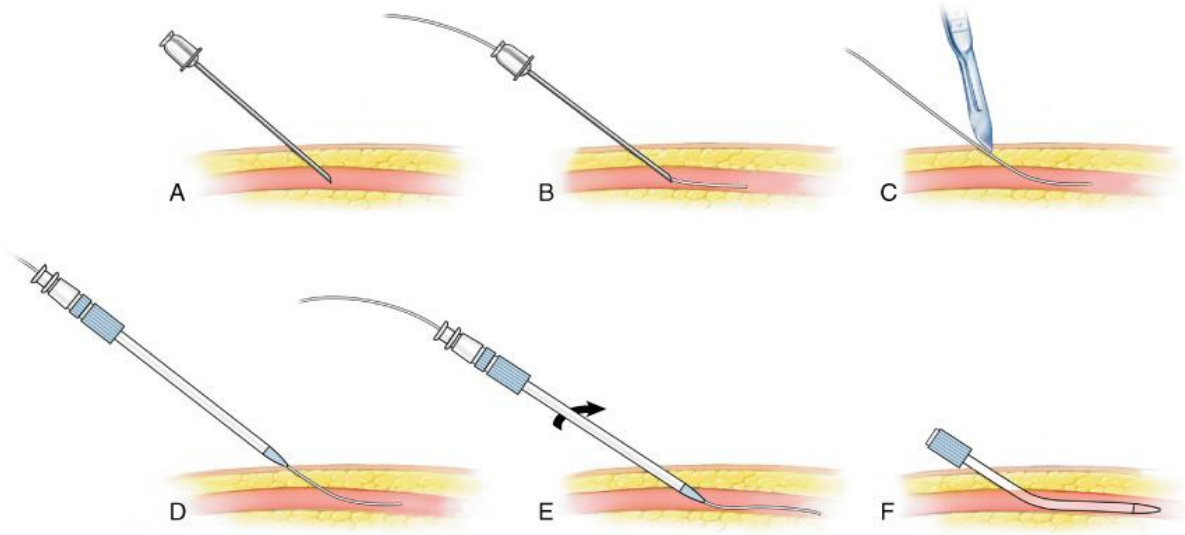

Figure 2.2 – Seldinger technique for percutaneous catheter sheath introduction [177]: the vessel is punctured by needle (a), a flexible guidewire is placed into the vessel through the needle (b), the needle is removed, the guidewire left in place, and the hole in the skin around the wire enlarged with a scalpel (c), the introducer sheath is placed over the guidewire (d) and advanced over the guidewire and into the vessel (e), and the dilator in the introducer sheath and guidewire removed while the sheath remains in the vessel (f). Catheters and guidewires can be advanced into the vessel through the introducer sheath from here on.

What was identified from this procedure is that if the introducer sheath can remain in-situ as shown in Figure 2.2f permanently or for a prolonged period, then repeatable transcutaneous vascular access can be achieved. Furthermore, if the introducer sheath was larger, it could accommodate for multiple catheters to facilitate organ isolation as the multiple catheters can be guided to the veins/arteries of the target organ to directly control the organ's blood flow. Thus, if both capabilities could be achieved, then a UVAS would be possible.

PICCs and CVCs are transcutaneous catheters that can remain in-situ for a prolonged period but if used for the purposes of organ isolation, multiple PICCS/CVCs would have to remain in-situ for the treatment period. The risks associated with such a setup would be unacceptable considering the entire length of each PICC/CVC must remain within the patient's vasculature and such a large surface area of foreign material from the catheter in contact with the patient's circulating blood is bound to lead to thrombotic reactions, catheter tip migration, and be a high infection risk from the multiple exit sites of the catheter. Conversely, this can be addressed by only having multiple introducer sheaths in-situ for a prolonged to provide long term access of transcutaneous catheters when required which would remove the need for multiple long term PICCs/CVCs. However, no introducer sheaths exist that can remain in-situ for the long term. Even if such an introducer sheaths were available, the requirement for multiple sheaths is still accompanied with the risk of infection associated with multiple entry sites into the vasculature. Furthermore, as introducer sheaths lack any type of fixation mechanism, it is unlikely it may remain in place for the long term without dislodgement or further penetration into the vessel which poses a high risk of vessel dissection.

The use of an introducer sheath capable of multiple catheters simultaneously is another option and one which does exist as shown in Figure 2.3 below. The system, known as the GORE® Dryseal Flex Introducer Sheath allows multiple catheters to be introduced through it simultaneously. However, like all other sheaths, it lacks any fixation mechanism and thus cannot remain in-situ for the longer term as needed. Due to the large profile of the device, dislodgement of such a sheath would result in significant and potentially fatal bleeding complications.

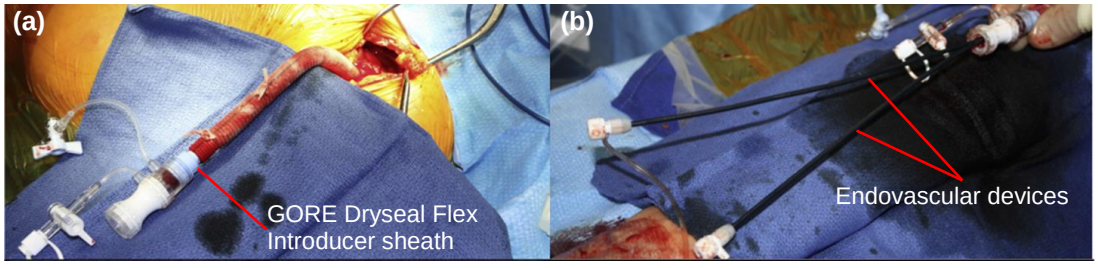

Figure 2.3 – The GORE® Dryseal Flex Introducer Sheath (a) with two endovascular devices being inserted through the seal in the hub (b) as shown in Wooster *et al* [178].

2.1.2 Port-Catheters

Port-catheters, as described previously and as shown in Figure 2.4, are percutaneously inserted catheters guided to a specific location. The non-endovascular end is attached to a reservoir with a pierceable septum. The entire system is implanted subcutaneously with the pierceable septum near the surface of the skin. The catheter and septum are typically silicone and the reservoir housing plastic or metallic.

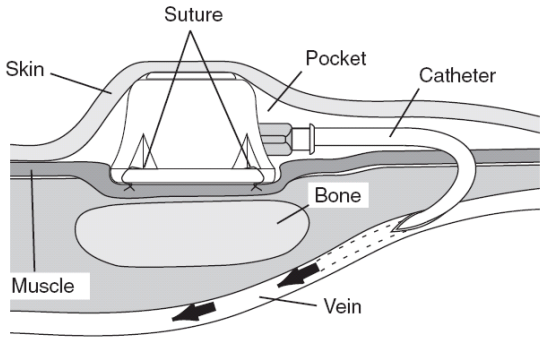

Figure 2.4 – Schematic of a port-catheter.

Port-catheters provide long-term vascular access but only in a single vessel and are only capable of infusions at low flow rates and cannot be used for flow obstruction. Thus, theoretically, even though multiple port-catheters can be implanted, and each catheter tip guided to the target an organ's arteries/veins, isolation cannot be achieved due to its inability to obstruct blood flow. Furthermore, such an implantation procedure of multiple devices would be surgically burdensome and the issue of accumulative risk of thrombosis and disturbance to the natural blood flow from the in-dwelling nature of the catheter remain. The key advantage offered by port-catheters is that the subdermal nature of the device greatly reduces the risks associated with infection compared to that of PICCs and CVCs that provide bacterial pathway directly into the patient's systemic bloodstream.

2.1.3 An Existing Solution – a Peripheral Access System

Based on the capabilities of transcutaneous catheters and port-catheters, it was identified that the most feasible solution for a UVAS was an introducer sheath that:

a) was large enough to accommodate multiple catheters, and
b) allows repeatable vascular access, and
c) possessed a fixation mechanism to prevent dislodgments, and
d) had no vessel-dwelling components when not in use.

A system with very similar features to this had already been developed by Lane *et al* [179] known as the peripheral access system (PAS). Although it was developed for a very different application to that of LRC, the functionality and capabilities described fulfilled the requirements described above. A schematic of the PAS and a photo of it in-situ is shown below in Figure 2.5.

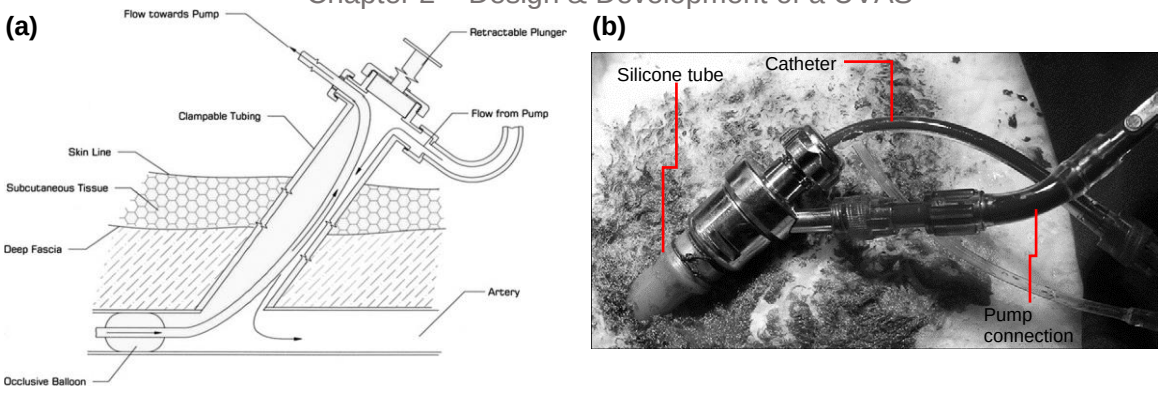

Figure 2.5 – Schematic of the PAS (a) and photo of it in use in an ovine model (b). Reproduced from Lane *et al* [179].

As can be seen, the PAS was a large silicone bore tube that was attached to a patient's artery via an end-to-end or end-to-side anastomosis tunnelled through the subcutaneous tissue transcutaneously to allow connection with extracorporeal components such as perfusion pumps. The system was developed and used to treat patients with critical limb ischemia. Such patients suffered from occlusive peripheral vascular disease of the limbs so extensive that amputation was the only treatment option available. The PAS was used to create an extracorporeal circuit to and from a major host artery, such as the common femoral artery, whereby the blood flow from the host artery was pumped back into the patient's limb at suprasystolic pressures using a centrifugal pump to promote collateral circulation to the limb promote angiogenesis [179].

The large bore nature of the PAS itself (21 Fr) was designed to allow for the amplified flow rates and pressures. While only a single balloon catheter was introduced through the PAS for this application, the size of the PAS would be more than capable of housing multiple catheters for LRC therapies. The PAS is like the GORE® Dryseal Flex Introducer Sheath but differs in length and fixation. The PAS is significantly shorter in length as it is designed to terminate at the vessel wall and therefore removes the risks associated with the presence of foreign materials dwelling within the artery/vessel itself. The PAS is also surgically affixed to the host vessel via an anastomosis mitigating the risks associated dislodgement of the device.

Provided the PAS could remain in-situ for the long term, it essentially fulfils all the design requirements of a UVAS that can be used for LRC therapies. As described in the previous sections, the PAS has combined the capabilities of port-catheters and percutaneous catheters, specifically introducer sheaths. Its implantable nature allows repeatable vascular access while its large profile allows for mulitcatheter access to allow for organ isolation.

Based on this review, it was decided that the design of the PAS could be used as a template for the development of a UVAS with minor modifications where necessary in order to ensure the safety and performance of the UVAS in the use of LRC.

2.2 Design of the UVAS

Using the PAS as a starting template, a UVAS was designed with the following key requirements in mind:

a) implantable and removable using standard vascular surgery techniques, and
b) functions in two different modes:
    a. when vascular access is required (Access Mode), and
    b. when vascular access is not required (Closed Mode).

"Vascular access" was defined as being able to host up to three 6Fr catheters simultaneously through the UVAS.

Based on these requirements and its intended use, the UVAS shown below in Figure 2.6 was designed and developed. The details of the design and the changes made from the PAS are described in detail in the subsections that follow.

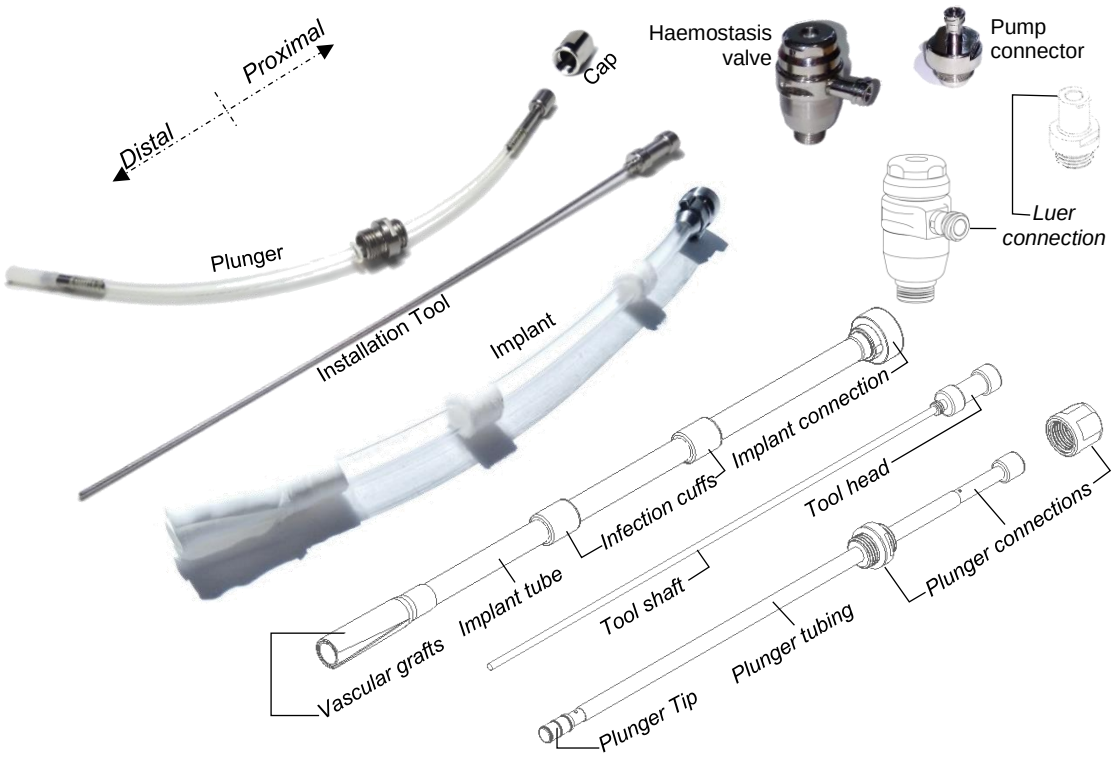

Figure 2.6 – Photos and schematics of the developed UVAS; subassemblies in normal text and individual components in italics.

2.2.1 The Implant

The implant design of the UVAS was kept very similar to that of the PAS. The key changes were the use of PVC (polyvinyl chloride) for the implant tube with a smaller profile (15 Fr), and the use of ePTFE (expanded polytetrafluoroethylene) for the dual vascular grafts. A smaller profile was chosen to reduce the size of the bacterial path for infection and allowed implantation onto smaller vessels. PVC was preferred over silicone after balancing the manufacturing limitations and security of the implant connections. Dual vascular grafts were used instead of a single graft as a safety precaution to prevent guidewire penetration through the anastomosis

as well as to provide extra fixation strength. ePTFE was used for the grafts due to their hemocompatibility as exhibited through its extensive use in vascular bypass grafts.

The Dacron infection cuffs used in the PAS were carried over to the UVAS. The cuffs prevent the migration of microorganisms through the subcutaneous tunnel the device exits through the body and also promotes tissue ingrowth to provide additional fixation strength.

Overall, the implant design allows for implantation and explantation using standard vascular surgery techniques. The implantation process is shown below in Figure 2.7 and is similar to that of the PAS.

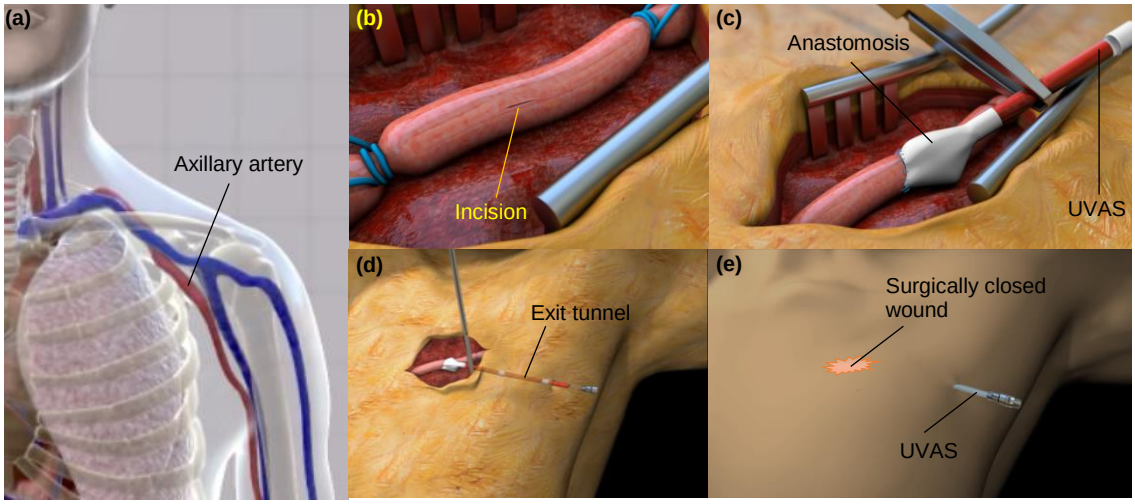

Figure 2.7 – Diagrammatic step-by-step process of the implantation procedure for the UVAS. A peripheral vessel such as the axillary artery (a) is mobilised, isolated with vessiloops and an incision made in the vessel wall (b). The dual vascular grafts of UVAS implant are then anastomosed onto the vessel wall, the tube clamped, and vessiloops removed (c). The UVAS can then be tunnelled through the subcutaneous tissue (d) after which the implant wound can be surgically closed and the UVAS closed with the plunger (e).

2.2.2 Haemostasis Valve & Pump Connector: Access Mode

The haemostasis valve of the UVAS was a newly designed and developed component while the pump connector was identical to the PAS apart from the connection being modified to fit the new implant connection. Both components were made from titanium and were designed to be used during the Access Mode. The use of the haemostasis valve during the Access Mode for LRC therapies is shown in Figure 2.8. The haemostasis valve houses a large pierceable seal that allows multiple catheters to be introduced through it via the Seldinger technique previously described.

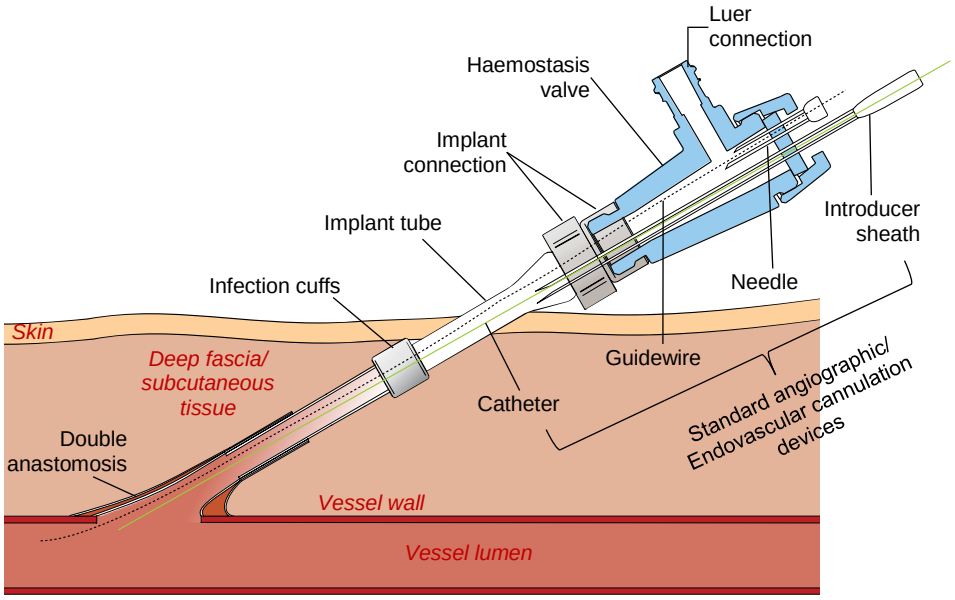

Figure 2.8 – Schematic of the UVAS in its Access Mode; the implant is connected to the haemostasis valve with a continuous flush line connected to the luer connection.

As shown in Figure 2.8, the Access Mode allows for multiple endovascular components such as catheters, guidewires, and introducer sheaths to be introduced into the patient's vasculature without the need for multiple vessel punctures. The valve can be detached and disposed of when access is not required, and a new valve used each time the access is required thus allowing repeatability. The luer connection of the haemostasis valve allows for the system to be connected to a saline drip so that there is a slow continuous flushing of the system thereby preventing a stagnant column of blood within the implant tube which may clot or thrombose.

The pump connector is not shown in Figure 2.8 but is similar to the haemostasis valve without the pierceable septum. Thus, like in the PAS, it is directly connected to a pump circuit line as needed.

2.2.3 Plunger & Installation Tool: Closed Mode

The plunger is used to close the lumen of the implant tube when the UVAS is not being used for vascular access. The system exists in this Closed Mode for most the time it is implanted. Similar to the PAS, the plunger's sole purpose is to provide a seal as close to the arterial wall as possible and prevent entry of blood into the lumen of the implant tube. The plunger used in the PAS was a stiff and solid design which is a cause for major discomfort to the patient during the period the system remains implanted. Additionally, it added the risk of the plunger being bent or broken due to the movements of the patient. This risk was mitigated in the UVAS by developing a flexible PVC tubing for the plunger system instead.

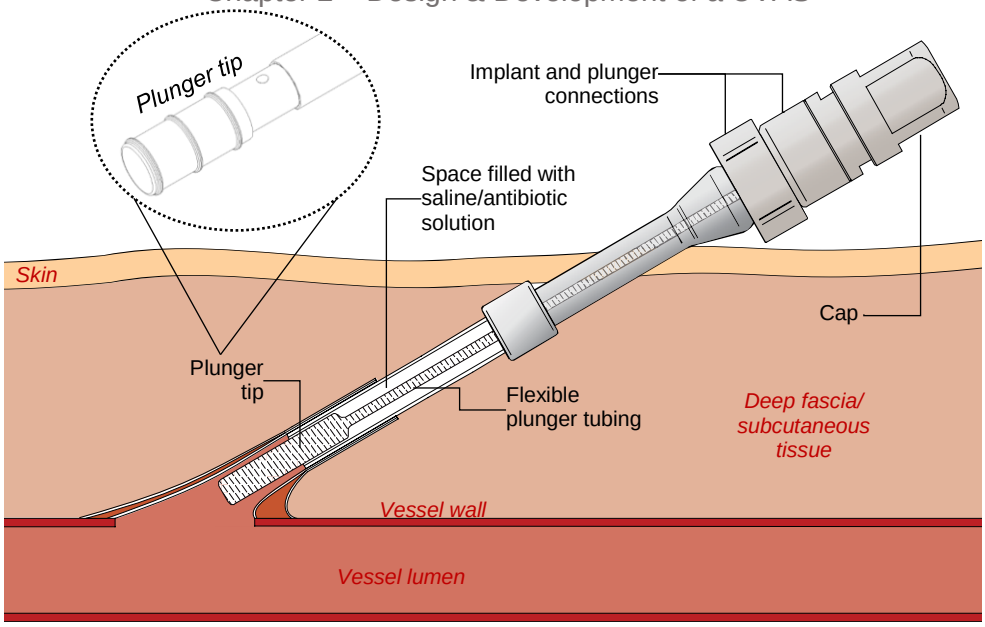

Figure 2.9 – Schematic of the UVAS in its Closed Mode; the plunger is inserted into the implant until the plunger tip is nearly level with the arterial wall and the region proximal to the tip backfilled with fluid.

The seal of the implant lumen was achieved by using a solid UHMWPE (ultrahigh molecular weight polyethylene) cylinder with three thin ribs slightly larger than the inner diameter of the implant lumen to create an interference fit. The use of multiple thin ribs ensured a seal while minimising the friction created by the seal. For the purposes of insertion, the plunger was stiffened using the installation tool which could be sheathed inside the plunger tubing. All elements of the installation tool and connection elements of the plunger were titanium. Upon complete insertion of the plunger, the installation tool can be retracted and discarded. Finally, the region behind the plunger tip can be flushed and filled with saline or antibiotic solution via the distal plunger connections before the cap is used to close the entire system as shown in Figure 2.9. The fluid behind the plunger tip provides an additional level of resistance to prevent blood from entering the implant lumen past the plunger tip. Finally, to prevent the build-up of thrombus at the plunger tip, clinicians using the UVAS were required to replace the plunger at least every 2 weeks.

2.2.4 Application to LRC Therapies

The final design of the UVAS that was developed and described above was deemed to have potential in facilitating LRC techniques based on the design concept as well as a similar proof of concept in the previous use of the PAS in an ovine model and humans [179]. Theoretically, the UVAS can be kept implanted in a peripheral artery in its Closed Mode for a prolonged period until treatment is required. In its Access Mode, the system can accommodate almost all the LRC techniques previously described in Chapter 1, Section 1.2.5. Its ability to accommodate for multiple catheters (Figure 2.10) makes it suitable to facilitate ASFI, CAI, SAI, TACE, SIRT, HAI, and PHP. It also allows for LRC techniques like IHP to be carried out through a minimally invasive procedure rather than through a laparotomy by using balloon catheters instead of external ligatures. Hence, this final design was used for the studies in this thesis

(Chapter 3 – 4) to assess the question of whether there is a role for such a system in facilitating LRC techniques.

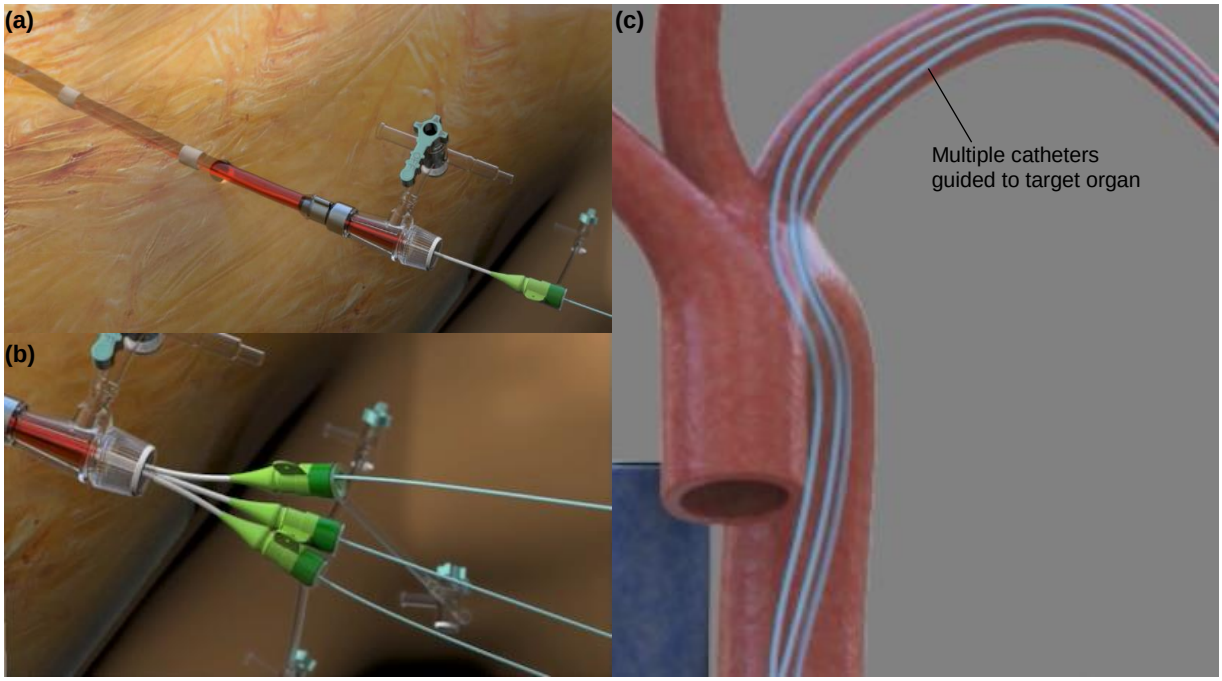

Figure 2.10 – Diagrammatic representation of the UVAS in its Access Mode accommodating a single or multiple catheters and introducers (a-b) which can be guided to the target organ/tumour to administer LRC treatments (c).

2.3 Identification of Critical Clinical Risks

Apart from the basic functionality requirements met and clinical risks that were mitigated through the design of the UVAS, the inherent residual risks involved in the use of the device needed to be considered. Therefore, it was necessary to identify the complications or side effects that may accompany the use of the UVAS so that the clinician can devise mitigation methods in advance or at least be forewarned.

To obtain a thorough understanding of the potential inherent risks of the use of the UVAS, a meta-analysis of clinical trial literature available for the use of devices or systems similar to the UVAS was carried out. The rationale, search process, and search results are described in the subsections below (Section 2.3.1-2.3.2) while the analysis of the data and the anticipated clinical risks of the UVAS are described in Sections 2.4 and 2.5 respectively.

2.3.1 Search Rationale

The assessment was focused on the features of the UVAS that may have a clinically significant impact on the safety and performance characteristics of the system. A specific emphasis was placed around the “features” of the UVAS as opposed to the device in its entirety since no published data exists for devices entirely equivalent to the UVAS other than the PAS which only reports data from 3 human subjects.

2.3.1.1 Features of the UVAS to Assess

The features of the UVAS that were deemed significant to warrant assessing, the safety and performance characteristics they may compromise, and the potential adverse events that could arise from such compromises were identified and listed below in Table 2.1.

Table 2.1 – Features of the UVAS that could potentially affect clinical safety and performance (S/P) characteristics and their associated potential adverse events.

No.	UVAS Features Potentially Affecting S/P Characteristics	S/P Characteristics Potentially Effected	Potential Adverse Event(s) from Compromised P/S Characteristic	S/P
1	Irregular arterial wall at anastomosis site	Haemodynamic Disturbance	Clot/emboli/stenosis	S
			Thrombosis	S
			Intimal hyperplasia	P
2	ePTFE Anastomosis	Graft/suture Integrity	Anastomotic leak leading to haemorrhage/haematoma	P
3	Transcutaneous tubing connected directly to artery	Contamination	Infection	S
4	Materials of the UVAS	Biocompatibility	Local/systemic side effects	P + S

2.3.1.2 Equivalent Feature Containing Devices for Literature Search

As mentioned earlier, due to the lack of clinical data other than from the PAS, the search for clinical literature was based on existing devices which possessed identical or very similar features to those of the UVAS features of interest listed in Table 2.1. The prerequisite for determining these "equivalent feature containing devices" (EFCD) were as follows:

a) The UVAS feature of interest must be a critical feature of the EFCD which has a direct effect upon the functionality of the EFCD, and
b) The application/mode of use of the specific feature being assessed in the EFCD must be similar or more demanding in terms of its safety and performance requirements compared to the UVAS feature.

Based on the above requirements, four devices were chosen as suitable EFCDs for literature assessment, and their suitability justified as shown in Table 2.2.

Table 2.2 – The four devices chosen as being suitable EFCDs to assess the critical features of the UVAS.

Equivalent Feature Containing Devices	Corresponding Features of the UVAS (refer to Table 2.1)	Justification of Suitability of EFCD
Synthetic ePTFE arteriovenous fistulas	1, 2, 4	- Graft material is identical to UVAS implant, - Surgical technique identical for end-to-side anastomoses with UVAS implant, - Flow disturbances introduced in the listed EFCDs have a more pronounced effect on performance/safety since the ePTFE acts as conduit rather than just as a fixation aid as in the UVAS implant
ePTFE peripheral bypass grafts		
Peripherally inserted central catheters (PICC)	3, 4, 5	- Transcutaneous tubing and infection cuffs are commonly used in both EFCDs as is in the UVAS implant, - These two EFCD subsets have a more pronounced effect on performance as they are vessel-dwelling (unlike the UVAS) which creates more haemodynamic disturbances. The reported rates of device occlusion would be higher than that to expect of the UVAS but provides a conservative starting point to define the risk of the UVAS.
Central venous catheter (CVC)		

2.3.2 Literature Search Protocol

Based on the above rationale, a literature search of clinical trials was carried out on the four EFCDs listed in Table 2.2. From the literature found, data related to adverse events that may be relevant to the corresponding UVAS feature of the EFCD (i.e. column 4 of Table 2.1) were collated as well as any other general performance and safety issues that may be relevant and applicable to the UVAS.

The literature search was carried out on PubMed using Mesh terms (Mesh), Title/Abstract terms (TAb), text words (TW), and document type (DT). The search terms used were the following: #1: humans (Mesh), #2: eptfe anastomosis (TAb), #3: ptfe anastomosis (TAb), #4: peripheral graft (TAb), #5: peripheral bypass (TAb), #6: bypass graft (TAb), #7: bypass (TAb), #8: arteriovenous fistula (TAb), #9: dialysis (TAb), #10: fistula (TAb), #11: PICC (TAb), #12: peripherally inserted central catheter (TAb), #13: CVC (TAb), #14: central venous catheter (TAb), #15: hickman (TAb), #16: peripheral (TW), #17: eptfe (TW), #18: ptfe (TW), #19: groshong (TW), #20: silicone (TW), #21: hickman (TW), #22: clinical trial (DT).

The search algorithms used were:

1. #1 AND (#2 or #3) AND #16 AND #22
2. #1 AND #4
3. #1 AND #5 AND #22
4. #1 AND #6 AND (#17 OR #18) AND #22
5. #1 AND #7 AND [16 AND (#17 OR #18)] AND #22
6. #1 AND #11 AND #22
7. #1 AND #12 AND #22
8. #1 AND #13 AND (#19 OR #20 OR #21) AND #22
9. #1 AND #14 AND (#19 OR #20 OR #21) AND #22
10. #1 AND #15 AND #22
11. #1 AND #8 AND (#17 OR 18) AND #22
12. #1 AND (#9 AND #10) AND (#17 OR 18) AND #22

2.3.2.1 Search Results & Filtering

As shown in Figure 2.11 a total of 375 results were obtained using the 12 search algorithms listed above. After 81 duplicate results were removed, the remaining 294 results were filtered based on the details provided in the abstract and or the title. All non-english studies and studies where their full texts were unavailable were excluded. The full texts for a total of 132 studies was read after which 64 were excluded with reason and a further 7 were excluded due to lack of comparable quantitative data. The remaining 61 studies were used for this assessment. The search queries, history, and each PMID number for the unique 294 studies found are provided in the Appendix A.

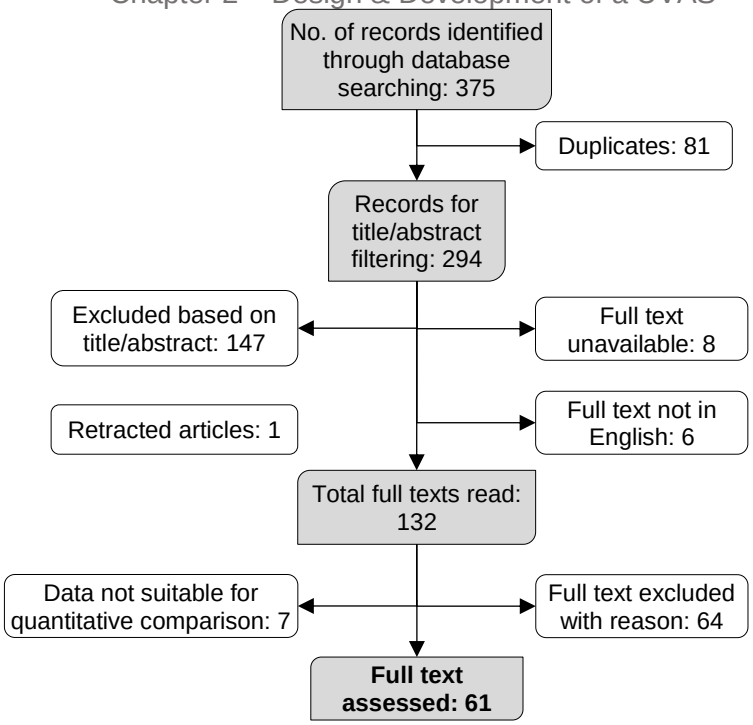

Figure 2.11 – Summary of literature filtering process.

2.4 Meta-Analysis of Data

The data obtained from the clinical literature for the 4 EFCDs are tabulated in the subsections below and their relevance to the safety and performance of the UVAS that need to be considered are discussed. The key complications identified during the assessment of this literature were related to infection and thrombosis. Of particular relevance were infections related to the surgical wound as well as the transcutaneous path provided by the UVAS, and thrombotic events related to the host artery that may eventuate due to the UVAS remaining in-situ for up to 3 months. A quantitative analysis was carried out on these two types of complications and assessed in detail. Other commonly reported complications within literature that were applicable to the UVAS, such as bleeding (haemorrhages and haematomas), pain, and catheter dislodgment were also noted and discussed qualitatively. “Prolonged implantation” was defined as an implantation period of the UVAS for up to 3 months to minimise the risks associated with a longer implantation period but to allow enough time for LRC therapies to be administered repeatedly.

2.4.1 Bypass Grafts and Arteriovenous Fistulas

The data extracted from the clinical trial literature found for bypass grafts and arteriovenous fistulas (AVFs) have been tabulated below in Table 2.3 and Table 2.4 respectively. Bypass grafts and AVFs are most similar to the internalised region of the UVAS implant; specifically, the anastomotic region of the implant. However, AVFs are regularly cannulated as they are typically used for haemodialysis and thus their reported infection rate must be interpreted with caution. Generally, the quantitative data sought after for analysis were complications related to patency and infection of the surgical wound. Patency was used as a symptomatic measure

of thrombosis. Other complications such as haemorrhage and haematomas were also reported but only assessed qualitatively.

Table 2.3 – Data extracted from the clinical literature found for bypass grafts.

Study	Underlying Disease/Medical History	Device Description	n	Results and Complications (% or n)								
				6-week patency	3-month patency	6-month patency	1-year patency	2-year patency	Infection	Haemorrhage	Haematoma	Others
Assadian & Eckstein, 2015 [180]	Claudication, rest pain and ulceration/localised gangrene	FUSION Vascular Graft (bilyaer graft with external ePTFE inner layer and outer polyester layer	117	-	-	-	85.6%	-	9	-	4	-
Lumsden & Morrissey, 2015 [181]	Claudication, rest pain and ulceration/localised gangrene	Standard ePTFE graft	100	-	-	70%	-	-	-	-	-	-
Lundgren, 2013 [182]	Critical limb ischemia	Below-knee bypass using PTFE graft with external support	167	-	-	-	54.9%	-	-	8	-	15
		Below-knee bypass graft using PTFE graft	162	-	-	-	41.5%	-	-	3	-	2
Lindholt, 2011 [183]	Intermittent claudication or chronically critical ischemia	Heparin-bonded PTFE graft	272	-	-	-	86.6%	-	-	-	-	-
		Same bypass with PTFE graft	274	-	-	-	79.9%	-	-	-	-	-
Hugh, 2009 [184]	Peripheral arterial disease	Heparin-bonded PTFE graft	87	-	-	-	80%	-	-	-	-	-
van Det, 2009 [185]	Claudication and critical ischemia	Femoro-popliteal bypass graft with ePTFE graft	114	-	-	-	-	64%	-	-	-	-
Matyas, 2008 [186]	Peripheral arterial disease	PTFE graft with external support	71	-	-	-	-	57.7%	5	-	-	3
		PTFE graft	38					63.2%				4
Solakovic, 2008 [187]	Claudication, rest pain and necrosis	PTFE/Dacron bypass graft	61	95.1%	91.8%	-	-	-	3	-	-	-
Bosiers, 2006 [188]	Peripheral vascular disease	Femoropopliteal bypass graft with Heparin-bonded ePTFE graft	86	-	-	-	82%	-	-	-	-	-
Kersting, 2004 [189]	Peripheral arterial disease	Infragenicular bypass with PTFE graft	50	-	82%	-	64%	-	-	-	-	-

Table 2.3 – Data extracted from the clinical literature found for bypass grafts.

Study	Underlying Disease/Medical History	Device Description	n	Results and Complications (% or n)								
				6-week patency	3-month patency	6-month patency	1-year patency	2-year patency	Infection	Haemorrhage	Haematoma	Others
		Same bypass with tapered PTFE graft	31	-	58%	-	50%	-	-	-	-	-
Ballotta, 2003 [190]	Claudication	PTFE graft	51	-	-	-	96%	-	-	2		1
Kreienberg, 2002 [191]	Limb-threatening ischemia	PTFE graft with a distal vein cuff	20	-	90%	83%	-	44%	1	-	-	2
Devine, 2001 [192]	Claudication, rest pain and ulceration	PTFE graft	103	-	-	-	41.7%	-	6	1	5	-
Burger, 2000 [193]	Severe claudication, rest pain and ulceration.	PTFE bypass	76	-	96.1%			92.1%	3	-	-	-
Johnson & Lee, 2000 [194]	Claudication, rest pain and tissue necrosis	Externally supported PTFE	265	-	-	86%	77%		3	-	-	6.1%
Johnson & Lee, 1999 [195]	Claudication, rest pain and tissue necrosis	PTFE	211	-	-	84.7%	77.2%		5	-	-	2
Tilanus, 1985 [196]	Intermittent claudication and rest pain	PTFE graft	24	92%	-	-	-	-	4	1	-	-
		Total no.	**2380**	80†	206†	493†	1360†	217†	39	15	9	-
		Sum of relevant study populations		85	238	596	1876	319	986	507	220	-
		Overall Mean Rate:		94.2%*	86.6%*	82.8%*	72.5%*	67.9%*	4.0%‡	3.0%‡	4.1%‡	-

‡ *Overall mean rate = Total no. of events / sum of relevant study populations*
† *Total no. events = overall mean rate × sum of relevant study populations*
* *Overall mean rate = Sum [study incidence rate x study population] / (sum of relevant study populations)*

Table 2.4 – Data extracted from the clinical literature found for arteriovenous fistulas.

Study	Underlying Disease/Medical History	Device Description	n	Follow-up (FU) Period	Results and Complications (% or n)									
					2-month patency	3-month patency	4-month patency	6-month patency	26-week patency	1-year patency	Infection	Haemorrhage	Haematoma	Others
Glickman, 2015 [197]	End-stage renal disease	Arteriovenous graft using Gore Accuseal Vascular Graft	138	12 months	-	-	-	-	-	35%	14	6	6	-
Ravari, 2010 [198]	End-stage renal disease	PTFE graft	25	2 years	-	-	-	-	-	64%	2	-	-	-
Ko, 2009 [199]	End-stage renal disease	ePTFE graft	42	3 years	-	80%	-	85%	-	-	-	-	-	-
		Cuffed ePTFE graft	47		-	90%	-	59%	-	-	-	-	-	-
Keuter, 2008 [200]	End-stage renal failure	PTFE loop	53	12 months	-	52%	-	45%	-	22%	6	-	1	-
Madden, 2005 [201]	Chronic renal failure	PTFE graft	27	16 months	-	58%	-	39%	-	-	-	-	-	-
Rooijens, 2005 [202]	Chronic renal failure	Radial-cephalic AVF with PTFE graft	84	1 year	-	-	-	-	-	52%	11	3	11	-
van Tongeren, 2003 [203]	End-stage renal disease	AVF with PTFE graft	33	12 months	-	-	-	-	-	51%	2	-	-	-
Lemson, 2002 [204]	Renal failure requiring haemodialysis	ePTFE graft	20	Mean FU: 1.25 years	-	-	-	-	35%	-	-	-	-	-
		ePTFE graft with venous cuff	20	Mean FU: 1.58 years	-	-	-	-	29%	-	-	-	-	-
Bacchini, 2001 [205]	Chronic renal failure	PTFE graft	53	N/A	-	-	-	-	-	16.7%	-	-	-	-
Biancari, 2001 [206]	Critical limb ischemia	PTFE graft only	9	2 years	-	-	-	-	-	19%	-	-	-	-
		Adjuvant AVF added	12		-	-	-	-	-	67%	-	-	-	-
Lemson, 2000 [207]	Renal failure requiring haemodialysis	Thin-walled stretch PTFE graft	61	Median FU: 1.4 years and FU Range: 7 days – 3.4 years	-	-	-	69%	-	-	1	1	-	-
		Thin-walled stretch PTFE graft with venous cuff	59	Median FU: 1.3 years and FU Range: 0 days – 3.6 years	-	-	-	62%	-	-	5	8	-	-
Cinat, 1999 [208]	Chronic renal failure	AVF with ePTFE graft	86	12 months	-	-	-	-	-	43%	10	-	-	1
Hamsho, 1999 [209]	Critical limb ischemia	ePTFE graft with adjuvant AVF	48	2 years	-	88%	-	69%	-	55%	-	-	-	-
		ePTFE graft only	41		-	65%	-	55%	-	53%	-	-	-	-

Table 2.4 – Data extracted from the clinical literature found for arteriovenous fistulas.

Study	Underlying Disease/Medical History	Device Description	n	Follow-up (FU) Period	Results and Complications (% or n)									
					2-month patency	3-month patency	4-month patency	6-month patency	26-week patency	1-year patency	Infection	Haemorrhage	Haematoma	Others
Hakim & Scott, 1997 [210]	Chronic renal failure	AVF with ePTFE graft	79	40 months	-	95%	-	88%	-	71%		-	-	-
Kaufman, 1997 [211]	Chronic renal failure	AVF with Goretex ePTFE graft	64	2 years	73%	-	69%	-	-	-	9	-	-	-
		AVF with Impra ePTFE graft	65		88%	-	70%	-	-	-		-	-	-
Jaffers, 1991 [212]	Patients requiring immediate dialysis	AVF with PTFE graft	25	N/A	-	-	-	-	-		3		3	
		Total no.	**1091**	**-**	25†	74†	39†	155†	27†	364†	63	18	21	-
		Sum of relevant study populations			129	337	129	457	40	661	693	342	300	-
		Overall Mean Rate:			80.6%*	78.1%*	69.5%*	66.0%*	32.0%*	44.9%	9.1%‡	5.3%‡	7.0%‡	-

‡ *Overall mean rate = Total no. of events / sum of relevant study populations*
† *Total no. events = overall mean rate × sum of relevant study populations*
* *Overall mean rate = Sum [study incidence rate x study population] / (sum of relevant study populations)*

2.4.1.1 Relevance to Safety & Performance of the UVAS

Infection

As summarised in Table 2.3 and Table 2.4, the likelihood of patients experiencing infection in the studies for bypass grafts and AVFs were 4.0% and 9.1% respectively.

A slightly higher occurrence of infection was reported for AVFs. This could be attributed to the fact this value encompassed both the peri-operative infections and events of infection due to continuous cannulation through the AVF when being used for haemodialysis. For example, Glickman *et al* [197] reported 11 out of 14 events of infection were caused by cannulation of the AVF while only 3 were related to implantation of the AVFs itself. For infectious risks associated with cannulation, it was deemed that the data from CVCs and PICC lines (Section 2.4.2) are more applicable to the UVAS due to their transcutaneous nature. Thus, infection rates reported from AVF clinical trials were considered irrelevant. The repeated percutaneous cannulation of AVFs confounds the data relating to infection that could be applicable to the UVAS.

Most of the infections reported by the bypass graft studies were wound infections caused by peri-operative conditions at the time of implantation of the grafts [180,186,187,192,193,196]. Hence, the reported occurrence rate of 4% provides an estimation of the risk of infection that can be anticipated from the implantation surgical wound of the UVAS. However, it must be noted that this estimate encompasses data dating back as far as 1985 which happened to report the highest infection rate of 17% [196]. With the improvements made in surgical techniques and peri-operative conditions since then, the actual probability of infection of the surgical wound experienced with the UVAS should be much lower than what was experienced with bypass grafts.

Thrombosis and Stenosis

A quantitative measure of the risk of thrombosis and stenosis that could be expected for the UVAS during its 3-month implantation period was made by reviewing the primary patency rates experienced with AVFs and bypass grafts. The primary patency rate was defined as the proportion of the study population remaining with a patent AVF or bypass graft that did not yet require intervention. This was considered as a good starting point for an appropriate measure of the thrombotic/stenotic risks of the UVAS since patency loss is mostly caused by successive events of intimal hyperplasia (resulting from vessel injury), stenosis, blood flow disruption and thrombosis. Although separate events of thrombosis and stenosis have been made in some studies, most of these events were limited to a specific phase of the treatment (early thrombosis) or event (complete graft failure due to thrombosis before allowing intervention). Simply put, patency loss was a measurable symptomatic outcome of the vascular aberrations (thrombosis/stenosis) caused by the implantation of the AVF or bypass graft and thus are directly applicable to the implantation of the UVAS.

The reviewed literature reported primary patency at various time points. Primary patency recorded at 3-month time points which were most similar to the implantation time specified for the UVAS were 86.6% and 78.1 % for bypass grafts and AVFs respectively. As these data sets were only available in a smaller volume, further reference to the results available for 6-month patency rates was useful although this was double the implantation time as what is anticipated for the UVAS. The primary patency rates for bypass grafts and AVFs at this time point were 82.8% and 66% respectively. Furthermore, a more detailed review of the studies revealed that the above results included studies conducted under special conditions and hence higher patency rates could have been achieved. For example, the dataset from Kersting *et al* [189] included the results of tapered PTFE grafts which were associated with significantly poorer primary patency rates compared to the normal non-tapered PTFE grafts (50% vs 82%). Excluding such data increases the mean primary patency rate at 3 months to 90.8%. This estimate is more applicable to the UVAS implant as it utilises a normal cylindrical ePTFE grafts instead of a tapered graft.

Additionally, the significantly lower rates of patency reported for AVFs compared to bypass grafts are also not applicable to the UVAS. It was observable from the literature that the majority of thrombotic complications associated with AVFs develop at the venous anastomosis or in the efferent vein rather than at the afferent atrial anastomosis [213-215]. Not only is the UVAS intended to be implanted only on an artery, when in-situ, it is most similar to the afferent arterial anastomosis. Thus, the primary patency results obtained from the literature for AVFs were not assessed any further.

The distinction between the modes of operation of bypass grafts and the UVAS is worth noting to assess the accuracy of the 90.8% patency rate observed in bypass grafts. Firstly, for majority of the time it is implanted, the UVAS is maintained in its closed configuration with the plunger which acts as a seal to prevent the entry of blood into the lumen of the UVAS implant. Additionally, as discussed for CVCs and PICCs (Section 2.4.2.1), the UVAS implant lumen can be flushed with heparinised saline or antibiotic solution so clotting of any remaining blood or blood that may somehow leak past the plunger tip is highly unlikely. Furthermore, if clots were to form in the UVAS implant tube, it poses no clinical risk as the retraction of the plunger would draw out these clots as well.

Secondly, the likelihood of thrombosis in the UVAS implant's anastomotic region and or lumen of the host artery is another risk location to consider. Thrombosis induced via haemodynamic disturbance in arteries are typically due to the discontinuities caused by divergent and convergent flow characteristics introduced to the blood flow path at the afferent (proximal) and efferent (distal) anastomoses of the bypass graft respectively. By comparison, arterial flow disturbances introduced via the UVAS are significantly less since there are no new divergent

or convergent flow paths introduced due to the plunger preventing any blood entry into the implant.

Thirdly, another contributor to thrombotic events around the anastomosis to consider is the sequence of intimal hyperplasia, stenosis and consequently blood flow disturbance. It has been reported in several studies that of the two anastomotic ends of bypass grafts, the primary site of intimal hyperplasia development was around the efferent anastomosis [216--218]. This is unsurprising considering that convergent flow paths are more unnatural for arteries and natural arterial bifurcations typically facilitate divergent blood flow. As the anastomosis of the UVAS implant is comparable to the afferent side of bypass grafts, a considerable proportion of thrombotic events due to intimal hyperplasia reported for bypass grafts are most probably inapplicable to the UVAS.

Lastly, the compliance mismatch between the host artery and the implanted synthetic graft is another contributing factor for intimal hyperplasia [219] that should be considered. The blood contacting surface area of the UVAS is significantly lower than that of synthetic AVFs and bypass grafts by comparison. Thus, while compliance mismatch still exists between the arterial wall and the synthetic materials of the UVAS Implant, the degree to which it contributes to intimal hyperplasia is markedly reduced due to the reduction of their blood flow contacting surface area. This reduction in the risk of intimal hyperplasia during the use of the UVAS is also likely to reduce the likelihood of thrombosis throughout the 3-month period compared to that of bypass grafts and AVFs.

In summary, from the review of clinical literature found for bypass grafts and AVFs, it was estimated that there is a 90.8% chance no symptomatic event will eventuate as a result of thrombosis/stenosis that may or may not be caused by the use of the UVAS for up to 3 months. However, the differences between the modes of operation between the UVAS and bypass grafts described above suggest that this risk estimation is likely to be overly conservative. A more accurate estimate of the 3-month patency/non-thrombotic event rate to expect for the UVAS would be much higher than 90.8% considering the implant does not act as a conduit for blood flow, the flow disturbances introduced by the implant are significantly reduced, and the contributing factors for intimal hyperplasia have been minimised.

Other Noteworthy Complications

Besides infection and thrombosis/stenosis, there were several other complications that were commonly reported for bypass grafts and AVFs, haemorrhage and haematoma. As summarised in Table 2.3 and Table 2.4, the occurrence rate for haemorrhage reported for AVFs and bypass grafts were 5.3% and 3.0% respectively. The haematoma occurrence rates were reported to be 7.0% and 4.1% for AVFs and bypass grafts respectively. The higher

occurrence rate found with AVFs could be attributed to the injuries caused by percutaneous cannulation into the AVFs. Nonetheless, these are complications that are commonly encountered during surgical procedures and since the UVAS requires surgical implantation and explanation, these risk estimates are to be anticipated postoperatively after device implantation and explantation.

2.4.2 CVCs and PICCS

The data extracted from the clinical literature found for CVCs and PICCs have been tabulated below in Table 2.5 and Table 2.6 respectively. CVCs and PICC lines are most similar to the UVAS implant in regard to the transcutaneous nature in which they act as an externalised vascular access device. However, CVCs are more akin to the UVAS implant as they have a larger and longer subcutaneous skin tunnel for the device to exit through. Additionally, the size of the UVAS implant will in most cases prohibit its ability to be implanted as peripherally as where PICC lines can enter/exit. As a result, due to a much smaller layer of skin/subcutaneous tissue, exit site infections were not commonly observed or reported in PICC lines as seen by the difference between Table 2.5 and Table 2.6. Generally, the quantitative data of relevance to the UVAS were complications related to infection and catheter occlusion. The “Overall Total” of incidence rates per 1,000 catheter days was calculated as a range; the lower range was the sum of “Total Events” divided by the sum of all “Total Days” and multiplied by 1000, and the upper range the average of all “per/1000 days” results. Other complications observed to be commonly reported throughout the studies were also noted but were used as qualitative data only.

Table 2.5 – Data extracted from the clinical literature found for CVCs.

Study	Indication, underlying disease, or CVC use	Arms	CYC Type	n	Mean Dwell Time (days) ‡	Total Days	Infection				Catheter Occlusion		Other
							Bloodstream		Exit site/tunnel				
							Total Events	Per 1000/days	Total Events	Per 1000/days	Total Events	Per 1000/days	
Worth, 2014 [220]	Leukaemia	a	H	43	34†	1917	5	2.6	4	1.51*	2	0.75*	-
		b	H	42	27†	1381	4	2.9	4	1.81*	0	0	-
Rinke, 2012 [221]	Paediatric oncology	-	H	-	-	5376	14	2.6	-	-	-	-	-
Hunst, 2011 [222]	Trauma & neurological	-	-	263	-	2122*	13	6.0	-	-	-	-	-
Larsen, 201 [223]	Paediatric Cancer & nutrition	-	-	51	260.5*	13283	51	3.84	-	-	-	-	-
Cesaro, 2009 [224]	Paediatric Cancer	a	BH	102	-	75249	9	0.24	14	0.38	41	1.11	Dislocation 0.54/1000 days
		b	BH	101	-		24	0.62	10	0.26	83	2.16	Dislocation 0.47/1000 days
Darouiche, 2005 [225]	Cardiopulmonary + neurological	-	Si	160	43.7 ± 37.9	6993*	10	1.43	-	-	-	-	-
Moller, 2005 [226]	Leukaemia	a	H	42	149.1*	6264	12	1.92	4*	0.64	-	-	-
		b	H	40	177.7*	7107	30	4.22	12*	1.69	-	-	-
Lange, 1997 [227]	Paediatric Cancer & nutrition	-	BH	348	167.5*	58290	184	3.16*	22	0.38*	-	-	-
Paz-Fumagalli, 1997 [228]	Antibiotics	-	-	13	10.8 (1-37)	140	1	7.14*	-	-	-	-	-
Mueller, 1992 [229]	Leukaemia & solid tumour	-	H	46	230 (6-948)	10592	17*	1.6	-	-	7*	0.7	Thrombosis 0.5/1000
Peugues, 1992 [230]	Cancer & antibiotics	-	H	47	-	3889*	7	1.8	-	-	-	-	-
Overall Total				**1298**	**146.7 to 149.5**	**192,603**	**381**	**1.98 to 2.86**	**70**	**0.36 – 0.95**	**133**	**0.69 – 0.94**	-

** calculated based on other data reported using equations [mean dwell time = Total days / n] OR [per/1000 days = total events x 1000 / total days]*
† median
‡ reported as mean +/- standard deviation OR mean (range)
BH = broviac-hickman line; H = hickman line; Si = silicone

Table 2.6 – Data extracted from the clinical literature found for PICCs.

Study	Indication, underlying disease, or PICC use	Arms	PICC Type	n	Mean Dwell Time (days) ‡	Total Days	Infection		Catheter Occlusion		Other
							Total Events	Per/1000 days	Total Events	Per/1000 days	
Webster, 2017 [231]	Antibiotics		Si	100	12.2 (2-42)	1109	2	1.8	-	-	-
Bertoglio, 2016 [232]	Cancer	-	PCU	291	-	6315*	6	0.95	7	1.11*	DVT and Dislodgement
Patel, 2014 [233]	Chemotherapy	-	-	36	115†	3627*	0	0	4	1.10*	Pain & partial dislodgements
Pittiruti, 2014 [234]	Chemotherapy	-	PU	61 60 59	56 ± 23 64 ± 31 65 ± 27	9901	0	0	6	0.61*	Thrombosis + PICC rupture
Alport, 2012 [235]	Nutrition	-	PU	25 28	23.3 ± 3.1 23.3 ± 3.3	1556	6	3.86*	8	5.14*	Skin fixation failure in 9 patients
Johnston, 2012 [236]	ICU	-	-	101	0.5-21.9*	1020	-	-	78	76	-
Rinke, 2012 [221]	Paediatric oncology	-	-	-	-	1411	1	0.71	-	-	-
Gunst, 2011 [225]	Trauma & neurological	-	-	37	-	454*	1	2.2	-	-	-
Ong, 2010 [237]	Infection, chemotherapy, nutrition	-	Si	194	23.3 (1-168)	4524	12	2.65	23	5.08*	6 dislodgements
		-	PU	198	27.8 (2-245)	5494	4	0.73	19	3.46*	5 dislodgements
Trerotola, 2010 [238]	Nutrition + antibiotics	-	-	50	17.1 ± 12.6	854	0	0	1	1.17*	-
Yamada, 2010 [239]	Cancer patients	-	-	38	23 ± 22	874*	0	0	3	3.43*	3 patients oedema of upper extremity
Periard, 2008 [240]	Antibiotics + nutrition	-	Si	31	9.4 ± 6.6	583*	1	1.72	-	-	Thrombosis was main AE observed
Yamamoto, 2002 [241]	Antibiotics & nutrition	a	-	85	35 ± 38	2934	8	2.73*	4	1.36*	12 dislodgements
		b	-	85	33 ± 42	2796	1	0.36*	3	1.07*	10 dislodgements
Hoffer, 2001 [242]	Infection & trauma	a	Si	48	37.5 (1-306)	1802	2	1.11*	7	3.88*	5 patients - accidental removal
		b	PU	52	35.1 (1-211)	1980	0	0.00*	5	2.53*	
Cowl, 2000 [243]	Pancreatitis + cancer	a b	Si	51 51	9.6 (1-36) 10.8 (2-27)	1015	5	4.9	8	7.88*	Thrombophlebitis
Hoffer, 1999 [244]	Infection & trauma	a	PU	180	33 (1-211)	6047	6	0.99*	6	0.99*	25 patients - accidental removal
		b	PU	182	35 (1-236)	6411	13	2.03*	13	2.03*	
Miller & Deitrick, 1997 [245]	Infection, GI disorders, cancer	-	Si	602	24 (1-353)	15314	4	0.26*	29	1.89*	Pain, swelling in 24 patients

Table 2.6 – Data extracted from the clinical literature found for PICCs.

Study	Indication, underlying disease, or PICC use	Arms	PICC Type	n	Mean Dwell Time (days) ‡	Total Days	Infection		Catheter Occlusion		Other
							Total Events	Per/1000 days	Total Events	Per/1000 days	
Paz-Fumagalli, 1997 [228]	Antibiotics	-	Si	38	48 (7-260)	1447	3	2.07*	-	-	-
Ng, 1996 [246]	Infection & nutrition	-	Si	89	19.1 ± 19	1666	1	0.6	3	1.80*	-
Loughran & Borzatta, 1995 [247]	Infection	-	-	289	NR	2506	2	0.80*	0	0	-
Overall Total				**2726**	**29.1 to 30.0**	**81640**	**78**	**0.96 to 1.32**	**227**	**2.78 to 6.34**	**-**

** calculated based on other data reported using equations [mean dwell time = Total days / n] OR [per/1000 days = total events x 1000 / total days]*
† median
‡ reported as mean +/- standard deviation OR mean (range)
BH = broviac-hickman line; H = hickman line; Si = silicone

2.4.2.1 Relevance to Safety & Performance of the UVAS

Infection

With data from over 192,000 catheter days and 1,298 CVCs, it was apparent that that infection via the CVC was the most commonly reported complication with an overall incidence rate ranging from 1.98 to 2.86 bloodstream infections per 1,000 catheter days. The overall reported infection rate for PICC lines were much lower than CVCs (0.96-1.32 cases per 1,000 day) which was probably due to the vast difference between the average dwell times between the two catheters (PICCs: 29.1-30.0 days; CVCs: 146.7-149.5 days). Hence, it was more appropriate to consider the infection rate reported by CVCs as it most likely provided a more reasonable estimation of the risk of infection that should be anticipated with the use of the UVAS implant for up to 3 months. However, this risk was conservative as it incorporated a study which treated patients with predisposed infectious risks (i.e. patients requiring antibiotics via the CVC) using the smallest sample size (n = 13) and total catheter days (140) to report an overly high incidence rate of 7.14 bloodstream infections per 1,000 catheter days [221]. Excluding the data reported from this study reduced the overall bloodstream infection incidence rate to 1.98-2.54 cases per 1,000 days. This would translate to approximately 0.17-0.22 bloodstream infection events every 3 months the UVAS is implanted. In addition, it can be seen from the overall mean dwell times of CVCs that they are used for almost 5 months; an extra 2 more months than that anticipated for the UVAS. One of the larger studies, reporting results over 13,000 catheter days [223], reported a higher bloodstream infection rate of 3.84 cases per 1,000 days. However, the mean CVC dwell time was 260.5 days which is almost 3 times as long as what the UVAS is anticipated to be implanted for. It was shown in a few of the studies, and shown to be statistically significant, that there was a direct correlation between infection incidence rates and the implantation time. Hence, it is quite possible that most of the infectious events reported in the studies occurred at least after the mean/median catheter dwell time was reached. This was already an additional 2 months longer than the UVAS's expected implantation time. This is especially relevant as the reported dwell times are only means and one of the studies that had reported a range showed CVC use for up to 948 days [229].

Finally, the studies also provided guidance for risk control measures that may be incorporated into the use and maintenance of the UVAS implant throughout its 3-month use period. The two studies by Cesaro and Møller demonstrated the role of patient education and heparinised saline [224,226]. The former demonstrated that the use of a heparinised saline flush through the lumen of the CVCs (Arm a) greatly reduced the incidence rates of infection compared to a normal saline flush (Arm b) and this was shown to be statistically significant. Additionally, the study by Møller demonstrated the effectiveness of patient education in general CVC and wound management (Arm a) to reduce the likelihood of infections and was shown to be statistically significant when compared against a control group who were not educated on these techniques (Arm b). These mitigations are both features that should be implemented with the UVAS via the information supplied to the clinician and patients. Specifically, clinicians

should be made aware of the need to use heparinised saline (or antibiotic solution) to backfill the UVAS implant lumen during its Closed Mode, and nursing staff/clinicians to advise the patient on wound management. Unlike CVCs, the patient is not required to maintain the UVAS device itself which reduces room for inadvertent errors and may possibly increase patient compliance in regular wound maintenance.

Infection of the exit site of the CVC or the skin tunnel was also commonly reported and is a risk that is directly applicable to the UVAS implant. The overall rate of exit site/tunnel infection was 0.36-0.95 cases per 1,000 catheter days (or 0.03 – 0.09 cases per 90 days). It should be noted though that the UVAS implant has two Dacron infection cuffs whereas most CVCs have a single infection cuff. Nonetheless, this is still an event to be aware of during use of the UVAS for up to 3 months. Unlike a bloodstream infection which led to the removal of the CVCs, infection of the exit site and skin tunnel was treated as a minor event in most studies and was typically addressed via cleaning of the exit wound, changing wound dressings, and general topical treatments if necessary. These mitigations should be incorporated into the wound and dressing management requirements specified in the UVAS's information to clinicians.

In summary, the overall infection rates calculated based on the data reported from the 11 CVC trials are most probably higher that the infection rate that should be expected of the UVAS. Thus, it is reasonable to define the risk of an infectious event arising from the use of the UVAS as being less than 0.17-0.22 events per 90 days of use given that:

a) the infection rate was shown to be correlated to the number of catheter days and the studies on average reported an extra 2 months use of CVCs compared to the expected implantation time of the UVAS,
b) heparinised saline was shown to be effective in reducing infection rates, and
c) patient education of general wound/dressing management was shown to be effective in reducing infection rates.

Catheter Occlusion and Thrombosis

Catheter occlusion and thrombosis of the vein (deep and or superficial) were observed in CVCs and PICC lines but were more prevalent in PICC lines with an overall reported rate of 2.78-6.34 catheter occlusions per 1,000 catheter days. This was most probably due to the smaller profile (and hence smaller luminal diameter) of PICC lines compared to CVCs. Since PICCs enter/exit from veins that are more peripheral and are smaller compared to the veins from which CVCs enter/exit, the higher occlusion rates reported were not unusual. This occlusion rate, however, is not applicable to the UVAS since the UVAS is sealed with a plunger that is regularly changed. If the tubing of the UVAS implant were to become coagulated/occluded at all, the retraction of the plunger upon each replacement would withdraw all the thrombus/occluding material out of the tube. The backfilled heparinised saline should also

prevent any thrombus/clot/occlusion within this tubing as well. Any thrombus build-up on the arterial lumen-facing surface of the plunger tip would also be withdrawn with the plunger as well.

Regarding the thrombotic events that were commonly observed in most studies (not quantitatively assessed in Table 2.5 and Table 2.6), they are not directly applicable to the UVAS since the total surface area and nature of contact of CVCs and PICCs are significantly different. Both CVCs and PICCs are venous in-dwelling devices whereas the UVAS terminates at the arterial wall. Therefore, CVCs and PICCs create haemodynamic disturbances to the natural blood flow along the entire length they reside within the vein. Conversely, the UVAS only imparts haemodynamic disturbances at the region of the arterial wall where the ePTFE anastomosis/graft and the plunger tip resides. Thus, it was more appropriate to define the risk of thrombosis based on the analysis of bypass grafts and synthetic AVFs (Section 2.4.1.1) rather than from CVCs and PICCs.

In summary, although the risks of catheter occlusion from CVCs/PICCs could be defined, they were not truly applicable to the UVAS. At best, they suggested that some minor thrombus build-up on the tip of the arterial lumen-facing surface of the UVAS plunger is to be expected upon changes of the plunger during the 3-month period the UVAS implant is used. The risk concerning the likelihood of thrombosis within the host artery due to the presence of the UVAS was previously defined by using the data from bypass grafts and synthetic AVFs (Section 2.4.1.1).

Other Noteworthy Complications

Several other complications that were commonly reported for CVCs and PICCS were catheter dislodgements, pain and swelling of the exit site, and phlebitis. Dislodgements of CVCs and PICCs are not truly applicable to the UVAS since CVCs and PICCs are not “fixed” in place. They rely on the skin/subcutaneous tunnel to hold the device in place. Some CVCs/PICCs are sutured onto the skin at the exit site but as this is an additional break to the skin layer which can become an infectious risk, most clinicians forego such a fixation. Consequently, especially in PICCs where the exit site is typically in the peripheral upper limb where there is frequent movement, it is prone to a higher risk of dislodgement. The UVAS implant, due to its size, is most likely be implanted on a larger peripheral artery (e.g. common femoral or axillary artery) where there is less movement. The direct suturing of the UVAS implant to the host artery itself via an anastomosis in addition to the infection cuffs which both promote subcutaneous tissue in-growth is expected to provide additional anchorage and fixation to the UVAS implant. Thus, based upon the design, the UVAS was expected to be highly resistant to any form of dislodgement.

The events of phlebitis in CVCs and PICCs probably directly related to the above issue of dislodgement. Any movement of the CVCs/PICCs lines results in direct abrasion between the venous wall and the outer surface of the shaft of the catheter. Such movements or micromovements that irritate the venous wall could prompt an inflammatory response of the venous wall. Such abrasive movements of the UVAS implant upon the arterial wall are not possible as the implant is directly sutured onto the artery as described previously. Hence, the incidence rates of phlebitis were not assessed in this analysis nor expected with the use of the UVAS.

Finally, the events of pain and swelling around the exit site/tunnel reported from the CVC/PICC studies are risks applicable to the UVAS implant throughout its 3-month use period. Such events were generally al grade I-II adverse events (when graded) and were typically treated (if at all) with standard oral analgesia. This provided guidance on a how such events can be managed with the use of the UVAS.

2.4.3 Overall Summary of Data

The key complications of concern to the UVAS during its 3-month implantation period were deemed to be infection and thrombosis of the host artery. Other complications such as pain, haemorrhage, and haematoma were also noted. The estimated risk of all these complications that could potentially arise from the use of the UVAS described in in detail previously (Sections 2.4.1-2.4.2) are summarised in the subsections below.

2.4.3.1 Bypass Grafts and Arteriovenous Fistulas

The clinical data reviewed for arteriovenous fistulas (AVFs) and bypass grafts has been summarised in Table 2.7. The risk that particularly stood out from the rest of the complications that can be expected for the UVAS was the risk of thrombosis within the host artery. The most accurate estimate obtained from the data was a 3-month patency of 90.8% for bypass grafts (refer to Section 2.4.1.1 for why the patency rates from AVFs were not applicable). This translated to a patency-loss rate of 9.2% and the best measure of the thrombosis rate to except for the UVAS implant throughout its 3-month implantation period. As discussed previously, the actual arterial thrombosis rate to expect for the UVAS implant will be significantly less than this as the system does not act as a conduit for blood flow, it imparts less blood flow disturbances within the host vessel, and the contributing factors for intimal hyperplasia have been minimised. Surgical wound infection, haematoma, and haemorrhage rates of 4.0%, 3.0% and 4.1% should be expected for the UVAS Implant throughout its 3-month period.

Table 2.7 – Summary of the reviewed clinical data for bypass grafts and AVFs.

Device	Reviewed Data	No. of Trials Reviewed	Total no. of devices reviewed	Average Result/ Probability of Occurrence
Bypass Graft (total no. of reviewed studies: 17)	**3-month patency:**	4	207	90.8%
	6-month patency:	4	596	82.8%
	Surgical wound infection:	9	986	4.0%
	Haemorrhage:	4	507	3.0%
	Haematoma	2	220	4.1%
Arteriovenous Fistula (total no. of reviewed studies: 16)	**3-month patency:**	5	337	78.1%
	6-month patency:	6	457	66.0%
	Surgical wound infection:	9	693	9.1%
	Haemorrhage:	3	342	5.3%
	Haematoma	4	300	7.0%

2.4.3.2 CVCs and PICCs

A summary of the data reported throughout the clinical trials for CVCs and PICCs are summarised below in Table 2.8. The most significant risk considered was the likelihood of a bloodstream infection arising from the use of the UVAS for the 3-month use period. A conservative estimation of this risks predicted rates of less than 0.17 - 0.22 events per 90 days the device is implanted (i.e. less than 1 event for every 4-5 UVAS used assuming each patient is implanted with the system for up to 3-months). The use of heparinised saline and educating the patient on wound management and wound dressing techniques is also expected to significantly lower this risk. The other risks of exit site/skin tunnel infection and catheter occlusion were also analysed but deemed to be insignificant and manageable as they were typically grade I-II events.

Table 2.8 – Summary of the reviewed clinical data for CVCs and PICCs.

Data	CVCs	PICCs
Total no. of studies analysed	11	20
Total no. of catheters from all studies	1,298	2,726
Sum of total catheter days	192,603	81,640
Average dwell time (days)	146.7 – 149.5	29.1 – 30.0
Complications	-	-
Bloodstream Infections (Total)	381	78
Bloodstream Infections (per/1000 days)	1.98 – 2.86	0.96 – 1.32
AVAS Implant: Bloodstream Infections (per/90 days)	< 0.17 – 0.22	0.09 – 0.12
Exit site/tunnel Infections (Total)	70	-
Exit site/tunnel Infections (per/1000 days)	0.36 – 0.95	-
AVAS Implant: Exit site/tunnel Infections (per/90 days)	0.03 – 0.09	-
Catheter Occlusion (Total)	133	227
Catheter Occlusion (per/1000 days)	0.69 – 0.94	2.78 – 6.34
AVAS Implant: Catheter Occlusion (per/90 days)	N/Ap	N/Ap
Other complications commonly reported	Dislocation and thrombosis	Dislocation, pain/swelling, haemorrhage, phlebitis, and thrombosis

2.5 Anticipated Clinical Risks of the UVAS

Based on the meta-analysis of the complications found for the EFCDs that could extend to specific features of the UVAS, the clinical risks that could potentially be associated with the use of the UVAS were identified and their likelihood estimated. Where possible, recommended

mitigation procedures for clinicians and patients for each risk were also established. This information has been summarised below in Table 2.9.

Table 2.9 – Clinical risks that should be anticipated with the use of the UVAS, their likelihoods, and treatment/preventative measures.

Expected Clinical Risk	Likelihood	Suggested Mitigations
Thrombosis	< 9.2%	Use heparinised saline in UVAS implant and regular changing of plunger.
Infection (implant surgical wound)	4%	Aseptic techniques during implant/explant and wound management.
Infection (exit tunnel)	3-9%	Aseptic techniques during implant/explant and wound management.
Infection (blood stream)	< 17-22%	Reduce implant days when possible, use heparinised saline in UVAS implant, patient education about wound management.
Haemorrhage	3%	None
Haematoma	4.1%	None
Pain and swelling	-	Oral analgesia if needed.

2.6 Chapter Conclusions

A new universal vascular access system has been designed based on the clinical requirements identified as being critical in facilitating LRC treatments. In theory, the developed design is capable of fulfilling the requirements stipulated (Section 2.1) but requires verification through clinical use as assessed in the Chapters that follow.

Based on the developed design and the meta-analysis of devices containing equivalent features to that of the system designed was performed. From the data analysed through the meta-analysis, the potential risks of the complications that could be associated with the use of the developed UVAS were identified, defined, and potential mitigation procedures developed where possible. This information must be communicated to the clinicians and patients participating in the studies carried out as part of this thesis. More importantly, without existing safety data in humans for this newly designed UVAS and the anticipated bloodstream infection rate of 17-22%, it was decided that the implantation period of the UVAS be reduced to a 1 month period as opposed to the preferred implantation time of 3 months during these initial human studies. Such a short implantation period imposes restrictions on the LRC therapies that can be developed but is in the interest of safety. However, depending on the safety profile established of the system from this thesis, the implantation period could be reviewed to determine whether a 3-month (or longer) implantation period is suitable.

CHAPTER 3 – THE UVAS AS A GENERAL VASCULAR ACCESS DEVICE

The safety and functionality of the UVAS developed in Chapter 2 required verification prior to its use as a platform for LRC therapies. Due to the similarities between the UVAS and the PAS device from which it was based upon, it was more appropriate to use the UVAS in the same setting as that of which was used for the PAS.

Therefore, the UVAS was first tested in patients suffering from critical limb ischemia (CLI) that had exhausted all other forms of therapy and were bound for amputation of the affected limb.

3.1 Aims

The aim of this chapter was to assess the safety and viability of the UVAS as an implantable vascular access device when used to provide very basic vascular access in the form of a blood flow conduit to and from the patient's peripheral arteries in a similar manner to how the PAS had previously been used.

3.2 Method

3.2.1 Trial Background and Design

The UVAS was designed and the development completed only after a new clinical trial for the PAS had already begun. The clinical trial was based on the original method of hyperperfusion developed in the initial ovine model and three patients treated in 2008 which were described by Lane *et al* [179]. Fifteen patients had already been treated with the PAS using this method before the UVAS was developed.

A clinical trial for the use of the UVAS for hypertensive extracorporeal limb perfusion (HELP) in patients with CLI was granted approval by the institutional human research ethics committee (Appendix B) and registered as on the national clinical trials registry (Appendix C). The primary endpoint of the trial was delayed limb amputation and aimed to enrol and treat 40 patients. However, due to challenges in patient recruitment, the trial was terminated prematurely after only 5 patients were treated with the UVAS. Therefore, Article I reports the results from the initial 15 patients treated with the PAS as well as the 5 patients treated with the UVAS. It should be noted that as Article I reports on the outcomes of the HELP treatment itself and no distinction has been made between the PAS and the UVAS. The former acronym, PAS, is used to refer to both systems in the Article.

3.2.2 Treatment Setup

The HELP technique varied slightly depending on whether it was used with the UVAS or the PAS. From the initial 15 patients treated, it was noted that high flows to the rotary pump were difficult to achieve due to the small lumen of the balloon catheter used obstruct the common

femoral artery. Thus, while higher flows back into the common femoral artery could have been achieved by the pump, the balloon catheter was a limiting factor. The rationale behind the HELP treatment was that higher flow rates would induce greater flow through the collateral flow to bypass the arteries obstructed from the peripheral vascular disease and therefore flow rates into the host artery would correlate with delayed amputation. Hence it was believed that using two UVAS devices implanted onto the same host artery with an obstruction made in the artery between the two anastomoses of the devices would allow greater flow rates to and from the centrifugal pump as the lumen of the UVAS devices were significantly larger than that of the balloon catheter used in the PAS setup. The PAS setup used in the first 15 patients has been described in the original PAS study [179] and in Figure 2.5, Section 2.1.3 of Chapter 2. The setup using the two UVAS devices is shown in Fig. 1 of Article I.

3.3 Results

The patient demographics, perfusion flows and pressure, clinical outcomes, and device and post-procedural complications have all been reported in Article I.

3.3.1 Results Specific to the UVAS

Of the twenty patients treated with HELP, a total of 10 UVAS devices were implanted in 5 patients on the common femoral artery. A total number of 22 successful connections to the centrifugal pump were made with the UVAS. A total of 11 hyperperfusion sessions were administered through the dual UVAS setup over a total of over an implantation of 15 days per patient on average (75 total implantation days). No device related serious adverse events were reported with the 10 UVAS devices used in the trial. More specific data relevant to the UVAS not reported in Article I are discussed later in Chapter 5.

3.3.2 Recruitment

The study failed to recruit all 40 patients as intended. This was due to an inability to fund the entire trial as the hospital costs exceeding the initial budgeted costs. The excessive costs were primarily a result of the requirement for the treatment to be administered in the intensive care unit throughout the entire stay of the patient. While this has implications upon the viability and feasibility of the treatment for this specific patient cohort, it has no influence upon the conclusions made pertaining to the UVAS's ability to function as an implantable vascular access device.

3.4 Article I

Khin NY, Dijkstra ML, Huckson M, et al. Hypertensive extracorporeal limb perfusion for critical limb ischemia. Journal of Vascular Surgery. 58(5), 1244–1253 (2013). DOI: http://dx.doi.org/10.1016/j.jvs.2013.05.004

Attached after Section 3.5.

The conference abstract reporting on some results for the external perivascular pressurised cuff used around the segment of the common femoral artery between the two UVAS devices is attached after the Article.

3.5 Chapter Conclusion

It was concluded in Article I that further research was required to assess the viability of using hyperperfusion to promote collateral circulation in patients with CLI to avoid major amputation of the affected limb. The data reported in Article I as well as the unreported but relevant data specific to the UVAS described above in Section 3.3.1 is evidence of the ability of the UVAS to:

(a) facilitate high flow rates and pressures, and
(b) function safely as an implantable transcutaneous conduit for blood flow into and out of the patient's host vessel.

Therefore, it was concluded that the UVAS was a safe and viable implantable vascular access system. Furthermore, it was concluded that although HELP was not a LRC technique, the arterial isolation of the limb achieved using the UVAS demonstrated its potential to serve as a platform for organ isolation techniques that could be utilised for LRC techniques.

Hypertensive extracorporeal limb perfusion for critical limb ischemia

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Objective: **This article reports the early results in humans of hypertensive extracorporeal limb perfusion (HELP) technology in the prevention of major limb amputation due to ischemia. The short-term aim was to dilate pre-existing collateral channels, and the long-term aim was to stimulate remodeling and new collateral development by increasing endothelial shear stress and wall tension.**
Methods: **This study evaluated 20 patients with critical limb ischemia who were treated with HELP. These patients had no other option but major amputation, as determined by at least two vascular surgeons. The arterial circulation to the ischemic limb was isolated from the systemic circulation by the use of an endoluminal balloon catheter in seven patients and by an implantable, inflatable, occlusive cuff in 13. The limbs were hyperperfused through the peripheral access system with an extracorporeal pump, producing a minimally pulsatile waveform at 200% to 300% of the mean arterial pressure. This was performed repeatedly in sessions of 24 to 36 hours, up to a maximum of 74 hours. The primary end point was avoidance of major amputation. The secondary end points were the clinical improvements in rest pain, ulcer healing, and claudication distance. Patients were analyzed and reviewed using infrared thermography and ultrasound imaging parameters of the limb.**
Results: **Given adequate arterial access, 39 of 40 connections developed flows four to eight times those supplied to the limb by the normal cardiac output. A progressive decrease was noted in peripheral resistance. All patients developed a pain-free, warm foot or hand while on the pump in the short-term. In the longer term at a mean of 22 months (range, 12-54 months), eight of 20 patients (40%) had avoided major amputation and four more had a delay in amputation of an average of 4 months. The ankle-brachial index changed from 0.04 ± 0.07 (range, 0.00-0.94) to 0.63 ± 0.39 (*t*-test, $P < .05$). Bleeding, infection, premature cessation of the treatment, and poor patient selection resulted in the failures. There were two short-term unrelated deaths that occurred at 1 and 3 months follow-up.**
Conclusions: **The collateral circulation of ischemic limbs can be augmented and regulated by a connection to an extracorporeal centrifugal pump, with isolation from the systemic circulation provided by balloons and with an access system providing repeatable pump connections. Major amputation may be avoided in selected cases. (J Vasc Surg 2013;58:1244-53.)**

Despite advances in endovascular and open surgical techniques for critical limb ischemia (CLI), lower limb amputation, particularly for patients with diabetes, remains a continuing challenge. The escalating costs to the health care system, particularly with repeat vascular procedures, demand a greater scientific effort to achieve a simpler and longer lasting solution.[1] Collateral circulation can be augmented and regulated by connection to an extracorporeal pump at suprasystolic pressures with isolation of the ischemic segment from the systemic circulation by the use of occlusive balloons.[2] This has been achieved by the design of a specific arterial access system to withstand the suprasystolic pressures and high flows similar to those obtained in physiologic peak exercise. In the longer-term, high levels of fluid shear stress (FSS) have been shown to be the moulding force in arteriogenesis.[3] The molecular factors mediating gene upregulation of vascular proliferation have been associated with changes of blood flow at the endothelial interface, particularly via monocyte chemoattractant protein 1.[4-7] Inherent in the concept is that new collaterals may be less susceptible to atheromatous degeneration than the native vessels.

The aims of this article are to:

1. Demonstrate the structure and function of the peripheral access system (PAS) in humans;
2. Report the results in 20 patients for whom major limb amputation was the only option available for their CLI;
3. Report the obstacles encountered in the developmental phase of the technique; and

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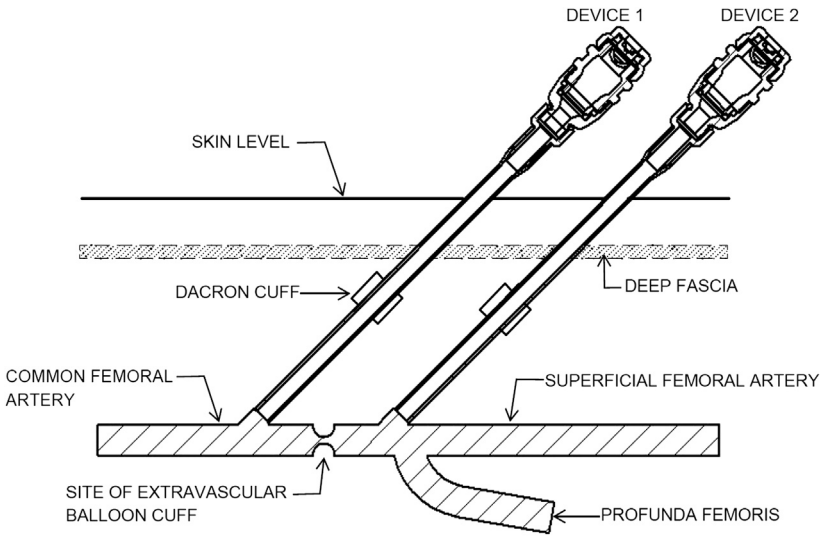

Fig 1. Schematic shows two peripheral access systems (PASs) with isolation from the systemic circulation via an inflatable extravascular balloon. *Device 1* is the inflow from the heart to the pump. *Device 2* takes blood from the pump to the isolated limb at high pressures and flows.

4. Demonstrate the device modifications undertaken to maximize the safety and efficacy of the technique.

METHODS

Patients. A cohort of 20 patients were evaluated for this report. Procedures in five patients were approved by the Northern Sydney and Central Coast Human Research Ethics Committee (NSCC HREC) New South Wales, Australia (Protocol 0501-021M). Ten patients were treated under the Special Access Scheme by the Therapeutic Goods Administration Australia, following a similar clinical protocol. Five more patients were part of a registered clinical trial (ACTRN1261000011 8000) approved by the NSCC HREC (Protocol 0911 -306M).

All 20 patients were destined for major amputation. Multiple vascular procedures (mean, 4.5) had failed in 19 of the 20 patients. Six patients had diabetes, and one had essential thrombocytosis.

The inclusion criteria were:

1. All patients had end-stage CLI with any or all of rest pain, tissue loss, or gangrene;
2. All standard operative and endovascular measures had been exhausted;
3. All had been offered amputation by at least one other vascular surgeon;
4. All had high-quality angiography at a small-vessel level with all three calf vessels occluded and no reconstitution distally;
5. There was clinical and angiographic evidence of good inflow.

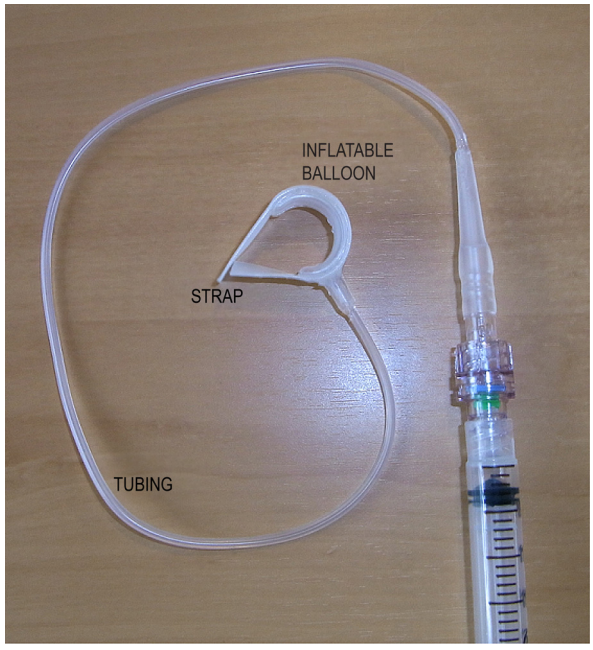

Fig 2. The inflatable balloon is placed circumferentially around the arterial inflow to isolate the ischemic limb. The diameter is fixed via sutures through the strap. The tube is passed externally for manual inflation and deflation as required.

The exclusion criteria were:

1. General cardiac, respiratory, and renal disease of significance;
2. Mental instability;

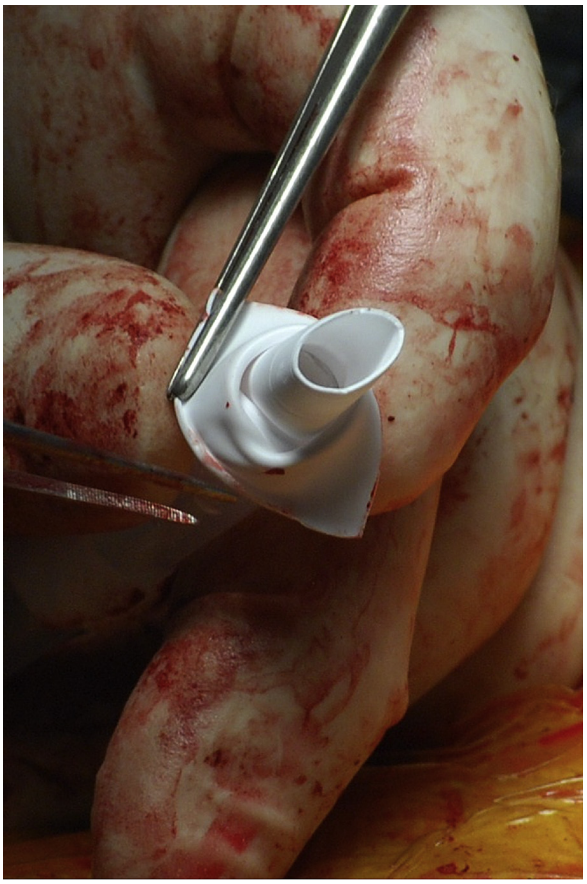

Fig 3. A polytetrafluoroethylene adventitia "skirt" is placed around the primary anastomosis to minimize bleeding. This is fixed to the adventitia by a continuous PROLENE suture (Ethicon, Somerville, NJ) after appropriate fashioning.

3. Uncontrolled infective/necrotic areas in the affected limb;
4. Vessels not capable of access and anastomosis;
5. Significant myonecrosis.

Materials. All PASs were supplied by AllVascular Pty Ltd (St. Leonards, New South Wales, Australia). The initial approach was to apply a single arterial access system using an endoluminal occlusion and saphenous system.[2] The preferred approach is shown in Fig 1, with inflow and outflow tubes with an extravascular inflatable cuff (Fig 2) between the two access systems. This setup facilitated for high pressure and large volume flows >500 mL/min, particularly where the superficial femoral artery was occluded.

The pumping system used was a Maquet Jostra ROTAFLOW centrifugal pump system (Hirrlingen, Germany). The thermographic imaging system used was the NECTH7800N Thermotracer (Tokyo, Japan). The thermographic assessment methodology has been described previously.[2]

OPERATIVE METHOD

Implantation. A standard surgical approach to the arteries of the groin or axilla was used. A standard

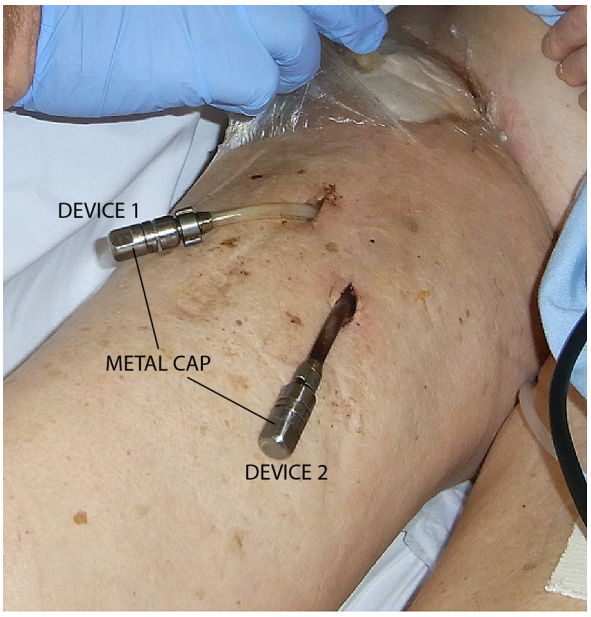

Fig 4. Two flexible access systems in situ in the right common femoral artery with exit cutaneous foramina. The extravascular balloon cuff is not visible. The metal caps lock the internal plunger in position to avoid patient tampering. *Device 1* is the inflow from the heart to the pump. *Device 2* takes blood from the pump to the isolated limb at high pressures and flows.

end-to-side anastomosis was performed, and a further polytetrafluoroethylene "skirt" was sutured around the primary anastomosis to minimize bleeding (Fig 3). These sutures were from the skirt to the adventitia of the host vessels and were circumferential around the primary anastomosis. The input and output PASs have their own individual cutaneous exit (Fig 4) with a hairy Dacron (DuPont, Wilmington, Del) cuff between each PAS and the subcutaneous tissue (Fig 1). The anastomoses were situated at least 1.5 cm apart to allow an inflatable occluder cuff to be implanted in between the two PASs. The inflatable occluder cuff has its own individual subcutaneous exit for its inflation port. The wounds were closed. Extracorporeal pumping was performed in the intensive care unit, and the patients were transferred to the standard ward accommodation after disconnection.

Explantation. Explantation occurred 5 to 18 days after implantation. The access wounds were reopened. After the vessels were controlled, the PASs and occlusive devices were removed, and no foreign bodies were left in situ. The arteriotomies were directly closed or patched with autogenous material. The wounds were irrigated with antibiotic solution and closed with drainage. Intravenous antibiotics were given according to the swab results from the ischemic ulcers during implantation, pump sessions, and explantation. Oral equivalents were given between these times.

Hematologic assessments. Serial full blood counts, biochemistry, and plasma free hemoglobin, D-dimer, and

creatinine phosphokinase were measured daily. During the pumping sessions, careful monitoring of the heparin anticoagulation was afforded by using an hourly measurement of the activated clotting time, which was kept between 160 and 180 seconds. Antiplatelet agents (clopidogrel) were used routinely to inhibit clot formation. Between pumping sessions, the patients had a standard anticoagulation with heparin as a continuous infusion, with a partial thromboplastin time of twice controls, or subcutaneous enoxaparin (1.25 mg/kg) if there was no intravenous access.

Pumping method. Connection can be at the time of the original operation or delayed to allow better hemostasis at the anastomosis. After pump connection, the infusion pressures are established at 300% of the mean arterial pressure (MAP; maximum of 300 mm Hg due to device limits). The MAP was monitored with an arterial catheter in the patient's lower arm. Pump pressure, suction pressure blood flows, and MAP were recorded every 30 minutes.

Baseline and subsequent progress evaluation. When the pump is connected and flow established, the pump revolutions are decreased so that the measured pressure through the system equals the MAP. The measured flow is the baseline. The initial resistance of the system and the limb can be calculated. The inflow pressures were increased to produce a clinically warm, painless limb. As time progresses, the flows increase and the pressures required decrease. When the revolutions are decreased so that the pressures are once again close to the MAP, then the resistance that the heart will face without the pump can be assessed.

When the flows are four to eight times the baseline flow, the pump can be disconnected. The indications for reconnection are recurrence of ischemic symptoms or a decrease in the thermographic and or ultrasound baseline parameters with poor monophasic flow. When the pump is reconnected, a low initial peripheral resistance indicates a good long-term prognosis and early disconnection.

Concerns about infection in recent wounds with transcutaneous foreign material connected to arteries are factors that promote early removal of the devices.

RESULTS

The pumping hours, mean flow rates, peak flows (mL/min), mean perfusion pressures, and peak pressures (mm Hg) are summarized in Table I. Peak pressures of up to 366 mm Hg (mean ± standard deviation: 240.6 ± 53.77 mm Hg) creating flows up to 1400 mL/min (694 ± 265.6 mL/min) were delivered safely to 19 of 20 ischemic limbs. One of the 20 limbs could not be perfused due to an unrecognized iliac dissection that prohibited adequate inflow. The overall mean perfusion pressure was 191 ± 39.54 mm Hg delivering 523 ± 195.4 mL/min through collaterals. These values were four to eight times the flow provided to the limb by the normal cardiac output. Patient outcomes at a mean of 12 months (range, 1-29 months) are summarized in Table II. While being treated with the pump, 18 of 19 patients (94.74%) were noted to have an essentially pain-free, well-perfused, warm extremity. The single exception was the patient with underestimated myonecrosis at the onset.

Limbs were intact in eight of the 19 who had adequate pump connection. Four patients had a mean delay of 4 months in the below-knee amputation, despite significant improvement in their initial post-treatment clinical picture (Table II). Seven of the eight patients had healed ulcers at the latest follow-up, with improvement in the single residual, who had a neurogenic component. Creatinine phosphokinase was elevated in two patients, one with pre-existing myonecrosis and the other with inadvertent balloon deflation due to a transient increase in distal ischemia. There was no evidence of hemolysis, with normal plasma free hemoglobin, or platelet activation due to pump-induced negative pressures. There were two long-term deaths >30 days. Complications are summarized in Table III.

Pain assessment documented in the visual analog score changed from 9.0 ± 0.1 to 1.1 ± 0.3 (*t*-test, $P < .05$) at the latest follow-up. The ankle-brachial index (ABI) measurements changed from 0.04 ± 0.07 (range, 0.0-0.94) to 0.63 ± 0.39 (*t*-test, $P < .05$) at the latest follow-up visit. Claudication was improved, but this variable was confounded by other factors such as coexisting osteoarthritis in the knee or contralateral peripheral vascular disease (Table II). The thermographic imaging system showed noticeable differences between the treated limb and the untreated limbs in 19 of the 20 patients while connected to the pump and in 11 patients at the last follow-up visit.

A typical pumping sequence for 24 hours is shown in Fig 5. There is progressive improvement in flow, with a decreasing pressure required to produce that flow. Fig 6 shows the relationship between pressure and flow at different times and at various pump speeds. The gradient is the peripheral resistance. When the limbs are initially hyperperfused, the resistance is high. If the pump speed is varied so that the inflow pressure equates to the MAP, the flow through the limb is almost undetectable. Because the pressure-flow relationship is a straight line, retrograde projection of the resistance gives an estimate of the resistance of the pump itself and its associated tubing at the MAP. In this example, the initial flow rates are <200 mL/min, but the flow rate at the MAP is ~450 mL/min after 24 hours of pumping. This has been designated as short-term pressure-induced collateral dilatation (PICD). The temporary PICD, along with the pressure gradient, results in an increased flow rated during the pumping session and thus greater FSS at the arterial walls to stimulate arteriogenesis and collateral growth. When the pump is initially reconnected after 3 or 4 rest days off the pump, the resistance resumes a similar, but improved, value from the base value. Thereafter, there is a gradual and long-term affect of the temporary PICD with each individual connection.

Table I. Pump flows and pressures

				Pumping hours			
	Patient	*Age/sex*	*Pumping sessions*	*S1*[a]	*S2*	*S3*	*Total*
Protocol 0501-021M	MB551[b]	52/M	2	19	28	…	47.0
	RB567	57/M	1	59.5	…	…	59.5
	FW853	85/M	2	6.5	18	…	24.5
	GH237[b]	61/M	2	33.5	24	…	57.5
	MM565	86/F	2	24	11.5	…	35.5
Special Access Scheme,	EC968[c]	86/M	2	27	29	…	56.0
Therapeutic Goods Administration	MB840	86/F	2	28.5	24.25	…	52.8
	IM879	79/M	1	17.5	…	…	17.5
	JV313[b]	65/M	2	26	36	…	62.0
	MI731	76/M	2	26.5	30	…	56.5
	GC319	72/M	2	19.75	22.75	…	42.5
	KH592[b]	73/M	2	24	24.75	…	48.8
	ED238[b]	62/M	2	26	25.42	…	51.4
	BB002	67/M	2	25	32.5	…	57.5
	SL314	67/F	3	23	23.5	24.33	70.8
	LP301	68/M	3	18.5	18.5	24	61.0
Protocol 0911-306M	GB304	79/M	1	20	…	…	20.0
	KW307	76/M	1	23.5	…	…	23.5
	CM305	70/F	3	25	24	27.5	76.5
	MP306	82/F	3	24	26	21	71.0

F, Female; *M,* male.
[a]Sn, nth pumping session.
[b]Superficial femoral artery open.
[c]Upper limb patient.

Table II. Clinical outcome of 20 patients

Patient	*1 week*	*Latest follow-up*	*Outcome at latest follow-up*
MB551[a]	Immediate pain relief	29 months	Forefoot amputation; leg viable, healed ulcer
RB567	Leg amputated	1week	AKA
FW853	No pain	3 days	BKA 3 months after treatment
GH237[a]	Pain negligible	15 months	Leg viable; ulcers healed
EC968 [b]	Pain-free fingers	13 months	Hand saved
MB840	Pain "low to medium;" gangrenous 1st toe amputated	4 months	Post-treatment infection; AKA
MM565	Minimized pain	1 month	Died of exacerbation of pre-treatment respiratory failure
IM879	No access, pumping abandoned	12 months	BKA
JV313[a]	Pain-free leg	18 months	Leg viable
MI731	Pain 4/10; leg appears warmer	3 months	Ulcer healed; forefoot amputated Amputation site viable, leg viable
GC319	Ulcer still sore; foot feels warmer than before	5 months	BKA at 5 months
KH592[a]	No pain when lying down; pain 3/10 in toe upon contact, 0/10 in leg	5 months	Delayed BKA
ED238[a]	Pain in ulcer negligible	3 months	Ulcer improved; some pain
BB002	Leg pain 2/10	6 weeks	BKA 6 weeks post-treatment
SL314	Pain absent	5 weeks	Infection, AKA at 5 weeks
LP301	Leg amputated; BKA	3 months	BKA
GB304	Leg viable; pain 1/10	6 months	Limb viable
KW307	Leg viable; pain 1/10	6 months	Limb viable
CM305	Leg viable; pain 8/10	3 months	BKA
MP306	Leg viable; pain 4/10	3 months	Died of cardiac and renal failure

ABI, Ankle-brachial index; *AKA,* above-knee amputation; *BKA,* below-knee amputation; *NA,* not applicable; *PPG,* photoplethysmograph; *VAS,* visual analog scale.
[a]Superficial artery open.
[b]Upper limb patient.

Table I. Continued.

Mean flow per treatment, mL/min			*Mean pressure, mm Hg*			*Peak flows, mL/min*			*Peak pressure, mm Hg*		
S1	*S2*	*S3*	*S1*	*S2*	*S3*	*S1*	*S2*	*S3*	*S1*	*S2*	*S3*
349	355	…	234	121	…	430	450	…	366	150	…
294	…	…	196	…	…	520	…	…	279	…	…
276	193	…	179	303	…	294	300	…	220	350	…
308	788	…	285	184	…	400	1006	…	330	233	…
894	474	…	181	200	…	1100	700	…	228	245	…
498	372	…	154	169	…	650	410	…	167	190	…
437	444	…	211	217	…	670	560	…	263	296	…
112	…	…	130	…	…	240	…	…	145	…	…
567	686	…	175	171	…	670	860	…	267	212	…
615	601	…	187	206	…	760	880	…	306	243	…
385	393	…	244	290	…	490	470	…	302	313	…
468	448	…	187	175	…	740	670	…	262	196	…
558	518	…	166	147	…	730	770	…	290	222	…
711	756	…	148	152	…	870	1000	…	179	190	…
486	656	634	205	204	188	690	770	770	221	230	207
808	744	858	204	198	206	1110	1020	1060	237	276	247
695	…	…	169	…	…	920	…	…	196	…	…
366	…	…	140	…	…	470	…	…	170	…	…
724	663	773	207	196	194	900	760	1400	248	257	299
326	433	258	149	187	181	450	510	290	180	204	209

Table II. Continued.

	ABI (PPG)			
Post-op walking distance, mm	*Before*	*After*	*Ulceration*	*VAS pain score*
≥500	(0.2)	(0.36)	Healed	0/10
NA	NA	NA	NA	NA
≥100	0.1	0.3	NA	NA
≥100	0	(0.21)	Healed	1/10
Unrestricted	0	1	Healed	0/10
≥100	0	NA	NA	NA
NA	0.1	0.35	NA	NA
≥100	0	NA	NA	NA
≥500	0.2	1	Healed	0/10
500	0	0.74	Healed	0/10
≥100	0	0.27	Ulcer neurogenic	NA
Contralateral BKA	0	0.3	Healed	1/10
≥100	0	1 (0.43)	Yes	3/10
50	0	0.47	Toe	2/10
50	0	0.4	NA	3/10
NA	0	NA	NA	NA
≥500	0	0.62	Healed	0/10
50	0	1.47	2 healing	0/10
NA	NA	NA	NA	NA
NA	0.94 (calcification)	NA	NA	NA

Table III. Complications: Device and procedural modifications

Complication	*Incidence*	*Etiology*	*Effect*	*Device/procedure change*
Hemorrhage	3	High infusion pressure Anticoagulation Repeat operation site Multiple exit cannulas	Blood transfusion required	Double "skirt" anastomosis Delay in pumping Suction drainage External compression
Infection	4	Gangrenous ulcers in feet	Amputation at a higher level (n = 1)	Dacron isolation rings on PAS
		Infected lymphatic Repeat groin procedures	Transient (n = 2) bacteremia	Early removal of device No residual foreign material Longer subcutaneous tunnel
Fistula	1	Inadvertent balloon deflation	Transient superficial skin ulceration (groin)	Routine balloon checks especially high flow with low resistance on monitors
Embolization	1	Long flow times Long pump lines Poor anticoagulation control	Transient muscle pain Transient CPK elevation Delay in ulcer healing	Use high-flow double PAS systems Limit pump time to 24 hours

CPK, Creatine phosphokinase; *PAS,* peripheral access system.

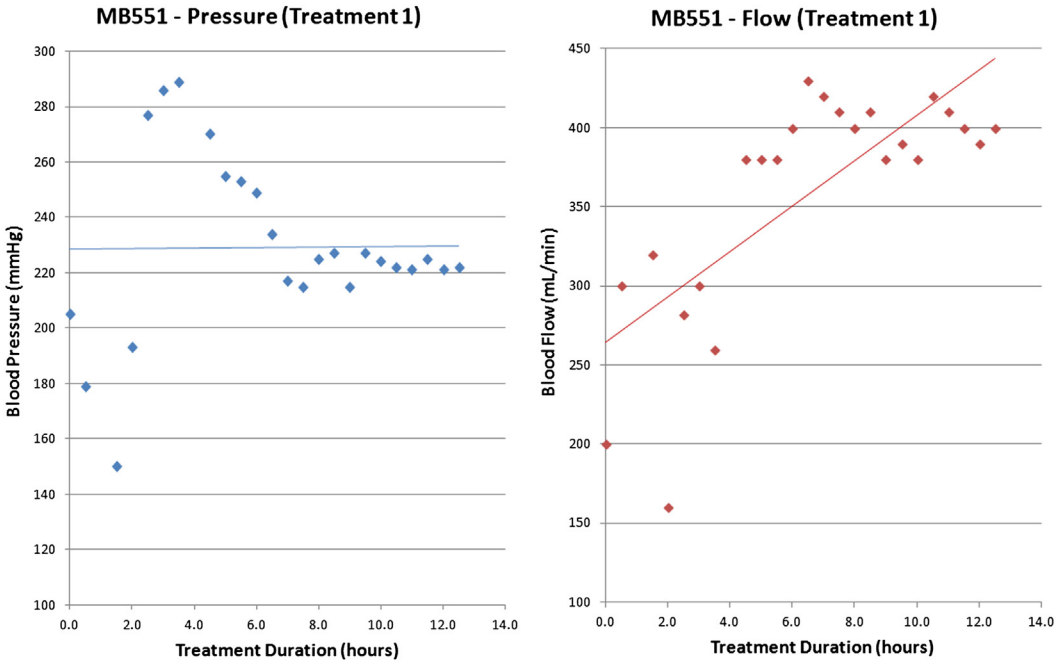

Fig 5. A 24-hour sequence with pressure and flow variation plotted against time. As time progresses, there is a gradual increase in flow with an associated decrease in the required pump pressure. This relationship reflects a decrease in peripheral resistance.

DISCUSSION

Given adequate inflow, the 40 connections to the pump allowed regulation, augmentation, and variation of the collateral circulation as required clinically in the short-term. The gradual reduction in peripheral resistance during a 24-hour period is shown in Fig 5. The changes are reflected in the clinical picture, with resolution of rest pain and the rapid development of a warm, pink limb. Thermography (Fig 7) is a simple noninvasive way to compare the preoperative superficial flow using the other limb as a control. Similarly, this imaging mode can be used to monitor postperfusion progress. The thermography was found to be helpful in deciding whether to reconnect the pump. The groin areas were scanned but uniformly showed increased temperature that did not correlate with the clinical situation.

The variation of pump speed allows control of the inflow pressure. Higher flow rates indicate a good PICD,

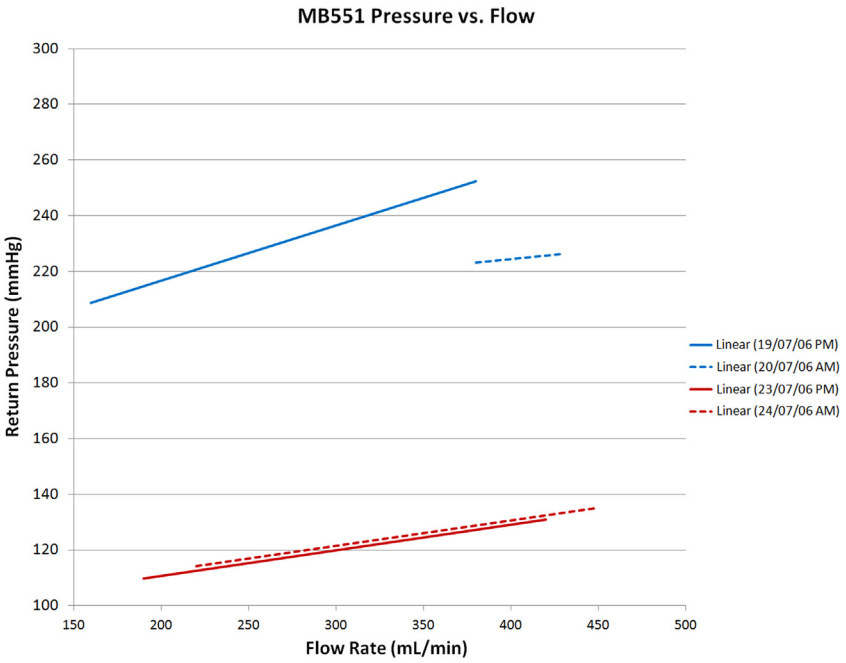

Fig 6. Graph shows pressure vs flow at different times. Initial flow rates are compared with those 12 hours later, after a rest period and after pump reconnection, and then again after 24 hours. Peripheral resistance improved after different pumping sessions.

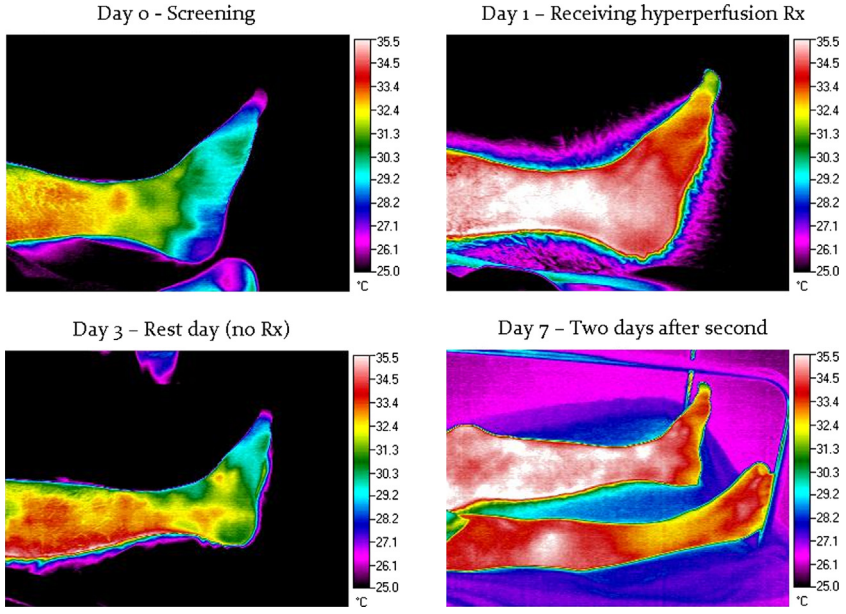

Fig 7. Monitoring thermogram is used to indicate the need for pump reconnection. This system is helpful for long-term follow-up. These images correspond to the clinical presentation. After receiving hyperperfusion, thermographic improvement is maintained.

and pump disconnection is appropriate. Similarly, when the pump is reconnected, the degree of return of collateral smooth muscle tone is reflected in the initial peripheral resistance. It is interesting that the pressure-flow rate gradient reduces slightly at different pump speeds (Fig 6). These changes suggest that the increased pressure induces dilatation of the vascular smooth muscle, which leads to a drop in the peripheral resistance, similar to that

induced by exercise.[2] After pump disconnection, there is recovery of smooth muscle tone. At the vascular endothelial level while on the pump, there is an enormous increase in blood flow velocity. Because velocity and FSS are intimately related and linked to the gradual upregulation of genes, there is an expectation of an increase in the formation of collaterals.[4-7]

The pump. The centrifugal pump was the pump of choice primarily due to its added safety measures. In an event of a blockage or obstruction in the circuit, a centrifugal pump would not continuously increase the pressure, which could lead to rupture of the PAS or the vessel(s), or both. In addition, it allowed for a heparinized circuit, was portable, and was easily connected to standard tubing. It also has automated alarm systems and a digitized reading of suction pressures, flows, and inflow pressures. Finally, it has been safely used for extended periods (days) for extracorporeal membrane oxygenation (ECMO) for cardiac patients, with minimal hemolysis. There was no significant cooling of the patient, as measured by standard temperature readings.

The evolution of the PAS. Repeated surgical groin dissections and anastomoses with expanded polytetrafluoroethylene grafts immediately subjected to high pressures, high flows, and aggressive anticoagulation create a strong predisposition for bleeding. The double skirt anastomosis was thus designed to address this issue. Since this concept has been instituted, bleeding at this site has been minimal. The development of separate input and output access systems allows for greater inlet and outlet diameters, thus eliminating the risk of hemolysis and platelet activation when using small catheters with a high negative pressure. This type of configuration also allows for more than one vascular bed to be isolated and hyperperfused, for example, a superficial femoral and profunda artery together, or by using another occlusive balloon, the profunda alone.

The use of an external inflatable occluder cuff also decreases the chance of thrombus compared with an endovascular occlusive balloon because no foreign body is in direct contact with the blood flow. No thromboembolic complications have been associated with external balloon occlusion. The disadvantage of having an external inflatable occluder cuff is the need for an additional small exit foramen, which, although only 2 mm, is nevertheless predisposed to skin bleeding at very high infusion pressures.

Because 19 of the 20 limbs had tissue loss or gangrene, the patients had a high infection potential due to colonization of their ulceration and potentially infected lymphatics. These patients often had multiple groin procedures, which also predisposes to an infective risk. In addition to appropriate antibiotics, technical changes have been instituted to minimize the infective complications. The length of the PAS and the length of the subcutaneous tunnel were increased with the addition of multiple circumferential Dacron infection shields. Other measures include a separate exit wound for the access system and the use of autogenous materials for arterial patches to close arteriotomies when the devices are removed. Often, the endarterectomized superficial femoral artery or residual autogenous grafts were used.

Repeatability. The long-term development of collateral circulation depends on the FSS. The optimal time for development of gene upregulation is ostensibly 3 weeks.[4-6] In 10 patients, despite very successful pumping procedures, the result was limb loss with the gradual redevelopment of rest pain, and the ulcer failed to heal completely in one patient.

External arteriovenous shunts have been used for long-term hemodialysis for periods of many months and years without insurmountable adverse events.[8-10] The HELP technology is an advancement of this but still requires a better understanding of collateral development to tailor flow requirements in the short-term and long-term. Further investigations could include analysis of the overall duration of the treatment, individual treatment durations, frequency of cycles, pressure profiles, and optimal adjuvant therapy (ie, physiotherapy or drug therapy, or both). There is an urgent need for measurable biochemical markers to reliably predict the development of adequate collateralization, thereby defining treatment repeatability. The ABI increase in these patients reflects this inadequacy. However, because many of these vessels were heavily calcified, no flow could be detected on presentation, then after hyperperfusion, the increased flow might be artificially elevated in the ABI.

Future developments. Optimization of the access system is ongoing. Pump specialization and size minimization may allow greater portability. The concept of regional hyperperfusion can be used for other ischemic organs and has already been shown in the carotid circulation.[2] Furthermore, the continuous perfusion dramatically increases the total flow through a vessel without the peak perfusion pressure having to be increased, largely due to increased diastolic flow. Theoretically, this may minimize the risk of intracerebral hemorrhage while increasing collateral flow for occlusive cerebral disease. Further basic research is required to demonstrate applicability in stroke patients and other ischemic vascular beds. In retrospect, shorter multiple hyperperfusion episodes (perhaps 8 hours, similar to hemodialysis) and accessing the blood flow from a remote source (axilla or either leg) might improve collateral distribution and growth.

CONCLUSIONS

The collateral circulation can be augmented and regulated by connection to an extracorporeal cardiac pump. Isolation from the systemic circulation provided by balloons and the PAS allows intermittent pump connection. Major amputation may be avoided in selected patients when all other measures have failed. Further research and definition of confounding variables are being defined in a prospective controlled clinical trial.

AUTHOR CONTRIBUTIONS

Conception and design: RL, NK, MP
Analysis and interpretation: RL, NK, MP, DM, MD

Data collection: MP, NK, MH, SI
Writing the article: RL, NK
Critical revision of the article: RL, NK, MP, DM, MD, MH, GR, SI
Final approval of the article: RL, NK, MP, DM, MD, MH, GR, SI
Statistical analysis: MP, NK, MD
Obtained funding: RL, GR
Overall responsibility: RL

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injection endothelial function was examined in mesenteric and femoral arteries. Endothelial function was differentially affected in arteries from the mesenteric and femoral beds. Endothelium-derived hyperpolarizing factor (EDHF)-mediated smooth muscle hyperpolarization and relaxation were halved in diabetes in mesenteric arteries. This was mediated by impaired activity of both intermediate (IK)- and small-conductance (SK) calcium-activated K^+ channels (K_{Ca}) in endothelial cells. mRNA expression of both channel types was upregulated in diabetes. Nitric oxide (NO) bioavailability in mesenteric arteries was reduced, underpinned by upregulation of NADPH oxidase isoforms. In contrast, endothelial function remained intact in femoral arteries in diabetes. Endothelial cell hyperpolarization due to activity of IK_{Ca} and SK_{Ca} channels was preserved. This hyperpolarization is unable to pass to the smooth muscle due to lack of myoendothelial gap junctions, therefore EDHF-mediated relaxation does not occur in this artery. The endothelium-dependent relaxation in femoral arteries is fully mediated by NO. Endothelial NO synthase expression and superoxide production were not altered in femoral arteries. This study demonstrates that the effects of diabetes on endothelial vasodilator dysfunction are region-dependent, with local mechanisms dictating functional outcomes.

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3',4'-DIHYDROXYFLAVONOL REDUCES SUPEROXIDE PRODUCTION AND IMPROVES NITRIC OXIDE FUNCTION IN DIABETIC RAT MESENTERIC ARTERIES

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3',4'-Dihydroxyflavonol (DiOHF) is an effective antioxidant that acutely preserves nitric oxide (NO) activity in the presence of elevated reactive oxygen species. We hypothesized that DiOHF treatment (7 days, 1mg/kg per day, s.c) would improve relaxation in mesenteric arteries from diabetic rats where endothelial dysfunction is associated with elevated oxidant stress. Mesenteric arteries were isolated from normal (N=12), normal+DiOHF (N=12), diabetic (N=12) and diabetic+DiOHF (N=12) groups. Superoxide levels, determined by lucigenin-enhanced chemiluminescence, were significantly increased in diabetic mesenteric arteries associated with an increase in Nox2 expression but treatment with DiOHF reversed that effect. ACh-induced relaxation of mesenteric arteries was assessed using wire myography. Diabetes significantly reduced the sensitivity to ACh and treatment with DiOHF prevented endothelial dysfunction (pEC_{50} diabetic, 6.86±0.12 versus diabetic+DiOHF, 7.49±0.13, N=11, $p<0.01$) in mesenteric arteries. When the contribution of NO to relaxation was eliminated by L-NNA (100 μM) and ODQ (10 μM), the sensitivity to ACh was significantly decreased in the diabetic arteries (diabetic, 6.63±0.15 versus normal, 7.14±0.12, N=12, $p<0.05$), and treatment with DiOHF (6.85±0.12, N=12) had no effect. Thus, DiOHF did not affect the contribution of endothelium-derived hyperpolarizing factor (EDHF) to relaxation. When the contribution of EDHF was inhibited with the potassium channel blockers, TRAM-34 (1 μM), apamin (1 μM) and iberiotoxin (100 nM), the maximum relaxation to ACh was significantly decreased in diabetic arteries (diabetic 31±9 versus normal, 68±10, N=8-9, $p<0.001$), suggesting that diabetes impaired NO activity which was associated with decreased endothelial nitric oxide synthase (eNOS) expression and eNOS uncoupling. DiOHF treatment preserved NO-dependent relaxation (69±6, N=11, $p<0.001$) via increasing eNOS expression and eNOS activity. Treatment with DiOHF in normal rats had no effect on any of the parameters that were assessed. In conclusion, we report that the antioxidant DiOHF prevents endothelial dysfunction by preserving NO activity via reducing Nox2-dependent superoxide production and preventing eNOS uncoupling.

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DEVELOPMENT OF OCCLUSION DEVICES FOR HYPERTENSIVE EXTRACORPOREAL LIMB PERFUSION

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Extracorporeal limb perfusion at supra-systolic pressures has been shown to improve collateral formation in ischaemic limbs. Limited clinical results to date indicate significant benefit, with complete recovery in patients in whom the lower limb has been recommended for amputation. The technique involves bypassing the arterial blood through a high pressure external pump, with the artery being occluded between the inlet and outlet ports. The efficiency of the perfusion is highly dependent on the complete occlusion using an external perivascular pressurized cuff. The aim of this study was to test the variation in pressure of occlusion cuff devices in segments of pressurized arteries in-vitro. Bovine carotid arteries (n=8) were pressurized using aqueous fluid. Segment length ranged from 50 to 80 mm and diameter from 6.45 to 9.84 mm. An occlusive cuff with an inner diameter of 12 mm was placed at the midpoint of the segments and pressurised with a fluid filled syringe. For the intra-arterial pressure (IAP) range of 150-400 mmHg, the cuff occlusion pressure (COP) ranged from 270-700 mmHg. There was a linear relationship between COP and IAP which was independent of arterial diameter ($COP = 1.2\ IAP + 140$). For a diameter range of 6.45 mm to 9.84 mm, complete occlusion was obtained for a mean COP range of 327.6 – 622.6 mmHg. Tests were conducted on bovine carotid arteries as models of human femoral arteries to test the efficiency of occlusive cuffs to be used for hyperperfusion of ischemic lower limbs. Findings indicate that a linear model can be used to predict the cuff pressure required for complete occlusion over a broad range of supra-systolic pressures typically used as clinical therapy for amputee patients in whom all standard therapy has been exhausted.

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HYPERTENSION OF 3rd GENERATION ω-3 FATTY ACID-DEFICIENT MICE

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Dietary ω-3 fatty acid deficiency has been demonstrated to induce hypertension. However, the effects of multiple generations of ω-3 fatty acid deficiency remain unknown. In the present study, we examined the effects of 3 generations of deficiency with or without repletion in the final generation. In addition, we examined the hypothesis that increased blood pressure of ω-3 fatty acid deficient mice is due to eicosanoid production from an arachidonic acid (AA)-cyclo-oxygenase (COX) pathway. Male C57BL/6J mice were bred for three generations and fed diets either deficient (DEF) or sufficient (SUF) in ω-3 fatty acids. At postnatal day 21, the third generation offspring were kept on the dam's diet or switched from dam's diet to the opposite diet, creating four groups [SUF-SUF; DEF-DEF; SUFF-DEF; DEF-SUF; n=15/group]. In addition, two groups that remained on the dam's diet were treated with a COX inhibitor [naproxen, 0.07mg/ml in drinking water; SUF-SUF(+); DEF-DEF(+); n=15/group]. At 25 weeks of age, systolic blood pressure was assessed by tail-cuff (CODA, Kent Scientific). Results obtained showed that DEF-DEF animals were hypertensive compared to SUF-SUF animals (108.7±1.6 vs 96.8±1.2 mmHg, $P<0.001$). DEF-SUF animals were not hypertensive (98.4±0.9 mmHg, *ns* vs SUF-SUF). SUF-DEF animals were hypertensive, but less so than the DEF-DEF animals (104.2±1.5 mmHg; $P<0.05$ vs SUF-SUF or DEF-DEF). In addition, treatment with the COX inhibitor prevented the hypertension of DEF-DEF animals (DEF-DEF(+) = 100.1±1.9 mmHg vs SUF-SUF(+) = 100.4±1.1 mmHg, *P*
ns]. Heart rate, body weight, food and water intakes were not different between groups. Thus, hypertension caused by 3 generations of ω-3 fatty acid deficiency appears to be mediated by products of AA-COX pathway and can be prevented by dietary repletion with ω-3 fatty acids.

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CHRONIC ANGIOTENSIN 1-7 TREATMENT PREVENTS L-NAME-INDUCED HYPERTENSION AND CARDIAC FIBROSIS INDEPENDENT OF MasR, AT_2R, NITRIC OXIDE AND PROSTAGLANDINS IN ADULT MICE

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We have previously reported that chronic treatment with Angiotensin 1-7 (Ang 1-7), reduces cardiac fibrosis in aged rats and mice. In these models, antifibrotic effects were inhibited by either PD123319 (angiotensin AT_2 receptor (AT_2R) antagonist) or A779 (MasR antagonist), however, whether or not this effect was specific to the context of aging was not investigated. Therefore the aim of this study was to determine the cardiovascular effects of chronic Ang 1-7 treatment in adult (12-16 weeks) FVB/N mice, in which cardiac fibrosis was induced by 4 week nitric oxide synthase (NOS) inhibition (L-NAME 100mg/kg/day in drinking water). Systolic blood pressure (SBP) and cardiac fibrosis were significantly increased by L-NAME administration (FVB/N SBP: vehicle 83±3 mmHg, L-NAME 114±2mmHg; FVB/N cardiac collagen content: vehicle 2.4±0.2%, L-NAME 7.0±0.1%, n=10-11/group, $P<0.05$). Ang 1-7 had no effect on blood pressure or cardiac fibrosis when given alone, but significantly inhibited detrimental effects of L-NAME when given simultaneously with NOS inhibition (FVB/N + L-NAME + Ang 1-7, SBP: 93±3 mmHg; cardiac collagen content: 4.5±0.3%, n=10. $P<0.05$ vs FVB/N + L-NAME). Importantly, Ang 1-7 also inhibited L-NAME-induced hypertension and cardiac fibrosis in mice deficient in AT_2R (AT_2R KO, SBP: L-NAME 116±6 mmHg, L-NAME + Ang 1-7 96±5 mmHg; AT_2R KO cardiac collagen content: L-NAME 6.4±0.6%, L-NAME + Ang 1-7 4.6±0.3%, n=9-10/group, $P<0.05$), suggesting that these effects were independent of AT_2R. Furthermore, blockade of pathways classically associated with Ang 1-7 signalling were also ineffective in reversing the effects of Ang 1-7 treatment; A779 (48μg/kg/hr, s.c. via osmotic minipump), and indomethacin (indo, 2mg/kg/day in drinking water) did not reverse the blood pressure-lowering or antifibrotic effects of Ang 1-7 in AT_2R KO (SBP: L-NAME + Ang 1-7 + A779 97±3 mmHg, L-NAME + Ang 1-7 + indo 111±5 mmHg; cardiac collagen content: L-NAME + Ang 1-7 + A779, 4.6±0.3%, L-NAME + Ang 1-7 + indo, 4.3±0.2%), suggesting that Ang 1-7 actions were independent of MasR, AT_2R, nitric oxide, and prostaglandins. These results are in direct contrast to those previously determined in aged models, in which chronic Ang 1-7 effects were mediated by MasR and AT_2R. Thus this study emphasises the context specific nature of the protective effects of Ang 1-7, and highlights the importance of further investigation into the mechanisms of cardiovascular effects of Ang 1-7 in age-specific models of hypertension and remodelling.

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THE EFFECT OF ACUTE GREEN TEA SUPPLEMENTATION ON VASCULAR FUNCTION IN YOUNG OVERWEIGHT MALES

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It is well-established that overweight individuals typically possess abnormal vascular function such as reduced forearm blood flow and high arterial stiffness. The purpose of this study was to examine the effects of acute supplementation of green tea containing epigallocatechin gallate (EGCG) on vascular function in young overweight males. Fifteen young males, with normal lipid profile, body mass index of 28.3 ± 0.4 (mean age 23 years) participated as subjects. Augmentation index (AIx), a measure of arterial stiffness, was assessed using applanation tonometry and was calculated as the ratio of augmented pressure and pulse

CHAPTER 4 – LIVER ISOLATION CHEMOTHERAPY USING THE UVAS

After the safety profile of the UVAS as an implantable general vascular access device was established in the Chapter 3 and used in facilitating HELP in a human clinical trial as reported in Article I, the use of the UVAS in administering a LRC treatment remained to be explored. The target organ and histology of the carcinoma chosen was based on what had been learnt in the existing LRC techniques and outcomes. As LRC was already a first line option in carcinomas in the limb and peritoneum, the options available were between the pancreas and the liver. As the study would be a single centre trial, the pancreas was ruled out due to the significantly higher incidence rates of hepatic carcinomas and to avoid another trial termination due to poor patient recruitment.

4.1 Aims

The aim of this chapter was to assess the safety and feasibility of using the UVAS to administer a newly developed LRC treatment to patients with advanced liver cancers.

4.2 Background

The clinical trial protocol (Appendix D) was granted approval by the institutional human research ethics committee (Appendix E) and registered on the national clinical trials registry (Appendix F). The study was intended to treat 10 patients with HCCs patients or CRCLM patients. However, patient recruitment proved to be too challenging due to the established therapies for patients with HCCs in the form of TACE and other systemic therapies. Consequently, upon completion of the trial all of the 10 patients treated were CRCLM patients.

4.2.1 Rationale for New LRC Technique

As the UVAS was a new instrument designed specifically for repeatable multicatheter access, it would have been redundant to replicate the existing LRC techniques (e.g. IHP, PHP, HAI etc.) which were developed within the confines and limitations of existing hardware prior to the availability of the UVAS. Instead, based on what was learned of the various hepatic LRC techniques in Chapter 1, it was identified that IHP had the most promising results despite its surgical complexity. Based on the phase II study data, IHP is believed to be able to offer a two-fold increase in OS compared to that of systemic therapy for patients with MOML [169]. While this is being assessed in a large randomised phase III trial [170], the surgical complexity of the procedure may prevent mainstream uptake even if the outcomes of the trial are positive in the same way ASFI and CAI were abandoned for advanced pancreatic cancers.

PHP was essentially a minimally invasive appropriation of IHP but with less convincing results. IHP directly ligated the portal vein while PHP did not control the blood flow into the liver via the portal vein in any way. Hence, it was believed that IHP was able to achieve a greater level of

liver isolation compared to that of PHP and thus the most probable contributor to the superior OS outcomes.

The hypothesis developed from this was that the degree of liver isolation that was achieved during a hepatic LRC treatment was directly proportional to its efficacy. The ability for repeatability was already designed into the UVAS which was also believed to contribute to the effectiveness of the treatment considering that not only LRC techniques involve repeat treatments (e.g. HAI and PHP), but even standard IV systemic therapy requires repeat treatment cycles.

With this rationale, the main clinical focus of the LRC technique developed was upon utilising the UVAS where possible to obstruct and or control the patient's:

a) hepatic inflows (the arterial and portal side), and
b) hepatic outflow, while
c) allowing repeatability of the process

As shown below in Figure 4.1, a catheter introduced via a peripheral artery can be easily guided to the hepatic artery to control one of the hepatic inflows. However, the portal vein cannot be accessed without a laparotomy as it converges from the venous output of multiple gastrointestinal organs. Hence the only means to control, or specifically to indirectly obstruct the hepatic portal blood supply using catheters is to deploy balloon catheters in the superior and inferior mesenteric arteries (SMA and IMA) and in the celiac trunk retrograde to the bifurcations of the splenic and gastric arteries.

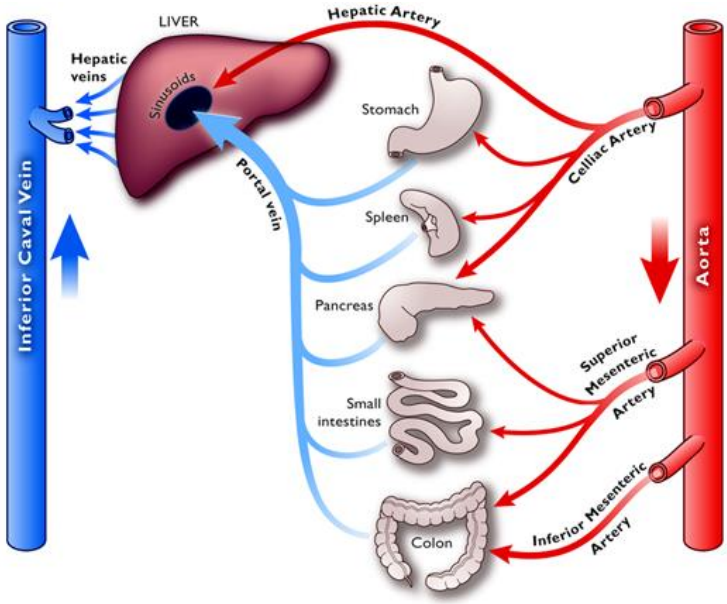

Figure 4.1 – Schematic of the direct hepatic blood supply (hepatic artery and portal vein), indirect hepatic blood supply (SMA, IMA, gastric, and splenic arteries), and hepatic venous outflow [248].

As the UVAS allowed simultaneous cannulation of multiple catheters, the hepatic arterial and portal inflow could be controlled by guiding catheters to all four locations described above

(hepatic artery, celiac trunk, SMA, and IMA). In the case of CRCLM patients, most patients would have had their IMA tied off from resection of their primary colorectal carcinoma and thus only 3 arteries would have required catheter access. Thus, hepatic inflow can be relatively well controlled in such patients. However, complete obstruction of the hepatic inflow has not previously been carried out in a minimally invasive manner and it is highly likely that the patient would experience ischemic liver pains even under sedation. Thus, it was decided that the patients should be sedated using general anaesthesia as pain induced patient movement could dislodge the catheters from their target arteries.

Control of the hepatic venous outflow is achievable via obstruction of each hepatic vein. Practically, since the left, right, and middle hepatic veins can join the IVC at different locations, a double balloon catheter system in the IVC like that used in PHP would be more appropriate. This could have been achieved through a UVAS implanted on the patient's peripheral vein but as the patient was already under general anaesthesia, it was believed to be more practical to reduce the patient's overall venous return by applying a positive end-expiratory pressure (PEEP) [249] which would reduce the number of catheters required as well as the procedure time.

In the interest of reducing the procedure to make repeat treatments feasible, it was decided that the chemotherapy should be administered as a bolus via the infusion catheter in the hepatic artery once all the balloon catheters were deployed and PEEP applied. The balloons and PEEP were to remain in use for up to 20 minutes to allow the chemotherapy to be spread and retained within the liver. The final setup developed for the hepatic LRC technique using the UVAS is shown in Fig 2 in Article II.

Oxaliplatin was chosen as the infusion chemotherapy based on its extensive use in an intra-arterial setting in HAI as discussed in Chapter 1. Patients were infused multiple times between the treatment window which was confined to a 1-month period as a precaution due to risks of infection through the UVAS as discussed in Chapter 2. Finally, oral capecitabine (a 5-FU prodrug) was prescribed to patients throughout the study to ensure they were not denied systemic therapy.

4.3 Aims, Methods, Results, and Discussion

The endpoints, methods, and results of the use of the UVAS and the new LRC technique developed are described in detail in Article II. The UVAS is referred to as the AVAS in the article.

4.4 Article II

Lane RJ, Khin NY, Rogan CM, *et al*. Safety and Feasibility of Repeatable Hepatic Vascular Isolation Chemotherapy: A Pilot Study. Annals of Surgical Oncology. 23(11), 3699–3708 (2016). DOI: 10.1245/s10434-016-5198-z

Attached after Section 4.5.

Two conference abstracts are attached after the Article. The first abstract presented the original clinical trial protocol prior to commencement of the study, while the second abstract presented the initial findings after 3 patients were treated.

4.5 Chapter Conclusions

As concluded in Article II, the UVAS was shown to be safe and feasible in administering the new LRC technique developed and allowed repeated treatments using standard interventional radiological techniques. Most notably, due to insignificant systemic toxicities, patients were able to be administered up to 5.7 LRC treatments on average in under a month that would normally take up to 3 months using conventional systemic chemotherapy. This hints at another potential of the UVAS system and the hepatic LRC technique developed in being utilised as an accelerated treatment to arm patients and clinicians with additional time to explore other therapies prior to further disease progression if the LRC treatment was ineffective. Finally, given the heavily pre-treated nature of the patients in the study, the response rates reported from Article II are promising although not statistically significant. The results from the pilot study warrants requires further assessment in a phase II study.

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ORIGINAL ARTICLE – HEPATOBILIARY TUMORS

Safety and Feasibility of Repeatable Hepatic Vascular Isolation Chemotherapy: A Pilot Study

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ABSTRACT

Background. The authors herein describe a novel method of repeatable hepatic isolation using an implantable access system allowing simultaneous control of hepatic arterial and portal flows by multiple endovascular catheters.

Purpose. The aim of this study was to assess the feasibility and safety of the system and to compress standard intravenous chemotherapy into 4 weeks of targeted intra-arterial delivery.

Methods. An arterial access system was implanted to the axillary artery via an anastomosis. Infusions of oxaliplatin were performed biweekly for 4 weeks, using balloon catheters to achieve hepatic isolation and segmental selectivity for 20–25 min. Fifty-seven treatments under general anesthetic were performed in ten patients with inoperable chemotherapy-refractory metastatic colorectal cancer. Systemic, intrahepatic, and hepatic venous pressures were recorded to assess vascular isolation, and platinum levels were measured to assess chemotherapy distribution.

Results. Pressure verified, multiple day-only hepatic vascular isolation infusions were achieved in nine of ten patients, with a single patient receiving multiple hepatic arterial infusions. Positron emission tomography–computed tomography (PET–CT) imaging confirmed partial response in three of ten patients and stable disease in three of ten patients. Systemic toxicity was minimal as all treatment-related gastrointestinal and neuropathic symptoms reported throughout the 4 weeks were grades 1–2.

Conclusions. Intra-arterial chemotherapy infusions with hepatic vascular isolation can be achieved repeatedly with targeted selectivity and minimal complications using an implantable multicatheter access system. Oxaliplatin infusions over a 4-week period may achieve tumor response in selected patients in the salvage setting. The technique should be further assessed in a phase Ib/II study.

There are approximately 132,700 new cases of colorectal cancer in the US alone each year,[1] with 18.9 % of these patients presenting with synchronous hepatic metastases and a further 8.1 % developing hepatic metastases.[2] While hepatic resection imparts a 47 % 5-year survival rate, only approximately 29 % of patients present with resectable metastases.[3] Despite improvements in treatments, the 5-year survival rates for unresectable patients remain poor at less than 19 %.[3] These patients are typically treated with systemic intravenous chemotherapy regimens: 5-fluorouracil and leucovorin paired with oxaliplatin (FOLFOX) or irinotecan (FOLFIRI) and coupled with monoclonal antibodies (MABs). However, only approximately 9 % of these patients are successfully downstaged to undergo resection[3]; hence, radiologically-based hepatic targeting treatments have been developed to improve results.

Recently, in first-line patients, the combination of FOLFOX, MABs, and intra-arterial Yttrium 90 spheres (Yt^{90}) have produced improvements of progression-free survival (PFS) in the liver of 20.5 months, which represents a 62 % improvement over controls with chemotherapy and MABs alone.[4] Alternatively, in hepatic arterial infusion (HAI) of oxaliplatin and intravenous 5-fluorouracil/leucovorin therapy in oxaliplatin-naïve patients, the response rate (RR) was 64 %, with a median PFS of 27 months.[5] The same

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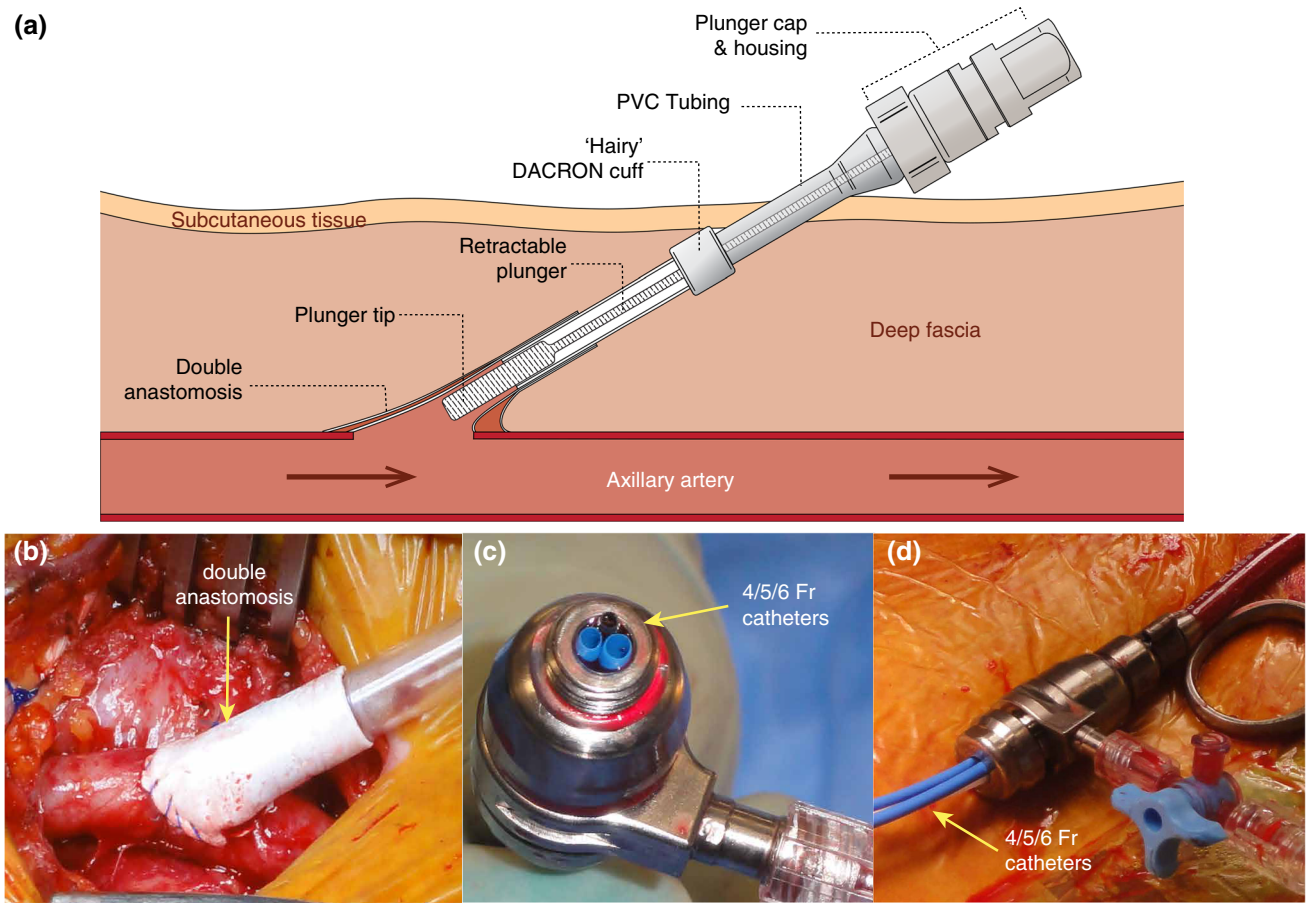

FIG. 1 **a** Cross-sectional schematic of the AVAS anastomosed onto the patient's axillary artery with the retractable plunger inserted when it is inactive and closed. **b** The implanted AVAS in the groin, with the double PTFE skirt anastomosis to provide more mechanical strength. **c** Close-up view of a disconnected hemoreduction valve and the orifices of the 4, 5, and 6-Fr sheaths inserted through it. **d** The access system in the resting phase with the valve and catheter locked in situ. *AVAS* Arterial and Venous Access System, *PVC* polyvinyl chloride, *PTFE* polytetrafluoroethylene

treatment, when administered as a salvage treatment for patients who have failed previous chemotherapy, resulted in PFS of 7 months and overall survival of 16 months.[6] However, mainstream uptake of HAI has been hindered by its cost, a surgical morbidity rate of 35 %,[7] and its inability for lobar/segmental targeting. Additionally, the conceptual problems with HAI relate to rapid washout of chemotherapy creating difficulties in maintaining a high maximum concentration (C_{max}) at the blood tumor interface. This concurrently decreases the total chemotherapy exposure, expressed as area under the concentration–time curve (AUC), and results in prolonged treatment times with subsequent reduction in quality of life (QoL).

To address the issues of low C_{max}, low AUC, and prolonged treatment-time-associated reduction in QoL, the logical progression was to intermittently control the hepatic blood flow (hepatic artery, portal vein inflow and hepatic vein outflow) within the known hepatic ischemic time.[8] The therapeutic advantage, compared with intravenous chemotherapy, relates to the relative mass of the liver compared with the whole body mass and also the portal venous washout. At 1.5 kg or 2 % of the body weight, this represents a mass ratio of 50:1 or 400:1 if one of the eight hepatic segments is selected. The portal vein supplies 75 % of the liver at pressures below 5 mmHg and hepatic vein pressure is approximately 0–5 mmHg.[9]

Oxaliplatin has a well-established colonic tumor response with a very rapid initial tissue uptake ($t_{½\alpha} \approx$ 8–15 min).[10] It is important to note that the drug is rapidly and irreversibly covalently bound to the plasma and red cells so that approximately 15 % is active and responsible for the therapeutic, as well as toxic, side effects.[10,11]

The concept of the mass ratio advantage, the absence of portal washout, the short half-life of oxaliplatin, and the minimization of plasma binding suggested that the total dose could be reduced. Hence, the potential of minimizing side effects and shortening the total administration time may have a positive effect on patient QoL. This study was undertaken to evaluate the feasibility and safety of repeated, organ isolated, intrahepatic oxaliplatin in patients

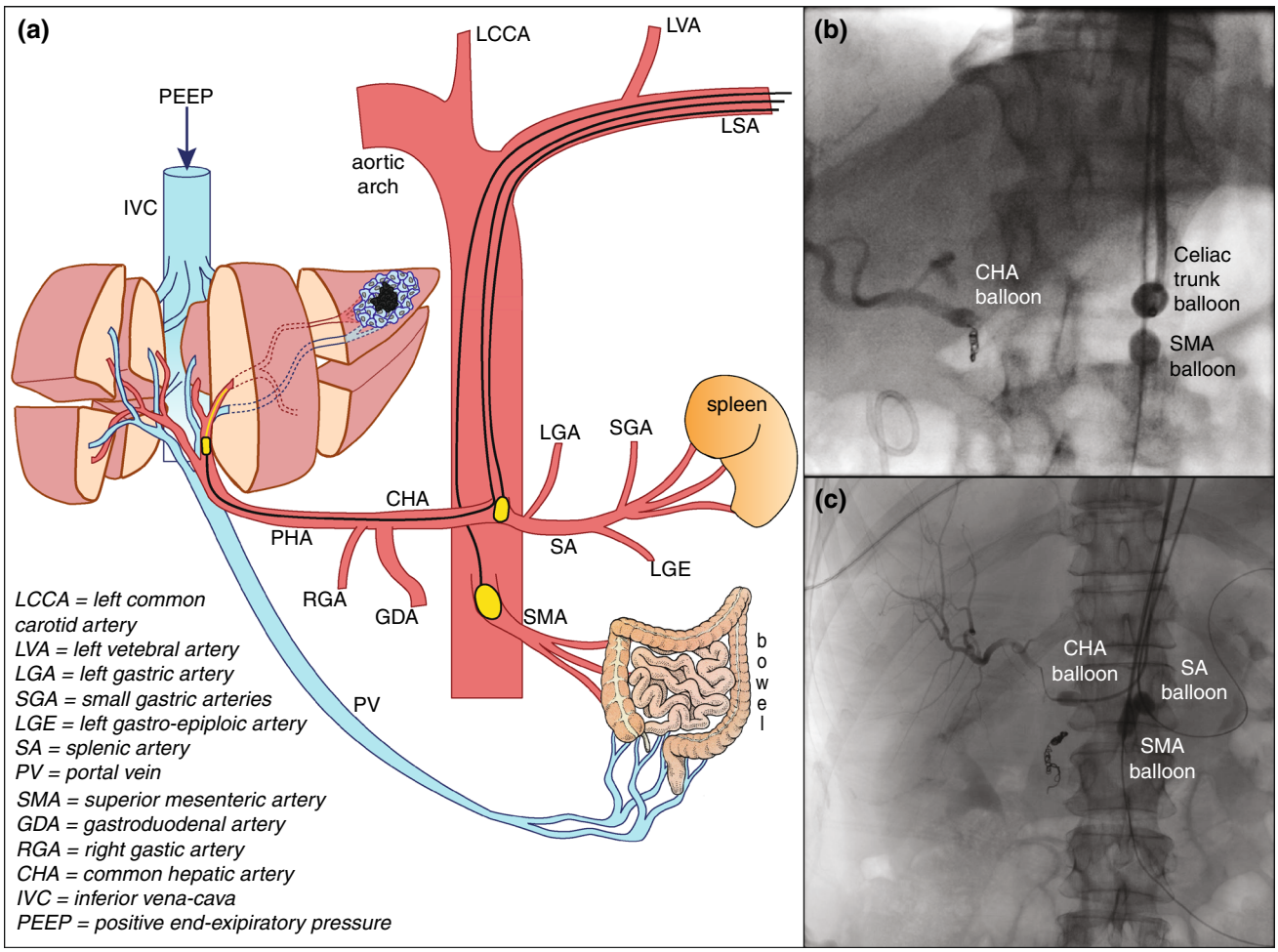

FIG. 2 **a** Schematic of the superselective isolated tumor infusion; the infused chemotherapy flows to the tumor by the branches of the hepatic segmental arteries as well as via the branches of the portal vein through the collaterals between the portal vein and the hepatic segmental arteries. The inferior mesenteric artery has been tied off in this cohort of patients and is not shown in the schematic. **b** Angiogram showing isolation via the Corail balloon system with infusion into the hepatic proper (**c**) angiogram with three Fogarty balloons, with a microcatheter infusing into a segmental artery

with colorectal liver metastases using an existing implantable vascular delivery system with multicatheter capacity. A similar implantable isolation system for performing regional hyperperfusion for critical limb ischemia has already been shown to be safe and efficacious.[12,13]

METHODS

This was a registered, single-arm, non-randomized pilot study (ACTRN12611001273976) approved by the institution's Human Ethics Committee and conducted in accordance with the Declaration of Helsinki. Ten patients who met the following inclusion criteria were enrolled between 2012 and 2015: histologically proven colorectal adenocarcinoma with inoperable hepatic metastases; failed at least one chemotherapy regimen; World Health Organization (WHO) performance status ≤ 2; adequate hematology, coagulation, renal, and hepatic function; and fit for general anesthesia (GA). Exclusion criteria consisted of the presence of dominant or life-threatening extrahepatic disease; clinically significant ascites or comorbidities; grade 3–4 peripheral neuropathy; technical inability to carry out the procedure (assessed via computed tomography [CT] angiogram); and patients under the age of 18 years.

The primary endpoints of the study were safety and feasibility of the treatment. Safety was assessed by complication rates associated with the vascular implant/explant procedures, as well as the catheterization and endovascular organ isolation procedures reported through adverse events (AEs) as per the Common Terminology Criteria for Adverse Events v3.0. Feasibility was assessed by the delivery system's capability for organ-isolated intra-arterial infusion. The secondary endpoint was the efficacy of the treatment assessed through systemic toxicity, tumor RR, and QoL.

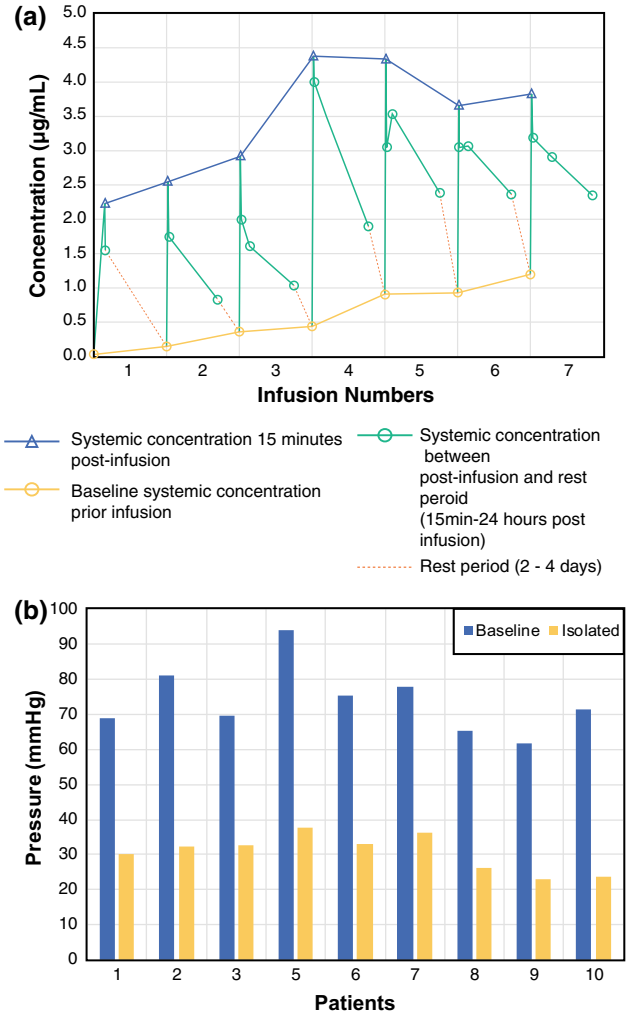

FIG. 3 **a** Platinum concentration levels over 4 weeks in one patient; the progressive high residual levels before the next infusion represent the terminal (non-active) excretory phase. **b** Level of hepatic isolation achieved as confirmed via mean intrahepatic pressures at the catheter tip. *Note* Patient 4 was treated with repeated hepatic arterial infusion, and intrahepatic pressures were not measured

Toxicity was measured by the patient's systemic platinum concentration levels and all relevant AEs; tumor response by comparison of positron emission tomography (PET)–CT scans taken at enrolment and 4 weeks post-treatment as per the Hick's criteria[14]; and QoL by comparison of QoL scores at enrolment and 4 weeks post-treatment and measured using European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 in conjunction with QLQ-LMC21.[15] Clinical review of the patient's hematology and biochemistry was performed prior to each treatment, and followed up for 6 months. Microbiological cultures of wound sites were taken and reviewed as clinically indicated.

Patients were administered GA in the operating theatre and, through a 6-cm skin incision, the Arterial and Venous Access System (AVAS; AllVascular, St Leonards, NSW, Australia) was implanted to the patient's common femoral or axillary artery, as shown in Fig. 1a, b. The device was then tunneled transcutaneously to appear immediately posterior to the lateral pectoral fold in the axillary or in the thigh in the lower limb. The wounds were closed in layers with drainage and the patient monitored during the overnight recovery.

Patients were then admitted to the angiography suite biweekly and were anticoagulated with enoxaparin (Sanofi–Aventis) 40 mg preoperatively. Under GA and following the administration of prophylactic cephalosporin 1 g intravenously and 5000–7500 units heparin intravenously, the AVAS was accessed by removing the retractable plunger from the shaft (Fig. 1a). An arterial clamp occluded the flow until a hemoreduction valve capable of accepting multiple sheaths simultaneously (Fig. 1c) was attached (Fig. 1d). The principles of isolation are shown in Fig. 2a. The aim was to control hepatic blood flow by balloons placed into the hepatic artery, as well as the celiac and superior mesenteric arteries, to minimize portal flow.

Through a 6-Fr 9-cm sheath, the hepatic artery was cannulated using an angled 6-Fr MPA catheter (Cook Medical, Bloomington, IN, USA) and a 0.035" 260-cm Glidewire Advantage (Terumo Medical, Tokyo, Japan) guidewire or 0.014" 300-cm Journey Guidewire (Boston Scientific, Marlborough, MA, USA). The catheter was then exchanged over the wire for a 5.5-Fr 80-cm Fogarty balloon catheter (Edwards Lifesciences, Irvine, CA, USA) and the catheter advanced into the hepatic artery proper or further into one of the segmental arteries. In selected patients, non-target vessels were occluded with detachable concerto microcoils (Covidien EV3, Dublin, Ireland) prior to the first infusion to isolate flow to the liver.

In order to indirectly occlude the remainder of the portal supply, two further 5.5-Fr Fogarty balloons were similarly exchanged through separate 6-Fr sheaths via the access system into the superior mesenteric artery (SMA) and the celiac trunk/splenic artery, as shown in Fig. 2b, c. Alternatively, the celiac trunk was occluded with a Corail 8-Fr balloon guide catheter (Balt Extrusion, Montmorency, France) and the hepatic artery occluded coaxially by a 3-Fr Fogarty balloon catheter. In earlier patients, semi-compliant Advance LP balloon catheters (Cook Medical, Bloomington, IN, USA) were used in place of the Fogarty balloons, but the Fogarty balloons were found to be preferable for this application due to their greater compliance. In one patient with difficult access, the portal flow was instead controlled via an occlusive balloon in the supraceliac aorta (Cordis Bridgewater, NJ, USA).

Pressures were measured within the hepatic artery at baseline and following inflation of all balloons to achieve hepatic inflow isolation. Positive end-expiratory pressure

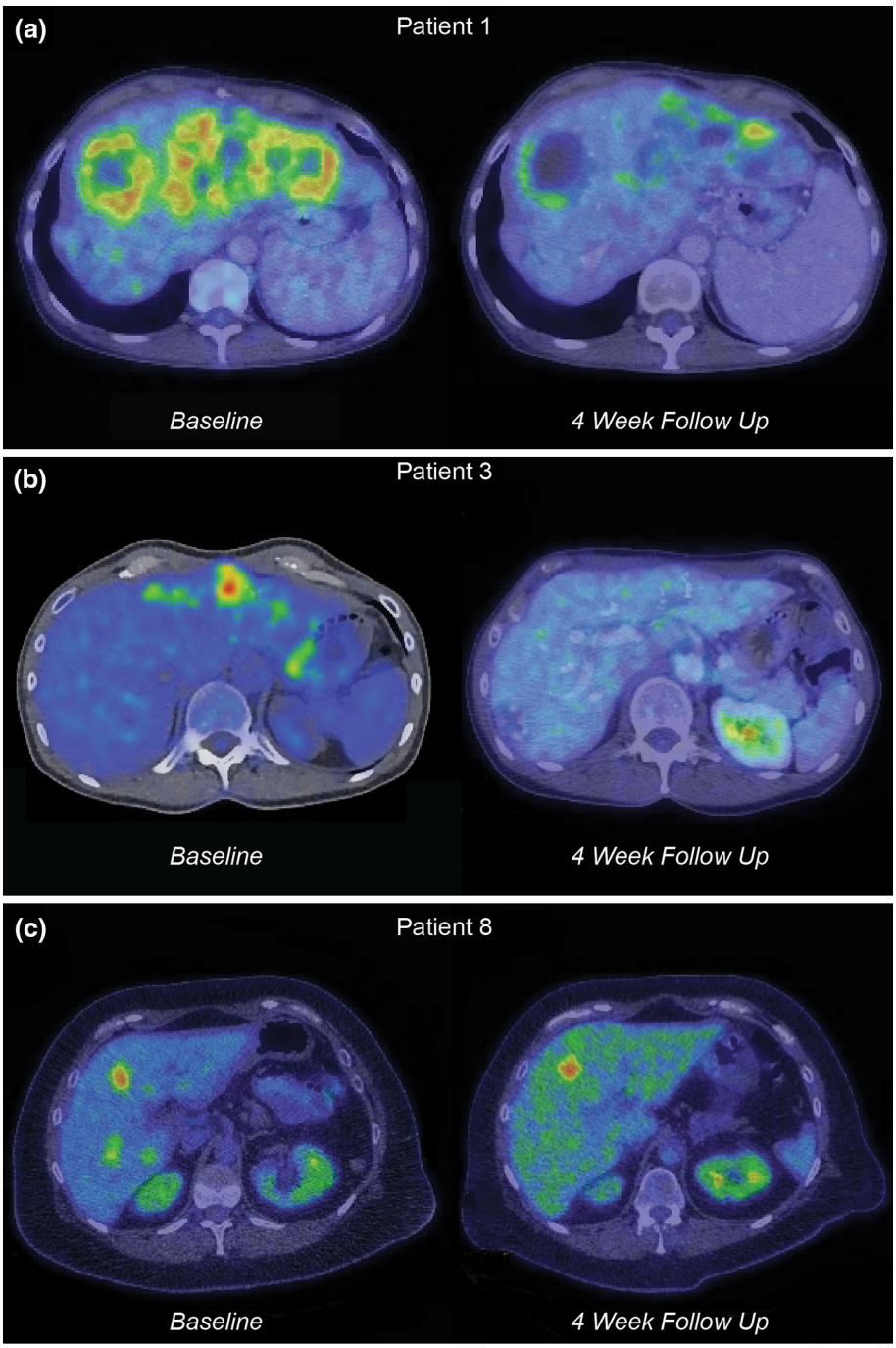

FIG. 4 PET–CT scans of the responsive patients at enrolment and at 4 weeks post-treatment. *PET–CT* positron emission tomography-computed tomography

(PEEP) was then increased to 20 mmHg to reduce systemic venous outflow and encourage preferential flow into the relatively low-pressure portal system. Following deflation of the balloons to reset the ischemic time, all balloons were reinflated and chemotherapy infusion commenced either through the hepatic artery occlusion balloon wire channel or via a Progreat microcatheter (Terumo Medical) introduced through the wire channel. In total, ten patients were catheterized a total of 57 times.

The segmental vascular volume was estimated and an average of 50 mL 5 % dextrose was infused to reduce oxaliplatin binding with plasma and erythrocytes. Due to the direct, isolated, and repeated nature of the treatment, lower doses of oxaliplatin (50–75 mg/m^2) were chosen for safety reasons. The oxaliplatin was infused by hand over approximately 5–10 min and all balloons were kept inflated for a total ischemic time of 20–25 min. Peripheral plasma platinum levels were measured (mass

spectrometry) immediately prior to infusion to establish baseline. Immediately prior to the end of the ischemic time, an average of 50 mL of 20 % albumen was then infused into the liver to bind and neutralize any residual oxaliplatin. All catheters, sheaths, and the hemoreduction valve were then removed and the AVAS plugged with a new plunger. Further plasma platinum levels were taken after the balloons were deflated at 5, 10, or 20 min following balloon deflation. Patients were usually discharged the following day and prescribed capecitabine (500 mg twice daily), rivaroxaban (20 mg in the morning), and keflex (500 mg three times daily) between treatments as systemic therapy, anticoagulants, and antibiotics, respectively.

Under GA, the AVAS device was removed by reopening the previous incision and clamping and fashioning the polytetrafluoroethylene (PTFE) as a patch. The access tube was removed retrogradely through the previous transcutaneous incisions. The wounds were closed in layers with drainage and the patient usually discharged the following day.

RESULTS

The demographics, management history, and treatment regimen details of the ten patients enrolled are summarized in Table 1. Of the ten patients treated, nine were able to be successfully cannulated with multiple catheters simultaneously to achieve isolated intra-arterial oxaliplatin. The average duration for the implantation ($n = 10$), explantation ($n = 10$), and infusion ($n = 57$) procedures were 123.9 ± 12.9, 70.0 ± 26.8, and 118.5 ± 32.8 min, respectively. After the initial learning curve, the infusion procedures were reduced to an average of 100.6 ± 32.8 min in the last six patients. Patient 4 received standard HAI via a single catheter eight times. The number of grade 4 and grade 3 AEs reported that were related to the study treatment were zero and four, respectively—three cases of hematomas (two from vessel dissection and one from a false aneurysm) from catheter access, and one case of pain at the surgical implant site. The mean global health status and QoL functioning scales at 4 weeks decreased by 8.3 and 9.7 %, respectively, from baseline. Similarly, an increase in the symptom scales and liver metastases symptom scales of 7.0 and 1.9 %, respectively, was observed. A typical platinum concentration curve throughout the 28-day period, as well as the change in the mean intrahepatic catheter pressure for each patient, are shown in Fig. 3a, b, respectively. Of the ten patients treated, the number of patients who resulted in progressive disease, stable disease, and partial response at 4 weeks follow-up were 4, 3, and 3, respectively, as summarized in Table 2. The PET–CT scans from enrolment and 4 weeks' follow-up for the three responsive patients are shown in Fig. 4.

DISCUSSION

The reported hepatic isolation system and technique was designed to improve upon the promising results of HAI in the first-line[5] and salvage settings[6] by addressing the weaknesses and limitations of conventional HAI. Theoretically, HAI is limited by the effect of immediate dilution by the forward flow of the hepatic artery (300 mL/min), and shunting of the portal vein and peribiliary anastomoses. Therefore, the chemotherapy transit time is high, resulting in low drug–tumor interface time that compromises the C_{max} and AUC to yield untoward side effects and prolong the time to response. A typical patient infused with oxaliplatin 85 mg/m^2 over 2 h produces an unbound (active) C_{max} of 0.69 μg/mL and an AUC of 4 μg/mL.[10] In contrast, the hepatic isolation system described may overcome the issue of immediate dilution, and a patient treated with optimal hepatic isolation produces a local unbound (active) C_{max} of 750 μg/mL, and the AUC of 300 μg/mL/h is added to the known 4 μg/mL with recirculation.[10] However, despite obstruction of the hepatic artery, celiac axis branches, and SMA, isolation was incomplete. The isolation pressures of 20–30 mmHg were similar to the PEEP pressures, encouraging vascular shunting of the chemotherapeutic agents into the portal system at 3–5 mmHg normally. These are less during hepatic isolation, which could be related to the balloon occlusion of the intestinal inflow. The effect is magnified by the hepatic arterial buffer response.[8]

The single case of a false aneurysm was the result of percutaneously cannulating through the brachial artery rather than through the implanted access device. The pallor and warmth of the limb was monitored but no intervention was required. All catheters were introduced through the access device (Fig. 1d) from thereon. The two cases of vessel dissection in the hepatic artery were a result of a ruptured balloon and treating a patient with excessively small arteries. Dual hepatic blood supply meant that the organ was not at risk, and covered stents were implanted to allow the continuation of treatment. The patient inclusion criteria were tightened and reinflation of balloon catheters were minimized to address such complications.

Two of the three patients who showed partial responses proceeded to surgery (downstaged and resection of the liver, as well as resection of primary colon cancer). However, progression was noted in four patients despite excellent hepatic isolation, as shown by the intrahepatic pressures and platinum levels (Fig. 3). A positive feature is the compressed treatment time to 4 weeks, which would enable patients to undergo other types of treatment such as Yt^{90}, TACE, or even HAI to be delivered through the same system. After the initial learning curve, the infusion procedure times were also comparable to that of Yt^{90}, TACE, and HAI. All ten patients reported grade 1–2 symptoms of peripheral neuropathy initially at enrolment and this was

TABLE 1 Summary of patient demographics, management history, and treatment regimen

Patient	Sex/age (years)	Treatment history[1]	Radiological details		Treatment regimen		
			Isolation method (Fig. 2b or c)	Intrahepatic pressure (mmHg) [mean (range)]	No. of infusions	Dose (mg/m^2)	Treatment period (days)
1	F/55	i. Whipple procedure[2] ii. FOLFOX iii. Hepatectomy + RFA iv. Capecitabine v. SIRT Gemcitabine (intravenous) vi. SIRT	Other[3]	30.3 (17.5–43.0)	3	50	14
2	M/67	i. Colon resection ii. FOLFOX	c	32.2 (19.0–50.5)	5	50	19
3	F/52	i. Surgical removal of polyp ii. FOLFOX (two cycles) iii. Hepatectomy + FOLFOX iv. Capecitabine + bevacizumab v. Hepatic arterial infusion vi. Cetuximab vii. Panitumumab + irinotecan viii. FOLFOX	c	32.6 (11.0–54.0)	6	50	28
4	M/61	i. Right hemihepatectomy ii. Bevacizumab + oxaliplatin + capecitabine iii. TACE (four sessions) iv. Cetuximab + F15 (3) v. Oxaliplatin + capecitabine	Other[4]	NA[4]	8	50–75	29
5	F/60	i. FOLFOX (ten cycles) ii. FOLFIRI + bevacizumab (nine cycles)	c	37.7 (31.0–45.5)	4	50	35
6	M/66	i. Ileostomy–rectal resection ii. Oxaliplatin (ten cycles) iii. 5-fluorouracil + irinotecan (28 cycles) iv. Ileostomy reversal v. 5-fluorouracil + irinotecan + cetuximab (12 cycles) iv. Regorafenib (one course)	c	32.9 (21.5–51.5)	5	50	28

TABLE 1 continued

Patient	Sex/age (years)	Treatment history[1]	Radiological details		Treatment regimen		
			Isolation method (Fig. 2b or c)	Intrahepatic pressure (mmHg) [mean (range)]	No. of infusions	Dose (mg/m^2)	Treatment period (days)
7	M/67	i. Laparoscopic resection ii. FOLFOX (12 cycles) iii. Left hemihepatectomy iv. Laparotomy: two lesions from segment 7, and three lesions via RFA v. RFA of three more lesions	c	36.3 (20.0–57.5)	6	50	28
8	F/59	i. Thyroidectomy (hemi) ii. Lower anterior resection iii. Radiation (Swedish protocol) iv. Oxaliplatin + capecitabine ± bevacizumab (five cycles) v. Capecitabine + bevacizumab (one cycle)	b	26.2 (23.0–31.5)	6	50	25
9	M/51	i. Oxaliplatin + 5-fluorouracil + bevacizumab (seven cycles) ii. FOLFOX ± bevacizumab (eight cycles) iii. 5-fluorouracil + bevacizumab (five cycles) iv. Capecitabine + bevacizumab	b	23.1 (13.0–32.0)	7	50	24
10	M/69	i. Hemicolectomy and hemihepatectomy ii. FOLFOX (12 cycles) iii. Bevacizumab iv. FOLFIRI (three cycles)	b, c	23.6 (15.0–34.5)	7	50–75	30
Overall mean			–	30.5	5.7	–	26

F female, *M* male, *HAI* hepatic arterial infusion, *NA* not applicable, *FOLFOX* 5-fluorouracil and leucovorin paired with oxaliplatin, *FOLFIRI* 5-fluorouracil and leucovorin paired with irinotecan, *RFA* radiofrequency ablation, *SIRT* selective internal radiation therapy, *TACE* transcatheter arterial chemoembolization

[1] In chronological order from diagnosis of primary cancer

[2] Histology of Patient 1's primary cancer was a duodenal adenocarcinoma; Patients 2–10 were all colorectal adenocarcinomas

[3] Occlusive balloons in the supraceliac aorta and common hepatic artery

[4] Isolation could not be achieved; HAI with a single balloon catheter administered via hepatic proper or left/right hepatic artery

TABLE 2 Summary of results at 4 weeks post-treatment compared with baseline

PET–CT outcome[a]	*n*	Patient no.	Mean (min, max) change in QoL score			
			Global health status[b]	Functioning scales[b]	Symptom scales[b]	Liver mets. symptoms scale[c]
Partial response[d]	3	1, 3, 8	+5.6 (−16.7, +41.7)	−1.1 (−9.3, +5.9)	0.0 (−9.9, +6.8)	−2.1 (−10.3, +4.3)
Stable disease	3	5, 7, 10	+8.4 (0.0, +16.7)	−1.7 (−3.3, 0.0)	+6.2 (+5.6, +6.8)	−8.0 (−15.4, −0.6)
Progressive disease	4	2, 4, 6, 9	−27.1 (−41.7, −8.3)	−20.2 (−32.0, −6.3)	+12.7 (+5.6, +17.9)	+9.9 (+6.0, +13.2)
Overall			−8.3 (−41.7, +41.7)	−9.7 (−32.0, +5.9)	+7.0 (−9.9, +17.9)	+1.9 (−15.4, +13.2)

All data are expressed as percentages

PET–CT positron emission tomography-computed tomography, *min* minimum, *max* maximum, *QoL* quality of life, *EORTC* European Organisation for Research and Treatment of Cancer

[a] Reported as per Hick's criteria[14]

[b] Scored as per EORTC QLQ-C30

[c] Scored as per EORTC QLQ-LMC21

[d] One patient downstaged for liver resection, another patient underwent resection of primary colon cancer

not escalated in any of the patients throughout the treatment period. Overall, the QoL scores revealed no significant signs of improvement or exacerbation of the patients' symptoms. When coupled with the low AE rate attributed to the treatment, the technique is considered safe and well-tolerated. A theoretical advantage of the time compression is the reduced opportunity for cell repopulation and mutation between cycles. In comparison with standard intravenous treatments, the relatively high local chemotherapy concentrations have an improved beneficial effect on more resistant cell lines. Given the observed clinical benefit in the six of ten patients with chemotherapy-refractory colorectal liver metastases, this technique has the potential for application in earlier clinical settings in patients with liver-dominant colorectal metastases to enhance tumor response, reduce systemic intravenous oxaliplatin exposure, and thus minimize the risk of chronic peripheral neuropathy. Furthermore, this technique can be explored with other agents.

Cost Ramifications

The system of hepatic isolation has the potential to reduce costs to the community related to the use of generic chemotherapeutic agents, same-day infusions, and standard radiological infrastructure. The time compression to 4 weeks allows earlier resumption of normal work activity, and the low incidence of side effects requires less medical intervention.

CONCLUSION

An implantable multicatheter hepatic isolation system designed for repeated vascular access was shown to be safe and feasible under radiological guidance. The high local and low systemic chemotherapy doses can produce positive results in the salvage setting. Tumor cells reliant on portal blood supply may also be vulnerable to chemotherapeutic agents by multicatheter control of pressure gradients. An important feature is the time compression of therapy delivery to 4 weeks, which could lead to an improved QoL by minimizing total treatment time and reducing overall exposure to oxaliplatin. The benefits of this technique should be further assessed in a phase II study in non-chemorefractory patients in conjunction with a phase Ib dosing study.

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Superselective Stop flow Chemotherapy for Solid Neoplasma with Chemoextraction

This abstract has been selected as a poster presentation for the Innovation in cancer treatment and care NSW conference.

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Background

A new implantable vascular access system has been developed which allows for complete control of blood flow (both arterial and venous) to treat patients with liver metastases from colorectal cancer or patients with hepatocellular carcinomas.

Methods

- The implantable vascular access system is surgically implanted in the patient's common femoral artery and exits through the patient's subcutaneous tissue. The ports on the device allow for repeatable access to the patient's vasculature.
- During the chemotherapy infusion sessions, the patient is ventilated with positive end-expiratory pressure (PEEP) to control the venous outflow whilst under general anaesthesia.
- Up to four catheters will be used to cannulate the patient's vasculature and control the arterial flow to the liver and bowels.
- A microcatheter (up to 800 microns) will be used to superselectively target the pre-determined liver tumour lesion and subsequently deliver chemotherapy locally. Extraction of the residual chemotherapy is achieved by back bleeding.
- The patient can be treated up to 8 times within 30 days before the vascular access system is explanted.

Results

The study has been assigned a Clinical Trial Notification by the TGA, registered on the Australian New Zealand Clinical Trial Registry (ACTRN12611001273976), approved by the institutional ethics and scientific committee, and is in the process of recruiting patients.

Conclusion

Further clinical trial protocols for pancreatic and solid gynaecological cancers are now in development.

Results: In pigs treated with 10 ml ethanol, treatment resulted in neural degeneration. We found a significant reduction of 53% in NE concentration in the kidney parenchyma ($p < 0.02$) compared with the untreated contralateral kidney. In pigs treated with 5 ml ethanol, no significant changes in histology or NE were observed. There was no evidence of renal arterial stenosis in MRI, macroscopy, or histology in any pig.
Conclusion: MR-guided periarterial ethanol injection was feasible and efficient for renal sympathetic denervation in pigs. This technique may be a promising alternative to the catheter-based approach in the treatment of resistant arterial hypertension.

1404.4

Irreversible electroporation (IRE) in an acute porcine liver model: effect of previous transarterial embolization with iodized oil on technical parameters and extent of coagulation

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Purpose: To evaluate the effect of transarterial embolization with iodized oil on technical parameters and extent of coagulation after irreversible electroporation (IRE) in an acute porcine liver model.
Material and Methods: In each of five landrace pigs, two IREs of the liver on the right (RL) and two IREs of the liver on the left (LL) were performed with identical system parameters (90 pulses, pulse length of 90 ns, electric field of 1750 V/cm) and applicator configuration (two applicators, applicator distance of 1.5 cm, tip exposure of 2.0 cm). A selective transarterial catheter embolization was performed before IRE of only the LL with iodized oil until stasis. Native and contrast-enhances CT examinations were performed to assess the extent of coagulation. Subsequently, animals were killed and livers were harvested. Mean resulting voltage and amperage were assessed during the electroporation cycle. The extent of coagulation (long, intermediate and short axes, volume, and sphericity index were analyzed using a 3D-segmentation software) was compared.
Results: Mean resulting voltage and amperage were 2545.3 ± 66.0 V and 26.1±1.8 A, respectively, for RL and 2537.3 ± 69.0V and 27.7 ± 1.8A, respectively, for LL without significant differences. Mean long, intermediate, and short axes were 37.4 ± 7.6 mm, 27.1 ± 3.5 mm, and 16.5 ± 4.4 mm for RL, respectively, and 37.5 ± 5.7 mm, 27.3 ± 5.3 mm, and 18.2 ± 3.4mm, respectively, for LL without significant differences. Volume and sphericity index were 8.6 ± 3.2 cm^3 and 1.7 ± 0.3, respectively, for RL and 9.8 ± 3.8 cm^3 and 1.7 ± 0.3, respectively, for LL without significant differences.
Conclusion: In this acute porcine liver model, previous transarterial embolization with iodized oil shows no effect on both technical parameters and extent of coagulation after IRE.

1404.5

Vascular organ isolation chemotherapy with extraction (voice)

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Purpose: A novel method of hepatic isolation using an implantable arterial access system that allows simultaneous control of hepatic arterial and portal inflows, superselectivity and repeatability is described. Safety and efficacy of the system was assessed, and the concepts of vascular volume displacement (VVD) and chemoextraction via reverse hepatic flow are introduced.
Material and Methods: An arterial access system was anastomosed to axillary or femoral vessels. Treatment was performed every 3–4 days, with three sheaths and balloons occluding the CA, SMA and HA with microcatheter superselection. Pressure measurements were obtained, and oxaliplatin infused to approximate segmental liver vascular volume and platinum levels were measured.
Results: Eight infusions (two patients with inoperable and treatment refractory secondary intestinal cancer) are described.
Infusions required day-only admissions under GA with minimal side effects/discomfort. Pressure measurements indicated minimal hepatic-systemic drug leakage. Wedge pressures were 0, and the platinum gradients were 20x systemic with contrast and 2–8x without. The CMAXs were 250 mg/ml (625 ml) and 375 mg/ml (94 ml) of platinum at 50 mg/m^2.
Haematological and biochemical findings indicated minimal systemic toxicity with marked improvement on PET.
Conclusion: A high CMAX continued for 2–25 min of ischaemic time to multiply the platinum exposure (AUC). VVD with glucose, oxaliplatin and contrast removes non-reversible binding effects, which typically nullifies 99% cytotoxicity. Initial uptake half-life of oxaliplatin is very rapid (Talpha ½ = 9–16min); hence, the minimal side effects. Delivered oxaliplatin concentration exceeded LD99.9% of in-vivo tested cell lines.
Hepatic isolation was possible using a multicatheter implantable access system. The delivery of cytotoxic agents is efficacious and repeatable.

1404.6

Are VX2 tumor cells sensitive to antineoplastic drugs used in chemoembolization?

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Purpose: Rabbit VX2 carcinoma is the most commonly used tumor model to evaluate the efficacy of chemoembolization procedures. However, sensitivity of VX2 cells and human liver cancer to antineoplasic drugs has not been compared. We assessed the cytotoxic effects of 10 anticancerous agents in VX2 cell cultures.
Material and Methods: A VX2-cell monolayer culture was established in 96 wells for 24 h (80% confluence). Cytotoxic effect, expressed as the half maximal inhibitory concentration (IC50), was evaluated after a 72-h incubation with various drug concentrations by colorimetric test and compared to human cancer cell data in the literature. Ten drugs of various classes were tested: anthracyclines (doxorubicin, idarubicin), platins (cisplatin, carboplatine, oxaliplatin), irinotecan, mytomicin-C, 5-fluorouracil, sunitinib, and bevacizumab.
Results: Anthracyclines (idarubicin and doxorubicin) were the most cytotoxic drugs (IC50 = 1.52 and 1.59 µM), followed by sunitinib (12.5 µM),

CHAPTER 5 – DISCUSSION PART 1: TRIAL OUTCOMES AND FUTURE DIRECTION

The purpose of this half of the Discussion is to analyse the outcomes from the two trials that were reported in Articles I and II together along with other relevant but unreported data to obtain a better understanding of:

a) the performance characteristics of the UVAS,
b) the safety profile of the UVAS,
c) the outcomes and safety profile of the LRC technique developed, and
d) the future direction of the technology and technique

The mechanisms and potential benefits of the new LRC technique developed in Article II, hepatic organ isolation (OIC), are discussed in Chapter 6, Article III.

5.1 Safety & Performance of the UVAS

Data compiled from the HELP (Article I) and OIC trials (Article II) relevant to the performance and safety of the UVAS are discussed below in Section 5.1.1 and 5.1.2 respectively.

5.1.1 Compiled Performance Data

The key clinical trial data relevant to the performance of the UVAS during the HELP and OIC trials have been compiled and tabulated below in Table 5.1. The data is indicative of the performance characteristics of the UVAS as an implantable vascular access device that allows intermittent repeated access either in the form of a general vascular access device or as a multicatheter access system.

Table 5.1 – Summary of relevant clinical data from the HELP and OIC trials.

Trial	Patient	Sex	Age	Implant site (CFA/AA) [a]	Implant Days	Devices Implanted	Total Plungers Used	Pump connections/ Catheter access procedures	Total pump connections [b]	No. of access devices used in each access procedure	Total no. catheters used
HELP Trial	LP-301	M	68	CFA	9	2	8	3	6	-	-
	GB-304	M	79	CFA	24	2	10	1	2	-	-
	CM-305	F	70	CFA	19	2	8	3	6	-	-
	MP-306	F	82	CFA	14	2	8	3	6	-	-
	KW-307	M	76	CFA	9	2	4	1	2	-	-
OIC Trial	KF-101	F	55	CFA	14	1	3	3	-	1, 2, 2	5
	MS-102	M	67	AA	19	1	5	5	-	3, 3, 3	15
	LS-103	F	52	AA	28	1	6	6	-	3, 3, 1, 2, 2, 2	13
	TB-104	M	61	AA	29	1	9	8	-	1, 1, 1, 1, 1, 1, 1, 1	8
	AT-105	F	60	AA	35	1	7	6	-	3, 3, 3, 3, 1, 1	14
	LG-107	M	66	AA	28	1	6	5	-	3, 3, 3, 3, 3	15
	JP-108	M	67	AA	28	1	6	7	-	3, 3, 3, 3, 3, 3, 3	21
	DL-109	F	59	AA	25	1	7	6	-	3, 3, 3, 3, 3, 3	18
	DB-110	M	51	AA	24	1	7	7	-	3, 3, 3, 3, 3, 3, 3	21
	TR-112	M	69	AA	30	1	8	7	-	3, 3, 3, 3, 3, 3, 3	21
TOTAL		**-**	**-**	**-**	**335**	**20**	**102**	**82[c]**		**-**	**151**

[a] *CFA = common femoral artery; AA = axillary artery*
[b] *total pump connections = pump connections x devices implanted (HELP trial only)*
[c] *total number of access procedures = total pump connections (HELP trial) + catheter access procedures (OIC trial)*

5.1.1.1 Implantation of the UVAS

Between the two trials, a total of 20 UVAS devices were implanted successfully in 15 patients. As there were no unsuccessful implantation procedures or premature device explantations due to improper implantation procedures, this provides clinical evidence that the workup, suitability criteria, and specified operative technique specified in the trial protocols (Appendix D) were appropriate. The implantation of the 10 UVAS devices on the axillary artery (AA) and common femoral artery (CFA) each verifies that the device is suitable to be implanted on the peripheral arteries of the lower and upper limbs as intended.

The number of days the UVAS was implanted for in both trials provides evidence that the device can still perform as intended when implanted for up to 4 weeks. Additionally, in the HELP trial, it was shown that two UVAS devices were able to be safely implanted on the same host artery approximately 10-20mm apart from one another.

Shown below in Figure 5.1 is a successful implantation of the UVAS implant on the AA in one of the OIC trial patients. As can be seen, the procedure was executed as per the planned method described in Figure 2.7 (Section 2.2.1, Chapter 2).

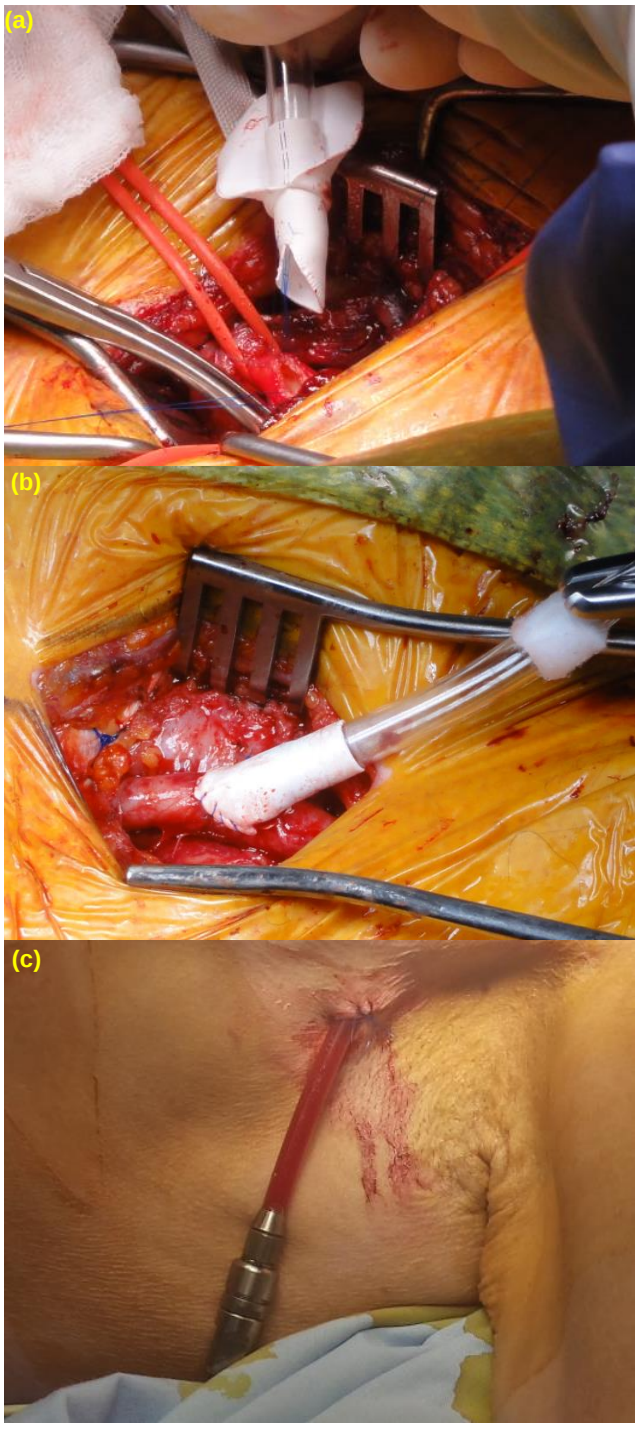

Figure 5.1 – Implantation of the UVAS implant on the AA in an OIC trial patient; the host vessel is exposed and tied off using vessiloops, and the inner and outer grafts of the UVAS Access Tube are trimmed to the desired anastomosis angle (a), the anastomosis is made (b), and the implant is tunnelled through a subcutaneous exit point under the pectoral muscle and the device closed with the plunger (c) before the exit site is dressed using routine wound care techniques.

5.1.1.2 Access Mode & Closed Mode with the UVAS

The capability of the primary function of the UVAS was demonstrated by the total number of successful access procedures (82) facilitated by the UVAS in the two trials; 22 successful connections to the extracorporeal pump and 59 catheter/guidewire/sheath access procedures were performed in the HELP and OIC trials respectively. In the OIC trial, this added up to a total of 151 catheter introductions through the UVAS implant via the haemostasis valve. This demonstrated the UVAS's ability to:

- be connected to standard vascular lines using a luer lock connection,
- withstand high pressures within the device without any clinically significant leaks at the anastomosis as the UVAS was pressurised up to 300mmHg in some cases in the HELP trial,
- facilitate simultaneous multicatheter access repeatedly, and
- maintain patency of the lumen of the UVAS implant via a continuous saline flush line during the multicatheter access procedure through the UVAS in the OIC trial.

The use of the UVAS in the HELP and OIC trials for connections to the pump circuit and for multicatheter access is shown below in Figure 5.2.

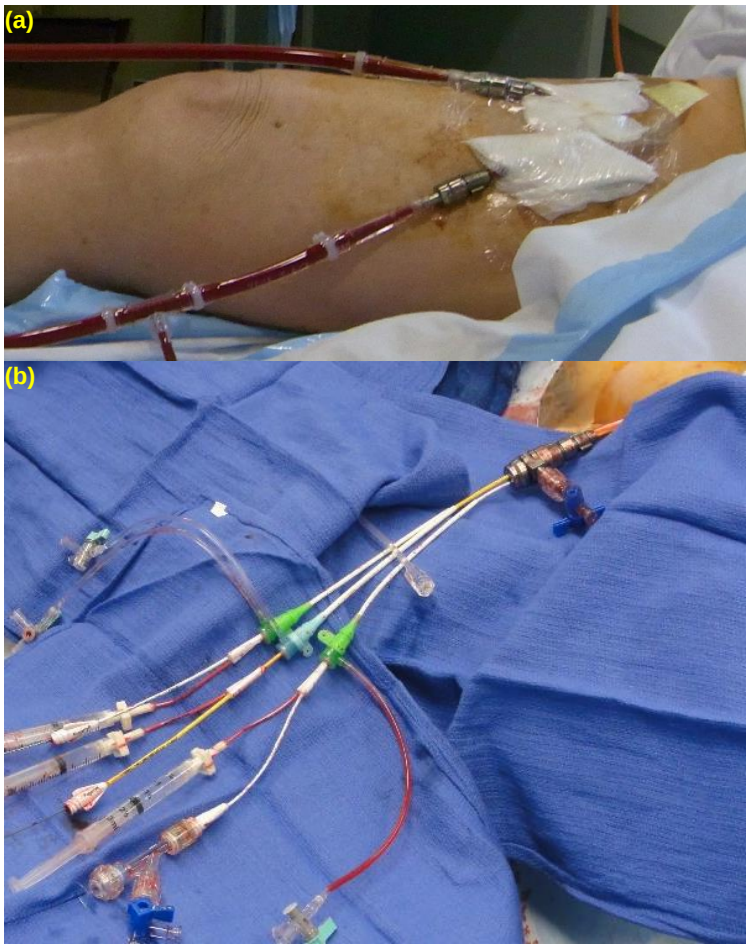

Figure 5.2 – The use of the UVAS in its Access Mode in the HELP and OIC trials; the two UVAS implants are connected to the extracorporeal pump circuit during HELP (a), and up to three catheters are introduced through the haemostasis valve with their sheaths and guidewires during OIC (b).

After each access procedure, the UVAS was closed using the plunger. The total number of plungers used (102) provides clinical verification of the safety and performance of the overall plunger design of the UVAS (i.e. a retractable seal of the lumen of the device approximately level with the host arterial wall) for the UVAS to safely remain in its Closed Mode. No leaks of blood or of the backfilled saline/antibiotic solution out of the device were observed throughout any of the plungers used which demonstrates the seal integrity achieved by the plunger. Additionally, no clots were observed in the space behind the plunger tip demonstrating the

adequacy of the seal at the plunger tip and regular changing of the plunger were sufficient in ensuring the patency of the UVAS implant tube.

5.1.1.3 Explantation of the UVAS

A total of 20 UVAS devices were explanted from 15 patients who were all followed up for 6 months thereafter. All explantation procedures were unremarkable. The implant site wound was cut down and the UVAS cut across the anastomosis and the segment of the remaining vascular graft was used as a patch to close the host artery. The UVAS was pulled out through the exit site tunnel and the exit wound closed with sutures. The implant site and device exit wounds were managed as routine surgical wounds and healed relatively quickly. Figure 5.3 shows the progress of the wounds over 3 months at which point it had healed completely. This data verifies that the wound management guidelines specified in the operative technique in the trial protocols were appropriate.

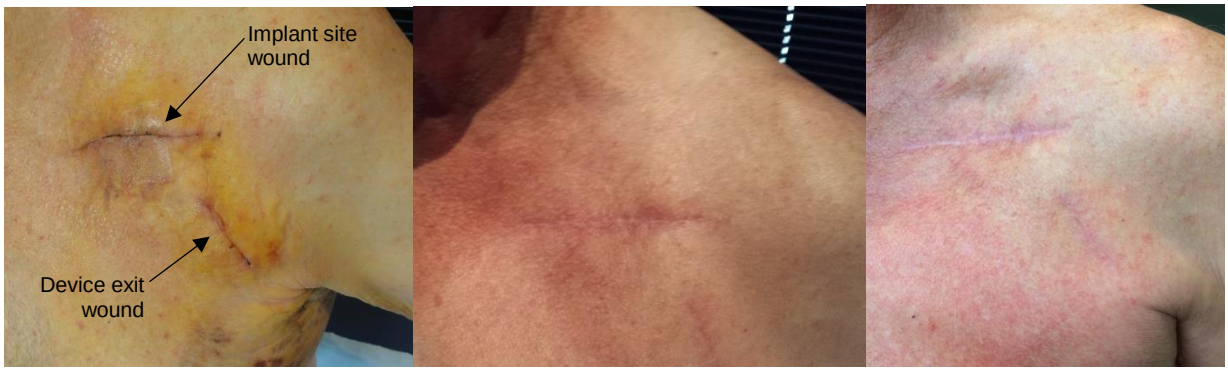

Figure 5.3 – Follow up photos of the implant site and device exit wounds of patient JP-108 from the OIC trial at 1 week (left), 1 month (middle), and 3 months (right) after explantation of the UVAS.

5.1.2 Compiled Safety Data

All adverse events (AEs) and serious adverse events (SAEs) in the two trials were reported using the common terminology criteria for adverse events (CTCAE v4.0) [250]. The relatedness of each AE to the study treatment was defined as either definitely, probably, possibly, unlikely, or entirely unrelated. AEs categorised as either “definitely”, “probably”, or “possibly” related to the study treatment were examined in detail as each AE reported explicitly mentioned any device related issues. A summary of the adverse AEs specifically related to the use of the UVAS have been extracted from the AE reports of the HELP and OIC studies and summarised below in Table 5.2.

Table 5.2 – Summary AE data from the HELP and OIC trials. All AEs and SAEs have been listed but only the device related SAEs/AEs are of interest.

Trial	Patient	All SAEs	Device related SAEs	All AEs	Device related AEs	Grades of device related AEs	Details of device related AEs as reported on the case report forms
HELP Trial	LP-301	2	0	19	2	Ungraded Ungraded	Heaviness & sensitivity of right leg Clot in distal plunger
	GB-304	2	0	31	3	Grade I Ungraded Ungraded	Discharge at the implant site Haematoma in explant wounds in proximal thighs Pain in left leg from mid-thigh to above knee

Table 5.2 – Summary AE data from the HELP and OIC trials. All AEs and SAEs have been listed but only the device related SAEs/AEs are of interest.

Trial	Patient	All SAEs	Device related SAEs	All AEs	Device related AEs	Grades of device related AEs	Details of device related AEs as reported on the case report forms
	CM-305	4	0	26	3	Ungraded Ungraded Ungraded	Large oozing and clot at implant site (around both access devices) Haematoma oozing from lower thigh wound (explant wound) Intermittent oozing at site of access device (x2)
	MP-306	2	0	30	4	Grade II Grade I Grade I Grade II	Severe pain in left thigh and hip (pain at implant sites) Bleeding from device exit sites Ooze from device exit site Bleeding and oozing at explant wound
	KW-307	1	0	20	4	Grade I Grade II Grade II Grade II	Pain at implant site Blood loss around the cannulation site and in the drain Leaking haemoserous fluid on lower wounds of left thigh Large ooze from left thigh wound
OIC Trial	KF-101	2	0	9	1	Grade II	Haemoserous ooze and some pus observable at explant site
	MS-102	0	0	13	3	Grade I Grade II Grade II	Patient had complaints of pain Chest wall displays small to moderate ooze Slight oozing around site under dressing
	LS-103	0	0	14	2	Grade I Grade II	Mild pain on operating area. Dressing on right breast, close to axillary area, oozing blood
	TB-104	1	0	13	2	Grade II Grade II	Slight oozing from under dressing, mostly clean, dry, intact. Slight oozing to left chest wound from removal of drain
	AT-105	1	0	11	3	Grade I Grade II Grade III	Small ooze from explantation site. Patient complained of 5/10 pain. Patient complaint of pain around chest, left clavicle, left shoulder, abdomen and back, mostly in inspiration. 5-7/10
	LG-107	1	0	16	3	Grade I Grade I Grade I	Minor oozing from implant site treated with drainage. Post surgical pain from implanted access system. Minor oozing from device explant wound site.
	JP-108	0	0	18	4	Grade I Grade I Grade I Grade I	2/10 pain complained around the implantation site Small ooze noted from device explanted surgical wound area. Slight oozing at implant site. Slight oozing at implant site.
	DL-109	0	0	13	3	Grade I Grade II Grade II	Mild pain Patient complaint of moderate pain with score of 6/10. Mild pain on the shoulder
	DB-110	0	0	17	3	Grade I Grade II Grade I	Numbness around the stitch line Insomnia attributed to presence of device Small ooze on primapore.
	TR-112	1	0	15	1	Grade I	Moderate bloody oozing from the wound site.
TOTAL		**17**	**0**	**265**	**41**	**-**	**-**

A total of 41 device related AEs were reported of which 16 and 25 were from the HELP and OIC trials respectively. The main types of device related AEs that were reported in both trials were typically reported as events of pain, infection, haemorrhage, thrombosis and clotting using the CTCAE coding system. Due to the strict CTCAE terms and codes available, various clinical research associates and investigators reported the same observations differently. For example, serous fluid around the UVAS implant would be reported as an “infection” event or

as a “haemorrhage” event depending on the reporting personnel. Therefore, the CTCAE terms and codes have not been included in Table 5.2 but have be discussed in the subsections below.

Generally, all device related AEs were either related to pain around the implant site or explant wound, “oozing” of serous fluid/blood around the UVAS implant tubes, and some clots between the ribs of the plunger tip. They were all mainly grade II or lower. Most importantly, there were no device related SAEs. This data verifies the overall safety of the UVAS system, its components, and intended use. The AEs that were observed provides qualitative information as to whether the anticipated side effects in the use of the UVAS in Section 2.5, Chapter 2 require updating for future use of the UVAS.

5.1.2.1 Pain

Pain was reported in 8 out of the 15 patients. Pain is always expected with postoperative surgical wounds especially in the limbs where there is more movement. Most of the pain related AEs were reported approximately immediately after the implantation and explantation procedures which suggests it was a result of the surgery itself. The wounds from the implantation and explantation of the UVAS system are unavoidable and thus it is probable that all 15 patients experienced these pains but was underreported by the more stoic patients.

Although pain is a subjective measure, most events of pain were able to be categorised as grade II or lower as all cases of pain could be either addressed through orally administered analgesia and or subsided over time. Overall, pain associated with the implantation and explantation of the device is to be expected as a general side effect of the surgical procedure. Based on the reported data and considering the minor intervention for the event throughout both trials, pain could be considered a minor side effect of implanting and explanting the UVAS.

5.1.2.2 Infection

Some of the fluid, haemoserous “ooze” or blood discharged around the implanted UVAS implants were reported as infections. This was the case in all 15 patients except for LP-103. This was most likely because the patients in the HELP trial had critical limb ischemia and thus already had multiple ulcers on their limbs with fluid discharge. Consequently, it may have been missed by the investigators who may have attributed it to the patient’s underlying condition.

It should be noted that a septic episode (fever) and septicaemia was observed in patients GB-304 and CM-305 respectively. However, these SAEs were ruled as not related to the device as swab analysis and observations of the anastomosis/implant site during the explant procedures showed no signs of infection around the device. The patient cohort treated in the HELP trial were highly prone to infectious events due to their underlying condition. Both patients had already developed gangrenous ulcers of their lower limbs prior to the implantation

and use of the UVAS. The same "oozing" of serous fluid observed in the OIC trial without any infectious SAEs gives merit to the idea the infectious SAEs in the HELP trial were most likely due to the patient's underlying condition.

The discharge at the device exit sites were addressed with standard wound management. Based on the combined data, this should continue to be anticipated as a grade II side effect at the exit wounds of the UVAS which should be dealt with via routine wound management. No device related blood stream infections were reported in either trial but due to the invasive nature of the UVAS, bloodstream infections should continue to be an anticipated AE.

5.1.2.3 Haemorrhage

Some of the fluid, haemoserous "ooze" or blood discharged around the implanted UVAS implant tubes were reported as haemorrhages. Haematomas in the surrounding tissue to the implant site and haemorrhage via the wound drains were observed in most patients as bruising. It is quite possible that the "ooze" was a result of subcutaneous haemorrhaging as well. The bruising subsided after a few days for most patients and thus was also reported as grade II events or lower. Therefore, and as anticipated, haemorrhaging is another side effect in the use of the UVAS that clinicians should be made aware of and which most likely is a consequence of the surgical procedure.

5.1.2.4 Clots Between Plunger Ribs

Plungers and the lumen of the UVAS implant tubes were inspected at every plunger changeover or access procedure. Occasionally, small clots were observed on the plunger, mainly in small quantities between the ribs of the plunger tip. This was noted to be old blood - present from when the plunger was inserted. There were no observed clots adhering to the blood-contacting surface of the plunger tips. The clot around the plunger tip can be considered a non-significant risk due to its small volume and its containment between the ribs. Thus, such a clot would always be removed from the system when the plunger is retracted.

The lack of clot on the surface of the plunger tip was considered to be a positive sign that there was no significant clot growth at the anastomosis site. This was confirmed when the UVAS was aspirated just prior to the access procedures with no observable thrombus being ejected.

The observed clots around the plunger tip provides confirmation of thrombus build-up that could eventuate to a clot within the host vessel but can be prevented via regular plunger changes.

5.1.2.5 Thrombosis and Clotting

One clot related SAE event was reported in the HELP trial for KW-307 but was not attributed to the device. Significant thrombus formation within the pump circuit and also within the UVAS was observed during aspiration. The cause of this event was positively identified as an

inadequate level of anticoagulation (ACT levels were allowed to decrease to around 130seconds for at least 2 hours from a recommended 180seconds minimum). Once the pump circuit was replaced and the anticoagulation was corrected, the patient successfully continued treatment for a further 15 hours with no clotting events. This SAE was ruled to be a result of the treatment procedure itself and not related to the UVAS since all blood perfusion procedures require appropriate anticoagulant drug management.

Overall, the risk of thrombosis/clotting will always be present in vascular implants like the UVAS regardless of whether any device related clots were observed during the two trials or not. Hence, the risk should continue be an anticipated side effect of the UVAS and should be managed with concomitant anticoagulation therapy as needed.

5.1.3 Summary of Performance & Safety Data

A summary of the performance (Section 5.1.1) and safety clinical data (Section 5.1.2) from the HELP and OIC trials is provided in Table 5.3 for which the details have been discussed in the sections above. A total of 5 patients were implanted with two UVAS devices each on the CFA in the HELP trial and a total of 10 patients were implanted with a single UVAS on the AA in the OIC trial. The devices were implanted for approximately 2 weeks and 4 weeks in the HELP and OIC trials respectively. The plunger was changed approximately 7-8 times (i.e. 3-4 times per implant) and the implant was accessed and connected to the extracorporeal pump circuit 4-5 times (i.e. 2-3 times per implant) in the HELP trial. In the OIC trial, the plunger was changed approximately 6-7 times and the implant was accessed between 6 times on average using 2-3 catheters/guidewires/sheaths per access procedure (i.e. a total of 14-15 endovascular devices per UVAS). No device related SAEs were reported in either of the two studies. Approximately 3-4 device related AEs and 2-3 device related AEs were reported per patient for the HELP and OIC trials respectively. Most device related AEs were either grade II or lower as per the CTCAE criteria.

This data provides clinical evidence of the UVAS's suitability to be safely implanted on a patient's peripheral arteries of the upper and lower limbs, the suitability of the implantation workup procedure, and the month-long implantation capability of the system. The plunger changes and ability to facilitate repeated extracorporeal pump connection and multicatheter access is clinical evidence of the overall functionality of the system's interaction with its sub-components in being able to safely facilitate the primary function of the UVAS system (i.e. safely providing repeatable vascular access).

The device related AEs were generally related to discharge of fluid (blood, serous fluid, etc.) around the implanted UVAS Access Tube, and minor pain and discomfort shortly after the implantation/explantation procedures. These were all common AEs and side effects of percutaneous implants (e.g. central venous catheters, peripherally inserted central catheters)

and anticipated with the UVAS as described in Chapter 2. The data generated from the two trials provide good guidance on the AEs and side effects to be expected with the use of the UVAS. Most importantly, these side effects are manageable and are outweighed by the performance characteristics offered by the UVAS.

Table 5.3 – Summary of clinical data available for the UVAS from the OIC trial, the significance of the data and its indication of overall safety/performance characteristics of the system.
Blue = data from HELP trial; Green = data from OIC trial

Data Type		Total	Mean	Significance of Data	Indicator of*	
					P	S
Number of patients		5	-	Demonstrates suitability of the UVAS for a broad demographic provided the specified patient workup in the trial protocols are carried out.	-	-
		10	-			
Age		68-82	75.0			
		51-69	60.7			
Sex (M:F)		3:2	-			
		3:2	-			
Implant Site		CFA†	CFA†	Evidence of UVAS implantation capability on peripheral arteries of the upper and lower limbs.	✓	✓
		AA‡	AA‡			
Implant Days		75	15	Evidence of prolonged implantation capability of the UVAS.	✓	✓
		260	26			
Number of:	**UVAS implants used**	10	2	Evidence of capability of dual device implantation per patient and suitability of workup procedures.	✓	✓
		10	1			
	Plunger and installation tools used	38	7.6	Evidence of functionality of the UVAS plunger system to seal the device as well as compatibility with the implant.	✓	✓
		64	6.4			
	Pump connections	22	4.4	Evidence of: • compatibility of the UVAS connector with the implant and an extracorporeal circuit. • implant being able to withstand high pressures & perfusion flow rates. • the implant being able to provide multiple access procedures	✓	✓
	Catheters used	151	15.1	Evidence of: • compatibility of the UVAS haemostasis valve with catheters, guidewires, and introducer sheaths. • capability of the UVAS haemostasis valve's flushing function	✓	✓
	Catheter access procedures	60ϕ	6	Evidence of the implant being able to provide multiple access procedures	✓	✓
	Device related SAEs	0	0	Evidence of overall safety of the system in its intended use.	-	✓
		0	0			
	Device related AEs	16	3.2	Evidence of overall safety and performance of the system in its intended use. Provides qualitative information on possible side effects associated with the system.	✓	✓
		25	2.5			

** P = performance; S = safety; † CFA = common femoral artery; ‡AA = axillary artery*
ϕ Article II reports 57 LRC procedures in total, however 3 additional catheter access procedures were also carried out (see Sections 5.2.1.3 and 5.2.1.4)

5.2 Analysis of the LRC Technique

In addition to the results reported in Article II for the OIC trial, the following section will discuss other relevant results relevant to the OIC technique itself.

5.2.1 Learning Curve

The OIC trial consisted of three main procedures: implantation of the UVAS, OIC infusion procedures, and explantation of the UVAS. The procedure time for the implantation and

explantation procedures were measured as the time from the first cut to the final stitch while the OIC infusion procedure time was measured from the time of the UVAS plunger being removed till the device was closed again post-infusion. The graph for the procedure times recorded for each patient is shown below in Figure 5.4 with the curve for the infusion procedure representing the mean of all the infusion times for each patient.

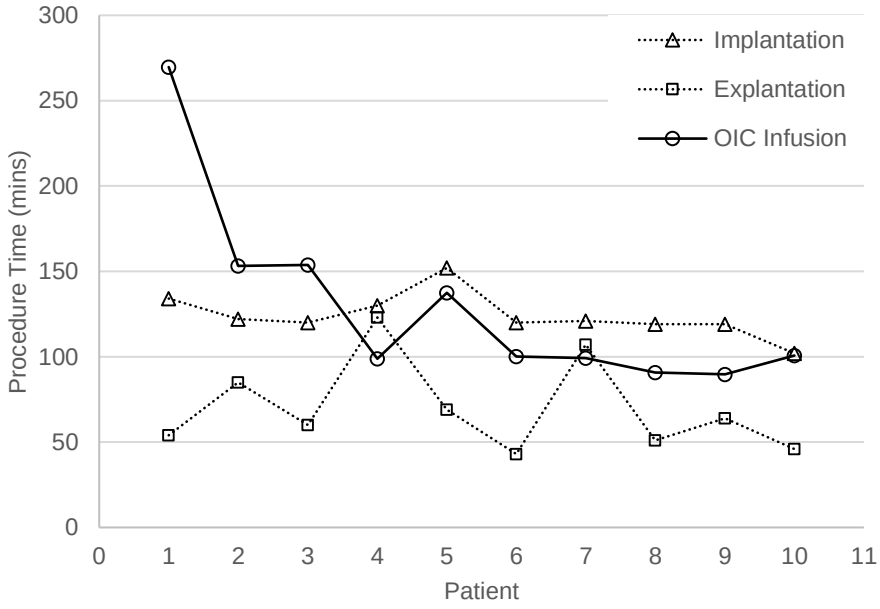

Figure 5.4 – Implantation, explantation, and mean LRC infusion procedure times for the 10 patients in the OIC trial (Article II).

The graph in Figure 5.4 shows that the implantation and explantation procedure times are consistent and hence there is really no learning curve associated with the procedure. This is unsurprising given the design of the UVAS which utilises standard vascular grafts which cater to any surgeon experienced in performing end-to-side anastomoses. However, an obvious learning curve can be observed with the OIC infusion procedure. Splitting the subjects into two even cohorts demonstrated a significant difference between in procedure times; 147.4 ± 69.6 versus 96.0 ± 29.6 for patients 1-5 (n = 25) versus patients 6-10 (n = 32) respectively (P < 0.01). It is important to consider whether this improvement was driven by the clinician's skill development or the iteration of the technique. The former would suggest that a similar learning curve should be anticipated for all clinicians while the latter suggests the absence of any learning curve provided the iterations to the technique are adopted.

As can be seen from Figure 5.4, the LRC procedure time for the first three patients were the longest and almost resemble to be outliers compared to the latter seven patients. It must be taken into account that not only was this the first time this OIC technique was being attempted by the investigators, but that this was a world-first technique and hence most the technical issues encountered were in the first half of the trial more so than the latter. The specific issues encountered are described below in Sections 5.2.1.1 to 5.2.1.4. All issues were unrelated to the clinician's technical skills and were addressed through technique iterations which were

implemented in patients 6-10 to avoid recurrence of any of the same issues and dramatically improve the infusion procedure time. Therefore, provided other clinicians or study groups are made aware of the issues identified in the first half of the patients in this study along with the prevention/mitigation procedures, it is reasonable to expect this LRC technique to be reproducible in other centres with procedure times similar to that of patients 6-10 from the OIC trial.

5.2.1.1 UVAS Implantation Location

The first patient treated (KF-101) with the new LRC technique using the UVAS took 269.7 minutes on average per infusion. The patient was implanted with the UVAS on the CFA as it was believed to be a suitable location based on the experience from the HELP trial. While introduction of the catheters through the UVAS was not an issue, the balloon catheters could not be guided into the celiac trunk or the SMA due to the tortuosity of the bends when approaching from the lower limb. Consequently, and as seen in Table 5.1, only one or two catheters were introduced via the UVAS in the first patient and the other balloon catheter percutaneously introduced via the brachial artery for each infusion. Also, organ isolation was not achieved on the second procedure and thus only a single infusion catheter in the hepatic artery was used to mimic HAI.

A treatment related SAE eventuated as result of the catheter introduced through the brachial artery percutaneously. The patient suffered a false aneurysm which was repaired during the UVAS explantation procedure after the three infusions.

The difficulty of guiding the catheters to their target arteries led to the procedure time for the first patient being considerably longer than all other patients. Such a lengthy procedure would also make the technique infeasible for repeat treatments. Consequently, the UVAS was implanted on the AA of the upper limb for the remainder of the patients. This change in location proved critical as all three balloon catheters were able to be guided to their target arteries via the UVAS alone and no percutaneous cannulations were required.

5.2.1.2 UVAS Implantation Angle

In the fourth patient (TB-104), the UVAS was implanted perpendicular to the patient's host artery. This angle presented a tortuous path for the clinician to introduce multiple catheters past the bend between the UVAS and the host artery. Consequently, only a single catheter could be introduced through the UVAS at any one time which prevented the patient from receiving the OIC treatment. Instead the patient was treated with repeated HAI through the single infusion catheter instead. This is reflected in Table 5.1 which shows that this patient, unlike all other OIC patients, received only a single catheter through the UVAS for each access procedure.

This issue also brought to light the risk of vessel dissection and perforation that are accompanied with a UVAS implant orientated perpendicularly to the host artery. Any catheter/guidewire introduced at such an angle is likely to hit the wall of the host artery directly as it is introduced through the UVAS. The issue was addressed by implanting the UVAS at an oblique angle to the host artery for the remaining patients in the trial who were all observed to be successfully cannulated with multiple catheters simultaneously.

5.2.1.3 Balloon Compliance

In the third patient (LS-103), a vasospasm was observed during the third session of the LRC procedure and consequently, the OIC infusion could not be delivered. This was believed to be a consequence of using longer non-compliant balloon catheters to occlude the target arteries. Such balloon catheters are typically reserved for angioplasty but were initially opted for as the lengthy nature of the balloons presented an opportunity to occlude all collateral arteries supplying non-target organs so that better isolation of the liver could be achieved. The spasm was self-resolved by the next infusion procedure but it was decided that softer more compliant balloon catheters would be used (Fogarty balloon catheters, Edwards Lifesciences). The difference between the balloons used in the first three patients compared to the remainder of the patients is shown below in Figure 5.5.

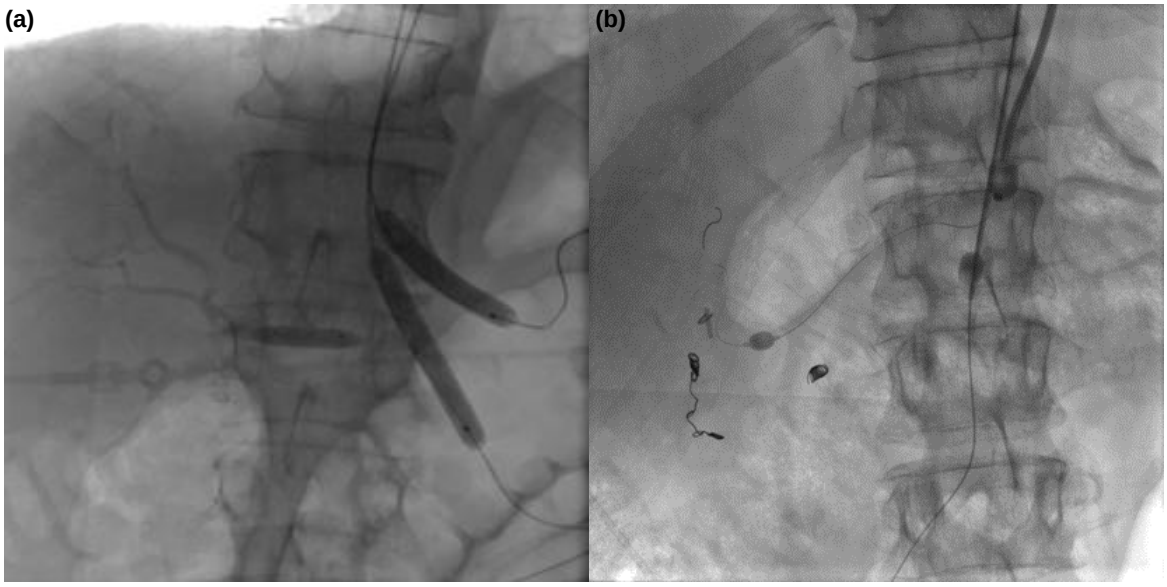

Figure 5.5 – Angiogram of the LRC infusion procedure showing the long non-compliant angioplasty balloons used for the first three patients (a) and the soft compliant Fogarty balloons used in the remaining seven patients (b).

5.2.1.4 Vessel Size

Finally, in the fifth patient (AT-106), a dissection of the hepatic artery with the infusion catheter occurred on the third OIC infusion procedure which was reported as another treatment related SAE. Patency of the artery was restored the following week by deploying a covered stent across the dissected segment of the artery (Figure 5.6). It was noted in the CT-angiogram during the patient workup and screening that this patient had smaller than average vessels.

As such, the dissection was attributed to poor patient selection and the patient inclusion criteria was made more stringent to exclude all patients with small vessels.

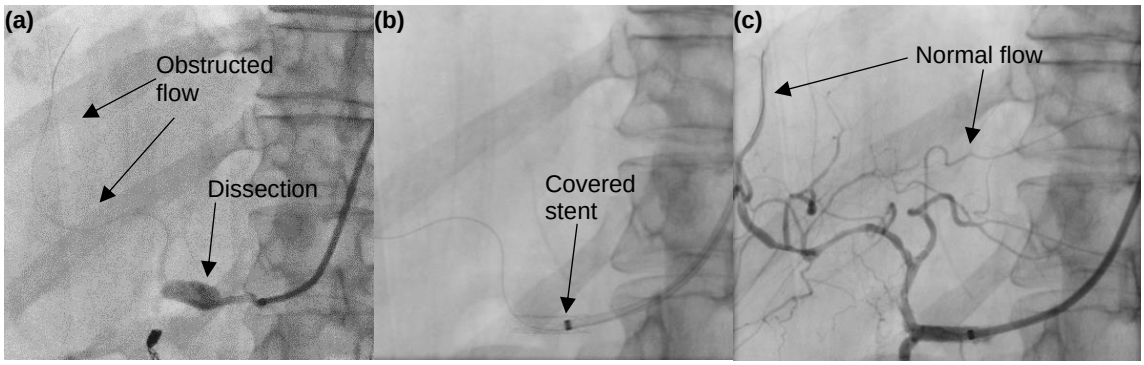

Figure 5.6 – Angiogram of the hepatic arterial dissection leading to obstructed flow (a). A covered stent was deployed (b) to restore normal flow (c).

5.2.2 Feasibility of Technique

Feasibility of the new LRC technique developed in the form of hepatic OIC treatment for patients with CRCLMs, can be assessed by reviewing the number of successful procedures where liver isolation was successfully achieved compared to the number attempts. This is tabulated in Table 5.4.

Table 5.4 – Overall success rate of OIC setup achieved in trial

Description		***n* (%)**
Total OIC attempts		60 (100%)
Unsuccessful	Patient 1 (HAI in 2nd procedure)	1 (1.7%)
	Patient 3 (vasospasm in 3rd procedure)	1 (1.7%)
	Patient 4 (HAI all 8 procedures)	8 (13.3%)
	Patient 5 (vessel dissection in 3rd procedure)	1 (1.7%)
Success rate		**49/60 (81.7%)**

For a first-in-human study of the newly developed OIC technique, a total success rate of 81.7% in being able to achieve the organ isolation setup sought after is a promising result. It must be taken into account that the all unsuccessful attempts were due to the learning curve which, as mentioned earlier (Section 5.2.1), could all be prevented as they were iterative steps rather than due to a lack or limitation of clinician skill. Assuming only the issues encountered in patients 1 and 4 (implant location and implantation angle) are addressed and that the vasospasm and vessel dissections are unavoidable, an event free rate of 96.7% (58/60) can be expected. It would even be reasonable to assume that a 100% success rate can be achieved as the issues of vessel dissection and vasospasm can be avoid as well provided the iterative improvements recommended (Section 5.4.2) are adopted in future use of the UVAS. The level of organ isolation achieved by the technique's indirect obstruction of the portal vein has been discussed in Article II and in particular Fig 3b of the article.

Finally, in terms of complexity, the technique developed is no more complex than that of HIPEC, IHP, or PHP. HIPEC has become a first line therapy while IHP and PHP have

progressed as far as phase III studies. The developed technique is actually significantly simpler as it was designed to be repeatable IHP-like technique. The surgical invasiveness of IHP has been significantly diminished and complex extracorporeal circuits and drug filtration systems like that of PHP are entirely unnecessary. Therefore, based on the success rate achieved through the OIC study as well as the reduced complexity of the technique compared to other LRC techniques, the developed technique can be considered feasible and warrants further investigation.

5.3 Other Outcomes from OIC Trial

Other outcomes and data generated from the OIC trial not reported in Article II have been discussed in the subsections below. The data discussed concern the non-UVAS related AEs and SAEs reported and OS data.

5.3.1 Analysis of AEs

The safety profile of the developed technique is best represented by the AEs reported throughout the trial from enrolment to 6-month follow-up. AEs related directly to the UVAS device has already been discussed in Section 5.1.2 and thus AEs related to the OIC treatment itself are discussed below. A total of 140 AEs were reported from the study. As summarised in Table 5.5 and depicted in Figure 5.7 below, the vast majority of all AEs reported were either grade I or II events (90%). Of the 14 events that were reported as grade III or higher, 8 were attributed to the study treatment or the UVAS device.

It is worth noting the low grades assigned to most AEs throughout the study. The lower grade AEs are discussed in Section 5.3.1.2 while the higher grades are discussed in Section 5.3.1.1.

Table 5.5 – AE grades and their relation to the treatment.

AE Grade	Relatedness to Treatment			Total
	*LRC Technique Related**	*UVAS Related**	*Unrelated*	
I	73	14	10	97
II	16	9	4	29
III	6	2	4	12
IV	0	0	0	0
V	0	0	2	2
TOTAL	95	25	20	140

** loosely related only (i.e. can vary between possibly, probably or definitely related)*

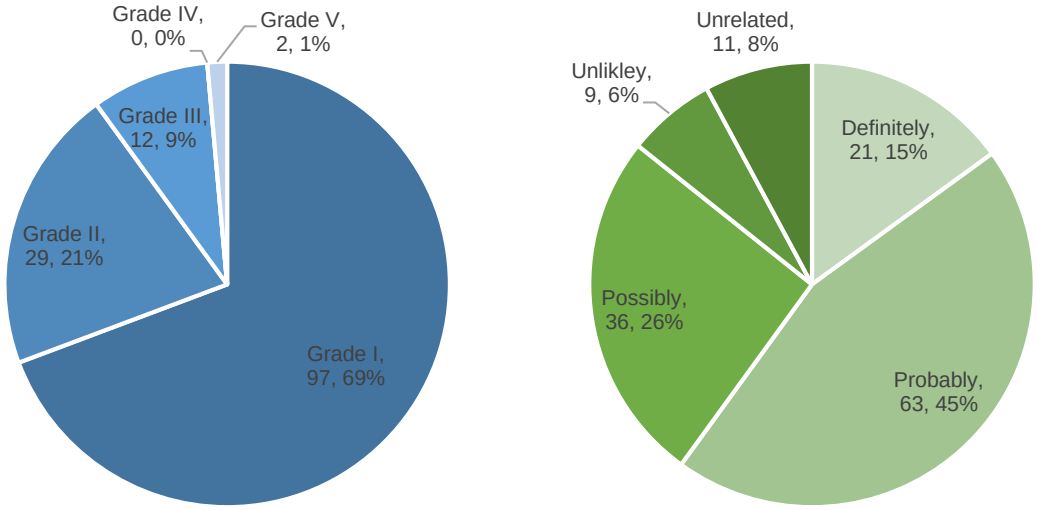

Figure 5.7 – Distribution of AE grades (left) and relatedness to the OIC treatment or UVAS device (right).

5.3.1.1 Grade III – V AEs and SAEs

Of the 14 grade III-V AEs, 6 were classified as SAEs of which 2 were related to the false aneurysm and dissection of the hepatic artery which have already been discussed in Sections 5.2.1.1 and 5.2.1.4. The 4 other SAEs were a result of the patient's underlying metastatic disease: one case of prolonged grade III abdominal pain, and three patient deaths. Two other grade III events were considered unrelated to the treatment (hypotension and atrial fibrillation). The remaining 6 grade III events and details have been provided below in Table 5.6.

Table 5.6 – Grade III AEs, details, relatedness, and interventions.

AE description	Details	Relatedness and Intervention
Pain x 3 cases	1 case: UVAS wound area 2 cases: abdominal pain	UVAS device related; oral analgesia Treatment related; oral analgesia
Hypertension	Blood pressure > 140/90 mmHg	Possible side effect of general anaesthesia on patient's hypercholesterolemia.
Haematoma in hepatic artery	From potential false aneurysm or dissection due to balloon rupture	Possibly treatment related; occurred post infusion and covered stent used to treat affected region at next infusion.
Suspected thrombus	In host artery around catheters due to not connecting the luer lock on the haemostasis valve to a continuous flush line.	Treatment related; vitals observed and anticoagulants administered. No symptoms reported by trial completion.

The treatment/UVAS related events of pain have already been discussed in Section 5.1.2.1, and the suspected thrombus formation within the host artery was a result of improper use of the UVAS. The hematoma in the hepatic artery as a result of a balloon rupture was most likely a result of the clinician inserting the balloon catheter through the seal of the sheath more than once.

Overall, apart from the 2 treatment/UVAS related SAEs discussed, the OIC technique did not have a substantial contribution to the more clinically significant adverse events.

5.3.1.2 Grade I – II AEs

Of the 97 grade I AEs, 73 (52%) and 14 (10%) were loosely attributed to the OIC treatment or the UVAS device respectively. Of these, only 9 (6%) and 6 (4%) grade I AEs were categorised as definitely or probably related to either the treatment or the UVAS. Similarly, of the 29 grade II AEs, 16 (11%) and 9 (7%) of them were loosely related to the treatment or the UVAS respectively. Of these, 8 AEs (6%) each were deemed as probably or definitely related to the OIC treatment and the UVAS device.

Most the grade I-II AEs were comprised of myelosuppression, nausea, vomiting, peripheral neuropathy, fever, and pain (UVAS wound/exit site plus abdominal). Due to the concomitant use of capecitabine, the pre-existing peripheral neuropathy from previous systemic oxaliplatin therapies, and the emetic side effects of general anaesthesia, it was difficult to discern whether these AEs were caused solely by the OIC treatment itself. Nonetheless, given that PEEP was used to reduce the hepatic venous outflow instead of any real physical obstruction, it is quite likely that there was a leak of the infused oxaliplatin into the systemic circulation. Therefore, it is quite probable that a portion of these grades I-II AEs reported are directly related to the OIC treatment although it is not quantifiable. Hence, to err on the side of caution, future studies replicating this technique should anticipate all these AEs as accompanying side effects of the OIC treatment.

5.3.2 Overall Survival Data

The 6-month survival reported for the study was 70%. Three patients (one with partial response and two with stable disease) had not yet reached OS upon writing this thesis with their OS > 2 years so far. However, OS was not a primary endpoint in the study and no firm conclusions about the OS data can be made. The three patients with OS > 2 years received post-treatment therapy in the form of systemic chemotherapy and stereotactic body radiation therapy thereby confounding any direct correlation that can be made between OS and the study's OIC treatment. The heterogeneity in the treatments of each patient prior to being enrolled to the study also prevents direct comparison between patients. Finally, the small sample size (n = 10) was also insufficient to allow any meaningful quantitative analysis of the OS data. The latter two reasons also limit any meaningful analyses that can be carried out on tumour response as well which were reported in Article II.

5.4 Future Direction

5.4.1 Improvements to the UVAS

The experience and user feedback of the UVAS throughout the HELP and OIC trials provided guidance on what features of the UVAS design could be improved upon. These features as well as a new UVAS design developed incorporating such have been discussed in the subsection below.

5.4.1.1 UVAS Implantation Angle

It was identified in Section 5.2.1.2 that the UVAS needed to be implanted at an oblique angle to the host vessel to be able to accommodate the multiple catheters that are required to be guided through the lumen of the UVAS implant to facilitate the OIC treatment. While this was carried out for the last six patients of the study with no untoward side effects, it increases the risk of thrombus formation at the plunger tip. The oblique orientation of the implant along with the cylindrical nature of the plunger tip results in a seal that is no longer in line with the vessel wall to create dead space at the plunger tip (Figure 5.8a). This dead space can act as a region for flow stagnation creating an unnatural blood flow profile which could either lead to thrombus formation or possibly be a contributing factor for intima hyperplasia of the host artery. Hence, it was suggested that the plunger tip of the UVAS be redesigned to minimise this dead space as much as possible. This could be done by converting the cylindrical shape of the plunger tip to a chamfered design to align with the vessel wall as shown in Figure 5.8b.

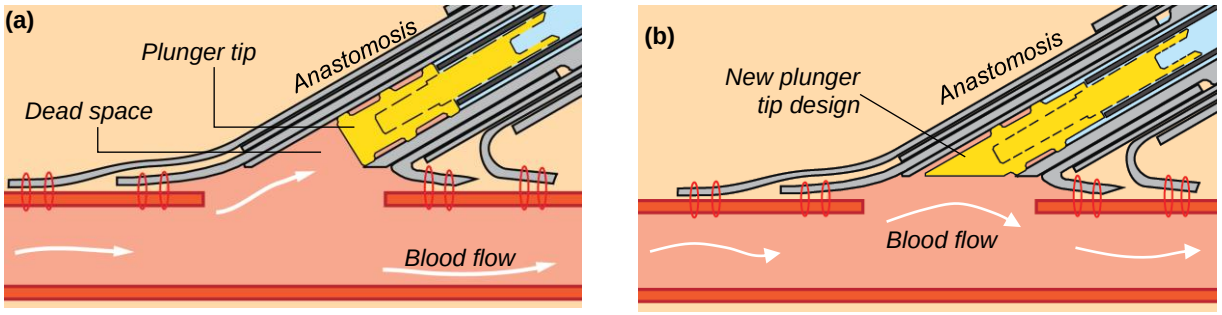

Figure 5.8 – Dead space created by the UVAS plunger tip design when the UVAS implanted is anastomosed obliquely (a) and the suggested design change for the plunger tip to reduce the dead space (b).

5.4.1.2 UVAS Haemostasis Valve

The haemostasis valve used in the OIC trial relied on a silicone septum that was pierced to allow the catheters and their sheaths to be introduced through it. The seal between the sheath/catheter pierced silicone septum relied on an interference fit. The study investigators reported that this added resistance in catheter tracking and limited its manoeuvrability. In addition, there were two access procedures where the silicone septum tore because of the repeated retraction and advancement of the catheters. Consequently, all catheters had to be removed, the haemostasis valve replaced, and the entire procedure restarted. While this only occurred in 2 out of the 60 (3.3%) catheter access procedures, it is still an avoidable risk.

It was suggested that this can be mitigated with the use of modular hand adjustable haemostasis valves instead of a single silicone septum. The use of a hand adjustable haemostasis valve to seal against the catheter/sheath would also negate the issue of friction while still allowing the user to lock the introduced catheter in position. Such a design would also make the need for a needle puncture unnecessary thereby removing a sharps hazard. Finally, a modulated design would avoid the issue of having to restart the procedure entirely when only one seal has failed as it could be replaced without compromising the seal around the other catheters.

5.4.1.3 UVAS Plunger Tip Seal

In both the HELP and OIC trails, it was observed that although the plunger tip was able to provide a seal with the UVAS implant, there was still some mixing of blood (distal to the seal) with the back-filled saline in the access tube (proximal to the seal). This was evident as the backfilled region in the UVAS implant tubing was always clear immediately after the plunger was inserted but gradually mixed with backfilled saline soon afterwards (Figure 5.9). Nonetheless, it would be ideal to improve upon the imperfect sealing capability of the plunger tip which was deemed to likely be a result of relying on an interference fit between a solid plug (i.e. ribs of the plunger tip) and a flexible PVC tube. Any bends that occur in the access tube could lead to leak paths past the solid ribs of the plunger tip.

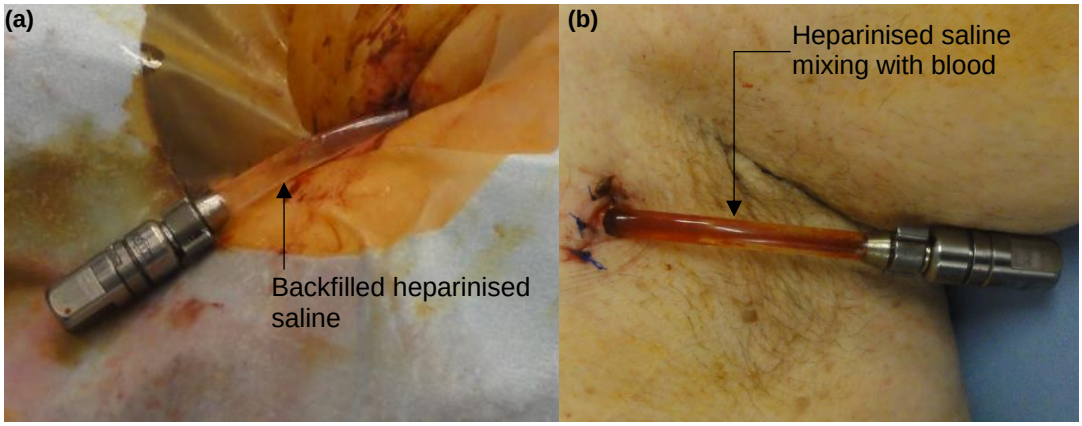

Figure 5.9 – The UVAS immediately after it has been closed with the plunger and backfilled with heparinised saline (a) and the gradual mixing with blood over time (b).

This could be improved by utilising a more compliant plunger tip to provide a seal against the flexible tube. In such a design, the ribs of the plunger would comply with the stretching/shape of the implant tubing as it bends and shifts in-situ to prevent any leak paths forming. While it may not entirely prevent any blood-saline mixing in the back-filled region of the tube it would most likely provide a better result compared to the current design.

5.4.1.4 UVAS Implant Material

The final and most critical feedback from the study investigators was their preference to be able to administer the OIC treatment over a longer period than the one month period the OIC patients were confined to. It was believed that a longer implantation period, such as up to 3 months, would allow patients to have a greater rest period between their OIC treatments instead of having to schedule each treatment so close to one another. The most significant advantage anticipated with this was that the adverse event rate (albeit generally grades II or lower) could be reduced as it was suspected that some AEs were a result of the accumulative effects of general anaesthesia. More importantly, it would provide more time for clinicians to assess patients between LRC treatments using CT scans to monitor the disease and to devise a tumour targeting plan. The most obvious solution to this was to change the PVC material of the UVAS implant tubing to silicone which has a far more established history of use in long term implants.

5.4.1.5 An Improved UVAS

Based on the potential improvements identified by the study investigators and discussed above in Sections 5.4.1.1 to 5.4.1.4, a new revised UVAS was designed and developed as shown below in Figure 5.10.

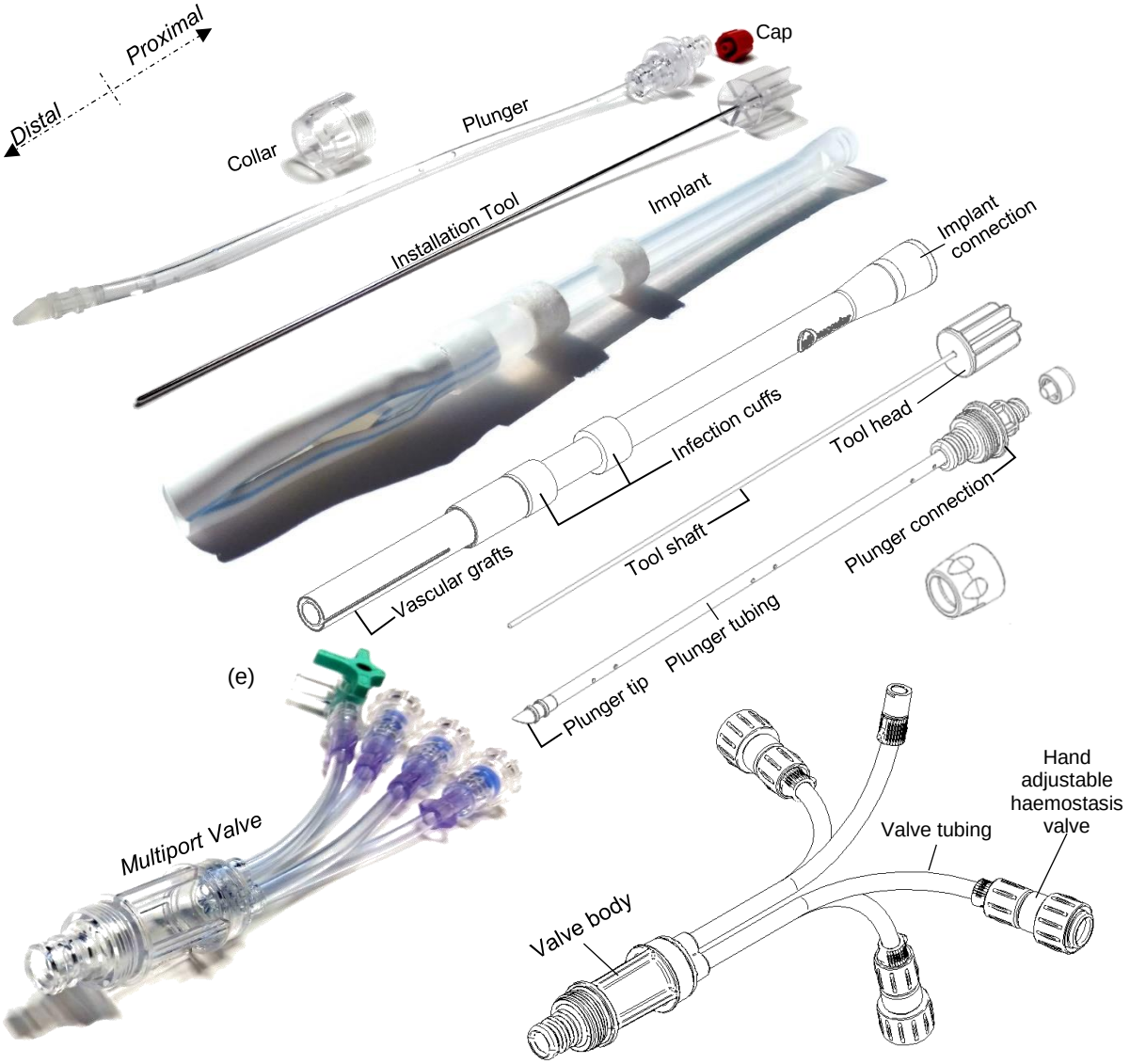

Figure 5.10 – The newly designed UVAS intended to improve upon the limitations and minor issues identified in the OIC and HELP trials.

All issues discussed in Sections 5.4.1.1 to 5.4.1.4 have been addressed with this new UVAS design. The plunger tip is designed with a 30° chamfer in order to reduce the dead space in the host artery when the system is implanted at an oblique angle. The plunger tip is also comprised of a compliant silicone now so that a soft seal is created with the UVAS implant tubing. The haemostasis valve has been replaced with a new multiport valve which has modular hand adjustable haemostasis valves at the proximal end to allow the clinician to adjust the friction/seal achieved with each catheter. The UVAS implant tubing has also been changed to a silicone material to allow for an extended implantation period. Finally, all the connecting elements have been converted to a transparent polymer (polycarbonate) in order to reduce the total weight of the device and to allow for visibility within the lumen.

It would be highly recommended that future studies use this newly developed UVAS as it is an iteration that addresses most the issues identified and lessons learned from the clinical studies throughout this thesis.

5.4.2 Improvements to the Hepatic OIC Technique

The improvements that can be made to the current hepatic OIC technique have all been identified through the issues identified and encountered during the initial learning curve which have been discussed in detail in Section 5.2.1. Therefore, in any future studies aiming to replicate this technique should take the following into account:

a) the UVAS should be implanted on the host artery at an oblique angle,
b) the UVAS should be implanted on the upper limb (preferably left side) when access arteries branching off the celiac trunk,
c) short compliant balloons should be used instead of long angioplasty balloon catheters when obstructing arterial blood flow, and
d) patients with small vessels should not be treated, and
e) the revised UVAS shown in Figure 5.10 should be used

If these suggestions are taken into account, it is highly likely that the rate of successfully cannulating multiple catheters and achieving organ isolation of the liver can be significantly improved from the success rate of 81.7% achieved in the OIC trial in Article II to potentially 100%.

5.4.3 Further Research for the Liver

The outcomes from the OIC trial as reported in Article II and in Section 5.3 suggest that further investigation into the LRC technique developed using the UVAS is warranted. The added benefits of a compressed treatment time, minimal side-effects, as well as promising data from other IHP studies [169] all suggest the potential of this repeatable hepatic OIC treatment for patients with CRCLMs.

Given the infancy of the OIC technique, it would be unlikely a large randomised controlled study would be approved by a scientific or ethics committee. Therefore, it would be most appropriate to progress onto a phase Ib/II study comprised of a systemic dosing study (phase Ib) combined with a single arm study assessing tumour response rate as the primary endpoint (phase II). Unlike the pilot study, this study should aim to recruit non-chemorefractory CRCLM patients preferably still on their first-line systemic chemotherapy.

Such a study has already been designed and reviewed by a scientific and ethics committee already with institutional approval pending. The full study protocol and the provisional entry on

the national clinical trial registry are provided in Appendix G and Appendix H respectively. The study design and details have been provided in the subsection below.

5.4.3.1 Prospective Phase Ib/II Study for Hepatic OIC in CRCLMs

The study will assess the potential of the hepatic OIC method using the UVAS combined with half the normal course of systemic therapy. In summary, patients with inoperable CRCLMs who have shown to have non-progressive disease after 6 cycles of FOLFOX ± bevacizumab with limited extrahepatic disease and a specific genotype (RAS mutant) will be considered eligible for the study. Eligible patients will be implanted with the new UVAS (Figure 5.10) and treated with the OIC treatment 5-7 times over a course of 2 months with concomitant oral capecitabine. After the treatments and explantation of the UVAS, patients will be followed up for 2 years.

The phase Ib component will be a dosing study comprised of an accelerated stage and a confirmation stage. During the accelerated stage patients will be treated one-by-one with the OIC oxaliplatin dose escalated between each patient until a dose limiting toxicity is observed. Form here, the confirmation stage will be initiated to enter a standard 3+3 design until a recommended dose is established. All patients will be treated with the recommended dose in the phase II component.

The study design is based on the well-known response rate of 50% for inoperable CRCLM patients with RAS mutations [251]. Based on this, the phase II study is designed to assess the OIC treatment against this known response rate to assess the following hypotheses:

- H_0 = OIC provides non-clinically significant improvements in response rates;
- H_1 = OIC provides clinically significant improvements in response rate

where “clinically significant” was defined as a response rate improvement of 20% or greater (i.e. $P_1 = 0.50$; $P_2 = 0.70$). To obtain a statistical power of 80% and a significance level of 0.05, a total of 37 patients must be enrolled in the phase II study. Of the 37 patients, at least 24 patients must show a partial response (via RECIST) or better to reject the null hypothesis (H_0) and demonstrate a clinically significant improvement.

5.4.4 Other Potential Applications

The outcomes of the two studies making up this thesis has confirmed that a UVAS can be developed to provided repeatable minimally invasive multicatheter access to the patient’s vasculature. This allows organs and or solid tumours to be isolated using standard endovascular catheters. The OIC technique developed in Article II was specific to tumours in the liver but can be extended to other organs and even in non-oncological applications.

5.4.4.1 Advanced Carcinomas of the Pancreas

Given the proximity of the pancreas to the liver and the shared blood supply by the celiac trunk and SMA, the hepatic OIC treatment developed can be modified slightly to isolate carcinomas of the pancreas. As shown below in Figure 5.11 as an example for carcinomas of the pancreatic head, an infusion microcatheter can be steered into a pancreaticoduodenal artery through a balloon catheter in the gastroduodenal artery, and balloon catheters can be deployed at the SMA and celiac trunk to shut off the remainder of the pancreatic arterial inflow to achieve organ isolation. All catheters could be introduced via a UVAS implanted in the upper limb. The duodenal mucosa can be indirectly protected from the intra-arterial chemotherapy by vasoconstrictions of its arteries induced through a large duodenal balloon (via endoscopy or colonoscopy) filled with cold water/saline. Similar to the hepatic OIC technique, venous outflow from the pancreas can be reduced using PEEP.

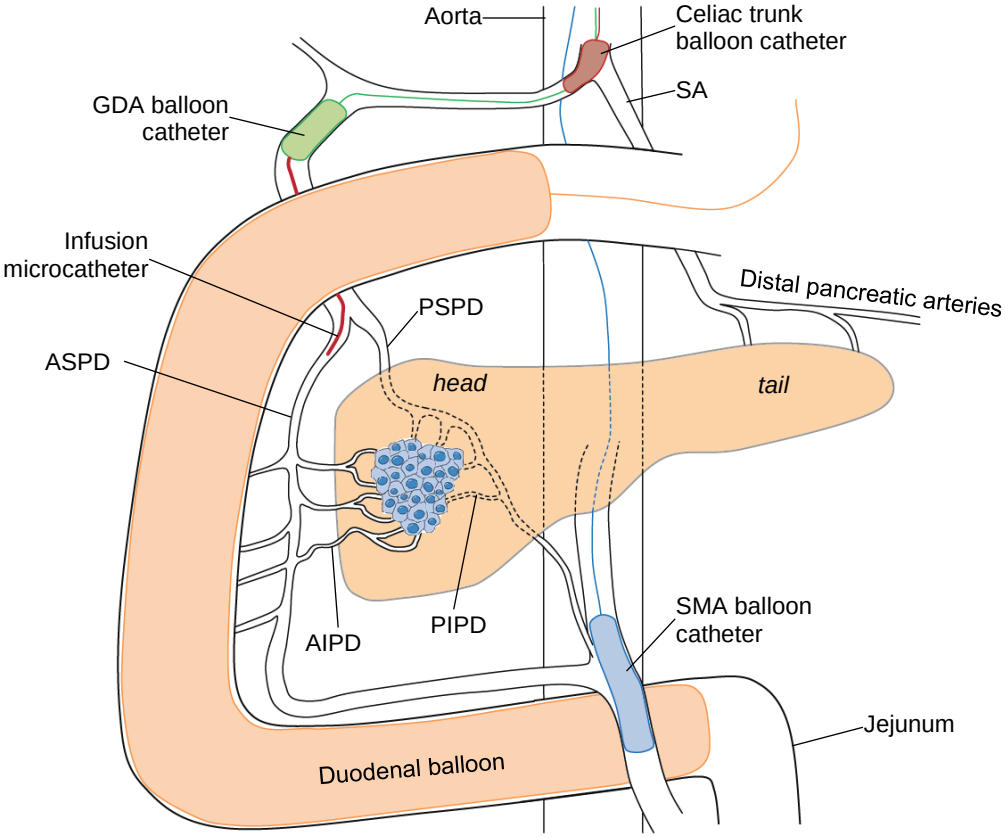

Figure 5.11 – Possible setup for pancreatic isolation chemotherapy of the head of the pancreas using three balloon catheters and one infusion microcatheter; *SA = splenic artery, GDA = gastroduodenal artery, ASPD = anterior superior pancreaticoduodenal artery, PSPD = posterior superior pancreaticoduodenal artery, AIPD = anterior inferior pancreaticoduodenal artery, PIPD = posterior inferior pancreaticoduodenal artery, SMA = superior mesenteric artery.*

Such a system would be no more complex than that of ASFI, CAI, and SAI which have shown to deliver promising results in advanced pancreatic cancers. However, the near-complete isolation achieved with this OIC technique as well as its mechanism of action (Chapter 6) has potential to improve upon what can already be achieved with these other LRC techniques. Provided the benefit achieved is clinically significant to offset its complexity and the grim

prognosis for patients with inoperable pancreatic carcinomas, there is potential for such a technique to be integrated as a standard treatment.

5.4.4.2 Carcinomas of the Breast
The OIC technique using the UVAS to treat carcinomas of the breast is discussed in Chapter 6, Article III.

5.4.4.3 Isolated Limb Perfusion
The UVAS and OIC technique can be applied as an alternative to ILP which, as discussed in Chapter 1, is already a first line treatment for those with melanomas and STS of the limb. Nonetheless, outcomes can always be improved further especially for patients with locoregional recurrent disease (35%) after an initial complete response where repeat ILP imparts a 5-year survival rate of only 35% [252]. Most these patients are only given a second round of ILP as well. In the same way IHP provided better blood flow control of the liver compared to PHP, the ILP technique can also be improved with OIC by replacing the gross obstruction techniques (i.e. tourniquets) with direct obstruction of the tumour supplying arteries and veins via balloon catheters. An example is shown below in Figure 5.12.

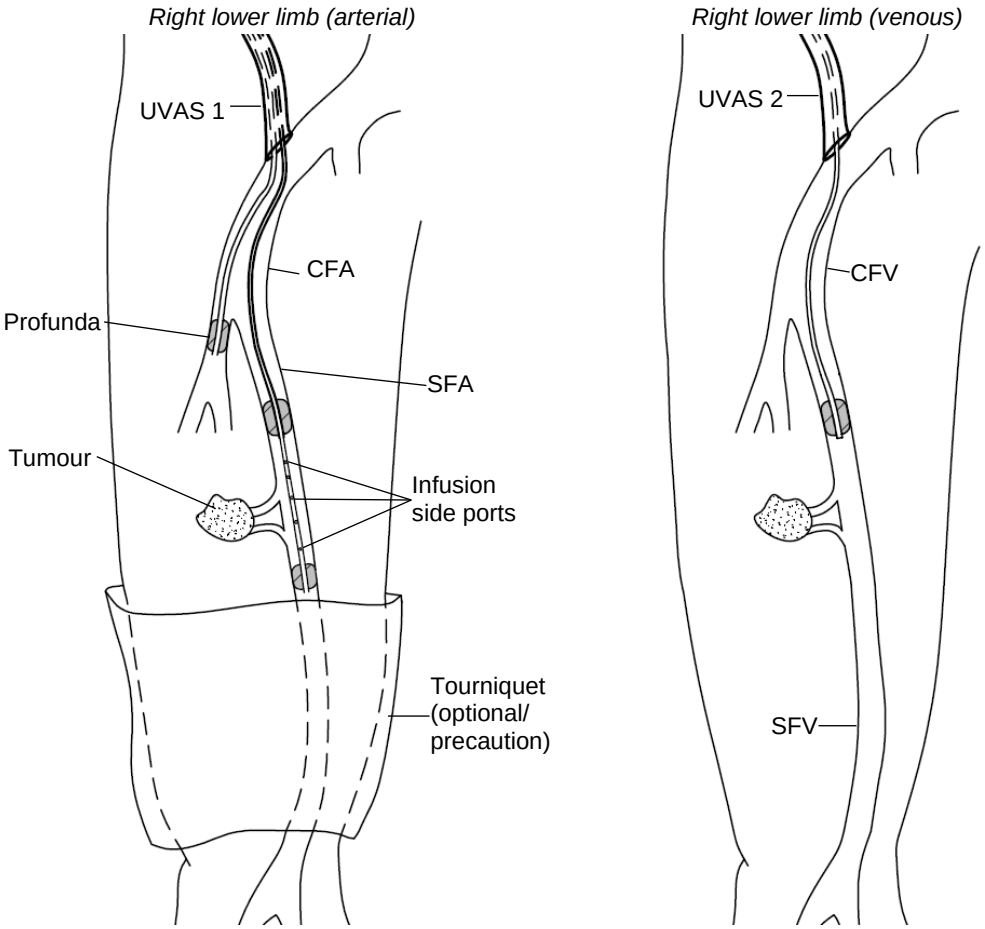

Figure 5.12 – Possible setup for limb isolation chemotherapy using two UVAS devices implanted on the CFA and CFV. A double balloon catheter with infusion side ports in the SFA can be used to isolate and infuse the tumour while another balloon catheter can be used to obstruct the profunda to obstruct collateral blood supply. A tourniquet distal to the infusion site can be used as a precaution and a balloon catheter from the venous side to the SFV can be used to obstruct the tumour outflow. *CFA = common femoral artery, CFV = common femoral vein, SFA = superficial femoral artery, SFV = superficial femoral vein.*

Such a setup would allow for more direct isolation of the tumour as well as repeatability. Improved isolation could potentially allow for higher tumour toxicity without higher local or systemic toxicity and thus more infusions over a short timeframe could be administered prior to reaching dose limiting toxicity. The higher toxicity achieved in the tumour could possibly induce responses that would otherwise have been unachievable using ILP and, if proven to be the case, could potentially become a replacement or supplementary technique to ILP.

5.5 Chapter Conclusions

The combined data from the two studies carried out in this thesis have shown that the UVAS that was developed can successfully perform its intended functions in and the AEs or side effects accompanied by its use are outweighed by the performance characteristics it can offer. The newly developed OIC technique can also be deemed as a feasible treatment that warrants further investigation especially when considered in the context of the current state of LRC treatments. The technique is no more complex than that of HIPEC (Figure 1.7, Section 1.2.2, Chapter 1) which is a first line treatment [86,87], has a far greater safety profile than that techniques like PHP which still imparts treatment related deaths [174], and is similar in setup to that of the most successful LRC technique of IHP to date [169] but allows for repeatability. As a precaution, it should be assumed that the developed OIC technique is not without side effects. Although a high level of hepatic isolation can be achieved, the use of PEEP to indirectly obstruct the venous outflow may account for minor chemotherapy leak into the systemic circulation albeit a small amount. Finally, the catheter combinations that can be used through UVAS presents opportunities to isolate various organs and treat a range of solid tumours with several possible setups already identified for that of the pancreas, lower limb, and breasts.

CHAPTER 6 – DISCUSSION PART 2: MECHANISMS OF THE HEPATIC OIC TECHNIQUE DEVELOPED

The purpose of this second half of the Discussion is to describe the potential advantages of the OIC technique developed using the UVAS compared to systemic IV chemotherapy as well as other LRC techniques. This Discussion, already published in Article III, specifically discusses the concepts of mass fluid transfer and bulk fluid flux by describing in detail the theoretical advantages of being able to reduce the arterial pressure to an organ, wash out the existing plasma proteins within arterial capillaries, and control the organ's venous pressure or flow. The Article also touches on the technique's applicability to solid tumours in other organs such as that of the breast.

6.1 Article III

Lane RJ, Khin NY, Pavlakis N, *et al*. Challenges in chemotherapy delivery: comparison of standard chemotherapy delivery to locoregional vascular mass fluid transfer. *Future Oncology.* 14(7), 647–663 (2018). DOI: 10.2217/fon-2017-0546

Attached after this page.

The conference abstract reporting on the device related results of the UVAS as well as the PAS used in the HELP trial (Article I) and OIC trial (Article II) is attached after the Article.

Systematic Review

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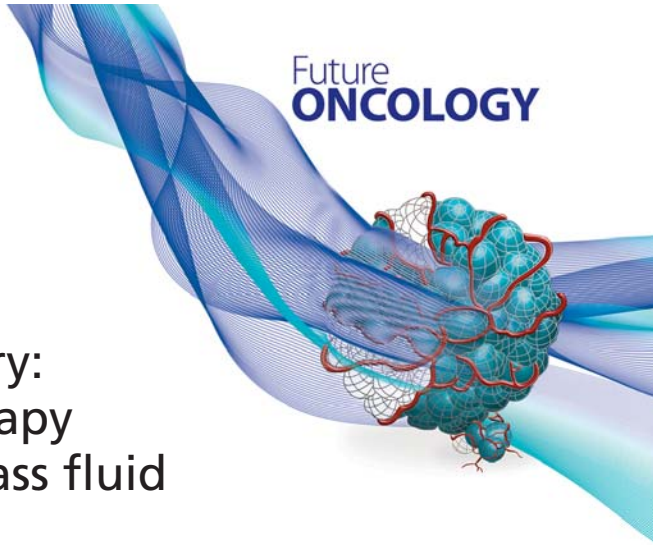

Challenges in chemotherapy delivery: comparison of standard chemotherapy delivery to locoregional vascular mass fluid transfer

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Standard intravenous chemotherapy delivery to neoplasms relies on simple diffusion gradients from the intravascular to the interstitial space. Systemic perfusion creates untoward effects on normal tissue limiting both concentration and exposure times. Regional intra-arterial therapy is limited by drug recirculation and vascular isolation repeatability and does not address the interstitial microenvironment. Barriers to delivery relate to chaotic vascular architecture, heterogeneous fluid flux, increased interstitial and variable solid tumor pressure and ischemia. To address these difficulties, a delivery system was developed allowing mass fluid transfer of chemotherapeutic agents into the interstitium. This implantable, reusable system is comprised of multiple independently steerable balloons and catheters capable of controlling the locoregional hydraulic and oncotic forces across the vascular endothelium.

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Keywords: bulk fluid flux • direct arterial chemotherapy delivery • drug eluding embolic particles • implantable multicatheter vascular access system • isolated hepatic infusion with recirculation and hemofiltration • mass fluid transfer • neoplasms • stop flow techniques • vascular mechanics

The intravenous (iv.) route is the standard pathway of delivering chemotherapy to neoplasms. As cancers have the propensity to disseminate, it is therefore logical to treat all body parts and circulating tumor cells and should always be an integral part of chemotherapy treatment.

Tumors and their draining lymph nodes reside in the interstitial or extravascular space and hence delivery requires the therapy to traverse the vascular endothelium [1]. The prime mechanism is simple diffusion down a concentration gradient aided by an increased intrinsic tumor vascular permeability [2]. The main obstacle is providing sufficient chemotherapy concentration to eradicate the tumor without causing deleterious side effects on normal structures remote from the tumor. The effective concentration of the delivered chemotherapy agent depends upon the relative mass of the organ compared with total body mass in attacking the neoplasm [3]. For example, a pancreatic head tumor may be 35 g in a 75 kg patient; this is a relative mass factor of 2000-times while the affected clearing lymph nodes may be 5–7 mm with a dilution factor of 10,000 to 1 [3]. The concentration limitation also prolongs the time requirement to produce an effective response. Cellular uptake depends on a series of complex biochemical interactions, some active and some passive, but all time dependent. Of equal importance is the desire to reduce the time taken to properly assess a treatment's effectiveness so that therapy can be changed promptly, if necessary. The combination of concentration and time restraints allows tumors to mutate, conjugate or develop mechanisms to mitigate chemotherapeutic actions thereby increasing cancer viability. Side effects may lead to early treatment

Future Medicine

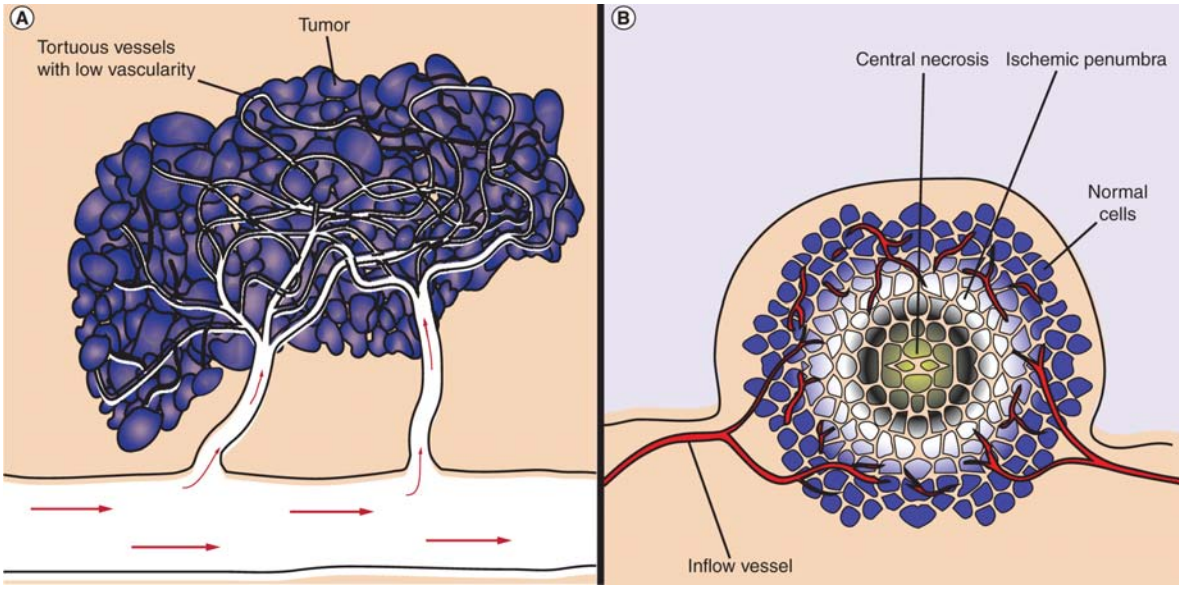

Figure 1. The intravenous route for chemotherapy delivery is impaired by the high resistance vasculature. The tumor vessels are often tortuous, heterogeneous, hypovascular with little or no flow **(A)**. Ischemic apoptosis liberates proteins centrally in the tumor with a resulting high oncotic pressure. This, combined with a decreased functional lymphatic drainage and high vascular permeability, results in an increase in central interstitial fluid pressure, which precludes adequate chemotherapy penetration **(B)**.

cessation and occasional premature death. Further, the intravenous route may also impair the natural immunological response to the tumor via bone marrow suppression and lympholysis.

In addition to the vascular endothelial barriers, the intravenous route for chemotherapy delivery is affected by multiple metabolic and excretory processes including plasma binding [4] as well as the dynamic tumor microenvironment [5]. The tumor vessels are often tortuous, heterogeneous, hypovascular or frequently associated with a low PO_2, which can initiate high protein transcription (Figure 1A) [6]. Ischemic apoptosis liberates protein centrally in the tumor with a resulting high oncotic pressure (Figure 1B) [1]. Combined with a decreased functional lymphatic drainage and high vascular permeability, the result is an increase in central interstitial fluid pressure (IFP) precluding adequate chemotherapy penetration [7,8]. A further confounding element is the increase in extracellular matrix density from elevated concentrations of collagen, hyaluronan and proteoglycans making the tumor stiffer and creating high pressure gradients [9]. The solid tumor pressure (STP) also relates to unregulated and often unpredictable cellular growth. Rapidly multiplying cells abut, compress and deform their neighboring tissue and may create a pseudo capsule within the host tissue [6]. There also exists a complex interplay between a multitude of physiological constituents including STP, IFP, infusion hydraulics, vascular heterogeneity, endothelial permeability and hypoxia [10–12]. All these erratic variables result in constant 3D spatiotemporal remodeling (Figure 2).

A number of treatment modalities have been proposed in an attempt to overcome these challenges that hinder effective chemotherapy delivery.

Direct arterial delivery/regional chemotherapy infusion

Part of the solution to increasing the efficacy of dose chemotherapy delivery is to directly infuse the vessels supplying the tumor. Regional infusion encompasses many diverse modalities, including intraperitoneal therapy (for appendiceal and ovarian cancers) [13], intrathecal therapy (for metastatic lesions to the brain) [14] and direct arterial infusion treatment (regional chemotherapy infusion).

One of the best studied areas of regional infusion is that of hepatic arterial infusion (HAI) for secondary colorectal cancer [15,16]. Here, patients undergo percutaneous implantation of an indwelling arterial hepatic catheter connected to an infusion reservoir (port-a-cath) or a transcutaneous catheter can be implanted in the gastroduodenal artery and is intermittently connected to an arterial pump thereby delivering chemotherapy continuously over several hours [17].

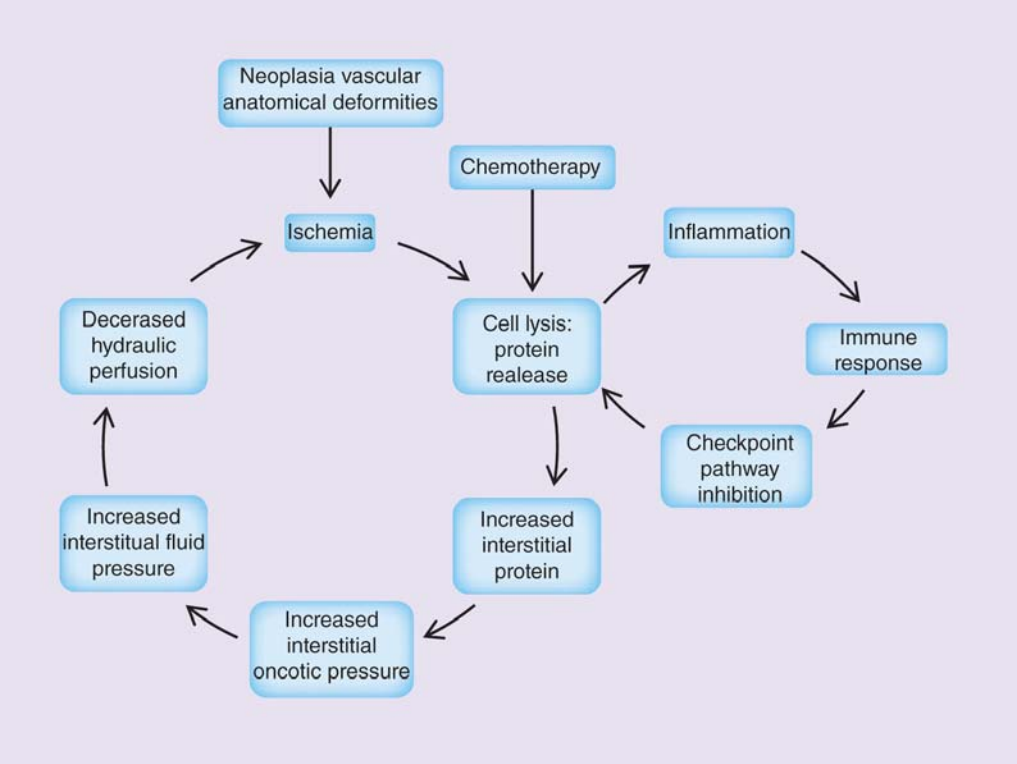

Figure 2. The interactions of anatomical vascular chaos, ischemia, high fluid pressure chemotherapy and immunotherapy are self-propagating. Chemotherapy and ischemia improve antigen exposure inducing inflammatory pathways and hence potentiating checkpoint pathway inhibition. Induced cell lysis releases proteins increasing interstitial fluid pressure and thence initiating hypoperfusion.

The relative advantage (RT) of HAI over the typical intravenous route is given by the following formula:

$$RT = 1 + \frac{TBC}{Q(1-e)} \qquad \text{(Equation 1)}$$

Where the total body clearance (TBC) is calculated by dividing the chemotherapy dose by the area under the time–concentration curve (AUC). Q and e denote the flow past the tumor and the extraction ratio, respectively [3,17]. An important deduction from this equation is that utilizing this treatment allows for a transient increase in local chemotherapy concentration with minimal plasma binding (Figure 3) [18–20]. Therefore, when intravenous and HAI variables are introduced into this equation a relative advantage can be deduced. This has relevance with some compounds that have a very high vascular extraction ratio on first pass removal, such as in fluorouracil derivatives [3]. Although this method has been shown to be modestly beneficial via meta-analysis [3,16], catheter migration and thrombosis [21] as well as the need for laparotomy for device insertion has resulted in limited universal acceptance [22].

Drug eluting embolic particles

Transcatheter arterial chemoembolization (TACE) involves the delivery of a chemotherapeutic agent, mixed with embolic material, administered selectively into the feeding arteries of the tumor to obtain higher intratumor drug concentrations compared with intravenous therapy, with occlusion of the blood vessel causing infarction and necrosis [23]. Microspheres are the most common embolic agents and can be made from various compounds including glass and resins. These compounds are usually bound to chemotherapeutics. No consensus exists as to the choice of agent [24].

The DC Bead (BTG International Ltd, London, UK) is a novel drug delivery embolization system [25–27].The beads vary in diameter of 100–700 μm and are typically hydrophilic, nonreabsorbable hydrogels usually impregnated

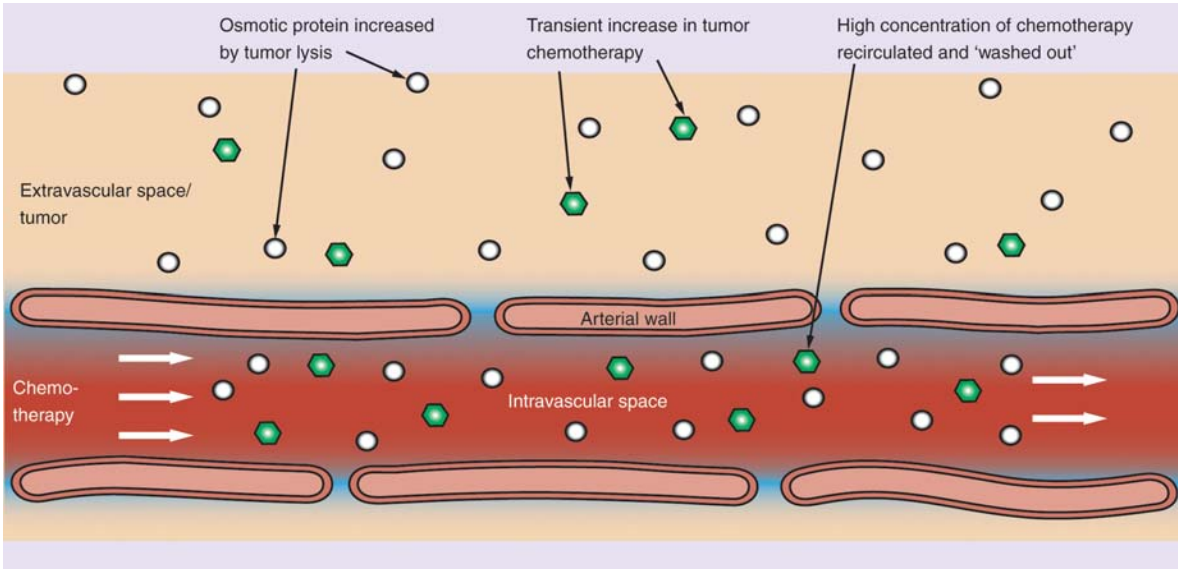

Figure 3. Standard intra-arterial chemotherapy at the tumor vascular interface. The transient increase in concentration of direct intra-arterial chemotherapy is washed out and recirculated. The induced side effects limit both the C_{max} and area under curve values.

with a chemotherapeutic agent such as doxorubicin [28]. Administration is similar to TACE without the need for lipiodol intermixing [29,30].

The therapeutic advantage of chemo-eluting particles relate to a controlled and sustained locoregional release of therapeutic agents in high concentration with prolonged administration at the targeted tumor thereby reducing its potential systemic toxicity [28]. Rapidly dividing neoplasms often have high vascular density and therefore facilitates self-selecting particle deposition. Embolic ischemia adds to this therapeutic advantage. Doxorubicin beads with TACE deployed in hepatocellular carcinomas have been shown to require fewer treatments compared with conventional TACE and have the same overall survival [31].

The disadvantages relate to occlusion of normal tissue with secondary ischemia. In addition, inadvertent migration of these particles into the systemic circulation can result in pulmonary embolization or infarction [32]. This concept is further complicated by arteriovenous shunts, which are commonly found in tumors [33]. Long-term ischemia induces collateralization related to surrounding endothelial shear stress and hormonal release. This may promote rather than inhibit tumor growth. In addition, the maximum chemotherapy concentration delivered usually remains intravascular and fails to address the problems of chaotic, tortuous and highly resistant vascular beds. In fact, some tumors themselves are hypovascular, which may result in the inability of beads to reach their target [34].

Stop flow techniques

Cessation of blood flow augments arterial chemotherapy delivery as well as the delivery of immunotherapeutic cancer treatments [35]. The goal of locoregional drug administration is to deliver a higher concentration of chemotherapy to the target compared with the delivery of chemotherapy systemically.

This treatment modality involves deploying an occlusion balloon catheter into the tumor feeding vessel thereby allowing chemotherapy greater time to traverse the vascular endothelium. In Equation 1, as the flow approaches zero and the extraction rate is high, the relative advantage improves dramatically [35]. Several techniques have been developed and include selective arterial infusion [36], celiac axis infusion [37], aortic stop flow infusion [38] and isolated hypoxic infusion.The last two treatment regimes offer the advantage of reducing regional active drug clearance as well as inducing hypoxia of the isolated compartment, which has been shown to increase the cytotoxic action of some anticancer agents, for example, mitomycin C and doxorubicin [39–41].

In the past, 'isolated' hypoxic abdominal perfusion has been reserved for patients with unresectable pancreatic cancer (stage III/IV) nonresponsive to traditional systemic chemotherapy [42,43]. During abdominal isolated perfusion, balloon catheters positioned within the aorta above the celiac axis and within the vena cava above the hepatic veins stop the blood flow of the abdominal vascular bed creating a virtual 'closed circuit' for perfusion

of the pancreas, liver and adjacent tissue. Despite leakage from the collateral circulation, a regional concentration advantage of perfused agents has been demonstrated in several studies [44,45]. An additional advantage of hypoxic abdominal perfusion is the decrease in tissue oxygenation and pH. Hypoxia increases the state of tumor cells and inhibits proliferation [40]. Hypoxia also enhances the cytotoxic activity of antiblastic agents such as mitomycin C and doxorubicin. The high incidence of local recurrence postradical pancreatic resection and the pattern of regional metastatic spread makes this technique practical for treating locally advanced pancreatic cancer, which is otherwise very difficult to treat using traditional surgical or medical intervention [46,47].

This technique does have shortcomings including prolonged end organ ischemic time, high hydraulic infusion forces required to adequately perfuse the tumor with chemotherapy as well as the potential genesis of collateral tumor circulation. Confounding deficiencies in this technique can occur during balloon deflation, which may result in the rapid exit of unwanted residual chemotherapeutic agents into the venous circulation [48]. Inability to repeat treatment and difficulty related to radiographic vascular superselection has resulted in a limited number of clinicians using this treatment modality.

Isolated & percutaneous hepatic infusion with recirculation & hemofiltration

Hepatic perfusion with high-dose chemotherapy directly into the liver via an open-surgical procedure, known as isolated hepatic perfusion (IHP), has been demonstrated to control disease and extend survival for patients with unresectable hepatic metastases [49,50]. It takes approximately 8 hours to complete and the recovery period is protracted with patients spending 2–3 days in an intensive care unit immediately after the procedure followed by an additional 10–15 days in the hospital prior to discharge. IHP has not been widely adopted as a treatment because it is an open-surgical procedure that is limited to one-time-only treatment and is associated with a high morbidity and mortality [51].

Percutaneous hepatic perfusion was developed to replace IHP. This technique utilizes a double-balloon catheter system (produced by Delcath Systems, NY, USA) positioned percutaneously in the retrohepatic vena cava [52–54]. The double-balloon catheter has a unique construction with a large central lumen, three accessory lumina and fenestrations throughout its length that allows the hepatic venous effluent to be isolated and filtered through an extracorporeal filtration system. The two balloons on either end of the catheter are positioned inferior and superior to the hepatic veins [55,56]. The venous outflow from the liver is filtered through this double-balloon catheter into the extracorporeal filtration system. Filtered blood is then returned to the systemic circulation through a catheter in the internal jugular or subclavian veins. Cannulation of the femoral artery with placement of a catheter into the proper hepatic artery allows for directed infusion of chemotherapy into the organ containing the pathologic tissue [57,58]. Once the extracorporeal circuit is established, chemotherapy can be delivered via the hepatic artery with simultaneous extracorporeal blood filtration via the inferior vena cava and systemic return by way of the neck veins [59].

Although initial results have been encouraging, numerous difficulties have been identified, namely, hematological, cardiovascular, hepatic, nephrotic and gastrointestinal toxicity [52,54,60]. Surgical morbidity, cost and repeatability are additional significant drawbacks. Also, this technique does not address the all-important tumor microenvironment.

Simple diffusion versus mass fluid transfer & bulk fluid flux

The delivery systems described have been unable to address the 3D spatiotemporal barriers that exist in the delivery of chemotherapy. In conventional chemotherapy delivery, the maximum concentration remains intravascular. However, cancer cells reside within the extravascular space and therefore therapy is required to traverse their semipermeable membranes to attain their maximum therapeutic concentration. The laws that govern basic diffusion were described by Fick [61]. The major variables of diffusion are solute concentration, time of exposure and cross-sectional vascular area. In the chemotherapeutic setting, the derived pharmacokinetic variables are of maximum concentration (C_{max}) and an estimate of exposure is described by the AUC. These values are important for describing response curves and potential side effects of chemotherapeutic agents. Darcy's Law expands on these principles adding blood viscosity and infusion velocity as further variables governing fluid flux across these membranes and hence the possible advantage of bolus delivery of therapeutic agents [62].

Mass fluid transfer can be defined as the delivery of soluble molecules across a semipermeable membrane while bulk fluid flux is the process used by lipid insoluble proteins to cross the capillary endothelium [7,8]. The latter has relevance to local antibody delivery to solid neoplasia. Bulk fluid flux is defined by Starlings law: "fluid movement due to filtration across the wall of a capillary is dependent on the balance between the hydrostatic pressure gradient

(ΔP) and the oncotic pressure gradient across the capillary ($\Delta\prod$)" [7,8,63]. Starling's equation is as follows:

$$J_v = K_f((P_c - P_i) - \sigma(\Pi_c - \Pi_i)) \quad \text{(Equation 2)}$$

1. Where J_v is the transendothelial solvent filtration in volumes per second;
2. K_f is the filtration constant that relates to the hydraulic conductance and capillary surface area;
3. P_c is the capillary pressure;
4. P_i is the interstitial pressure;
5. σ is the reflection co-efficient related to the re-absorption of albumen;
6. $\prod_i$ is the oncotic interstitial pressure; and
7. $\prod_c$ is the capillary oncotic pressure.

In the delivery of chemotherapeutic agents to solid tumors, the filtration constant can be manipulated by changing ΔP (P_c - P_i) and also $\Delta\prod(\prod_c - \prod_i)$. One way to improve ΔP_i is to increase the infusion pressure above normal cardiac infusion pressures. To improve $\Delta\prod$, the intravascular oncotic pressure can be reduced optimally by decreasing the plasma protein concentration. K_f can be improved by physical factors such as hyperthermia and ischemia [64]. Venous end capillary bed reabsorption of chemotherapy can be manipulated by increasing venous pressure.

Starling's equation can therefore be summarized in chemotherapy delivery as the flux across the tumor circulation. The focus of chemotherapy delivery is therefore dependent on three central concepts, in other words, inflow hypertension, removing plasma proteins and obstructing venous outflow [65].

Vascular mechanics

To remove blood and plasma proteins locoregionally from the tumor, the inflow pressure must be reduced so that there is no discernible flow. This requires pressure to be reduced below critical closing pressure (20 mmHg at capillary level) [66]. Achieving this allows plasma proteins and blood to be washed out into the venous system with saline. The net effect is an outward oncotic flux of 30 mmHg.

The concept of generalized hypoproteinemia and interstitial edema is well known in clinical equivalents such as Kwashiorkor and nephrotic syndrome. The mechanical requirement to reduce inflow below critical closing pressure requires occlusion catheters and balloons usually placed superselectively to occlude not only the axial inflow system but also collateral flow. This important step needs to be modulated and regulated by continuous pressure transduction assessment. Once the oncotically active components are removed, the venous outflow can then be occluded via various means such as positive end expiratory pressure (PEEP) or balloon occlusion of the hepatic veins via catheterization of the internal jugular vein. PEEP has the added advantage over selective venous occlusion as it results in a generalized increase in venous pressure thus avoiding shunting of the venous flow from one segment of the organ to the other.

Venous outflow obstruction ensures retention of chemotherapy in the interstitial space. Therapeutic agents can then be infused at suprasystolic pressures to overcome elevated vascular resistance intrinsic to many tumors. Most importantly the measured chemotherapy infusion pressure is designed to remain less than the measured outflow venous pressure to avoid systemic contamination (Figure 4).

There are a multitude of intrinsic physical factors that can also affect membrane permeability. One such factor is ischemia or oncosis, which plays an integral part of the mass fluid transfer concept [67]. Others include hyperthermia, Ph and osmolarity variation all of which may assist in the therapeutic delivery of substances across the neoplastic cells semipermeable membranes.

Hyperperfusion

Of paramount importance to cellular chemotherapy absorption is the concept of 'cellular hyperperfusion' which is defined as an increase in inflow pressure beyond the pressure that can be attained from the normal cardiac cycle. In the past, the technique of limb hyperperfusion has been successfully utilized to overcome high peripheral resistance in critical limb ischemia [68–70]. Figure 5 shows thermographic images of a gangrenous foot hyperperfused at 150% of the normal inflow pressures throughout the cardiac cycle [71,72]. The same basic hardware was modified to hyperperfuse solid tumors with chemotherapy.

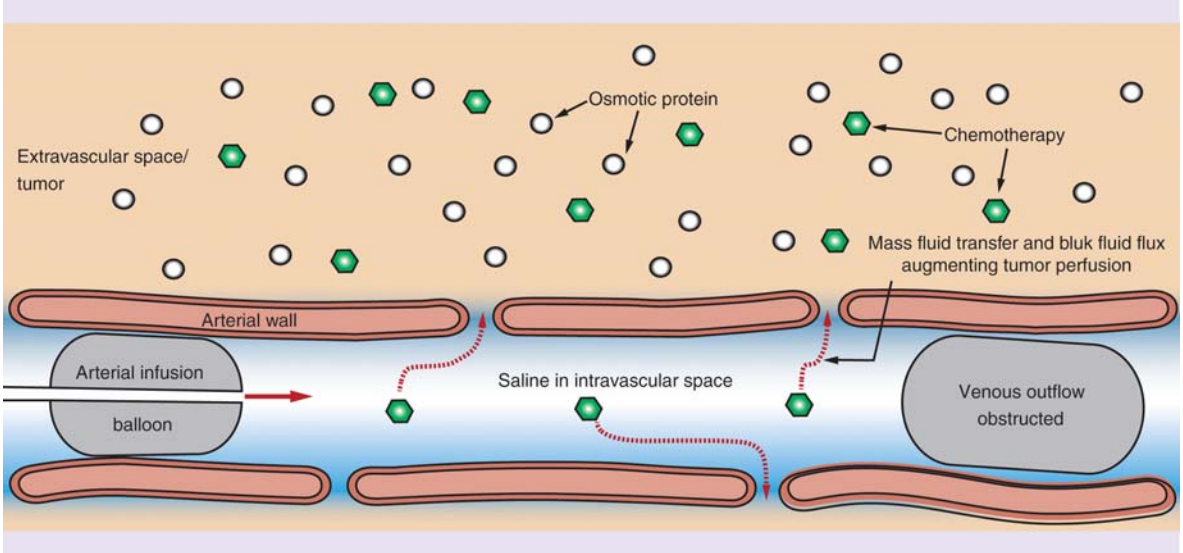

Figure 4. Mechanisms of vascular isolation and mass fluid transfer. To remove blood and plasma proteins locoregionally from the tumor, the inflow pressure must be reduced so that there is no discernible flow (vascular isolation). This requires intravascular pressures to be reduced below critical closing pressure (20 mmHg at capillary level). Achieving this allows plasma proteins and blood to be washed out into the venous system with saline. The net effect is therefore an outward chemo-oncotic flux of 30 mmHg. It is this chemo-oncotic flux that ensures that delivery of chemotherapy to the tumor across the vascular semipermeable membrane (mass fluid transfer) is augmented. The mechanical requirement to reduce inflow below critical closing pressure requires occlusion catheters and balloons usually placed superselectively. Venous outflow can then be occluded via various means such as positive end expiratory pressure or balloon occlusion.

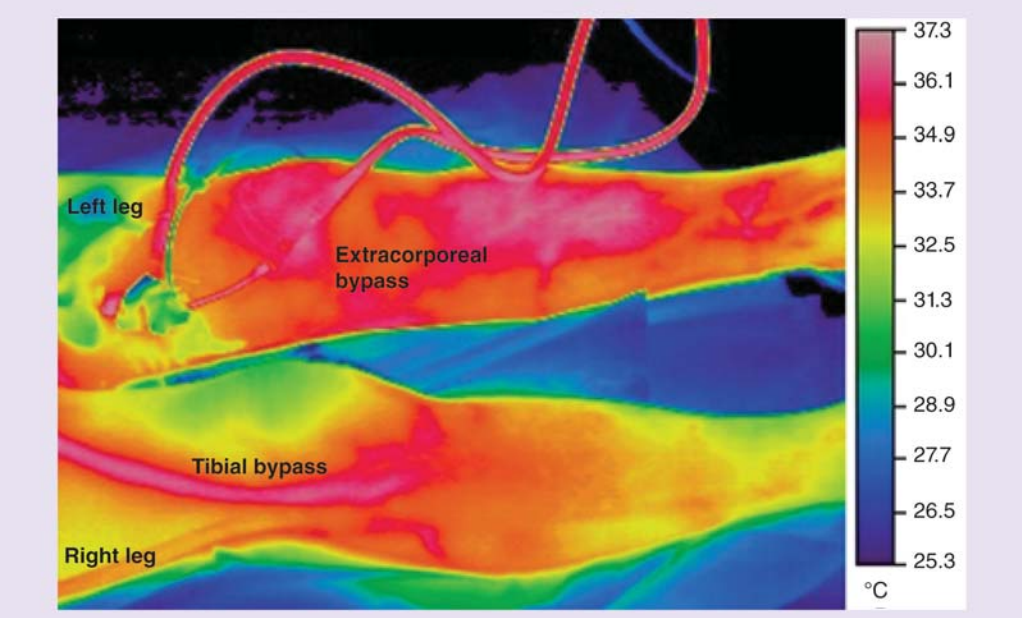

Figure 5. Thermographic images of a gangrenous foot hyperperfused at 150% of the normal inflow pressures throughout the cardiac cycle. Gangrenous left leg hyperperfused with extracorporeal bypass. Outcomes were shown to be superior to standard to tibial bypass (right leg).

Multicatheter access system

To optimize cellular endothelial permeability, mass fluid flow as well as hydraulic and oncotic forces, an implantable multicatheter vascular access system was developed (AllVascular Pty Ltd, St Leonards, Australia). The system's

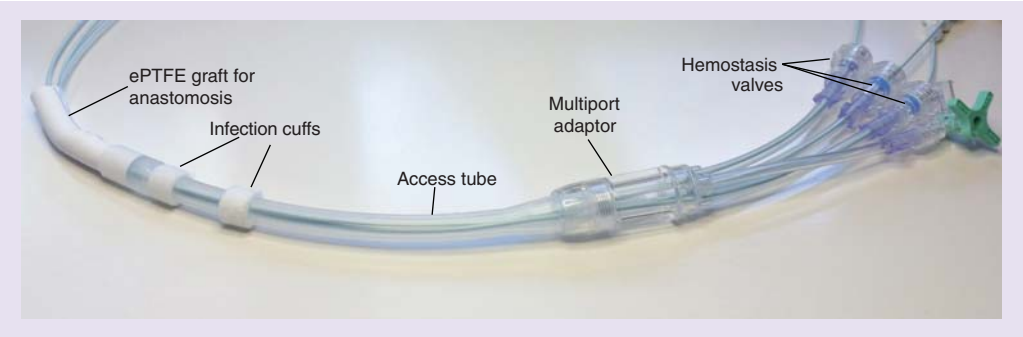

Figure 6. Implantable multicatheter access system.

prerequisites for mass fluid transfer are an implantable, tunneled, transcutaneous large bore port. In the dormant phase, the device is plugged with a disposable flexible plunger with a chamfered tip.

This abuts the anastomosis to create a continuous interface with the vascular endothelium and maximizes laminar flow. The plunger shaft is perforated allowing for anticoagulation of the potential space between the plunger and the internal surface of the silicone port. These features minimize thromboembolic complications. To activate the system, the plunger is removed and the access system is connected to a multiport adaptor which can accommodate up to six cannulas (Figure 6). Each port on the adaptor is equipped with a hemostasis valve to provide a seal to avoid blood loss when introducing catheters.

Superselecting target vessels using this system are made possible with the aid of radiological guidance. The system design enables carefully modulated pressure control via pressure transduction. Importantly the delivery process is easily repeatable and is controlled from a single point source. Access is possible to both the primary and secondary tumors either simultaneously or individually. Additionally, the device has been developed to minimize potential complications. The implantable access tube is silicone, minimizing tissue reaction and flexible to accommodate independent catheter steerage. The ePTFE in the anastomosis is resilient and difficult to perforate with guide wires. The arterial anastomosis is double layered and the two suture lines are offset to minimize guidewire perforation, hemorrhage and false aneurysms. It is also designed to withstand elevated suprasystolic pressures. Polyester felt placed circumferentially around the silicone access tube serves as an infection barrier and promotes dense fibrous ingrowth, minimizing inadvertent patient dislodgement (Figure 6).

Potential complications relate to multiple catheter deployments remote from the device, including dissection and thromboembolism.

Pilot study system deployment

The safety and feasibility of a multicatheter access system has previously been assessed in a pilot study involving patients with secondary colorectal liver tumors [73]. A total of 57 infusions were delivered across a total of ten patients each treated over a 4-week interval [73]. To obtain capillary closing pressure (normally 20 mmHg at the precapillary level), balloon catheter control of the celiac axis, superior mesenteric axis as well as hepatic artery isolation at two levels was required (Figure 7). In addition, the venous outflow was controlled by PEEP which ensured pressures in excess of 30 mmHg within the liver were sustained during bolus infusion of chemotherapy delivery. The tumor was subsequently washed out with saline and infused with a chemotherapy solution. This method gives an oncotic gradient of 30 mmHg into the interstitial space, which may be supplemented by a high protein concentration contents within the tumor.

To minimize rapid re-absorption of fluid and chemotherapy from re-entering the systemic circulation, the induced venous hypertension was maintained for several minutes after the gradual arterial inflow was reconstituted. Some systemic washout was inevitable once the balloon inflation was released. In the pilot study, evidence of this systemic recirculation was confirmed by the accumulation of platinum levels after an infusion had been completed [73].

The results confirmed chemotherapy infusions with hepatic vascular isolation can be achieved with targeted selectivity and minimal complications using this implantable multicatheter access system. Biweekly administration of chemotherapy and compressing treatment time into 1 month minimizes the time for the tumor to mutate or introduce mechanisms to mitigate chemotherapy effectiveness and allows patients to promptly return to normal

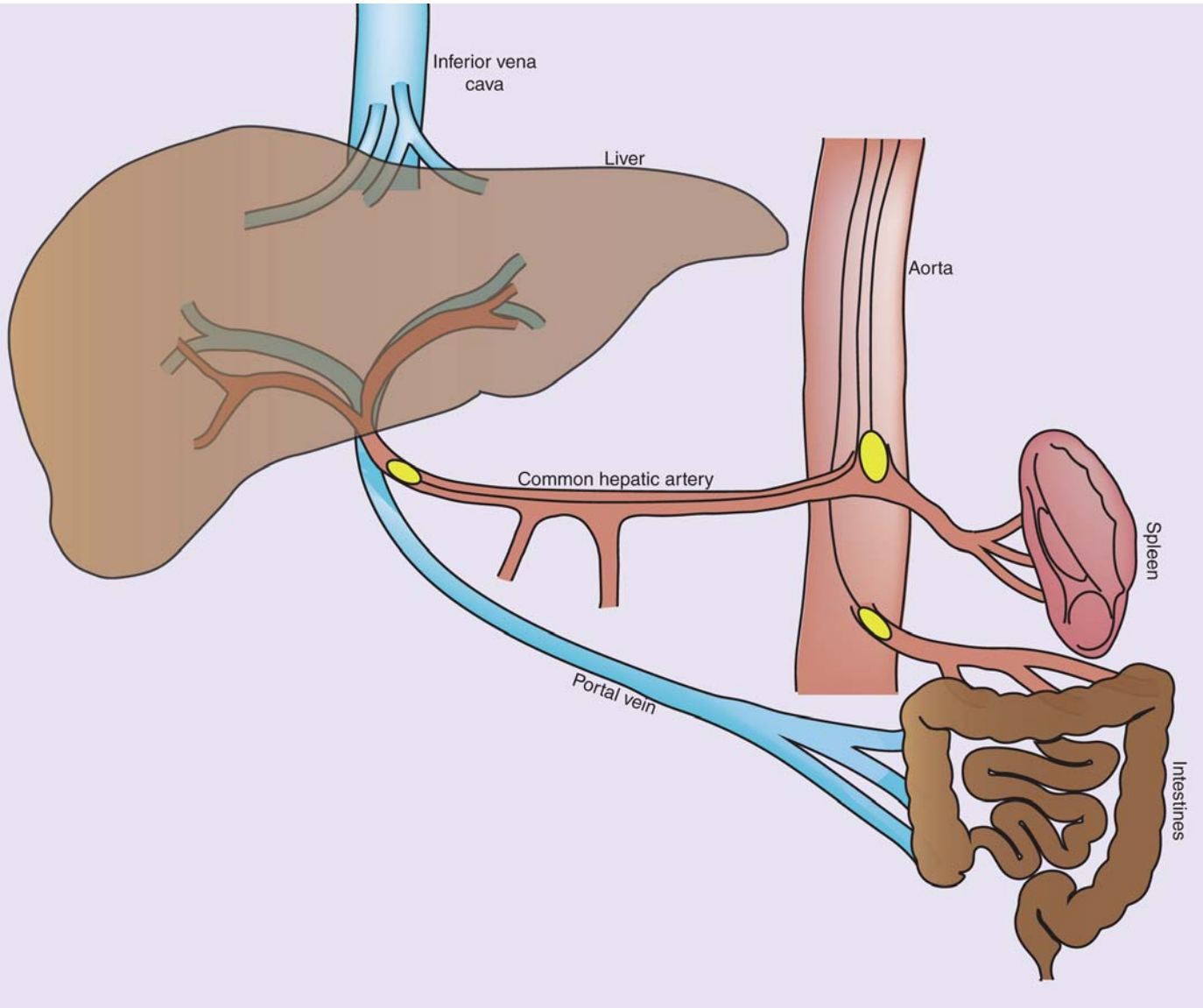

Figure 7. A schematic of the superselection of the hepatic artery for targeted chemotherapy delivery while simultaneously occluding the remaining branches of the celiac axis and inferior mesenteric artery.

life [73]. This time compression also allows the oncologist to assess progression/regression and modify therapy technique.

Direct comparison of mass fluid transfer with routine systemic intravenous therapy

A typical patient infused with systemic iv. oxaliplatin of 85 mg/m^2 over 2 hours can be expected to produce an unbound (active) C_{max} of 0.69 μg/mL and an AUC of 4 μg/mL/h [73]. In contrast should a clinician utilize the hepatic closed segment isolation system with mass fluid transfer, one can expect a local unbound (active) C_{max} of 750 μg/mL and an AUC of 300 μg/mL/h in addition to the known 4 μg/mL/h with recirculation [73]. As the closed segment system relies on artificially high venous pressures supported by elevated inflow hyperperfusion pressures, the resultant chemotherapy exposure time is high.

Figure 8 summarizes some of the obstacles in delivering intravenous chemotherapy to target cells. Vascular isolation liver therapy allows the dilution factor to be reduced to the mass of the target organ compared with total body mass. This approach minimizes the perfusion of unwanted effects on sensitive organs. Checkpoint immune inhibition is maximal locoregionally [74]. As the plasma proteins are removed locally before infusions, the plasma binding of active agents is minimized; oxaliplatin is 85% rapidly and irreversibly inactivated by plasma proteins [75].

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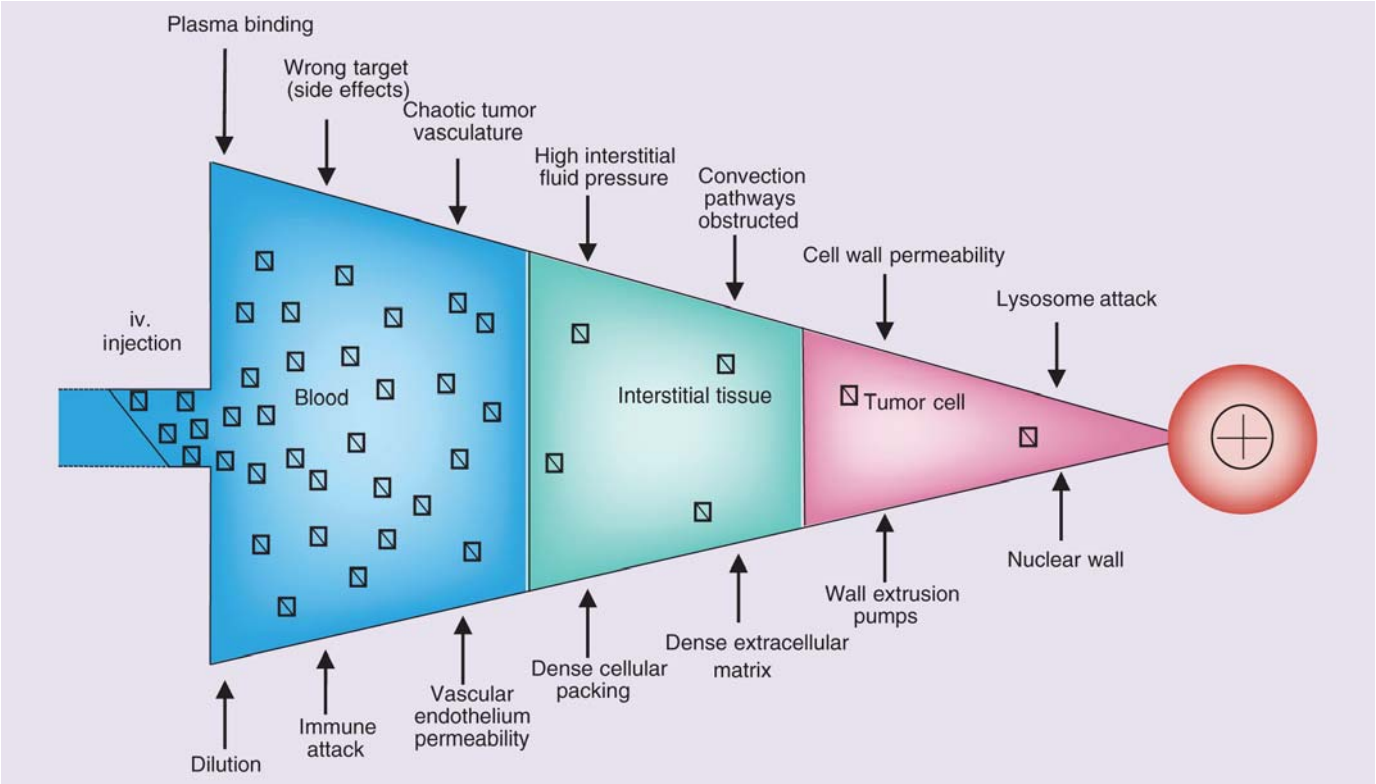

Figure 8. Standard intravenous chemotherapy delivery to neoplasms relies on simple diffusion gradients from the intravascular to the interstitial space. Summarizes numerous barriers which prevent efficient iv. chemotherapy delivery to the target tumor cell.
iv.: Intravenous

Removing the intravascular oncological active plasma protein creates an intravascular to extravascular transfer gradient of approximately 30 mmHg. This is then augmented by the higher protein concentrations often in the tumor interstitium [7,8]. High pressure bolus injection (Darcy's Law) improves the vascular endothelium mass fluid flux to counter elevated vascular resistance associated with the chaotic vascular architecture. The local permeability is improved by the synergistic effects of the elevated hydraulic and oncotic gradients. The induced interstitial edema may also improve the dense cellular packing and convection pathways [9,62]. Local tumor defences, including lysosome engulfment, are concentration dependent and may be neutralized by overwhelming intracellular chemotherapy gradients [9,62]. However, these optimal hemodynamics may have minimal effect on the genetic capability of tumors to mutate and become multidrug resistance.

After resumption of normal flow when the catheters are removed, the high vascular tumor resistance and increased interstitial edema renders intravascular reabsorption of chemotherapy difficult. This combined with a known tumor hypoplastic lymphatic system results in the chemotherapy now 'locked in'. Increased lymphatic flow through surrounding normal lymphatics may be helpful in treating lymph node deposits.

Direct comparison of mass fluid transfer with hepatic arterial infusion

HAI takes advantage of the fact that a proportion of the arterial blood volume delivered to the liver and particular liver tumors is via the hepatic artery [76]. There is therefore a transient increase in hepatic artery chemotherapy concentration during activation of the forward flow chemotherapy perfusion pump. This concentration increase is limited by recirculation. Confounding chemotherapeutic factors include an immediate chemotherapy dilution as blood flow within the artery reaches 300 mL/min within the hepatic artery and 1200 mL/min while transversing the portal system intrahepatically. In total, 15% of the tumor vascular supply is by the portal system.

The hepatic chemotherapy mass fluid transfer method requires intermittent obstruction of both portal and hepatic arterial inflows with multiple catheters selected segmentally, lobar or the liver in its entirety. Plasma proteins are subsequently removed allowing the transfer of chemotherapy to the interstitium of the tumor. This is achieved due to the elevated oncotic gradient that exists between the intravascular and extracellular compartments. During

infusion venous outflows are obstructed minimizing systemic contamination. Chemotherapy is delivered as a bolus to its intended target at suprasystolic pressures. Reduction of the portal flow activates the hepatic artery buffer response increasing global hepatic arterial blood flow and also shunts chemotherapy into the portal system via the peribiliary anastomosis [76].

A method of addressing the 15% of blood supply to the tumor by the portal system involves balloon occlusion and perfusion of the splenic artery at the splenic hilum. As the spleen is an end organ, chemotherapy delivered into the splenic hilum results in indirect perfusion of the portal system via the splenic vein. This method is repeatable.

Relevance of mass fluid transfer to *in vitro* testing

The known safe peak dose of unbound oxaliplatin delivery at 130 mg/m^2 is about 0.9 μg/mL [77]. In comparison, a concentration of 37 μg/mL (67.5 micromoles) of oxaliplatin is the lethal dose required to kill 99.9% ($LD_{99.9}$) for squamous cells (SM1573) [78]. This can only be achieved safely with locoregional treatment. The relative sensitivity of the tumor to therapy may be more predictable, as delivery capabilities become more objective. Local environment manipulation may also be easier to achieve and therefore becomes less unpredictable. In the above example, heating to 41°C improves the $LD_{99.9}$ by 180%. Local measures to combat increased solid intratumor pressure, such as hyaluronidase, collagenase and abraxane delivery may also be efficacious.

Future perspective: direct comparison of mass fluid transfer with previous locoregional approaches

The breast

Many of the principles of locoregional delivery of chemotherapy were incorporated by Stephens in stage III breast cancer treatment [79,80]. Intra-arterial infusion with superselection was possible from the groin and localization of the tumor blood supply was achieved with selective blue dye infusion. The results were impressive but the side effects due to chemotherapy recirculation were extensive. Suggested improvements would include the use of a long balloon to occlude all the collateral arteries that are not involved in direct arterial supply to the tumor (Figure 9A).

Plasma protein washout is possible before venous outflow is occluded via a single long balloon occluding the internal and lateral thoracic and pectoral veins supplemented by PEEP. This maneuver also minimizes intercostal perforating venous outflow (Figure 9B). The essence of the locoregional isolation technique allows the clinician to manipulate the tumor microenvironment. A simple needle into the breast allows measurement of local chemotherapy concentration and interstitial pressure surrounding the tumor. The interstitial chemotherapy dilution may indicate local lymphatic perfusion.

Mass fluid transfer has the potential to treat most solid tumors

Immune-checkpoint modifiers offer a broad and diverse opportunity to enhance antitumor immunity with the potential to produce promising clinical responses [81–83]. However, local tumor inflammation is needed to precipitate the activation of the checkpoint inhibitory pathway (Figure 2) [84].

Multicatheter local vascular isolation of organs may be helpful in initiating inflammation by triggering tumor lysis. Ischemia, elevated intrafluid pressure and high-concentration chemotherapy may combine to create a local aggressive immune response and hence a better response to locally delivered checkpoint inhibition (Figure 2). The advantage of delivering these checkpoint modifiers locally minimizes the potential for more serious systemic autoimmune complications.

Although mass fluid transfer has the potential to treat most solid tumors. Several tumors, such as brain and pancreatic tumors, present unique physical and biochemical barriers that will need to be overcome. Brain capillary endothelial cells are interconnected by tight junctions, with limited fenestrations and pinocytotic vesicles that form a barrier to prevent unimpeded diffusion into the brain. Therefore, progress in treating this disease may be dependent on the disruption of this blood–brain barrier. Also, given the number of agents that are substrates for active efflux at the blood–brain barrier there will need to be a modification of drug structures to diminish efflux transporter affinity and perhaps co-administration of transport inhibitors are required to enhance delivery of anticancer drugs. Pancreatic tumors harbor a dense, desmoplastic stroma that serves to limit the delivery of chemotherapeutic agents to these tumors. Efficacious delivery of chemotherapy to these tumors via mass fluid transfer requires further investigation.

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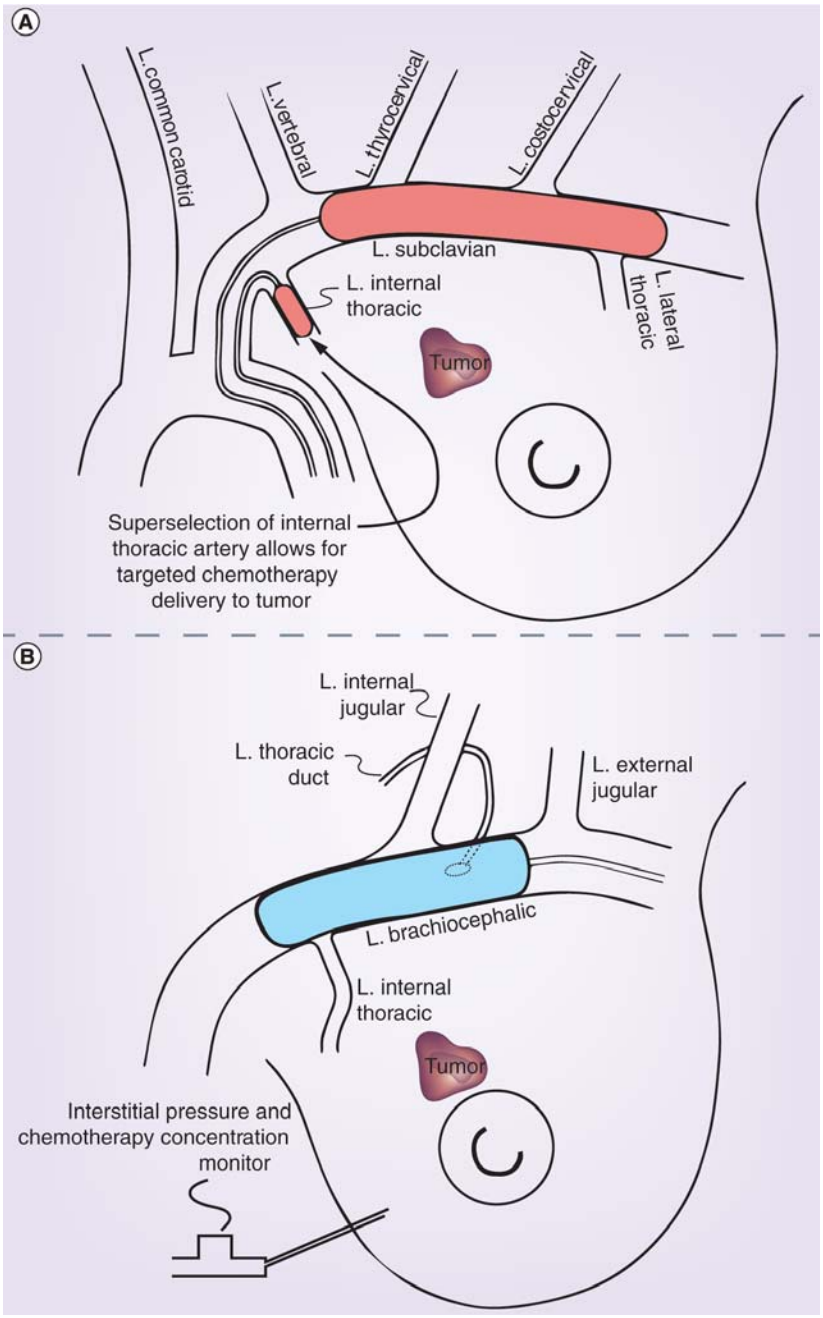

Figure 9. Locoregional intra-arterial breast chemotherapy delivery (A) with venous outflow obstruction (B).

Interaction with new technology

The US FDA has recently approved fluciclovine F18 for PET imaging in males with suspected prostate carcinoma recurrence based on PSA elevation [85,86]. Prostate arterial isolation has been shown to be safe and efficacious for benign prostatic hypertrophy [87]. The use of bulk fluid flux and multicatheter isolation may prove helpful in the focal treatment of pelvic recurrence in an otherwise difficult area to treat.

Conclusion

The current paradigm to treat solid neoplasia using systemic treatment alone encounters intrinsic difficulties related to the perfusion penetration and permeability of chemotherapy. The barriers relate to the chaotic tumor vasculature and elevated pressure within the tumor. Mass fluid transfer and bulk fluid flux combines intravenous, intra-arterial, stop flow and superselective locoregional chemotherapy delivery. The technique adds venous outflow obstruction

for chemotherapy retention and locoregional hypertension for added penetration and intravascular protein removal. Most importantly, the system is repeatable, measurable and addresses the tumor microenvironment. The essential components needed to manipulate mass fluid transfer and bulk fluid flux are therefore inherently dependent on specifically designed vascular hardware.

Executive summary

Background

- The standard treatment of solid organ neoplasms relies on the systemic delivery of intravenous chemotherapy.
- Effective treatment relies on the administration of a sufficient chemotherapy concentration to eradicate the tumor without causing deleterious side effects on normal structures remote from the tumor.
- In an attempt to overcome the challenges of effective chemotherapy delivery a number of treatment modalities have been proposed:
  1. Direct arterial delivery;
  2. Drug eluting particles;
  3. Stop flow techniques;
  4. Isolated hepatic infusion with recirculation and hemofiltration;
  5. Implantable multicatheter access system.

Simple diffusion versus mass fluid transfer & bulk fluid flux

- Mass fluid transfer can be defined as the delivery of soluble molecules across a semipermeable membrane.
- Bulk fluid flux is the process used by lipid insoluble proteins to cross the capillary endothelium.

Vascular mechanics

- Optimal delivery of chemotherapy is dependent on locoregional control of the tumor microenvironment.
- Vascular inflow pressure is required to be below critical closing pressure.
- Venous outflow obstruction ensures retention of chemotherapy in the interstitial space.
- Therapeutic agents can be infused at suprasystolic pressures to overcome elevated vascular resistance intrinsic to many tumors.

Multicatheter access system

- An implantable vascular access system with the capacity for multiple independently steerable targeting catheters.
- The system allows for repeatable vascular isolation that optimizes endothelial permeability and bulk fluid flow.

Direct comparison of mass fluid transfer with routine systemic intravenous therapy

- Locoregional delivery enables an improvement of 2–3 orders of magnitude compared with intravenous therapy.

Direct comparison of mass fluid transfer with hepatic artery infusion

- Hepatic artery infusion results in a transient increase in hepatic artery chemotherapy concentration during activation of the forward flow chemotherapy perfusion pump.
- The hepatic mass fluid transfer method requires intermittent obstruction of both portal and hepatic arterial inflows with multiple catheters.
- Plasma proteins are removed allowing the transfer of chemotherapy to the interstitium of the tumor.
- Obstruction of venous outflows prevents systemic contamination and therefore chemotherapy is delivered as a bolus to its intended target at suprasystolic pressures.

Relevance of mass fluid transfer to *in vitro* testing

- The relative sensitivity of the tumor to therapy may be more predictable, as delivery capabilities become reliable, for example, squamous cells SM1573 have a $LD_{99.9}$ of 37 μg/mL (67.5 micromoles) of oxaliplatin. This can only be considered possible by local treatments.
- In the above example, heating to 41°C improves the $LD_{99.9}$ by 180%.

Direct comparison of mass fluid transfer with previous locoregional approaches

- In the previous locoregional treatment of stage III breast cancer, superselection and intra-arterial chemotherapy achieved good results with severe side effects.
- The repeatable vascular hardware system allows manipulation of inflow, outflow and oncotic gradients minimizing systemic chemotherapy contamination.
- A simple needle into the breast allows measurement of local chemotherapy concentration and interstitial pressure within the tumor. The interstitial chemotherapy dilution may indicate local lymphatic perfusion.

Mass fluid transfer has the potential to treat most solid tumors

- Multicatheter local vascular isolation of organs may be helpful in initiating inflammation by triggering tumor lysis.
- Ischemia, elevated interstitial fluid pressure and high-concentration chemotherapy may combine to create a local aggressive immune response and hence a better response to locally delivered checkpoint inhibition.

Interaction with new technology

- The use of bulk fluid flux and multicatheter isolation may prove helpful in the focal treatment of pelvic recurrence of prostate cancer with the recent approval by the US FDA of fluciclovine F18.

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P119
EMERGING TREATMENTS USING AN IMPLANTABLE LARGE BORE VASCULAR ACCESS SYSTEM
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Introduction: An implantable large bore arterial/venous access system (AVAS) was developed to address the limitations of repeatability and frequency of the current minimally invasive vascular access technology available. New treatment options introduced from this improvement were explored.
Material and methods: The AVAS was used to administer local hyperperfusion therapy to twenty patients with critical limb ischemia (CLI) facing imminent amputation, and vascular isolation chemotherapy to ten chemorefractory patients with inoperable colorectal liver metastases (CRC-LM). The AVAS was implanted and explanted under general anaesthesia in all patients. In the CLI group, the device was connected to a centrifugal pump to intermittently hyperperfuse-affected limbs over a 4-week period. In the CRC-LM group the AVAS was used to facilitate simultaneous cannulation of multiple balloon catheters into the superior mesenteric and common hepatic arteries and the celiac axis to isolate hepatic blood flow. Chemotherapy was infused via a microcatheter through the lumen of the hepatic arterial balloon. Chemotherapy infusions were administered up to twice a week over a four-week period.
Results: Forty-three devices were implanted with no device related serious adverse events reported. Forty AVAS-pump connections were made for hyperperfusion sessions that spanned from twenty-four to thirty-six hours in CLI patients. Forty-seven multicatheter cannulations were made through the device for vascular isolation chemotherapy in CRC-LM patients.
Discussion: An implantable large bore access system allowing repeatable vascular access and its application for novel treatments has been demonstrated. The system presents an opportunity to explore the potential of repeatable and localised infusion/perfusion of organs with or vascular organ isolation.

P121
EXPANDED PTFE MEMBRANE PREPARATION FOR VASCULAR PROSTHESIS
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Introduction: Expanded PTFE is prepared by thermo-mechanical stretching. Obtained morphology shows the suitable structure for vascular prosthesis. Direct cell contact and MTT demonstrate the non-toxic feature of expanded PTFE prepared at present study.
Material and methods: PTFE is prepared by thermo-mechanical stretching from PTFE powder and lubricant. PTFE was first mixed with lubricant, extruded and subsequently stretched. Finally, the lubricant was extracted from the membrane. The samples were characterized by SEM, liquid entry pressure (LEP) and cytotoxicity to evaluate the efficiency for vascular prosthesis. In addition quantitative cell viability measurement was performed by MTT assay.
Results: SEM images revealed that, lubricant presence and stretching ratio increment lead to increase in IND, which demonstrates the traditional definition of ePTFE membrane porosity. Presence of lubricant brings about high porosity of ePTFE, whereas absence of the lubricant resulted in low porosity. Fibril length increased by stretching ratio and causes the high porosity ePTFE. In addition LEP is decreased by increase of stretching ratio for whole the studied samples. On the other hand, absence of lubricant lead to decrease in IND compared to the lubricated samples. Direct cell contact method shows non-toxic feature of lubricated samples. MTT assay shows decrement in cell viability because of hydrophobicity of PTFE.
Discussion: Expanded PTFE prepared in this study shows the adequate morphology for vascular prosthesis applications. High porosity ePTFE achieves by increase of stretching ratio and lubricant utilization. It seems that lubricant diffuses between crystal cells and facilitated the fibrillation during process, which subsequently leads to high porosity ePTFE.

Poster Session - Biomeasurements, Robotics and Navigations, P123-P132

P123
THREE-DIMENSIONAL NANO- AND MICROSTRUCTURAL ANALYSIS OF BIOLOGICAL OBJECTS BY SCANNING PTOBE NANOTOMOGRAPHY
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Introduction: Progress in development of technologies of micro-and nanostructural analysis of artificial and native biological objects and tissues is crucially significant for tasks of structural biology, medical diagnostics, and development of new materials and bioengineered constructions for medical

CHAPTER 7 – CONCLUSIONS

The aim of this thesis was to determine whether a universal vascular access device could be developed which could provide general vascular access but also facilitate LRC treatments and if so, to assess the potential of the treatment it can facilitate.

A design for a UVAS was made based on an existing transcutaneous vascular access device as well as the clinical requirements deemed necessary for it to be able to facilitate LRC therapies. The design was developed into a functional device and a meta-analysis of devices with similar features was carried out to develop an understanding of the potential risks and side effects to anticipate with the use of the device. Initially, 10 UVAS devices were implanted and used in 5 patients in a general vascular access setting where the UVAS served as a conduit for pressurised blood flow to and from the patient's host artery. The treatment, hypertensive extracorporeal limb perfusion, was administered to patients with end-stage critical limb ischemia.

Based on the functionality and safety profile established through this first study, a new LRC technique was developed for the liver in the form of OIC which utilised the capabilities made available by the UVAS. Another human clinical trial was completed to assess the safety and feasibility of the hepatic OIC treatment with the UVAS. Ten patients with inoperable colorectal liver metastases that had previously failed all systemic chemotherapy along with other treatments were administered the OIC treatment using the UVAS.

The outcomes from the OIC and HELP studies confirmed that the designed UVAS could safely perform its intended function under the user specifications and patient suitability criteria developed. It was shown that in addition to being able to serve as a general vascular access device as was the case in the HELP study, the UVAS was able to facilitate a repeatable LRC technique in the form of repeated hepatic OIC. The outcomes reported from the OIC study not only demonstrated that the OIC treatment was safe and feasible, but that it warrants further investigation in a larger phase II study. The complications and adverse events encountered form the two studies also provided insight into what design features of the UVAS could be improved upon as well the aspects of the OIC treatment that could be refined in order to prevent the recurrence of such complications and or improve the potential of the OIC treatment. Furthermore, an iteration of the UVAS incorporating the improved design features has already been developed and a phase Ib/II study utilising this revised UVAS design to further explore the efficacy of the hepatic OIC treatment has been initiated.

Finally, the level of control of the hepatic inflow and outflow achieved during the OIC treatment initiated a re-evaluation of the mechanisms by which chemotherapy is transported and distributed throughout the microvasculature of the tumour and organ. Based on first principles,

it is believed that the hydrostatic and oncotic pressure gradients across the capillary walls can be directly controlled via the OIC method developed unlike that of other LRC techniques or standard IV chemotherapy which relies on simple diffusion to cross the vascular endothelium into the tumour and interstitium. Manipulation of these parameters via OIC allows for chemotherapy penetration into and retention within the tumour via mass fluid transfer and bulk fluid flux. Based on these potential advantages as well as the universal nature of the UVAS, further potential applications of OIC using the UVAS have also been identified with possible device and catheter setups identified in instances of carcinomas of the pancreas, breast, and limbs.

Overall, the outcomes observed and the insights gained from the processes undertaken throughout this thesis could serve as a platform to launch further endeavours in thoroughly exploring LRC treatments. The UVAS device developed allows for institutions resourced with standard skillsets in vascular surgery, interventional radiology and endovascular surgery to replicate or tinker with the OIC technique and develop new repeatable and minimally invasive LRC techniques of their own. In doing so, it could potentially shift the current research paradigm from one that is drug design centric to one that seeks to achieve same leaps of progress in drug delivery techniques. Only then can the question be answered as to whether the magic bullet for cancer is already on the shelf and all that is needed is the right gun.

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APPENDIX A – ALL LITERATURE FOUND FROM META-ANALYSIS

All the PMID numbers for the 294 unique search results (i.e. duplicates removed) from the 12 algorithms used for the literature search (Section 2.3.2, Chapter 2) are listed below in Table A1.

Table A1 – List of all 294 unique PMID numbers for all clinical literature found using the literature search protocol.

1379968	6375089	8817948	10496704	11854728	15684902	18360062	20574104	22893096	25649214
1381642	6407410	8852178	10541127	11859986	15696040	18381133	20598573	22945408	25720929
1406473	7609278	8872599	10587392	12105254	15780111	18541001	20599208	23023470	25876977
1453208	7630459	8984428	10609902	12127802	15878264	18544146	20629557	23332688	25907772
1538510	7648588	9091836	10687256	12382087	16005107	18705719	20638981	23532614	25953016
1548889	7661253	9123925	10742435	12469051	16041209	18843613	20667751	23538636	25998123
1675136	7666089	9154475	10776036	12514593	16075346	18981642	20886210	23765173	26026264
1837550	7747826	9175232	10826736	12566672	16171591	19103988	20926105	23816388	26464072
1839703	7763121	9201160	10860694	12578294	16199481	19125710	21051729	23817954	26842716
2149042	7769738	9208965	10864199	12620263	16476607	19127226	21055087	23823005	26904891
2149048	7779730	9214926	10885719	12829157	16485206	19172346	21285898	23892494	26996592
2149049	7844604	9261781	10917292	12831411	16635031	19231253	21349747	23972437	27020965
2149051	7944033	9269607	10917986	12917893	16672064	19242336	21376643	24005884	27092784
2261941	7945084	9335673	10917987	14597359	16783143	19273702	21514114	24018351	27191518
2529814	8000128	9413642	10952794	14603216	16798772	19321052	21622670	24096801	27203778
2599125	8078010	9423389	11012957	14611735	17047181	19327750	21663812	24113369	27240799
2663980	8134457	9444795	11107088	14612164	17098527	19329916	21941231	24268631	27258204
2698562	8201387	9516200	11153622	14695501	17321952	19389904	21945145	24464053	27259529
2777728	8313125	9552036	11199311	14709686	17379979	19602895	22063233	24625519	27514445
2886533	8353432	9591592	11237786	14979400	17472536	19628360	22284636	24699511	27818170
2915237	8365459	9607475	11241124	15041577	17709365	19660993	22341495	24717908	27957644
3079838	8398318	9793013	11336362	15111342	17767451	19693022	22378114	24732230	28077611
3278258	8530241	9884940	11506514	15122605	17880315	19718588	22444157	24811603	28278167
3422694	8559494	10072461	11532113	15164262	17919374	19788736	22466981	24983260	28526171
3525990	8562348	10092890	11585883	15218464	17928580	20010613	22505280	25063013	
3834009	8630289	10160070	11720831	15351854	18155872	20218943	22622651	25198813	
3907550	8671969	10230263	11723017	15385346	18161677	20306091	22633423	25421369	
4014571	8677035	10380274	11758266	15503612	18202556	20443681	22710497	25453876	
6339139	8696545	10436450	11788698	15557906	18241756	20478686	22790185	25498193	
6350971	8735325	10465471	11854727	15621100	18296081	20546160	22840340	25527695	

APPENDIX B – HUMAN RESEARCH ETHICS COMMITTEE APPROVAL: HELP TRIAL

NORTHERN SYDNEY CENTRAL COAST NSW HEALTH

18 March 2010

Professor R Lane
C/-Consulting Rooms, Suite 13, Greenwich Square
130-134 Pacific Highway
ST LEONARDS NSW 2065

Dear Professor Lane,

Re: LEAD HREC MULTI-CENTRE APPLICATION APPROVAL
NSW HEALTH ACCREDITED HREC: HARBOUR
NORTHERN SYDNEY CENTRAL COAST HEALTH (NSCCH)
LOCAL REFERENCE: Protocol 0911-306M(CTN-dev) **- R Lane, C Fisher, V Puttaswamy, W Mohabbat, R Harris, M Neale, A Johnston, D McMillan, M Huckson, J Hyvarinen, M Evtushenko**
A Multicentre, Controlled Trial to Determine the Safety and Efficacy of Hypertensive Extracorporeal Limb Perfusion (HELP) in Treating Patients with Critical Limb Ischaemia. (AU RED Ref. HREC/09/HARBR/160)

Thank you for providing additional information as requested at the meeting on the **22 February 2010** by the **HARBOUR** Human Research Ethics Committee (HREC) of Northern Sydney Central Coast Health (NSCCH). Please be advised that your study has now been approved.

It is noted that the study has been assessed by the HREC for *'HREC review only'* (i.e. the NSCCH HREC has reviewed the project as the external site does not have an in-house HREC to review the research). It is acknowledged that the *'Authority'* for the trial is Chief Executive Officer Dalcross Private Hospital. The external site/s approved are:

- **Dalcross Private Hospital, Killara NSW**

The study is approved with the following conditions:

Conditional Approval - Monitoring:

- **The HREC requires a Progress Report for each patient, 3 months after surgery. The report is to include a copy of the Patient Consent Form and any relevant (de-identified) patient notes.**
- **The researcher is required to submit a Quarterly Progress Report on the overall data of the trial.**
- **The HREC will conduct annual monitoring visits at the site where the study is to be conducted.**
- **All Adverse Events (AE) and Serious Adverse Events (SAE) should be submitted immediately to the HREC for review.**

It is noted that the study has been assessed by the HREC for *ethical* and *scientific review* ONLY and that clearance on the Site Specific aspects of the trial (local sign-off's, legal documentation etc) *MUST* be obtained *prior* to commencement of research. Each site has different requirements, NSW Area Health Service sites require submission and approval of a Site Specific Assessment (SSA), which can be completed at www.ethicsform.org/au. Please contact each site for advice on any local requirements.

Research Business Unit
Level 2 Building 51, Royal North Shore Hospital
St Leonards NSW 2065 Ph: (02) 9926 8106 Fax: (02) 9926 6179

North Shore Private Hospital:
The Harbour HREC is unable to provide approval for the study to be conducted at the North Shore Private Hospital (NSPH). There is no agreement between the NSPH and the Area Health Service to conduct research at that site. The researcher will be required to submit an application to conduct the study at NSPH, to the NSPH Management Committee for approval prior to commencement of the study.

The documentation included in the approval is as follows:

- Master Patient Informed Consent and Information Sheet CT1-066 revision1 (Released 19MAR2010)
- Dalcross Hospital Patient Informed Consent and Information Sheet CT1-081 revision3 (Released 15MAR2010).
- Investigators Brochure Peripheral Access Device (PAD) Version 1.0 dated 13 October 2009.
- Peripheral Access Device Instructions for Use (PAD IFU) Version 1.0 dated 22 September 2009.
- Instructions for Use – Inflatable Occluder Cuff Version 1.0 dated 22 September 2009.
- HELP Clinical Trial Protocol CT1-001 Version 1.0 dated 13 October 2009.
- Investigators Declaration for Recruitment Version 1.0 dated 13 October 2009.

*If you wish to add an additional site to the project within the area you will be required to complete a *'Site Specific Assessment Form'*, that can be accessed from www.ethicsform.org/au.

The HREC recommends that you consult with your Medical Defence Union to ensure that you are adequately covered for the purpose of conducting this clinical trial.

At this time, we also remind you that, in order to comply with the *Guidelines for Good Clinical Research Practice (GCRP) in Australia*, and in line with NSCCH HREC policy, the Chief Investigator is responsible to ensure that:

1. The HREC is notified of anything that might warrant review of the ethical approval of the project, including unforeseen events that might affect the ethical acceptability of the project.
2. The HREC is notified of all Serious Adverse Events (SAEs) or Serious Unexpected Suspected Adverse Reactions (SUSARs) in accordance with the Serious Adverse Event Reporting Guidelines. Please refer to the Research Office website.
3. Proposed amendments to the research protocol or conduct of the research that may affect the ethical acceptability of the project are submitted to the HREC on an amendment form (including any relevant attachments). For multi-centre studies, the Chief Investigator should submit to the Lead HREC and then send the amendment approval letter to the investigators at each of the sites so that they can notify their Research Governance Officer.

4. Proposed changes to the personnel involved in the study are submitted to the HREC on a Change in Personnel Form (accompanied by the investigator's CV where applicable).
5. The HREC must be provided with an annual progress report for the study by the 31st October each year. For multi-centre studies the Chief Investigator should submit to the Lead HREC on behalf of all sites.
6. The HREC must also be provided with a final report upon completion of the study. For multi-centre studies the Chief Investigator should notify the Lead HREC and the investigators at each site should notify the relevant Research Governance Officer.
7. The HREC must be notified, giving reasons if the project is discontinued at a site before the expected date of completion.

Please refer to the NSCCAHS Research Office website to access forms such as the amendment form, Annual/Final Report Form, Change in Personnel Form and Serious Adverse Event Guidelines and Forms;

Intranet:
http://intranet01.nsahs.nsw.gov.au/intranet/rns/research/Ethics/HREC/default.shtml

Internet:
http://www.nsccahs.health.nsw.gov.au/services/research/default.shtml

HREC approval is valid for four (4) years from the date of the approval letter. **Your approval will therefore expire on the 18 March 2014. The Annual Progress Report is to be submitted on the 31st October each year.**

Yours sincerely,

Dr Liz Newton
Chairperson
HARBOUR HREC
NORTHERN SYDNEY
CENTRAL COAST HEALTH

NORTHERN SYDNEY
CENTRAL COAST
NSW HEALTH

18 March 2010

Professor R Lane
C/-Consulting Rooms, Suite 13, Greenwich Square
130-134 Pacific Highway
ST LEONARDS NSW 2065

Dear Professor Lane,

Re: Protocol 0911-306M(CTN-dev) **- R Lane, C Fisher, V Puttaswamy, W Mohabbat, R Harris, M Neale, A Johnston, D McMillan, M Huckson, J Hyvarinen, M Evtushenko A Multicentre, Controlled Trial to Determine the Safety and Efficacy of Hypertensive Extracorporeal Limb Perfusion (HELP) in Treating Patients with Critical Limb Ischaemia. (AU RED Ref. HREC/09/HARBR/160)**

I can confirm that the **HARBOUR** Human Research Ethics Committee is constituted and functions in full compliance with NHMRC Guidelines.

Currently there are nineteen (19) members of this Committee including:

- Laywomen
- Laymen
- 2 Ministers of Religion
- a Lawyer
- 5 Medical Graduates
- a Scientist with research experience
- a Clinical Trials Pharmacist
- an alternate Clinical Trials Pharmacist
- a Neuropsychologist
- a Psychologist
- Registered Nurses

We can confirm that none of the researchers involved in the study are members of the NSCCH HREC.

Yours sincerely,

Mrs Judy Wells
Ethics Officer
Harbour Human Research Ethics Committee

Adventist HealthCare
yours for life

24 November 2014

Professor Rodney Lane
c/o Mr Nyan Khin
Suite 13
130-134 Pacific Highway
St Leonards NSW 2109

Dear Professor Lane

HREC Project ID: 16/10
Project Title: A multicentre, controlled trial to determine the safety and efficacy of hypertensive extracorporeal limb perfusion (HELP) in treating patients with critical limb ischaemia.

The Adventist HealthCare Limited Human Research Ethics Committee (HREC), previously known as the Sydney Adventist Hospital Human Research Ethics Committee, is a registered HREC with the National Health and Medical Research Council (Australia) Registration Number EC00141. The HREC is constituted and operates in accordance with Section 35 of the *National Health and Medical Research Act 1992;* the *National Statement on Ethical Conduct in Human Research* and the *CPMP/ICH Note for Guidance on Good Clinical Practice.*

The HREC is a registered Institutional Review Board with the U.S. Department of Health and Human Services, Office for Human Research Protections Registration Number IRB00005340

The HREC accepted the Lead HREC's (RNSH) ethical approval in July 2010 and granted approval for the above research study to continue at Dalcross Adventist Hospital.

None of the HREC members were involved with the conduct of the research study and no conflict of interest existed between their membership and the study. Professor Rodney J Lane was not a member of the HREC during the conduct of the study.

Yours faithfully

Jenelle Quick BScOT
Research Governance & Ethics Officer
Adventist HealthCare Limited
Ph: +61 2 9487 9604
Fax: +61 2 9487 9615
Email: ethics@sah.org.au
Web: www.sah.org.au/ahcl-ethics-committee

APPENDIX C – NATIONAL TRIALS REGISTRY: HELP TRIAL

Trial Review

VIEW TRIAL AT REGISTRATION VIEW HISTORY

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Trial registered on ANZCTR

Trial ID	ACTRN12610000118000
Ethics application status	Approved
Date submitted	9/12/2009
Date registered	4/02/2010
Date last updated	16/12/2014
Type of registration	Prospectively registered

Titles & IDs

Public title	A Multicentre, Controlled Trial to Determine the Safety and Efficacy of Hypertensive Extracorporeal Limb Perfusion (HELP) in Treating Patients with Critical Limb Ischaemia (CLI)
Scientific title	In treating patients with Critical Limb Ischaemia (CLI) using Hypertensive Extracorporeal Limb Perfusion (HELP) when compared to conventional treatments the study evaluates Safety and Efficacy via a multicentre, controlled trial.
Secondary ID [1]	CTN 036/2010
Universal Trial Number (UTN)	U1111-1112-6971
Trial acronym	Hypertensive Extracorporeal Limb Perfusion (HELP)
Linked study record	

Health condition

Health condition(s) or problem(s) studied:

Critical Limb Ischemia

Condition category

Cardiovascular

Condition code

Diseases of the vasculature and circulation including the lymphatic system

Intervention/exposure

Study type	Interventional
Description of intervention(s) / exposure	The Hypertensive Extracorporeal Limb Perfusion (HELP) procedure involves the temporary surgical implantation of two large bore access ports (Peripheral Access Devices - PAD) in to the femoral artery (thigh). The devices will be implanted (2hour procedure duration) for a maximum duration of 28 days after which the devices are removed. Pressure and Flow are then generated by an extracorporeal pump taking the patients blood from one device and returning it in to the the treatment limb. This increased flow allows an improvement in perfusion to the diseased/occluded limb. Pumping sessions will last for around 24 hours at a time and may be repeated every other day for the total treatment period (28 days)
Intervention code [1]	Treatment: Devices
Intervention code [2]	Treatment: surgery
Comparator / control treatment	Historical Data of CLI Amputees determined by a literature review (worldwide meta analysis of published

	papers)(taken from within previous 10 years) along with a review of the investigative teams own patient databases
Control group	Historical

Outcomes

Primary outcome [1]	Determine safety and efficacy of Hypertensive Extracorporeal Limb Perfusion in preventing major limb amputation by examination for harm (Serious Adverse Events - including Minor Amputations ,Significant infection. haematoma or haemorrhage, Clinically significant thrombosis, Haemolysis) or further treatment (amputation)
Timepoint [1]	6 months after explantation of the PAD devices
Secondary outcome [1]	Relief of symptoms of peripheral vascular disease - determined by thermography, ultrasound, physical examination, questionnaires
Timepoint [1]	6 months after explantation of the PAD devices
Secondary outcome [2]	Healing of ulcers determined by photographic records and physical examinations
Timepoint [2]	6 months after explantation of the PAD devices
Secondary outcome [3]	Increased distal perfusion determined by ankle brachial index (ABI) and also by ultrasound exam
Timepoint [3]	6 months after explantation of the PAD devices

Eligibility

Key inclusion criteria	1) Only alternative treatment is imminent (within 8 weeks) major limb amputation 2) At least two vascular surgeons must agree that the treatment is the only remaining option for the patients 3) Patients must be over 18 years of age 4) Patients have critical limb ischaemia 5) Patients must be able to understand the risks and benefits of the trial and give written informed consent to participate 6) Patients must be fit for anaesthesia 7) Patients must have suitable anatomy determined by pre-operative imaging and physical examination
Minimum age	18 Years
Maximum age	No limit
Gender	Both males and females
Can healthy volunteers participate?	No
Key exclusion criteria	1) Patients must not be in a concurrent clinical trial 2) Patient must not have compartment syndrome 3) Patients must not have an active systemic infection 4) Patient must not have serum abnormalities or high Creatine Phosphokinase (CPK) (greater than 3x the upper limit of normal for the testing laboratory) as deemed by the clinical investigator 5) Patients must not have general advanced debilitation or intercurrent organ failure 6) Patients must not have a serious wound infection (for example, Methicillin-resistant Staphylococcus aureus (MRSA) of the ulcer) that in the opinion of the Clinical Investigator may impede the response to treatment 7) Patients must not have disseminated intravascular coagulation (DIC) as deemed by the clinical investigator

Study design

Purpose of the study	Treatment
Allocation to intervention	Non-randomised trial
Procedure for enrolling a subject and allocating the treatment (allocation concealment procedures)	All patients are end stage referrals with no other options. They are approved to the trial by two independent co-investigators. All recruited patients if deemed suitable will be treated.
Methods used to generate the sequence in which subjects will be randomised (sequence generation)	There are no randomisations
Masking / blinding	Open (masking not used)
Who is / are masked / blinded?	
Intervention assignment	Single group
Other design features	
Phase	Not Applicable

Type of endpoint(s)	Safety/efficacy
Statistical methods / analysis	

Recruitment

Recruitment status	Completed

Date of first participant enrolment

Anticipated	1/02/2010	**Actual**	7/05/2010

Date of last participant enrolment

Anticipated		**Actual**	3/11/2010

Date of last data collection

Anticipated		**Actual**	

Sample size

Target	40	**Accrual to date**	**Final**

Recruitment in Australia

Recruitment state(s)	
Recruitment hospital [1]	Dalcross Adventist Hospital - Killara

Funding & Sponsors

Funding source category [1]	Commercial sector/Industry
Name [1]	Advanced Surgical Design and Manufacture
Address [1]	2/12 Frederick St, St Leonards, NSW 2065
Country [1]	Australia
Primary sponsor type	Commercial sector/Industry
Name	Advanced Surgical Design and Manufacture
Address	2/12 Frederick St, St Leonards, NSW 2065
Country	Australia
Secondary sponsor category [1]	None
Name [1]	
Address [1]	
Country [1]	

Ethics approval

Ethics application status	Approved
Ethics committee name [1]	Northern Sydney Central Coast Human Research Ethics Committee (HREC)
Ethics committee address [1]	Research Office Level 2, Building 51, Royal North Shore Hospital ST. LEONARDS NSW 2065
Ethics committee country [1]	Australia
Date submitted for ethics approval [1]	16/11/2009
Approval date [1]	18/03/2010
Ethics approval number [1]	HREC/09/HARBR/160 HREC Protocol Number 0911-306M

Summary

Brief summary	The HELP treatment implants two Peripheral Access Devices (PAD) in to a patients thigh. The devices are connected to a pump (outside of the body). Blood is taken from the upper device and pumped at higher pressure back in to the lower device. The higher pressure increases perfusion in to the diseased limb, reducing pain and promotes growth of new vessels.
Trial website	

Trial related presentations / publications	Lane RJ, Phillips M, McMillan D, Huckson M, Liang SW, Cuzzilla M,"Hypertensive extracorporeal limb perfusion (HELP): A new technique for managing critical lower limb ischemia" J Vasc Surg. 2008 Nov;48(5):1156-65
	Khin NY, Dijkstra ML, Huckson M, Phillips M, McMillan D, Itoh S, Roger G, Lane RJ. "Hypertensive extracorporeal limb perfusion for critical limb ischemia"J Vasc Surg. 2013 Nov;58(5):1244-53
Public notes	

Contacts

Principal investigator

Name	Dr Rodney Lane
Address	AllVascular Pty Ltd Suites 13, Greenwich Square, 130-134 Pacific Highway, St Leonards NSW 2065
Country	Australia
Phone	+61 2 9438 5228
Fax	
Email	HELP-Trial@asdm.com.au

Contact person for public queries

Name	Dr Dr Rodney Lane
Address	AllVascular Pty Ltd Suites 13, Greenwich Square, 130-134 Pacific Highway, St Leonards NSW 2065
Country	Australia
Phone	+61 2 9438 5228
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Email	HELP-Trial@asdm.com.au

Contact person for scientific queries

Name	Dr Dr Rodney Lane
Address	AllVascular Pty Ltd Suite 13, Greenwich Square, 130-134 Pacific Highway, St Leonards NSW 2065
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Email	HELP-Trial@asdm.com.au

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APPENDIX D – CLINICAL TRIAL PROTOCOL: OIC TRIAL

Protocol Number: 5201100434

Assessment of the Safety and Efficacy of Intra-Arterial Liver Isolation Chemotherapy Using an Implantable Vascular Access System

Prepared by:

Nyan Khin
(Clinical Trial Monitor)

Signature 12 MAR 2013 Date

Reviewed and approved by:

Dr Rodney J Lane
(Vascular Surgeon)

Signature 12 / MAR / 2013 Date

Revision History

Version	Changes/Lab Book/Meeting/ Report Reference	Date	Author
1.0	Initial	06FEB2012	NK
2.0	Modified to allow for inclusion of hepatocellular carcinoma (HCC) patients. Primary changes include inclusion/exclusion criteria, specifying a dosage regimen for HCC patients, updating the equipment/chemotherapy agents table, and minor wording changes to other sections.	25JUL2012	NK
3.0	Modified to include option to implant PAD in patient's subclavian artery, updated equipment/chemotherapy agents table, added another schematic in Appendix 3, and minor wording changes in other sections.	03NOV2012	NK
4.0	Table in Section 11, and 11.6 modified to include the use of the power infuser to inject the chemotherapy. Sections 12.2 12.3 updated to provide a more extensive list of anticipated adverse events.	12MAR2013	NK

Table of Contents

1 General Information

1.1 Testing Centres

Testing centres involved in this trial can be found in Appendix 1.

1.2 Study Sponsor

Sponsor: Professor Rodney J Lane
Address: Suite 13, 130-134 Pacific Highway
St Leonards NSW 2065
Australia
Phone: +61 2 9638 5228
Fax: +61 2 9438 4114

1.3 Study Monitor

Sponsor: Nyan Khin
Address: Suite 13, 130-134 Pacific Highway
St Leonards NSW 2065
Australia
Phone: +61 2 9638 5228
Fax: +61 2 9438 4114

1.4 Medical Expertise

This trial is intending to use Dr Rodney Lane as a medical expert adviser on all clinical decisions with regard to the implantation, operation, and explantation of the vascular access system. Dr Stephen Clarke will be the lead oncologist and will make all clinical decisions with regards to the patient's treatment regimens. Dr John Magnussen will be the lead interventional radiologist and will carry out the specified treatment regimen(s). Further, the nominated investigators will be consulted as a panel on clinical matters related to the trial.

1.5 Participating Personnel

A list of personnel positions is provided in Appendix 2.

2 Introduction

Use of combination chemotherapy has improved survival for patients with metastatic colorectal cancer. Around 80% of patients have liver involvement, and it is often the predominant site of disease. A higher chemotherapy dose reaches the tumor using hepatic arterial infusion. In the past, surgery was required to place a device permanently in the hepatic artery and portal system, which resulted in local complications. Recent developments using percutaneous techniques still require the use of indwelling catheter systems. A new device is now available which is placed in the artery of the common iliac, or axilla, and catheters inserted into the liver just for the duration of the chemotherapy, which reduces local complications, whilst also allowing for repeatability. Second, multiple catheters allow for complete control of the hepatic circulation. The aim of this study is to demonstrate the feasibility of this approach and also replicate results from a recent study (Boige et al 2008) where 43% of colorectal cancer (CRC) patients responded following failure of first and second line combination chemotherapies.

Responses to hepatic arterial infusion (HAI) chemotherapy for patients with colorectal cancer with inoperable liver metastases (CRC-LM) have been seen for patients for whom these same drugs have ceased working via the intravenous route. Early studies using HAI required surgical placement of an indwelling device which remained in the liver. A new device is now available which is implanted into the artery in the groin or axilla. At the time HAI is administered, catheters are inserted into the hepatic artery, whilst also

controlling both portal and arterial hepatic perfusion. Post procedurally the catheters are removed following completion of therapy and the treatment process can be repeated multiple times.

Our study plan is to recruit patients with CRC-LM and patients with hepatocellular carcinoma (HCC) who have failed systemic treatment with first and second line combination chemotherapy. We will assess the feasibility of delivering oxaliplatin via HAI using the new vascular access technique in combination with systemic oral administration of Xeloda for CRC-LM patients and delivering doxorubicin via HAI for HCC patients. We will assess tumour response after each treatment cycle using new imaging technology. A baseline PET/CT scan will be performed and then target lesions followed with volume matched ultrasound (US) after every treatment cycle.

The primary outcome of the study will be the feasibility and safety of HAI via the access system (including the median number of cycles delivered, reasons for discontinuation of HAI and or complications of the vascular access systems, multiple catheters and chemotherapy).

Our secondary outcome is to assess the response of the liver lesions, and record time to tumor progression and overall survival.

A successful outcome of the study may result in improved response rates for patients with hepatic metastases/carcinomas and improved survival. With further study, this may increase the number of patients suitable for curative resections of their hepatic metastases/carcinomas, which would result in long term survival.

A further literature review may be found in the Investigators Brochure (CT-HAI-02).

3 Overview

3.1 Proposed Completion Date

01 June 2016

3.2 Expected Duration of Treatment for each Patient

Each patient treated is expected to undergo 3 to 8 treatments to the liver depending on the clinical need and tolerance. Each treated lesion will be treated twice where appropriate and if possible. The expected time the access device will remain implanted will be approximately 29 days. The patient will be admitted into hospital for implantation, treatment sessions, and education. Following the patient's discharge from hospital after explantation, they will be followed up as per standard protocols for CRC-LM and HCC patients by the respective oncology departments.

3.3 Number of subjects for the study

10 patients consisting of 5 colorectal cancer patients with liver metastases and 5 patients with hepatocellular carcinomas.

3.4 Description of Study Population

This trial intends to recruit patients from a diverse population. Male and female patients, over 18 years of age, of any ethnicity who meet the study inclusion/exclusion criteria and are capable of complying with study requirements will be recruited. Patients will be recruited from any Australian population centre, but will only be treated at the nominated study sites.

3.5 Inclusion/exclusion criteria

This clinical investigation involves screening patients for suitability for the Trial. Once these patients are identified, and informed consent is obtained, they will be enrolled as subjects. A candidate will be accepted and enrolled into the trial if he/she meets all of the inclusion criteria (Section 3.5.1 and 3.5.3) and is not excluded by the exclusion criteria (Section 3.5.2 or 3.5.4).

In addition to the inclusion and exclusion criteria, the following points should be taken into consideration by the clinical investigator whilst determining a patient's suitability for the trial:

- Physically and psychologically able to comply to the procedures required in the protocol
- Likelihood of an inability to attend follow-up consultations

3.5.1 Inclusion Criteria for Patients with Colorectal Cancer Liver Metastases

- Patient must be over 18 years of age
- Patients must be able to understand the risks and benefits of the trial and give written informed consent to participate
- Patients must be fit for anaesthesia
- Histologically proven colorectal cancer
- Unresectable hepatic metastases
- Patient has failed 1st line therapy
- World Health Organization performance status ≤ 2 (see Appendix 4 for classifications)
- Adequate bone marrow (hemoglobin ≥ 10 g/L, neutrophil count ≥ 1.5×10^9/L, platelet count ≥ 75×10^9/L)
- Adequate renal function (Serum Cr < 1.5 × ULN)
- Adequate liver function (bilirubin 1.0 - 2.0 × ULN, AST/ALT/AlkPhos < 5 × ULN)
- Normal coagulation (INR < 1.5)

3.5.2 *Exclusion Criteria for Patients with Colorectal Cancer Liver Metastases*

- World Health Organization performance status > 2 (see Appendix 4 for classifications)
- Dominant extra-hepatic disease
- Clinically significant ascites
- Technical inability to perform HAI
- Previous treatment with SIR spheres (yittrium-90) in the past 3 months
- Grade 3 or 4 peripheral neuropathy
- Significant co-morbidities

3.5.3 *Inclusion Criteria for Patients with Hepatocellular Carcinoma*

- Patient must be over 18 years of age
- Patients must be able to understand the risks and benefits of the trial and give written informed consent to participate
- Patients must be fit for anaesthesia
- Child-Pugh score of A or B
- Patient has failed 1st line therapy
- Adequate hematology/bone marrow (platelet count $\geq 50\times10^9$/L, prothrombin activity 50%)
- Adequate liver function (AST/ALT < 5 × ULN)
- Normal coagulation (INR < 1.5)

3.5.4 *Exclusion Criteria for Patients with Hepatocellular Carcinoma*

- Child-Pugh score of C
- Dominant extra-hepatic disease
- Previous treatment with SIR-spheres (yittrium-90) in the past 3 months
- Technical inability to perform HAI
- Significant co-morbidities
- Advanced liver failure/complications

3.6 Ethical treatment of human subjects

The handling of all human subjects enrolled in this trial will strictly adhere to all principles outlined in the current version of the World Medical Association's Declaration of Helsinki (Seoul, 2008) for the ethical treatment of human subjects involved in medical research, and the Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95). Furthermore, the trial is conducted under the monitoring of the Human Research Ethics Committee (HREC) responsible for overseeing ethical research within the Macquarie University Hospital, and shall comply with all regulatory requirements of the local authorities. The conduct of the trial shall also conform to requirements of NHMRC National Statement on Ethical Conduct in Human Research (2007).

3.7 Cessation of the Trial

The trial can be stopped for a number of reasons. The trial can be stopped on a patient basis, an investigator basis or completely stopped.

3.7.1 Complete Trial Closure

The trial may be stopped completely, as determined by the principal clinical investigator, if there are any device related mortalities. The study will be re-evaluated before continuation. Note that the patient demographic may contain critical patients and mortality is not an automatic indicator for trial cessation.

The Steering Committee may decide to completely cease the trial if it is decided that there are significant safety issues due to the treatment itself.

3.7.2 Investigator Trial Closure

The trial may stop an individual investigator from proceeding in the trial if they are unable to follow the protocol, especially if this is related to adverse event reporting. An investigator may also be removed from the trial if after discussion with them, they are noted to have a disproportionate amount of complications.

3.7.3 Patient Trial Closure

The trial may be suspended or stopped for a specific patient if they develop prohibitive co-morbidities (both device related, treatment related and or non-related).

3.8 Study flow and synopsis

Each subject in the study group receives an operation to have the vascular access device implanted prior to receiving chemotherapy treatment sessions. The treatment sessions will subsequently be given as part of the treatment regimen determined by the clinical investigator based on clinical observations. The subjects in the study group will then undergo a second operation to remove the device at the end of the treatment plan or if the treatment is determined to be no longer necessary or possible (e.g. persistent LFT abnormalities).

All subjects in the study group will be followed up during treatment, at discharge and after 1 week, 1 month, 3 months, and 6 months following explantation of the access device to monitor the patient's quality of life, full blood count, biochemical profile, liver function, and tumor markers. Also see Figure 1 for a study flowchart. After cessation of treatment and device explantation, patient follow up will be as per protocol for CRC-LM or HCC patients by the oncology department.

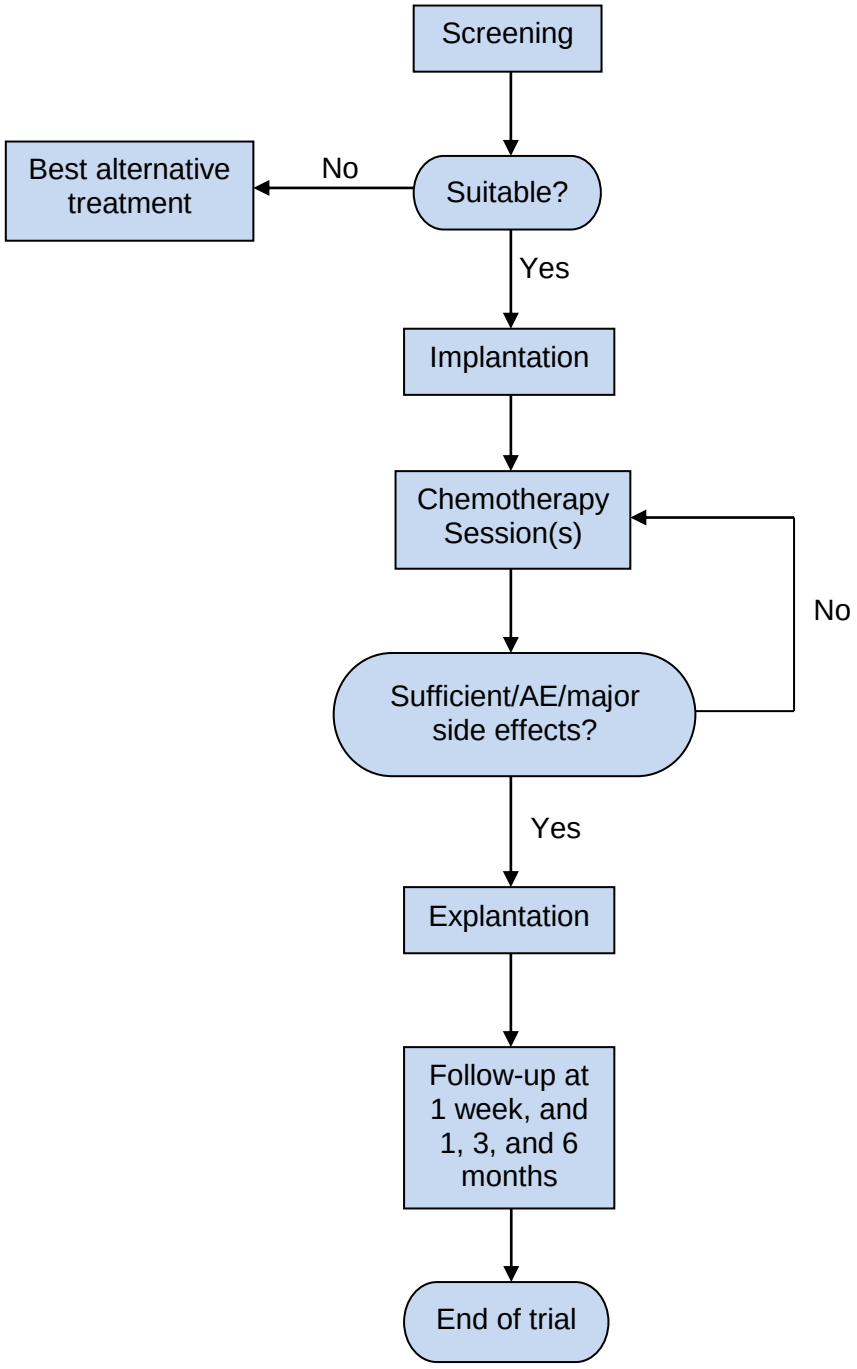


Figure 1 - Flow chart of key stages of the clinical investigation for each subject

4 Objectives

The primary objective of this pilot study is to assess the safety and efficacy of intra-arterial liver isolation chemotherapy using an implantable vascular access system.

5 Method

5.1 Study Design

This is a prospective pilot clinical trial and is a non-randomized, controlled study. Each subject will be under the treatment of the oncology department. Each patient will be reviewed by the oncologist, vascular surgeon, and an interventional radiologist to develop a consensus. Furthermore, a clinical expert panel will review all of the results at the end of the study and prepare a report on the findings.

5.2 Endpoints

5.2.1 Primary Endpoints

The desired endpoints, which can be assessed upon device explantation, of the study of intra-arterial liver isolation chemotherapy are:

1) Feasibility - functionality of the device and its ability to facilitate the infusion treatments
2) Safety - device related complications
3) Safety - organ related complications

5.2.2 Secondary Endpoints

Other endpoints of this study include the following:

1) Overall survival
2) Response rate as determined by clinical imaging and PET scan
3) Systemic side effects to chemotherapy
4) Quality of life

These endpoints can be measured by the blood samples taken during the infusion treatment sessions as well as during the post-explantation follow up (at 1 week, 1 month, 3 months, and 6 months), and PET-CT scans and quality of life surveys taken at baseline and at 1 month follow ups will be done via the oncology department according to the standard post chemotherapy surveillance and the device implant site monitored.

The study will be stopped on an individual patient basis should a serious adverse event occur that prevents the continuation of the trial for that particular patient.

6 Study Events

The following section defines the flow of a patient passing through the various stages of the trial.

6.1 Referral

Patients are referred to the trial via the oncology department.

Data are to be collected using the following documents:

1.	Investigators Declaration for Referral

6.2 Consent

Once the patient has been referred to the trial, and is being consulted by one of the study investigators, the patient must be consented to participate in the trial as below. Once a patient has consented, a Study ID is assigned consisting of the patient's initials followed by a sequential 3-digit code.

1.	Patient Informed Consent - Site Specific
2.	Assign Study ID on Subject Referral and Enrolment Log

6.3 Pre Enrolment Consult and Screening

After the patient has been referred to the trial, it is the responsibility of the investigator dealing with the patient to perform a pre enrolment consultation. The purpose of this consult is to ensure that the patient is suitable for the trial. At this stage, the patient should have relevant tests and examination results such that the enrolment review can subsequently take place.

Pre-enrolment CTA is reviewed by the radiologist for:

- Arterial anatomy (hepatic / access via femoral / access via subclavian)
- Tumor
    - Locations
    - Volume
    - Accessibility
    - Central necrosis ie. modified inflow pressure

Data are to be collected using the following documents:

1.	Pre Enrolment Consult and Screening Worksheet/CRF

6.4 Enrolment

A review of the screening visit data are carried out by at least two of the investigators involved in the study. This review is signed off on the patient folder identification page. Once the patient is deemed suitable for isolated liver perfusion, the patient is enrolled into the trial.

1.	Patient enrolled on Subject Referral and Enrolment Log

6.5 Imaging

Baseline imaging, consisting of PET-CT, target ultrasonography and in some cases MRI, is available on enrolment. Post-enrolment imaging will consist of standard imaging such as PET-CT, and ultrasonography as requested by the oncologists. The PET-CT imaging is to be done at the 1 month follow up after explantation. An ultrasound image (baseline) is to be taken prior to the first infusion session and then taken prior to every second treatment session thereafter. Further ultrasound images may be taken at follow up at the discretion of the oncologist.

Data are to be collected using the following documents:

1.	Pre Enrolment Consult and Screening Worksheet/CRF
2.	Treatment and Chemotherapy Worksheet/CRF
3.	Follow Up Worksheet/CRF

6.6 Patient Admission

Once the patient has been enrolled on the trial, they will be planned for implantation of the device.
The screening visit results can be used as a baseline.

Data are to be collected using the following documents:

1.	General Hospital Procedure Consent Forms

6.7 Implantation

Each PAD access system is surgically implanted in accordance with the manufacturer's Instructions for Use (IFU), preferably on the common femoral artery or the subclavian artery.

Data are to be collected using the following documents:

1.	Implantation Worksheet/CRF

6.8 Patient Monitoring

Once treatment has commenced, (i.e. implantation has been completed and patient has received the first round of chemotherapy), patient observations shall be recorded on a daily basis whilst in hospital. Second, pain scores (VAS) will be done by the visiting nurses throughout the duration of treatment. A Quality of Life assessment will be done pre-implantation and at the 1 month follow up after explantation.

Data are to be collected using the following documents:

1.	Pre-Enrolment Consult and Screening Worksheet/CRF
2.	Follow Up Worksheet/CRF
3.	Patient Visit Worksheet/CRF

6.9 Chemotherapy treatment

Intra-arterial liver isolation chemotherapy is performed by radiologists and vascular surgeons. Refer to Appendix 3 for a diagrammatic representation. The procedure outline is as follows:

- Cannulate coeliac trunk and the common hepatic artery using a balloon catheter via access from either the subclavian artery or common femoral artery
- Super select tumor area using a microcatheter (i.e. CXI, Cantata, or any other suitable microcatheter) going through the balloon catheter in the celiac trunk/hepatic artery
- Cannulate superior mesenteric artery and inferior mesenteric artery with balloon catheters (if not already occluded/tied off). Note: if the superior/inferior mesenteric arteries are not tied off and cannot be cannulated, use an aortic balloon catheter at the junction of the aorta and SMA
- Measure arterial pressure (before and after HABR activation)
- Anesthetist to measure portal pressure via the occluded hepatic catheter, and central venous pressure (CVP)
- Anesthetist increases positive end-expiratory pressure (PEEP) to > CVP (or to standardize use PEEP 20)
- Optional: Inflate and deflate the balloon catheter in the common hepatic artery 3 times to activate the HABR
- Inflate all balloon catheters with PEEP on to isolate the liver blood flow
- Infuse chemotherapy dose via hand injection or power infuser and keep all balloon catheters inflated for over 20 minutes
- The microcatheter is removed while the PEEP is still active to allow for back bleeding of chemotherapy agents not taken up by the tumor via back-bleeding through the balloon catheter in the hepatic artery using a syringe.
- All balloon catheters are let down after the back-bleeding and removed.
- Systemic toxicity will be measured during treatment sessions through blood samples collected from the patient's peripheral circulation
- NOTE: if the interventional radiologist has trouble isolating the organ (due to cannulation or other technical difficulties), for their benefit, the patient should be infused with the prepared chemotherapy dose via a different/standard technique (e.g. hepatic arterial infusion) and should be noted.

Standardized drug regimen (for CRC-LM):

- Heparin during procedure, standard dose
- Xeloda administered orally as prescribed by oncologist
- Escalating oxaliplatin intra-arterial 20 min infusion dosage regimen: Patients 1-3, for reasons of safety, will be treated with 50 mg/m^2 which is 50% dosage of similar trial (Boige et al 2008). Patients 4-6 will be treated with 75 mg/m^2 and patients 7-10 will be treated with 100 mg/m^2.

Standardized drug regime (for HCC):

- Heparin during procedure, standard dose
- Intra-arterial infused doxorubicin of 45-100 mg/m^2 per session
- No systemic chemotherapy during or between infusion treatments

Data are to be collected using the following documents:

1.	Treatment and Chemotherapy Worksheet/CRF
2.	IR operative report

6.10 Explantation

Each PAD access system is surgically removed in accordance with manufacturer's IFU.

Data to be collected using the following documents:

1.	Explantation Worksheet/CRF

6.11 Follow Up

All subjects in the study group will be followed up during the hospital admission and according to the oncologists follow up scheme.
Patients are to be followed up at the following time points:

- On treatment days
- 2 days post-treatment
- 1 week, 1 month, 3 months, and 6 months post-explantation
- Per protocol thereafter according to oncology department.

The clinical investigators participating in this trial are responsible for the follow-up of trial patients to assess effectiveness of intra-arterial liver isolation chemotherapy treatment and to monitor the device implant site.

Data to be collected using the following documents:

1.	Follow Up Worksheet/CRF

7 Patient Withdrawal

A patient has the right to withdraw from the trial at any time. There are three main stages when this withdrawal could occur and each has implications on the study results. Note - these points consider when a patient decides themselves to withdraw. Any decision made by an investigator to remove a patient requires the approval of the Sponsor and a full justification for the removal would be required.

7.1 Pre enrolment

If a patient withdraws from the trial before enrolment they can be replaced directly, and have no effect on the results.

7.2 After Enrolment and Initial Implantation

Once the patient has had started on the intra-arterial liver isolation treatment (and devices implanted), they may withdraw from treatment at any stage. This will involve explantation of the devices. For the purposes of the trial, depending on the number of inclusions up until that point, a new patient will be required to replace them. Note - follow up of the withdrawn patient is still attempted to monitor any adverse events but if the patient withdraws then their results will not be included in the study. Also if they withdraw and refuse to allow follow up, they are no longer considered to be part of the trial or its liabilities.

A patient shall also be withdrawn from the final statistical analysis, and replaced by another patient, if the study protocol was not followed during surgery or application of the intra-arterial liver isolation chemotherapy treatment.

7.3 After Explantation

Once the appropriate amount of treatments has been given and the device has been explanted, any withdrawal from the trial will preferably require a replacement patient with regards to the study results. Any patient data collected up until the withdrawal of the patient will be used in the study. Follow up of the patient should still be attempted with regards to tracking adverse events but will not be enforced if the patient withdraws from the study.

8 Medications

The effect of all patient medications needs to be considered. A list of all concomitant medications will be established (Concomitant Medication worksheet). Each medication will be assessed by the Investigator with regards to the effect that the medication is likely to have on the outcome of the intra-arterial liver isolation chemotherapy treatment for the specific patient.

9 Compliance Statement

The compliance of an enrolled patient is considered to be a simple case. Due to the chemotherapy administration route, there are no opportunities for the patient to be non-compliant with regards to receiving treatment.

10 Timeline for Review of Patient Cases

Once a patient has been discharged from hospital their case will be reviewed by the Investigator and the Principal Investigator. A summary report of the case will be prepared by the sponsor within 1 month of their discharge and will include a full discussion of any adverse events occurring, along with an opinion on the outcome of the device usage and the effectiveness of the treatment at that stage.

11 Chemotherapy Agents and Equipment

The following devices are required for the trial. Any modifications to the design of the components shall be documented, along with a justification of its use. Part and lot numbers of all components used in each subject shall be recorded such that full identification and traceability is maintained.

Equipment/Chemotherapy Description	Manufacturer /Trade name	Application	Standard approved/Experimental Use
Peripheral Access Device Kit	ASDM Ltd	Implantable vascular access system	Standard approved use
Peripheral Access Device Flex Connector/hemostasis Valve	ASDM Ltd	Allows for repeated cannulization through the Peripheral Access Device	Experimental use
Guide wires, guide catheters, flush catheters, measuring	Cook Medical Ltd	Isolation and regulation of the hepatic blood flow	Standard approved use

Equipment/Chemotherapy Description	Manufacturer /Trade name	Application	Standard approved/Experimental Use
catheters, and sheaths			
Microcatheters	Cook Medical Ltd	Site specific chemotherapy drug infusion	Standard approved use
Pressure Transducers	ITC	Measuring intra-tumoral pressures and intra-arterial pressures	Standard approved use
Power Infuser - Avidia Angiographic Contrast Injector	Imaxeon	Infusion of contrast.	Standard approved use
		Infusion mixture of chemotherapy, contrast, and or dextrose solution.	Experimental agent
Oxaliplatin	Eloxatin	Chemotherapy agent for intra-arterial administration	Experimental route
Capecitabine	Xeloda	Chemotherapy agent to be administered orally throughout treatment	Standard approved use
Doxorubicin	Adriamycin	Chemotherapy agent to be administered orally throughout treatment	Standard approved use

11.1 Peripheral Access Device Kit (20-000844, 20-000912)

The Peripheral Access Device (PAD) Kits (Part No. 20-000844 and 20-000912) were developed by AllVascular Pty Ltd (St Leonards NSW, Australia) in conjunction with ASDM Ltd (St Leonards NSW, Australia) and manufactured at ASDM's facilities. Each kit consists of a temporary implant designed to provide intermittent, repeatable access to the vascular system for treatments where moderate-sized access is required. The Peripheral Access Device is made of a PVC tube bonded to the expanded polytetrafluoroethylene (ePTFE) suture foot at one end and a titanium housing at another. This allows the PAD to be anastomosed to the patient's artery and achieving haemostasis in a short period of time. The Pad Kit is approved for vascular access.

Each patient will be supplied with a PAD Kit (see manufacturers IFU for details).

Instructions for the safe use and operation of the PAD are described in the following documents

1. The PAD Access Device Instructions For Use
2. The PAD Access Device Product Insert

All surgeons, perfusionists and nursing staff shall be trained in the relevant IFU prior to using the device.

11.2 Peripheral Access Device Flex Connector (20-000792)

Second to the PAD for the repeated cannulizations, a Flex Connector haemostatic valve (Part No 20-000792) will be used during the chemotherapy infusion / treatment procedures. The component is the access point to the PAD for the catheters that are required to isolate and regulate the patient's hepatic flow as well as for the delivery of the chemotherapy drugs. The device is disposable and a new part will be used for each treatment session. Although the use of this component in conjunction with the PAD is experimental, bench top testing has been carried out on the flex connector in conjunction with the PAD. Furthermore, the component is *only* used during the treatment sessions and thus is always monitored by the investigator. Any component related complications would immediately be identified and tended to by the investigator.

11.3 Catheters/Guide Wires/Sheaths

Standard peripheral interventional equipment such as guide wires, guide catheters, flush catheters, measuring catheters, and sheaths will be introduced through the PAD Flex Connector, the PAD, and into the patient's vasculature to isolate and regulate the patient's hepatic flow (see Appendix 3). All catheters and other peripheral intervention equipment, apart from the PAD and PAD Flex Connector, will be supplied by Cook Medical. All devices will be used following the manufacturer's IFU.

11.4 Microcatheters

Microcatheters, supplied by Cook Medical (such as the Cantata or CXI), will be introduced through the PAD Flex Connector, the PAD, and the patient's coeliac trunk to the common hepatic artery (see Appendix 3). The chemotherapy agent will be administered through this catheter during the treatment sessions. The catheter is approved for chemotherapy administration and all surgeons and interventional radiologists will be trained in the use of the device prior to use. All investigators will follow the IFU provided by the manufacturer.

11.5 Pressure Transducers

The pressure transducers, manufactured by ITC, will be used to take measure pressures in the tumor and or in the patient's vasculature. The transducers are approved for standard pressure measurements and will be used as per the manufacturer's IFU. The transducers will only be used during the infusion treatment sessions and thus any device related complications would be identified and tended to immediately by the investigator.

11.6 Power Infuser - Angiographic Contrast Injector

The infuser, provided by Imaxeon, will be used to infuse the chemotherapy mixture into the microcatheter. The infuser is approved for injecting contrast but not for injecting a mixture of chemotherapy, contrast, and dextrose solution. The infuser will be connected to the infusion catheter via a standard luer mechanism. In the unlikely event of a malfunction, the infusion catheter can be disconnected from the infuser and the treatment resumed via hand infusion.

11.7 Chemotherapy Agents

As described in Section 6.9, the CRC-LM patients will be treated with Eloxatin (oxaliplatin) and Xeloda throughout this study. The patient will be administered with two 750 mg Xeloda tablets per day orally (1500 mg/day) as a complementary systemic treatment. During the treatment sessions, the patient will be administered with oxaliplatin intra-arterially via hand injection or via a power infuser and the bolus kept isolated for over 20 minutes. Since the intra-arterial administration of oxaliplatin is experimental, an escalating dosage regimen will be used for reasons of safety (described in Section 6.9).

HCC patients will be treated with Adriamycin (doxorubicin) arterial infusions only during the treatment sessions. The dose will range from 45-100 mg/m^2 as mentioned in Section 6.9. No systemic chemotherapy will be administered during or in between the infusion treatments.

11.8 Other External Laboratories and Testing Equipment

All laboratories used in the collection of clinical data need to be registered, accredited facilities.

11.8.1 Ultrasonography

Ultrasound assessment of targeted liver lesions will be conducted using standard duplex scanning methods by qualified ultrasonographers. Ultrasound imaging sites should have an approved Location Specific Practice Number (LSPN).

11.8.2 Imaging Centres

All imaging carried out for study patients should be performed in accordance with the relevant sites and oncology protocols for imaging by an approved imaging department or company.

11.8.3 Blood testing

All laboratories used for haematology will be approved by the relevant site and be a registered laboratory.

12 Adverse Events

Adverse events are distinguished using various criteria, including severity, unexpectedness and whether or not it is related to the treatment/device itself. A serious adverse event is an untoward medical occurrence in a patient or clinical investigation subject that has resulted in a death or a serious deterioration in health. Serious adverse device events are serious adverse events occurring as a result of use of a medical device under the trial. Unanticipated adverse device effects may necessitate an amendment to the study protocol or the study's termination should risks be deemed too great. This section outlines the responsibilities and procedures for reporting adverse events. CT-HAI-03 Adverse Event Procedure summarizes the reporting requirements for the Study Sponsor and the Clinical Investigator.

12.1 Procedures for Adverse Events

The study is operated under the control of ICH:GCP, the TGA guidelines on Clinical Trials and under the control of the regional HREC for Sydney. Each of these authorities stipulate requirements for adverse event monitoring and reporting. All adverse events will be recorded and processed according to the outline given in this protocol plus the instructions provided in the sponsors procedures document - CT-HAI-03 Adverse Event Procedure.

12.2 Potential Directly Related Anticipated Adverse Events

Adverse events associated with the device implantation and intra-arterial liver isolation chemotherapy treatment that can be reasonably anticipated include the following:

12.2.1 Local Effects of Implant Device

- Hemorrhage
- Haematoma
- Infection
- Dissection / thrombus
- Anastomotic leak

12.2.2 Effects of Intra-Arterial Liver Isolation Chemotherapy

- Standard risks associated with endovascular catheter access:
  - Permanent ischaemic damage
  - Sepsis
  - Infection
  - Pseudoaneurysm
  - Haematoma
  - Vessel wall damage/trauma
  - Inability to access the required site
- Extra-hepatic infusion / systemic toxicity / liver toxicity
- Additional IR procedures necessary
- Hemorrhage / dissection / thrombus
- Reddening of urine
- Burning sensation in digestive tract (mouth, throat, food pipe, rectum or vagina)
- Skin infections or blisters

12.3 Potential Non-Directly Related Anticipated Adverse Events

These are events that are not expected to be directly related to the intra-arterial liver isolation chemotherapy treatment. Note that these are general conditions and are expected in both the treatment and control study demographic but which are monitored and could include:

12.3.1 Natural Progression of the Treated Disease

This is a safety and efficacy trial and cannot be assumed that the treatment provided in this study will lead to tumour response or regression (although it is the aim of the study to do so). Hence, these adverse effects associated with the natural progression of the carcinoma/metastatic disease should be anticipated.

Metastatic Liver Disease	**Hepatocellular Carcinoma**
• Abdominal pain (right upper quadrant) • Anorexia • Early satiety • Weight loss • Fatigue • Fever • Jaundice • Ascites • Intestinal effects (nausea, vomiting and diarrhea) • Sweats • Biliary obstruction/blockage • Local pain • Anemia • Liver failure • Metastatic spread to other organs	• Abdominal pain (right upper quadrant) • Anorexia/cachexia • Early satiety • Weight loss • Fatigue • Fever • Jaundice • Ascites • Intestinal effects (nausea, vomiting and diarrhea) • Palpable liver mass • Nodular liver • Hepatic bruits • Pruritus • Splenomegaly • Peripheral edema • Asthenia • Liver failure

Note: If any of these potential adverse effects are ***triggered or exacerbated as a result of the study/treatment***, it will no longer be considered as the "natural progression" of the treated disease and hence will be considered as an unanticipated directly related adverse event.

12.3.2 Natural Progression of Pre-Existing Conditions

The study is aimed at treating CRC-LM and HCC patients only. Therefore, the potential adverse effects associated with the natural progression of any other pre-existing condition should be anticipated. All adverse events stemming from pre-existing conditions in the following systems should be anticipated:

- cardiovascular system
- circulatory and lymphatic systems
- respiratory system
- nervous system
- renal system
- endocrine system
- digestive system
- Immune system
- Musculoskeletal system
- Reproductive system

Note: If any of these potential adverse effects are ***triggered or exacerbated as a result of the study/treatment***, it will no longer be considered as the "natural progression" of the pre-existing disease and hence will be considered as an unanticipated directly related adverse event.

12.3.3 Adverse reactions to medication

Medication/drug regimen after the patient has been explanted and during the follow up period is not stipulated by the study as the patient is under the care of their physician/oncologist. Thus all potential adverse reactions to any medication/drugs post explantation and not prescribed by a study investigator are not directly related to the study. Alternatively, adverse reactions to any medications/drugs between implantation and explantation will be considered to be directly related to the study.

12.3.4 Unforeseeable Injuries

These are adverse events that are a direct result of unforeseeable or natural occurrences that are beyond clinical control inclusive but not limited to:

- natural disasters (e.g. flood, bushfire, tsunami etc.)
- endemics/epidemics
- accidents (e.g. falls, burns, vehicular etc.)

  Note: accidents ***as a result of the patient's physical or psychological state being compromised from the treatment*** will be classified as being directly related to the treatment.

12.4 Review of Adverse Events

It is intended that any adverse events will be reviewed on a monthly basis. This review is intended to be carried out by the Steering Committee. The following personnel must be present for the monthly review meeting:

- the Principal Investigator (can also hold one of the three positions below)
- at least one interventional radiologist
- at least one oncologist
- at least one vascular surgeon
- the Study Monitor

In the event that one of the above personnel is absent during the meeting, the minutes and outcomes must be forwarded to them for review and approval. All minutes and correspondences must be filed and forwarded to the HREC. Copies of the minutes, outcomes, and correspondences of the monthly Steering Committee meetings are to be forwarded to the HREC monthly or quarterly (as decided by the HREC).

Note - the monthly adverse event review is required for the full duration of all patients. Any adverse events occurring towards the end of the follow up period for a specific patient will necessitate an extension to the monitoring of that patient for a further 3 months.

12.5 Clinical Investigator Responsibilities

In the occurrence of an adverse event, the Clinical Investigator shall record all adverse events on 'SITE - Adverse Event Report'.

If the Adverse Event is deemed to be an **Unanticipated Serious Adverse Event** (excluding those noted in section 12.2) that is directly related to the devices used in giving the intra-arterial liver isolation chemotherapy treatment. The Clinical Investigator must report to the study Sponsor **as soon as possible (within 24hours)** for the timely reporting to the Therapeutic Goods Administration.

Adverse events shall be reported to the Human Research Ethics Committee as specified under conditions of ethics approval for conducting this study.

12.6 Sponsor Responsibilities

The Sponsor is responsible for compiling reports of all adverse events encountered during the trial. Where an **Unanticipated Serious Adverse Event** has occurred, the event shall be reported to the Therapeutic Goods Administration using form '*#MDIR01 – Medical Device Incident Report*'.

If an Adverse Event is deemed to pose significant concerns regarding the ongoing safety and efficacy of the trial, the Sponsor and the Principal Clinical Investigator shall discuss to determine any corrective actions required address such concerns. If amendments to the study are required, these shall be made in accordance with Section 20 of this protocol. If safety concerns remain, termination of the trial should be considered.

13 Statistical Review

Patients eligible for this study are those who have CRC with liver metastasis, not suitable for surgical resection. These patients already underwent 1st and 2nd line combination chemotherapy and as such do not have other treatment options. The proposed design is a single arm Phase I study where eligible patients would be offered intra-arterial liver isolation chemotherapy through a new peripheral access device which allows for multiple subsequent cannulations. Primary outcomes are feasibility of the procedure and safety of both the procedure and the device. Earlier studies on HAI using percutaneous placement of an indwelling port-catheter showed a device related complication rate of 21% (de Baere et al) versus a complication rate of 34 for surgical implantation.

Data will be summarized by Kaplan-Meier time-to – event curves as well as proportions and 95% confidence intervals. Continuous outcomes will be summarized using means in appropriate together with standard deviations and 95% confidence intervals.

The results of the analysis will be reviewed by the principal clinical investigator and another vascular surgeon.

Secondary endpoints are response rate, overall survival, Quality of Life. These results will be compared to historical controls, although the numbers are probably not sufficient for statistical analysis they will be reported.

14 Data Collected and Purpose

The data collected in the trial is summarised below. The purpose for collection is stated. Note that this treatment regimen is still investigational and the parameters for it are being evaluated. For this reason, a number of parameters are being recorded which are not being used directly in this study but may be potentially used in the future.

14.1 Patient Quality Of Life Data

Patient quality of life will be assessed at initial screening and then at the follow-up points. The data will be used as an indicator of the patient's general health and mental opinion of themselves. A QOL (Quality of Life) metric shall be calculated from the responses. It will be analyzed by comparing the scores of the QOL parameters against time to see if there is any trend with time, especially immediately after the treatment in the study group. The QOL questionnaires, QLQ-C30, QLQ-LMC21, and QLQ-HCC18 are that of the European Organisation for Research and Treatment of Cancer (EORTC) and the results will be analyzed using the EORTC scoring manual.

14.2 Patient Physical Assessment and Imaging

Patients will undergo a physical assessment at screening, daily at the hospital and then at the follow-up periods. Patients will undergo ultrasound, CT scans, and PET-CT of the liver during pre-enrolment screening, and during follow ups. Pain will be recorded using VAS for the implant site as well as the abdominal region, which will be monitored to determine whether the treatment has been able to reduce the patient's discomfort. Results will be normalized to the baseline value obtained at screening. Data will be evaluated for significance using an appropriate statistical method.

An arteriogram shall be taken at the Clinical Investigators discretion. Pre-operative imaging shall be compared with images taken at follow-up to determine the changes in resectability. This shall be assessed by a clinical investigator.

14.3 Patient Blood Data

Blood samples shall be taken at screening, on a daily basis whilst the patients are in hospital and then at each follow-up after discharge. At screening stage the blood results will be used to assess whether the patient is suitable for the study (no pre-existing liver failure, bone marrow failure etc.)

Blood data shall also be collected at the follow-up periods after treatment. These samples are sent to the relevant site laboratory for analysis. The blood data shall be analyzed for any clinically significant variations in serum levels that may have been caused by the device and/or treatment, and to determine whether the affect continues after the treatment is stopped.

14.4 Patient Histology

Tissue samples may be taken at the time of explantation of the PAD, at the discretion of the clinical investigator. The biopsy shall be taken of the fatty tissue around the PAD incision site. It will be examined for possible vasculogenesis and the associated tissue factors. This data will not be used in the final statistical analysis, but will be used to understand potential changes in local tissue morphology due to implantation.

14.5 Infusion Data

During the infusion treatment sessions, the chemotherapy infusion pressure, infusion rate, and total volume of infusion will be recorded. The area of the tumor, segment, or lobe will be recorded as well as the total portal pressure, PEEP pressure, and arterial pressures.

14.6 Device Observations

Observations on the device and device site shall be recorded on a daily basis whilst the patient is in hospital. These shall be captured to detect device related issues, such as leaks and thus determine the safety and efficacy of the device. A key parameter which will be monitored is thrombus formation especially within the PAD device and at the anastomosis site. Observations on thrombus formation shall be taken of the plunger tip when it is replaced and the access tube upon explantation.

15 Access to Source Data

All investigators are required under regulatory compliance to allow access to all source data related to the trial for a period of 15 years. This access is required to be given to the sponsors nominated monitors, the sponsors appointed auditors. Access is also required to be permitted at any time to the TGA or other equivalent regulatory bodies.

15.1 Record retention

Records and raw data shall be retained by the clinical investigator through which the data are generated or the sponsor for a minimum period of 15 years after the completion of the clinical trial.

16 Data and quality management

16.1 Treatment of data

Data collected for this trial shall be handled in such a way that quality and integrity of the data maintained throughout all stages of the study. The following points are to be followed:

1) Data shall be recorded in blue or black ink ONLY
2) Dates shall be recorded as DD/MMM/YY or DD/MMM/YYYY where DD=day, MMM=month and YYYY=year
3) Record time as XX:XX in 24 hour time format.
4) Each page of data collection forms shall be marked with the subject's Study ID
5) All forms are to be signed and dated only by authorised study personnel
6) Incorrect entries must be corrected by the following:
   a) Draw a single line through the incorrect entry
   b) Write correct entry next to incorrect entry
   c) Sign (or initial) and date the correction
7) Where queries regarding recorded data arise, clarification shall be sought from the authorised person(s) responsible for recording the data
8) When data transcribed into electronic format, the following shall be noted:
   a) When transcribing numbers, the correct number of decimal places shall be maintained
   b) Once the data is entered, it shall be verified against source data and the source data retained.

Any deviations to the protocol shall be recorded on Deviation from Protocol form. A justification shall be recorded for the deviation. The sponsor and the principal clinical investigator shall determine the relevance of each deviation, its impact on the results of the trial and subsequent action necessary.

17 Quality Assurance and Control

17.1 Monitoring Plan

The trial will be monitored by a sponsor appointed monitor. The monitor will perform tasks as defined by - CT-HAI-04 Monitoring Plan.

17.2 Procedure for CRF System

The clinical trial will be administered using a paper based data capture system.

18 Financial Agreements

All peripheral intervention equipment (i.e. catheters, guide wires, flush catheters etc) are supplied by Cook Medical. The PAD and the PAD Flex Connector are manufactured by ASDM Ltd and purchased and supplied by the Principal Investigator - Dr Rodney J Lane.

19 Publication Policy

All information from this study will be written up by the Principal Investigator. Any secondary publications should be approved by the sponsor and Principal Investigator before they are published. All intellectual property from the trial becomes the property of the sponsor and requires prior approval.

20 Deviations and amendments

Any deviations from this protocol as prescribed shall be recorded. A justification shall be recorded for the deviation. The Sponsor and the Principal Clinical Investigator shall determine the relevance of each deviation, its impact on the results of the trial and subsequent action necessary. This may require amendments to the current clinical trial protocol, or, where safety and wellbeing of subjects are placed under excessive risk, termination of the trial. A justification shall be recorded for amendments made to the protocol. Approval shall be sought from the Sponsor, all Clinical Investigators and the HREC prior to implementation of the amended protocol.

21 References

Boige V, Malka D, Elias D, Castaing M, De Baere T, et al. 2008. Hepatic arterial infusion of oxaliplatin and intravenous LV5FU2 in unresectable liver metastases from colorectal cancer after systemic chemotherapy failure. *Annals of Surgical Oncology* 15:219-26

22 Appendix 1 - Trial Site Details

The trial is planned to be carried out at a Macquarie University Hospital in Australia. The site details are shown below. Additional sites will be recorded in a document listing all site and personnel involved in the trial. Changes to this document will be notified to HREC immediately.

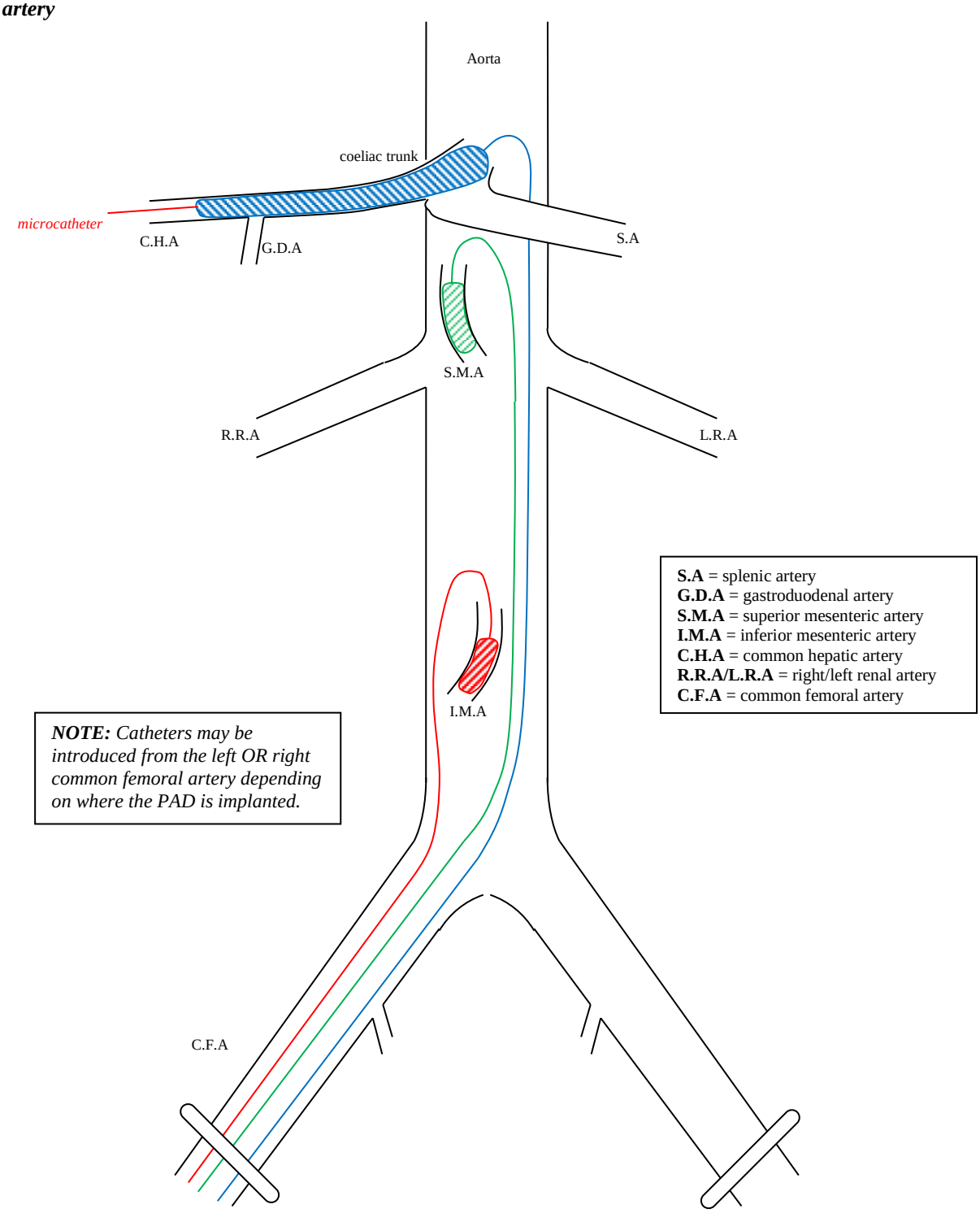
Institution: **Macquarie University Hospital**
Address: Macquarie University, 3 Technology Place,
North Ryde NSW 2109
Australia

23 Appendix 2 - Participating Personnel

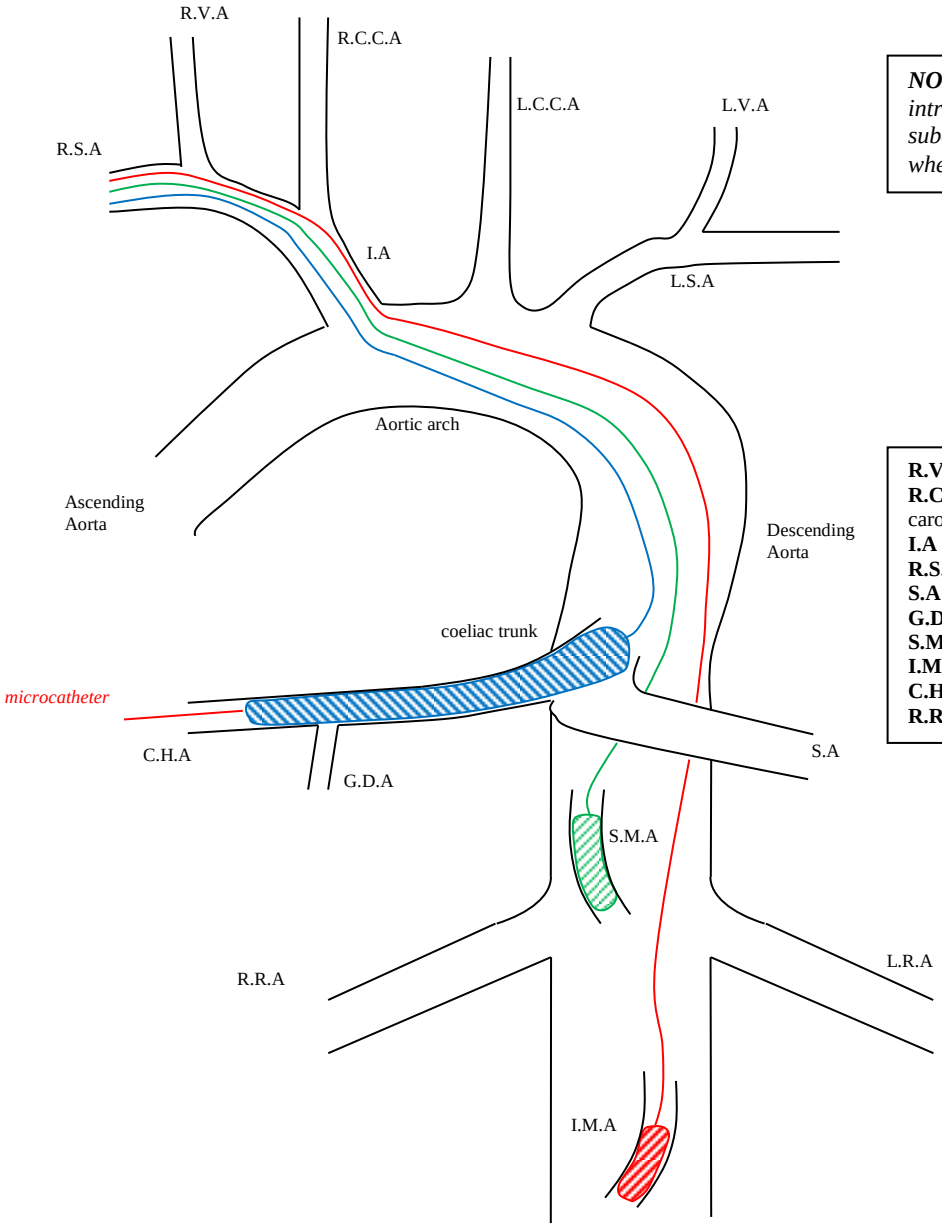
- **Principal Investigator**
- **Study Monitor**
- **Clinical Investigators**
- **Perfusionist Staff**
- **Ultrasound and Imaging Staff**
- **Clinical Co-ordinators - Investigator**
- **Clinical Trial Staff –-Sponsor**
  - Clinical Trial Monitor
  - Consultant CRA

24 Appendix 3 - Diagram of Treatment Layout

Catheter access via common femoral artery



Catheter access via subclavian artery



NOTE: *Catheters may be introduced from the left OR right subclavian artery depending on where the PAD is implanted.*

R.V.A/L.V.A = right/left vertebral artery
R.C.C.A/L.C.C.A = right/left common carotid artery
I.A = innominate artery
R.S.A/L.S.A = right/left subclavian artery
S.A = splenic artery
G.D.A = gastroduodenal artery
S.M.A = superior mesenteric artery
I.M.A = inferior mesenteric artery
C.H.A = common hepatic artery
R.R.A/L.R.A = right/left renal artery

25 Appendix 4 – World Health Organisation Performance Status

Grade	Explanation of activity
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

APPENDIX E – HUMAN RESEARCH ETHICS COMMITTEE APPROVAL: OIC TRIAL

MACQUARIE UNIVERSITY

Research Office
Research Hub, Building C5C East
MACQUARIE UNIVERSITY NSW 2109 AUSTRALIA

Phone +61 (0)2 9850 8612
Fax +61 (0)2 9850 4465

Ethics
Phone +61 (0)2 9850 6848

Email ethics.secretariat@ro.mq.edu.au
Web www.research.mq.edu.au/researchers/ethics/human_ethics

30 September 2011

Professor Rod Lane
Dept of Vascular Surgery
Greenwich Square, Suite 13,
130-134 Pacific Highway
ST LEONARDS NSW 2065

Reference: 5201100434

Dear Professor Lane,

FINAL APPROVAL

Title of project: ***"Assessment of the safety and efficacy of intra-arterial liver isolation chemotherapy using an implantable vascular access system"***

Thank you for your recent correspondence. Your response has addressed the issues raised by the Human Research Ethics Committee and you may now commence your research. This approval is subject to the below mentioned condition:

1. Please submit quarterly progress reports for your study. Please refer to the below mentioned website address to find the progress report.

   http://www.research.mq.edu.au/for/researchers/how_to_obtain_ethics_approval/human_research_ethics/forms

The following personnel are authorised to conduct this research:

Prof James Lane – Chief Investigator
Dr Michael Evtushenko & Mr Nyan Ye Khin – Co Investigators

NB. STUDENTS: IT IS YOUR RESPONSIBILITY TO KEEP A COPY OF THIS APPROVAL LETTER TO SUBMIT WITH YOUR THESIS.

Please note the following standard requirements of approval:

1. The approval of this project is conditional upon your continuing compliance with the National Statement on Ethical Conduct in Human Research (2007).
2. Approval will be for a period of five (5) years subject to the provision of annual reports. Your first progress report is due on **30 December 2011**.

If you complete the work earlier than you had planned you must submit a Final Report as soon as the work is completed. If the project has been discontinued or not commenced for any reason, you are also required to submit a Final Report for the project.

Progress reports and Final Reports are available at the following website:

http://www.research.mq.edu.au/for/researchers/how_to_obtain_ethics_approval/human_research_ethics/forms

3. If the project has run for more than five (5) years you cannot renew approval for the project. You will need to complete and submit a Final Report and submit a new application for the project. (The five year limit on renewal of approvals allows the Committee to fully re-review research in an environment where legislation, guidelines and requirements are continually changing, for example, new child protection and privacy laws).

4. All amendments to the project must be reviewed and approved by the Committee before implementation. Please complete and submit a Request for Amendment Form available at the following website:

   http://www.research.mq.edu.au/for/researchers/how_to_obtain_ethics_approval/human_research_ethics/forms

5. Please notify the Committee immediately in the event of any adverse effects on participants or of any unforeseen events that affect the continued ethical acceptability of the project.

6. At all times you are responsible for the ethical conduct of your research in accordance with the guidelines established by the University. This information is available at the following websites:

   http://www.mq.edu.au/policy/

   http://www.research.mq.edu.au/for/researchers/how_to_obtain_ethics_approval/human_research_ethics/policy

If you will be applying for or have applied for internal or external funding for the above project it is your responsibility to provide the Macquarie University's Research Grants Management Assistant with a copy of this letter as soon as possible. Internal and External funding agencies will not be informed that you have final approval for your project and funds will not be released until the Research Grants Management Assistant has received a copy of this letter.

Please retain a copy of this letter as this is your official notification of final ethics approval.

Yours sincerely

Dr Karolyn White
Director of Research Ethics
Chair, Ethics Review Committee (Human Research)

APPENDIX F – NATIONAL TRIALS REGISTRY: OIC TRIAL

Trial Review

VIEW TRIAL AT REGISTRATION VIEW HISTORY

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Trial registered on ANZCTR

Trial ID	ACTRN12611001273976
Ethics application status	Approved
Date submitted	9/12/2011
Date registered	12/12/2011
Date last updated	28/07/2017
Type of registration	Prospectively registered

Titles & IDs

Public title	Assessment of the Safety and Efficacy of Intra-Arterial Liver Isolation Chemotherapy Using an Implantable Vascular Access System
Scientific title	Treating patients with colorectal liver metastases or hepatocellular carcinoma with intra-arterial liver isolation chemotherapy delivered through an implantable vascular access system and to determine its feasibility, safety and efficacy.
Secondary ID [1]	Nil known
Universal Trial Number (UTN)	U1111-1126-1877
Trial acronym	
Linked study record	

Health condition

Health condition(s) or problem(s) studied:

1. Secondary hepatic metastases from colorectal cancer
2. Hepatocellular carcinoma

Condition category

Cancer

Condition code

Liver

Intervention/exposure

Study type	Interventional
Description of intervention(s) / exposure	SCREENING & WORK UP: The patient is screened by the trial staff and a comprehensive patient history is recorded. Baseline blood tests and a CTA scan is carried out to determine patient suitability. A baseline PET-CT scan is also performed to determine treatment lesions. A Quality of Life (QOL) Survey will be filled in by the patient at this time also. DEVICE IMPLANTATION PROCEDURE: The procedure involves the surgical implantation under general anaesthetic of a large bore temporary access port (a peripheral access sytem) in either the common femoral artery or the subclavian artery. The device is implanted by anastomosing the ePTFE graft skirt of the device onto the patient's common femoral artery and tunnelling the tubing of the device through the patient's subcutaneous tissue in the upper thigh/pectoralis and out through the skin. The implantation procedure can take between 1-3 hours and the patient can be discharged after recovery.

CHEMOTHERAPY INFUSION PROCEDURE: During the chemotherapy infusion sessions the patient will be ventilated with positive end-expiratory pressure (PEEP) whilst under general anesthesia. Depending on the specific patient anatomy up to 4 catheters will be used to selectively cannulate and obstruct the target visceral vessels. Once the flow to the liver is isolated, a microcatheter will be used via the coeliac trunc to superselectively target a pre-determined liver lesion and subsequently deliver chemotherapy locally for 20-30 minutes. All catheters are removed after the infusion and the patient discharged after recovery. The procedure is expected to take between 60-200 minutes. Depending on the patient response, the patient will be infused 3-8 times over the 30 day course.

DEVICE EXPLANTATION PROCEDURE: After the final chemotherapy infusion, and on the same day, the patient undergoes an explantation procedure where the implanted access device is removed and the vessel sutured, either with or without a patch angioplasty. This procedure takes approximately 1-2 hours and the patient is discharged after recovery.

FOLLOW UP PROCEDURE: The trial staff will follow up on the progress of the patient at 1 week, 1 month, 3 months, and 6 months from the date of the explantation procedure. A PET-CT scan and a QOL Survey will be carried out during the 1 month follow up period.

Intervention code [1]	Treatment: surgery
Intervention code [2]	Treatment: Devices
Comparator / control treatment	This is a feasibility and safety/efficacy study as there is no comparator/control treatment.
Control group	Uncontrolled

Outcomes

Primary outcome [1]	To determine the feasibility of the implantable access port in its ability to facilitate the administration of chemotherapy via intra-arterial liver isolation. Outcome is assessed through evaluation of all the operative reports of the standardised chemotherapy infusion sessions carried out.
Timepoint [1]	At every chemotherapy infusion session
Primary outcome [2]	To determine the safety and efficacy of intra-arterial liver isolation chemotherapy using the implantable vascular access system. Outcome is assessed through monitoring serious adverse events and adverse events such as significant infection, haematoma/haemorrhage, septicaemia, or significant thrombosis.
Timepoint [2]	From implantation to 3 months post-explantation
Secondary outcome [1]	To increase the overall survival rate of patients. Assessed by survivorship through post-treatment follow ups.
Timepoint [1]	Follow-ups beyond 3 month post-explantation
Secondary outcome [2]	To increase the patient's response rate to the chemotherapy. Assessed by resectability of tumour post-treatment and changes in tumour size.
Timepoint [2]	Baseline PET-CT and ultrasound of the liver and at 1 month post-explantation
Secondary outcome [3]	To minimise the systemic side effects of chemotherapy. Assessed through blood samples during the chemotherapy infusion sessions.
Timepoint [3]	During chemotherapy infusion sessions
Secondary outcome [4]	To improve patient's overall quality of life. Determined through questionnaires.
Timepoint [4]	Baseline and 1 month post-explantation

Eligibility

Key inclusion criteria	Colorectal cancer liver metastases patients: 1) Patients must be over 18 years of age 2) Patients must be able to understand the risks and benefits of the trial and give written informed consent to participate 3) Patients must be fit for anaesthesia 4) Patients must have histologically proven colorectal cancer 5) Patients have unresectable hepatic metastases 6) Patient has failed first line therapy 7) Patients' World Health Organization performance status less than or equal to 2 8) Patients have adequate bone marrow 9) Patients have adequate renal function 10) Patients have adequate liver function 11) Patients have normal coagulation Hepatocellular carcinoma patients: 1) Patient must be over 18 years of age 2) Patients must be able to understand the risks and benefits of the trial and give written informed consent to participate 3) Patients must be fit for anaesthesia 4) Patients have a Child-Pugh score of A or B 5) Patients have failed 1st line therapy

	6) Patients have adequate hematology/bone marrow 7) Patients have adequate liver function 8) Patients have normal coagulation
Minimum age	18 Years
Maximum age	No limit
Gender	Both males and females
Can healthy volunteers participate?	No
Key exclusion criteria	Colorectal cancer liver metastases patients: 1) World Health Organization performance status > 2 2) Patients have clinically significant ascites 3) Patients have dominant extra-hepatic disease 4) Technical inability to perform HAI 5) Patients have had previous treatment with SIR spheres 6) Patients have Grade 3 or 4 peripheral neuropathy 7) Patients have significant co-morbidities Hepatocellular carcinoma patients: 1) Child-Pugh score of C 2) Patients have dominant extra-hepatic disease 3) Patients have had previous treatment with SIR-spheres 4) Technical inability to perform HAI 5) Patients have significant co-morbidities 6) Patients have advanced liver failure/complications

Study design

Purpose of the study	Treatment
Allocation to intervention	Non-randomised trial
Procedure for enrolling a subject and allocating the treatment (allocation concealment procedures)	
Methods used to generate the sequence in which subjects will be randomised (sequence generation)	
Masking / blinding	Open (masking not used)
Who is / are masked / blinded?	
Intervention assignment	Single group
Other design features	
Phase	Not Applicable
Type of endpoint(s)	Safety/efficacy
Statistical methods / analysis	

Recruitment

Recruitment status Completed

Date of first participant enrolment

Anticipated 30/01/2012 **Actual** 26/09/2012

Date of last participant enrolment

Anticipated 2/09/2014 **Actual** 13/01/2015

Date of last data collection

Anticipated **Actual** 30/09/2016

Sample size

Target 10 **Accrual to date** **Final** 10

Recruitment in Australia

Recruitment state(s) NSW

Funding & Sponsors

Funding source category [1]	Self funded/Unfunded
Name [1]	Dr Rodney Lane
Address [1]	Suite 13, Greenwich Square 130-134 Pacific Highway St Leonards NSW 2065
Country [1]	Australia
Primary sponsor type	Individual
Name	Dr Rodney Lane
Address	Suite 13, Greenwich Square 130-134 Pacific Highway St Leonards NSW 2065
Country	Australia
Secondary sponsor category [1]	None
Name [1]	
Address [1]	
Country [1]	

Ethics approval

Ethics application status	Approved
Ethics committee name [1]	Macquarie University Human Research Ethics Committee (HREC)
Ethics committee address [1]	Research Office Research Hub, Building C5C East Macquarie University NSW 2109
Ethics committee country [1]	Australia
Date submitted for ethics approval [1]	
Approval date [1]	30/09/2011
Ethics approval number [1]	HREC Reference No: 5201100434

Summary

Brief summary	The study will be recruiting patients with colorectal cancer with liver metastases (CRC-LM) or patients with hepatocellular carcinomas (HCC). The inclusion and exclusion criteria for both CRC-LM and HCC patients can be found in the relevant sections. This study involves the temporary surgical implantation of a large bore access port (a peripheral access system) in the common femoral artery or the subclavian artery. This procedure will take approximately 2 to 3 hours. You will undergo an operation to have the vascular access device implanted prior to receiving chemotherapy treatment sessions. The chemotherapy treatment sessions will subsequently be given as part of the treatment regime determined by the clinical investigator based on clinical observations. Depending on your response, you will be administered with the liver isolation chemotherapy treatment between 3 to 8 times during the month the device is implanted. After you the final chemotherapy treatment and on the same day, you will then undergo a second operation to remove the device.
Trial website	
Trial related presentations / publications	
Public notes	

Contacts

Principal investigator

Name	Prof Rodney Lane
Address	Suite 13, Greenwich Square, 130-134 Pacific Highway, St Leonards NSW 2065
Country	Australia
Phone	+61 2 9438 4500
Fax	+61 2 9438 4114
Email	profrodlane1@gmail.com

Contact person for public queries

Name	Prof Rodney Lane
Address	Suite 13, Greenwich Square,

	130-134 Pacific Highway, St Leonards NSW 2065
Country	Australia
Phone	+61 2 9438 4500
Fax	+61 2 9438 4114
Email	profrodlane1@gmail.com

Contact person for scientific queries

Name	Prof Rodney Lane
Address	Suite 13, Greenwich Square, 130-134 Pacific Highway, St Leonards NSW 2065
Country	Australia
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Email	profrodlane1@gmail.com

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APPENDIX G – CLINICAL TRIAL PROTOCOL: PIb/II OIC TRIAL

ABN 54 106 760 427 ACN 106 760 427
Suite 13, Greenwich Square, 130 – 134 Pacific Highway
ST LEONARDS, NSW, 2065, AUSTRALIA
P: +61 2 9438 5228 F: +61 2 9438 4114 W: www.allvascular.com

Document Title: Clinical Investigation Plan
Protocol No: AV-LIVPIBII-01 **Version:** 2.0 **Date**: 07 AUG 2017
Protocol Title: Phase Ib/II Study of Intra-Arterial Liver Isolation Chemotherapy in Patients with Hepatic Metastases from Colorectal Cancer

Prepared by:

Nyan Khin _____ ____/_____/_____
(Sponsor Project Manager) Signature Date

Reviewed by:

Nick Pavlakis _____ ____/_____/_____
(Co-ordinating Investigator) Signature Date

INVESTIGATOR'S SIGNATURE

I have reviewed this protocol, including the investigator's brochure, and agree to adhere to the requirements and responsibilities listed herein. I am trained to the contents of this protocol, and the specific use of the device listed in this protocol. I will ensure that the study is conducted in compliance with the protocol, Good Clinical Practices, ISO14155-2011, Declaration of Helsinki and all applicable regulatory requirements.

Reviewed and approved by:

_____ _____ ____/_____/_____
Name Principal Investigator Signature Date

Confidentiality Statement

Table of Contents

1 General Information

1.1 Study Site(s)

The clinical trial study will be carried out at 2-4 sites in Australia.

1.2 Study Sponsor

Sponsor: AllVascular Pty Ltd
Address: Suite 13, 130-134 Pacific Highway
St Leonards NSW 2065
Australia
Phone: +61 2 9638 5228
Fax: +61 2 9438 4114

1.3 Study Monitor

Name: ReSQ Clinical Research Pty Ltd
Address: 2/40 Hardy St, Dover Heights, NSW 2030
Phone: +61 2 9371 7897
Email: tracey@resqclinical.com.au

1.4 Investigational Device Manufacturer

Name: AllVascular Pty Ltd
Address: Suite 13, 130-134 Pacific Highway
St Leonards NSW 2065
Australia
Phone: +61 2 9438 5228
Fax: +61 2 9438 4114

1.5 Medical Expertise, Investigator Role & Responsibilities

Personnel	Site	Role	Responsibility
Oncologist	Royal North Shore Hospital	Co-ordinating Investigator	Responsible for conducting the trial and trial site related medical decisions regarding the patient's treatment regimen (dosage and frequency). Responsible for ensuring all study site staff are educated/trained/informed in providing standard patient care for study patients.
	All	Principal Investigators	
Interventional radiologists	All	Co-Investigators	Responsible for trial-site medical decisions regarding the patient's treatment regimen (dosage and frequency) as well as administering the specified treatment regimen.
Vascular surgeons	All	Co-Investigators	Responsible for carrying out the implantation and explantation of the vascular access system.

Personnel	Site	Role	Responsibility
Radiologists	All	Site staff	Responsible for assessing the patient's CT scans as per RECIST v1.1.

1.6 Laboratories and Other Institutions

Lab/Institution Address	Description of Service
Macquarie Medical Imaging Macquarie University Hospital Ground Floor, 3 Technology Place Macquarie University NSW 2109 Australia P: +61 2 9430 1100 F: +61 2 9430 1199	To provide all imaging that are critical for the study; specifically CT and CTA. Investigation site. Any additional imaging procedures that are not critical to the study but requested by an Investigator/physician will also be referred to this address.
North Shore Radiology & Nuclear Medicine 38 Pacific Highway St Leonards 2065 NSW P: +61 2 9468 1900 F: +61 2 9438 4697	
Douglass Hanly Moir Pathology Suite 205 Level 2, 2 Technology Place Macquarie University NSW 2109 Australia P: +61 2 9812 3655 F: +61 2 9812 3719	To provide all haematology services that are critical for the study site (e.g. FBC, EUC, LFT, CEA, etc.).
Sydney Adventist Hospital Pathology Laboratories Level 5, Sydney Adventist Hospital, 185 Fox Valley Road Wahroonga 2076 NSW Australia P: +61 2 9487 9500 F: +61 2 9487 9535	
Pathology North Royal North Shore Hospital, Outpatient Clinic Pacific Highway St Leonards NSW 2065 P: +61 2 9926 4118 F: +61 2 9926 4069	

2 Abbreviations

The following is the list of the acronyms of the abbreviated terms used in this clinical investigation plan:

- CRC-LM: Colorectal Cancer – Liver Metastases
- RR: Response rate

- PFS/OPFS: Liver Progression Free Survival/Overall Progression Free Survival
- OS: Overall Survival
- AVAS: Arterial Venous Access System
- QoL: Quality of Life
- DLT: Dose-limiting toxicity
- RD: Recommended dose
- RP2D: Recommended Phase 2 dose
- MTD: Maximum tolerable dose
- FBC: Full blood count
- EUC: Electrolyte, urea, creatinine
- LFT: Liver function test
- ANC: Absolute neutrophil count
- PLT: Platelet count
- TBC: Total bilirubin count
- SOC: Standard of care

3 Declaration of Compliance

This clinical investigation plan for "Phase Ib/II Study of Intra-Arterial Liver Isolation Chemotherapy in Patients with Hepatic Metastases from Colorectal Cancer" has been prepared in compliance with ISO 14155:2011 and the requirements of National Statement on Ethical Conduct in Human Research (NHMRC, 2007). The clinical investigation will not be commenced until the required approval/favourable opinion from the Ethics Committee or NHMRC has been obtained. Any additional requirements imposed by the EC or TGA shall be followed.

4 Background

The medical products to be used in this study are summarised below in Table 1. A more detailed description of these products can be found in the *Investigator's Brochure.* As per the definitions of "investigational medical device" under International Organisation for Standardization (ISO) 14155:2011 Clinical Investigation of Medical Devices for Human Subjects – Good Clinical Practice, the investigational products in this clinical trial are the AVAS device and oxaliplatin. The use of capecitabine in this trial will not deviate from its approved use and standard of care. Table 1 summarises the details on the medical devices used in this clinical study.

Table 1 - List of all devices and chemotherapy agents used in the proposed treatment

Devices/Chemotherapy	Manufacturer	Application	Approval Status
AVAS	AllVascular Pty Ltd	Implantable vascular access system	Indication: Unapproved
Oxaliplatin	Accord Healthcare Pty Ltd, Fresenius Kabi	Chemotherapeutic agent	Indication: Approved Delivery Route: Unapproved Frequency: Unapproved

The treatment proposed in this clinical investigation plan is to repeatedly administer intra-arterial chemotherapy to hepatic metastases from colorectal cancer when the blood flow to and from the liver has been isolated via balloon catheters. The objective of this study is to evaluate the tumour response, progression-free survival (PFS), morbidity and mortality of repeated and isolated intra-arterial hepatic infusion of oxaliplatin against the standard 5-FU/leucovorin/oxaliplatin (FOLFOX) treatment. The most common adverse events that should be anticipated, directly resulting from the study treatment, are mild pain on the operating area, minor haemoserous oozing around the implant site, and chemotherapy side effects (as listed in Section 9.2 of this Clinical investigation plan and in the Investigator's Brochure).

The treatment proposed in this study is based on the hypothesis that direct chemotherapy arterial infusion to metastatic tumours of the liver whilst the blood flow to the organ is isolated could potentially yield benefits that cannot be achieved with existing treatment regimens. The detailed justification for this can be found in the Investigator's Brochure.

4.1 Ethics and GCP

The management of all human subjects enrolled in this trial will strictly adhere to all principles outlined in the current revision of the World Medical Association's Declaration of Helsinki (2013) for the ethical treatment of human subjects involved in medical research, and the Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95). Furthermore, the trial is conducted under the monitoring of the Human Research Ethics Committee (HREC) responsible for overseeing ethical research for the testing centres listed in Section 1.1 and shall comply with all regulatory requirements of the local authorities. The conduct of the trial shall also conform to the requirements of NHMRC National Statement on Ethical Conduct in Human Research (2007).

5 Trial Objectives and Purpose

The primary objective of this Clinical Trial study is to evaluate the liver specific Response Rate (RR) of the patients who will receive repeated intra-arterial hepatic isolation chemotherapy using the AVAS device to determine whether there is a clinically significant improvement to warrant further investigation in a Phase III study.

6 Trial Outline

6.1 Primary Endpoint

The desired endpoint which can be assessed 4-5 weeks after device explantation will be:

1. Liver specific response Rate (RR) as determined by clinical imaging and tumour markers under the RECIST criteria

The RR of standard FOLFOX for the patient cohort enrolled in this study (described in 7.1 - 7.2) is well established and is approximately 50% [1] [2]. The RR achieved from the study treatment will only be considered 'clinically significant improvement' if the RR can be increased by at least a further 20% (i.e. RR ≥ 70%).

6.2 Secondary Endpoints

Other endpoints of this study include the following:

1. Two-year survival
2. Liver progression free survival (PFS) and overall progression free survival (OPFS)
3. Systemic side effects to chemotherapy
4. Organ isolation capability as determined by pressure readings on catheters
5. Conversion to resection rate
6. Quality of life (QoL)

6.3 Summary of Trial Design

The study is a Phase Ib/II open label, non-randomized, single-arm study using a binary primary endpoint of liver specific response rate to serve as a "go/no-go" study for a larger Phase III study. It is an open-label study since the study treatment requires the use of an implantable medical device which prevents blinding. It is a non-randomized, single-arm study since there is well established data for the response rate for the standard management regimen and therefore, there is no need to enrol a control group. Finally, the Phase Ib dose determination stage is built into the study to prevent using a sub-optimal dose for the Phase II study. The statistical plan for the Phase II study has been explained in Section 11. The key study stages are summarised below in Table 2 and Figure 1.

The patients who are selected and who consent to participate in this clinical trial will receive the repeated intra-arterial hepatic isolation chemotherapy of oxaliplatin using the AVAS. After the patient is screened, the patient will proceed through the appropriate preparation procedures. After the patient is implanted with the AVAS (Day 0), during the treatment period, the patient is re-admitted to the study site up to twice per week to receive the study treatment until the treatment regimen is completed. The patient is then re-admitted to the study site to have the AVAS surgically explanted. The patients will also be prescribed oral capecitabine throughout and possibly past the oxaliplatin infusion sessions. Refer to Section 8.2 for a detailed description of the study's treatment modality, dosage regimen and patient preparation.

The treatment may be discontinued prior to the completion of the treatment in the event of a serious and unanticipated adverse device effect (USADE) that is directly related to either the treatment and or the medication/devices used in the study. In such circumstances, the patient will be re-admitted to the study site to have the AVAS surgically explanted at the patient's earliest convenience.

Regardless of whether the patient's treatment regimen is completed or discontinued, and provided that the patient does not refuse to allow follow-ups, patients will be followed up as per the planned schedule summarised in Table 2. Also refer to Section 8.3 for more detailed description of the follow-up procedures.

Below is a summary of the general outline of the clinical trial:

- Number of patients: up to 47 patients: approximately 10 patients (Phase Ib, the number of patients required may change depending on the dose modification study) + 37 patients (Phase II)

- Expected duration of each patient's participation: up to 8 weeks of treatment plus 5 weeks for the primary end point follow-up. The patient will be followed up for 2 years after the primary end point is assessed, but is not restricted from proceeding to other treatment regimens.

- Total expected duration of the clinical trial: 2.5 years per patient; 3.5 – 4 years for all patients to complete the study.

- Number of investigational devices to be used: Sufficient quantities of the AVAS Implant, AVAS Occluder, and AVAS Multiport Valve will be provided for all patients.

- Estimated time required for patient recruitment: 1 – 1.5 years to enrol all patients.

- Max. number of patients to be included for each investigation site: 47 patients

Table 2- Timeline and summary of key study stages

Data/Event Description	Screening between 7th & 8th FOLFOX cycles	Treatment Phase																									Follow-up Phase						
		Day 0			1st infusion			2nd infusion			3rd infusion			4th infusion			5th infusion			6th infusion (optional)			7th infusion (optional)			AVAS Explantation			4-5 weeks from AVAS explantation	3 months from AVAS explantation (± 1 month)	6 months from AVAS explantation (± 1 month)	9 months from AVAS explantation (± 1 month)	12 months from AVAS explantation (± 1 month)	18 months from AVA explantation (± 1 month)	24 months from AVAS explantation (± 1 month)
		AVAS Implantation (Enrolment)																																
		Admission	Implantation	Discharge	Admission	Infusion	Discharge	Admission	Infusion	Discharge	Admission	Infusion	Discharge	Admission	Infusion	Discharge	Admission	Infusion	Discharge	Admission	Infusion	Discharge	Admission	Infusion	Discharge	Admission	Explantation	Discharge						
Patient information & consent	X																																
Last CT scan prior FOLFOX commencement	SOC																																
CT scan after 6th FOLFOX cycle	SOC																																
CT-Scan																												X	SOC[b]	SOC[b]	SOC[b]	SOC[b]	SOC[b]	SOC[b]
CT-Angiogram	X																																
RECIST v1.1	SOC																												X	SOC[b]	SOC[b]	SOC[b]	SOC[b]	SOC[b]	SOC[b]
Review of imaging data	X																																
Haematology: full blood count	SOC	SOC			SOC			SOC			SOC			SOC			SOC			SOC			SOC			SOC			SOC	SOC[b]	SOC[b]	SOC[b]	SOC[b]	SOC[b]	SOC[b]
Chemistry: electrolytes, urea & creatinine	SOC	SOC			SOC			SOC			SOC			SOC			SOC			SOC			SOC			SOC			SOC	SOC[b]	SOC[b]	SOC[b]	SOC[b]	SOC[b]	SOC[b]
Chemistry: liver function tests	SOC	SOC			SOC			SOC			SOC			SOC			SOC			SOC			SOC			SOC			SOC	SOC[b]	SOC[b]	SOC[b]	SOC[b]	SOC[b]	SOC[b]
Laboratory test: CEA	SOC	X			X			X			X			X			X			X			X			X			X	X[b]	X[b]	X[b]	X[b]	X[b]	X[b]
Laboratory test: INR	X	X[a]																																
Adverse Event Collection & Monitoring (CTCAE 4.03)		X			X			X			X			X			X			X			X			X			X	X[bc]	X[bc]	X[bc]	X[bc]	X[bc]	X[bc]
Review of medical history	X																																
Final approval for enrolment	X																												X					
Quality of Life (EORTC QLQ-C30 and QLQ-LMC21)	X										X																		X					
Concomitant medication	X	X			X			X			X			X			X			X			X			X			X	X[b]	X[b]	X[b]	X[b]	X[b]	X[b]
Device implantation/Explantation Procedure			X																								X							
Discharge Follow-up				X																								X						
Oxaliplatin infusion						X			X			X			X			X			X			X										
Procedure Details & DICOM files			X			X			X			X			X			X			X			X			X							
Device Accountability			X			X			X			X			X			X			X			X			X							
Capecitabine administration (frequency as per standard eviQ protocol)					SOC			SOC			SOC			SOC			SOC			SOC			SOC			SOC								
Post-treatment status																													X	X	X	X	X	X	X

a Can be omitted if result available within last 2 weeks

b Activity can be omitted once the patient commences another treatment regimen for the underlying disease. Trial Co-ordinator must continue to obtain data/results from new treatment as per schedule.

c Any serious adverse event leading to a patient's death will always be reported if it is within the 2 year follow-up period regardless of whether the patient has withdrawn from the study or commenced another therapy.

Patient Workup, Screening, and Approval for Enrolment

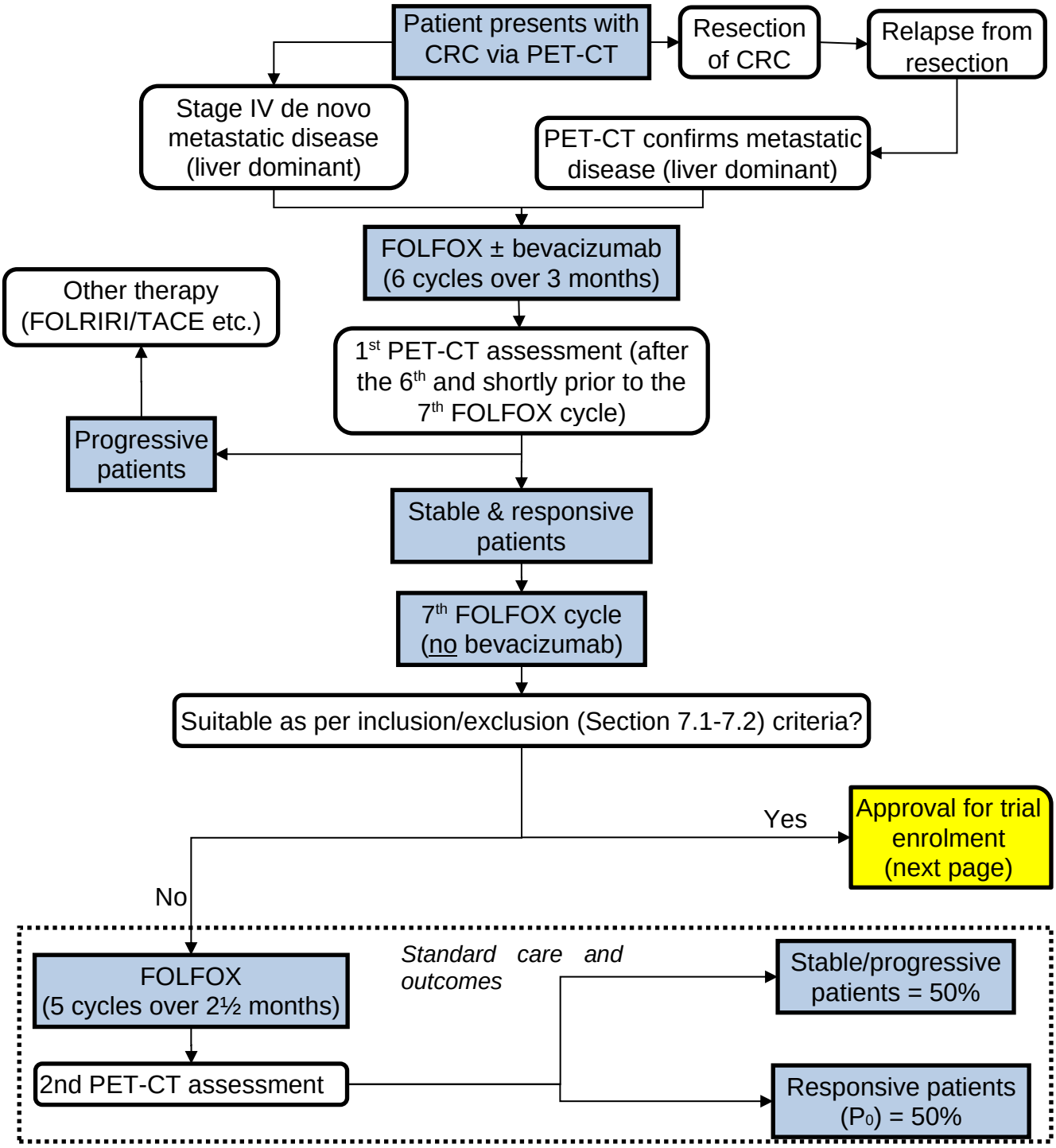


Figure 1 - Synopsis of study flow for the proposed study treatment: Pre-enrolment

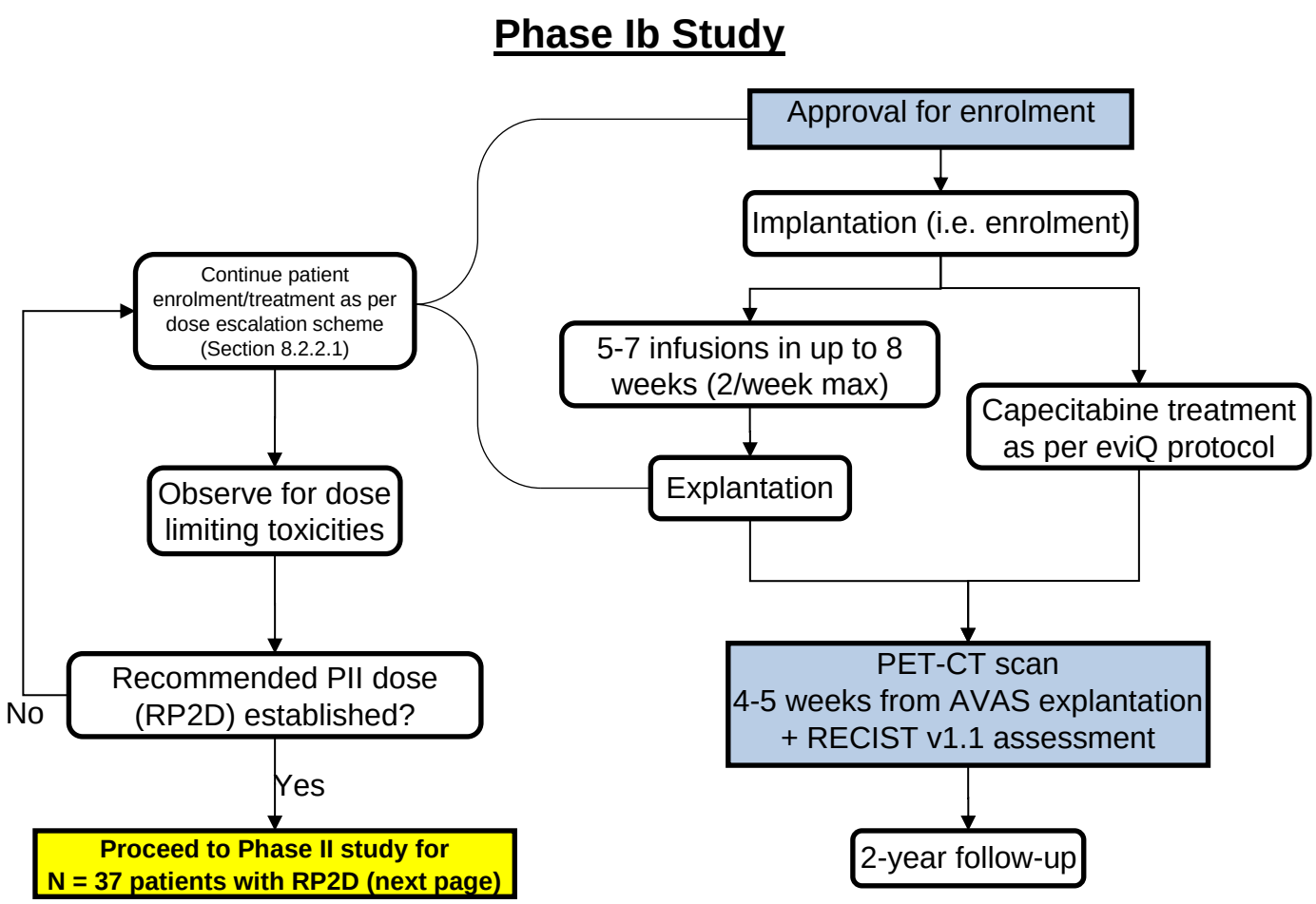
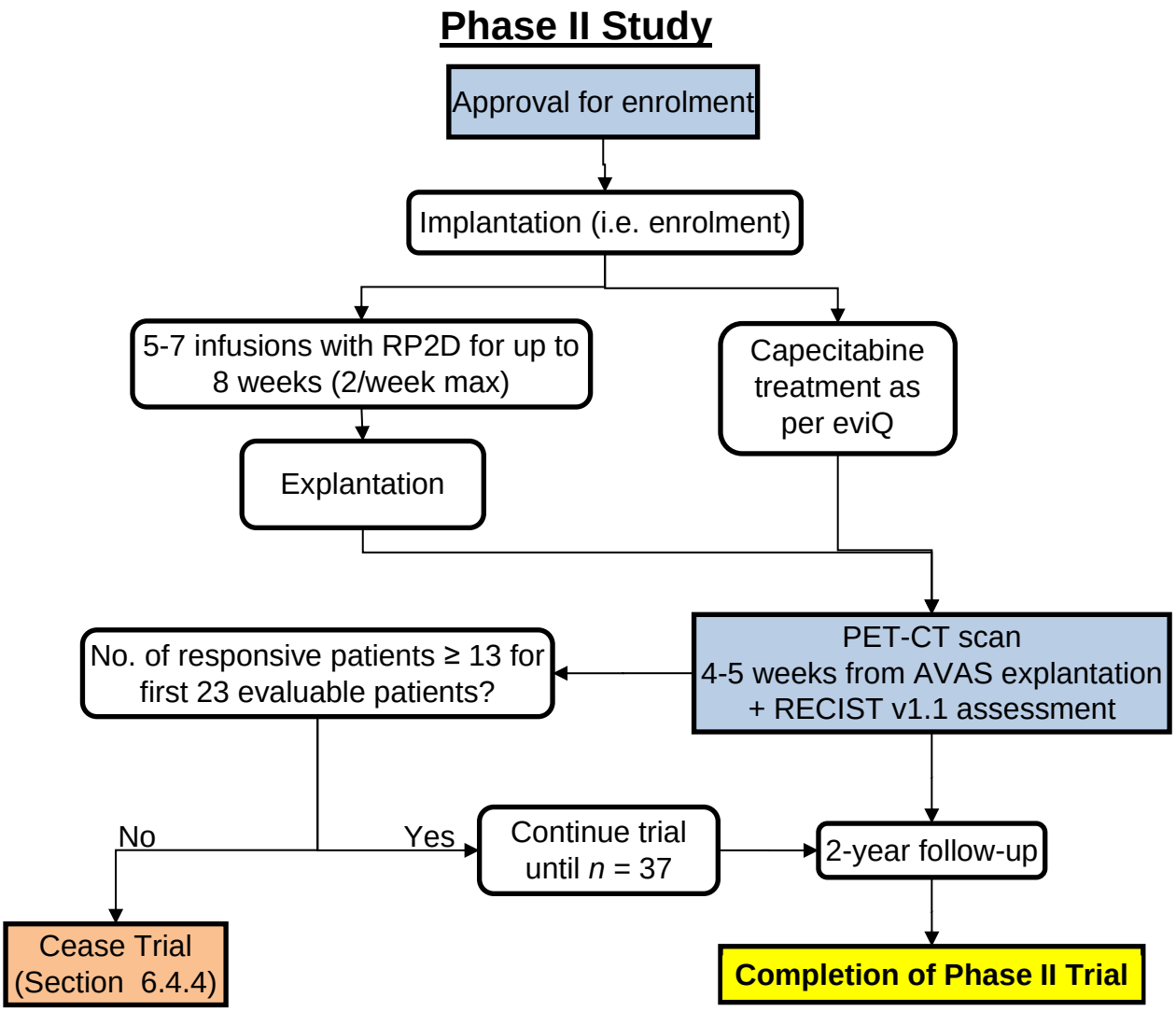


Figure 1 (Cont.) - Synopsis of study flow for the proposed study treatment; refer to Section 11 for details on the statistical analysis.



Primary endpoint = response rate (RR)

H_0: non-clinically significant improvement in RR

H_1: clinically significant improvement in RR

$P_0 = 0.50$; $P_1 = 0.70$; $\alpha = 0.95$; $1-\beta = 0.80$

Phase II = 2 stage design

Stage 1: 13 out of the first 23 patients must be responsive to continue study

Stage 2: 24 out of 37 must respond for null hypothesis to be rejected

Figure 1 (Cont.) - Synopsis of study flow for the proposed study treatment; refer to Section 11 for details on the statistical analysis.

6.4 Stopping Rules

The trial can be stopped for a number of reasons. The trial can be stopped on a patient basis, an investigator basis or completely stopped. Follow-ups will still be carried out on patients that have stopped provided they have been treated with at least one intra-arterial oxaliplatin infusion.

6.4.1 Individual Patient Stopping Criteria

The trial may be suspended or stopped for a specific patient if they develop co-morbidities, regardless of relatedness to the study treatment, and which, in the opinion of the investigator, require discontinuation in the best interests of the patient.

6.4.2 Investigator Trial Closure

Participation by any investigator's may be discontinued for non-compliance with the CIP, regulatory, GCP or adverse event reporting requirements. An investigator may also be removed from the trial if there is a consensus from the Steering Committee/DSMB that a disproportionate number of complications has occurred at that site.

6.4.3 Complete Trial Closure

The trial may be stopped completely in one, multiple or all of the investigation sites, as determined by the co-ordinating clinical investigator in conjunction with the sponsor, if there are any treatment-related mortalities. The study will be re-evaluated before continuation. Note that the patient demographic may contain critical patients and mortality is not an automatic indicator for trial cessation. The Steering Committee or DMSB may decide to completely cease the trial if it is decided that there are significant safety issues due to the treatment itself (see Section 9.4).

6.4.4 Significant Statistical Outcome

If the number of subjects treated responding to the study treatment at the end of Stage 1 of the Phase II component of the study is too low, the study may be prematurely terminated for reasons of safety/futility. Refer to Section 11.2 for a detailed statistical criterion.

7 Selection and Withdrawal of Subjects

7.1 Inclusion Criteria

- Patients with hepatic metastases from histologically proven adenocarcinoma of the colon/rectum
- Patients with limited extrahepatic metastases in the lung or lymph nodes (fewer than 5 nodules ≤ 1 cm diameter or a single nodule ≤ 1.7cm diameter in the lung, and lymph node involvement in a single anatomical area < 2 cm diameter)
- Patients in whom CT at screening has confirmed non-progressive disease, as per RECIST v1.1, after the first 6 cycles of FOLFOX ± bevacizumab
- Patients who have had no more than 7 cycles of FOLFOX ± bevacizumab or other chemotherapy

- Patients with Genotype: RAS mutant
- Estimated time between last monoclonal antibody treatment and anticipated date of first infusion will be at least 6 weeks
- Patients must be fit for repeated general anaesthesia
- Patients with World Health Organization performance status < 3
- Patients with haemoglobin ≥ 100 g/L, ANC ≥ 1.5×10^9/L, platelet count ≥ 100×10^9/L
- Patients with adequate renal function (serum creatinine < 1.5 × Upper Limit of Normal)
- Patients with adequate liver function (bilirubin 1.0 - 2.0 × Upper Limit of Normal, AST < 5 × Upper Limit of Normal)
- Patients with normal coagulation (INR < 1.5)
- Patient over 18 years of age
- Patients who are able to understand the risks and benefits of the study and give written informed consent to participate
- Patients who are available for follow-up at the study sites for the length of the study

7.2 Exclusion Criteria

The following exclusion criteria apply:

- CT-angiogram confirms unsuitable vascular anatomy
- All lesions in the liver are not measurable (RECIST v1.1) in the CT scan prior to FOLFOX commencement
- All lesions in the liver are not measurable (RECIST v1.1) in the CT scan between the 6^{th} and 7^{th} FOLFOX cycles
- Evidence of ascites, cirrhosis, portal hypertension, main portal venous tumour involvement or main portal venous thrombosis
- Allergies to contrast agents
- Previous hypersensitivity or laryngo-pharyngeal dysaesthesia associated with oxaliplatin
- Previous allergies associated with 5-FU or oxaliplatin
- Grade > 2 peripheral neuropathy
- Significant co-morbidities (i.e. life expectancy ≤ 3 months)
- Pregnant or breastfeeding women, or women of child bearing potential and who are not on a reliable form of birth control
- Patients who are enrolled or intend to participate in another clinical trial (of an investigational drug or device, new indication for an approved drug or device, or requirement of additional testing beyond standard clinical practice) during this clinical study
- Patients with medical conditions that preclude the testing required by the protocol, or limit study participation

7.3 Patient Withdrawal and Replacement

A patient has the right to withdraw from the trial at any time. There are three main stages when this withdrawal could occur and each has implications on the study results. Note – this section only considers situations where the patient him/herself decides to withdraw from the trial. Any decision made by an investigator to remove a

patient requires the approval of the Sponsor and a full justification for the removal would be required. Depending on the stage at which the patient chooses to withdraw from the study, another patient may or may not be enrolled to replace the withdrawn patient in the final statistical analysis. The same applies to patient death during the various stages of the study. Whether a patient can be replaced in the event of a death or a patient choosing to withdraw from the study depends on a combination of factors such as:

- What stage in the study the patient withdraws/dies;
- Relatedness of the death to the study treatment;
- Relatedness of the death to the underlying disease being treated;
- Whether the patient allows follow-ups to the primary endpoint; and
- Whether the primary endpoint has already been assessed

7.3.1 Pre-treatment

If a patient withdraws from the study or dies before the implantation of the device, another patient can be enrolled to replace the patient. Similarly, if a patient withdraws from the study or dies after device implantation but prior to the first intra-arterial oxaliplatin infusion, the patient will not be included as part of the study and will be replaced by another patient.

7.3.2 During Treatment

Patient replacement rules for patient deaths and patients who withdraw from the study after they have been administered with at least one oxaliplatin intra-arterial infusion are shown in Table 3. Patients withdrawing at this stage must still undergo device explantation regardless of whether they allow post-withdrawal follow-ups or not.

The Investigator should always refer to the Stopping Rules (Section 0) for patient deaths deemed definitely or probably related to the study treatment or the progression of the underlying disease being treated.

Table 3 – Patient replacement rules during treatment.

No. of oxaliplatin infusions administered prior withdrawal:	**Patient withdraws but allows follow-up to:**		**Patient death and relatedness to the study treatment or progression of underlying disease being treated**	
	Primary endpoint	***No follow-up allowed***	***Definitely or probably related***	***Definitely NOT related***
1-4	Replace patient [a]	Replace patient [a]	Cannot replace patient [b]	Replace patient [a]
5-7	Cannot replace patient [b]			

[a] *patient being replaced will not be included in final statistical analysis but the replacement patient will*

[b] *patient result must be included in final statistical analysis*

7.3.3 Post-treatment (Follow-up)

Patient replacement rules for patient deaths and patients who withdraw from the study after they have undergone device explantation are shown in Table 4.

The Investigator should always refer to the Stopping Rules (Section 0) for patient deaths deemed definitely or probably related to the study treatment or the progression of the underlying disease being treated.

Table 4 – Patient replacement rules during follow-up.

Primary Endpoint	Patient Withdrawal	Patient death and relatedness to the study treatment or progression of underlying disease being treated	
		Definitely or probably related	***Definitely NOT related***
Already assessed	Cannot replace patient [a]	Cannot replace patient [a]	Cannot replace patient [a]
Not yet assessed	Replace patient [b]	Cannot replace patient [a]	Replace patient [b]

[a] *patient result must be included in final statistical analysis*
[b] *patient being replaced will not be included in final statistical analysis but the replacement patient will*

8 Treatment of Subjects

The procedures outlined in the sub-sections below applies both to Phase Ib and Phase II of the clinical trial, except for Section 8.2.2.1 which instructs on how the optimum oxaliplatin dose level for the Phase II trial is determined through the Phase Ib trial.

8.1 Referral & Screening (< Day 0)

Before the screening stage, all patients would have had a CT scan followed by 6 cycles of FOLFOX over a 12-week period. Generally, bevacizumab may also have been administered concomitantly at the discretion of the patient's oncologist but Investigators should hold off bevacizumab for the last 4-5 weeks prior to patient screening for the study. Given a RAS mutant genotype is a prerequisite for this study, withholding monoclonal antibodies (such as bevacizumab) at the discretion of the oncologist is not diverging from the standard of care.

After the 6th cycle and shortly prior to the 7th cycle of FOLFOX, the patient will undergo another CT scan which will be compared to the original diagnostic scan to assess tumour response/progression. Provided the patient has no progressive disease and the metastases are still unresectable, the oncologist will refer the patient to the study team for screening along with the CT scan and the original diagnostic CT scan. The referred patient is consulted by one of the study Principal Investigators, and the Participant Information and Consent Form (PICF) will be explained to the patient. Once a patient has consented and signed the PICF, the patient will be assigned a study ID. The Principal Investigator is to perform a pre-enrolment consultation/screening (as per Section 7.1) to assess the patient's suitability for the clinical trial.

As part of the screening, the Principal Investigator should:

- collect quality of life (QoL) data (EORTC QLQ-C30 and QLQ-LMC21);
- collect adverse events being experienced by the patient (CTCAE 4.03)
- record the concomitant medication(s) the patient is currently taking
- review the patient's medical history
- review the patient's haematology (FBC, EUC, LFTs, CEA, and INR) and request tests for any missing results

- refer the patient for a CT-angiogram and for the scan to be sent to the Co-investigator interventional radiologist intended to administer the treatment and a Co-investigator vascular surgeon
- ensure that copies of the most recent CT scans are sent to the Co-investigator interventional radiologist intended to administer the treatment as well as a Co-investigator vascular surgeon
- ensure that copies of the two CT scans and their completed RECIST assessment forms are sent to the radiologist(s) who will be assessing the patient's scans in the study

The interventional radiologist intending to administer the treatment should:

- review the CT-angiogram and the more recent CT scan to assess accessibility of the patient's arterial anatomy to the liver lesions,
- review the patient's haematology results, and
- inform the Principal Investigator of his/her assessment regarding the patient's suitability for enrolment

A vascular surgeon should:

- review the CT-angiogram and the more recent CT scan to assess the patient's suitability to be implanted with the AVAS device,
- review the patient's haematology results, and
- inform the Principal Investigator of his/her assessment for the patient's suitability

The radiologist(s) who will be assessing the patient's scans should:

- review the two CT scans and their corresponding RECIST assessment forms to ensure that the patient has measurable target lesions in the liver (RECIST v1.1) in both CT scans, and to otherwise
- inform the Principal Investigator not provide approval for enrolment

A summary of all the data to be collected and reviewed by each study personnel is summarised below in Table 5.

Table 5 – Summary of data to be collected and reviewed at screening.

Data	Study Personnel			
	Principal Investigator	**IR**	**VS**	**Rad**
Patient information and consent	Consent and Sign			
QoL data (EORTC QLQ-C30 and QLQ-LMC21)	Collect			
eviQ chemotherapy induced peripheral neuropathy screening	Conduct			
eviQ antineoplastic drug assessment	Conduct			
Patient's current concomitant medication(s)	Collect, review			
Patient's medical history	Collect, review			
Haematology (FBC, EUC, LFT, CEA, INR)	Refer, review, send to IR & VS	Review	Review	
CT-angiogram	Refer, send to IR & VS	Review	Review	
Last CT scan prior FOLFOX commencement	Send to Rad			Review
CT scan after 6th FOLFOX cycle	Send to IR & Rad	Review	Review	Review
RECIST assessment forms	Send to IR & Rad			Review

Table 5 – Summary of data to be collected and reviewed at screening.

Data	Study Personnel			
	Principal Investigator	**IR**	**VS**	**Rad**
Final approval for enrolment	Conduct	Send feedback to PI		

IR = interventional radiologist (co-investigator) intended to administer the treatment to the patient;
VS = vascular surgeon (co-investigator)
Rad = radiologist intended to assess the patient's follow-up scans. Qualified IRs may also take on this responsibility

8.2 Study Treatment (up to 8 weeks from AVAS Implantation)

Patients will go through three different treatment stages; implantation of the AVAS, intra-arterial chemotherapy infusions, and explantation of the AVAS. The specifics for each of these procedures are described below.

8.2.1 Implantation/Enrolment (Day 0)

Once the patient has been approved for enrolment, implantation of the AVAS will be scheduled by a vascular surgeon. The patient will be admitted to the study site as each AVAS system is surgically implanted in the operating room (OR) under general anaesthetic (GA) in accordance with the manufacturer's Instructions for Use (IFU). The AVAS is implanted preferably on the axillary artery or on the common femoral artery. The patient will only be considered as being enrolled on the trial once the device has been implanted.

Postoperatively, the patient will be monitored overnight. The patient will be prescribed anticoagulant medication (Table 9, Section 8.4) and the implant/device exit wounds will be dressed by the nursing staff. The patient will be educated on wound care/dressing management by trained nursing staff or a clinical investigator prior to being discharged and permitted to go home the following day.

The Clinical Trial Co-ordinator should be present at the implantation procedure and assist the vascular surgeon in recording the procedure details.

8.2.2 Study Treatment & Chemotherapy Regimen (Day 1 up to Week 8)

Patients will be treated with a combination of oxaliplatin and capecitabine (XELOX). Apart from the mode of delivery of the oxaliplatin, the patient will be managed as closely as possible to the eviQ XELOX protocol for colorectal metastatic patients [3]. Intra-arterial hepatic isolation oxaliplatin infusions are to be performed by an interventional radiologist as described in Section 8.2.2.3 below. For each scheduled infusion session, the patient is admitted to the study site and the treatment carried out in the angiography suite while the patient is sedated under GA. Provided a patient is well enough, the Investigator may give permission for the patient to be discharged and permitted to go home after each infusion procedure.

The patient should be scheduled for the infusions with the following constraints:

a) 5 ≤ total number of infusions ≤ 7; patients who receive less than 5 oxaliplatin infusion sessions will be considered to have received incomplete treatment.
b) total device implant period must be ≤ 8 weeks
c) number of infusions must be ≤ 2 over any 7 consecutive days

d) a rest period ≥ 2 full calendar days is required between any 2 infusions; e.g. a patient receiving an infusion on Tuesday can receive the next infusion no earlier than the Friday of the same week.
e) the capecitabine schedule is followed as closely as possible to the eviQ XELOX protocol [3].

A *sample* treatment schedule, considering the above rules, is shown below in Table 6. As shown in the table, depending on the availability of the OR, a hybrid procedure is recommended to increase the chances of facilitating 7 oxaliplatin infusions and to reduce the number of general anaesthetics. Note: the schedule is an *example* and is adjustable depending on theatre/staff availability.

Table 6 – Example of a treatment schedule

Suggested Intra-arterial Oxaliplatin Schedule	**Days**	**Capecitabine Schedule (eviQ XELOX protocol** [3]**)**
Implantation/hybrid procedure [a]	D0 – D14	Cycle 1: Oral capecitabine twice daily (as per eviQ protocol)
Rest period		
Oxaliplatin infusion session 1		
Rest period		
Oxaliplatin infusion session 2		
Rest period		
Oxaliplatin infusion session 3		
Rest period		
Oxaliplatin infusion session 4	D15-D21	Rest period
Rest period		
Oxaliplatin infusion session 5		
Rest period	D21-D35	Cycle 2: Oral capecitabine twice daily (as per eviQ protocol)
Explantation/hybrid procedure [a]		

[a] *hybrid procedure = implantation immediately followed by an oxaliplatin infusion session or an oxaliplatin infusion session immediately followed by an explantation procedure.*

8.2.2.1 Phase Ib - Determining the Optimum Oxaliplatin Dose

This section applies only to the Phase Ib part of the clinical trial which is intended to determine the optimum oxaliplatin dose to be used in the Phase II stage. The starting dosage (SD) of oxaliplatin will be 50mg/m^2, which is the dose level used in the pilot study for which its safety and tolerance was proven in 10 patients. The dose escalation thereafter will depend on the patient's tolerance of the administered dosage using an accelerated titration design. However, intra-patient dose escalation will be disallowed to avoid difficulties in interpretation. Figure 2 provides a graphical view of a typical dose control scheme under the accelerated titration design.

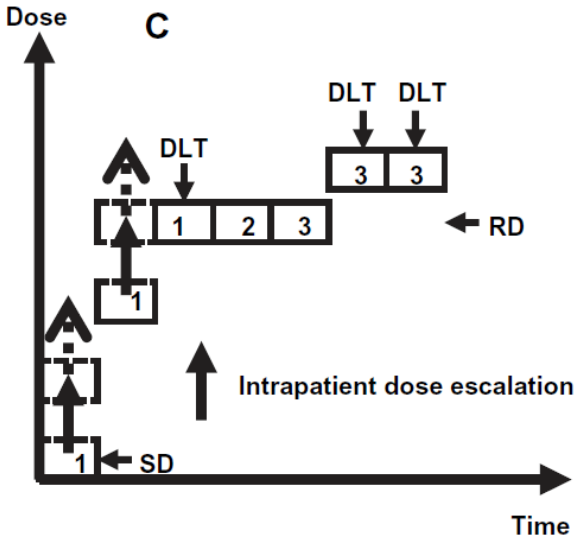


Figure 2 - A typical accelerated titration design [4] with intrapatient dose escalation. NB: the numbers in each box represent the number of patients treated with a dose – not the patient number.

Figure 3 shows how the accelerated titration design will be used in this Phase Ib study. Doses will be escalated in increments of 5 mg/m^2 and the study will be split into the accelerated stage and the confirmation stage. During the accelerated stage, no two patients will be treated over the same period and each patient will receive a dose 5mg/m^2 higher than the previous patient until a patient exhibits signs of dose-limiting toxicity (DLT) which initiates the confirmation stage. From here on, the study mimics that of a traditional 3+3 design where patients are treated in groups of three until 2/3 patients or 2/6 patients exhibit DLT. As shown in the flow diagram (Figure 3), the dose is escalated if there are 0/3 patients with DLT. Otherwise, the Phase Ib study is completed with the previous dose chosen as the recommended dose (RD) for the Phase II study if 2/3 patients or more exhibit DLT. Alternatively, if 1/3 patients exhibit DLT, the dose is kept unchanged and another 3 patients are treated with the same dose. If the total number of patients exhibiting DLTs at this dose is 1/6, the dose will be escalated for the next 3 patients. Otherwise, if there are 2/6 or more patients with DLTs, the Phase Ib study is ended with the previous dose chosen as the RD for the Phase II study.

A DLT will be defined as toxic symptoms experienced by the patient whereby a dose reduction of oxaliplatin or a discontinuation of oxaliplatin is required as per the dose modification criteria in Section 8.2.2.4. DLTs will NOT be defined by the dose modification requirements for capecitabine. When a patient exhibits signs of capecitabine related DLT prior to the end of the treatment period, the patient may continue to be treated as per the dose modification plan in Section 8.2.2.4.

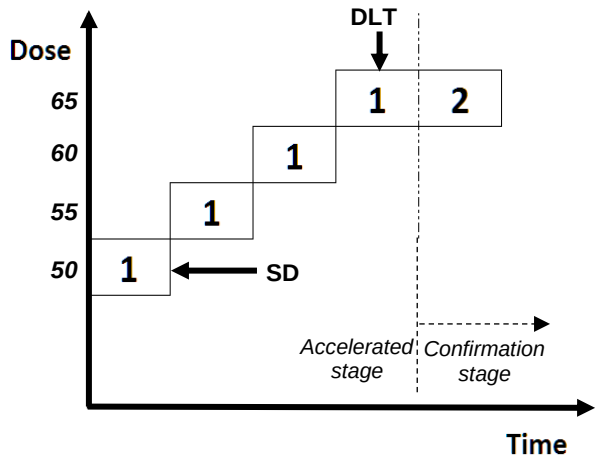
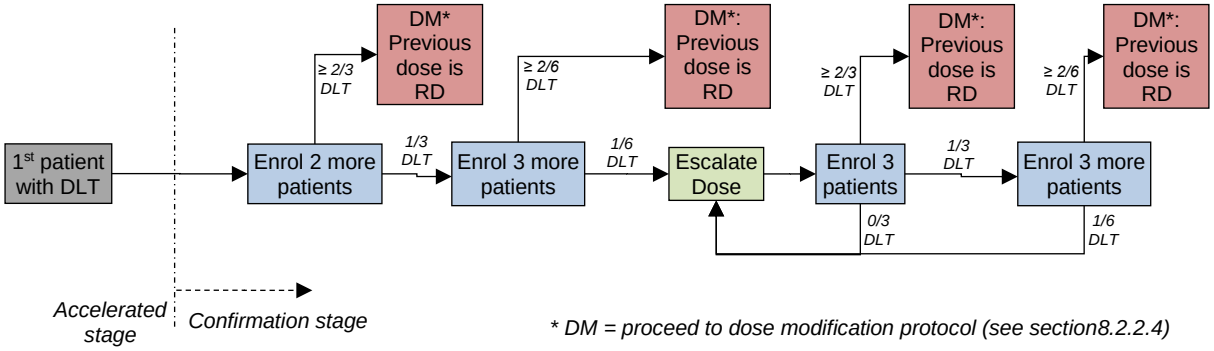


Figure 3 - Accelerated titration design: during the accelerated stage, patients will be treated one-by-one and the dose escalated after each patient until the first patient exhibits signs of DLT. The confirmation stage is then initiated which follows the rules of a 3+3 design until a recommended dose for the Phase II study is determined as shown in the flow diagram.



8.2.2.2 Pre-Infusion Workup

As part of standard care and as per the eviQ XELOX protocol [3], prior to *each* intra-arterial infusion session and either upon or prior admission, the patient must:

a) Have had haematology tests (FBC, EUC, LFTs, and CEA)
b) Review any adverse events experienced (using CTCAE 4.03)

Based on the above assessments, the Investigator should adjust/maintain the intra-arterial oxaliplatin dose to be administered or cease the treatment as per the dose modification requirements (Section 8.2.2.4).

Upon approval to proceed to intra-arterial oxaliplatin infusion, the patient should be administered with enoxaparin 40mg (IV bolus or SC) pre-operatively and be prepped for GA and the infusion procedure.

8.2.2.3 Intra-Arterial Oxaliplatin Infusion

A stepwise summary of the critical steps involved in the intra-arterial oxaliplatin infusion is shown below:

1) The patient is sedated under GA and administered:
   - heparin (5000-7500 units, IV bolus)
   - cephalosporin (1g, IV bolus)
   - palonsetron (0.25mg, IV bolus)
   - dexamethasone (8mg, IV bolus)

- a 5-HT3 antagonist (IV bolus; refer to Section 8.4 to assess appropriateness for patient)

2) The AVAS is accessed as per the device's IFU.
3) Under angiographic guidance, guidewires, sheaths, and catheters are introduced through the AVAS and into the patient's vasculature as required to achieve the best level of hepatic isolation as practically possible. Figure 4a-c shows an example schematic and an angiogram. An attempt should be made to control the arterial and portal blood flow to the liver.
4) After all catheters have been placed in position, baseline intrahepatic pressures should be measured and recorded by connecting the infusion catheter to a pressure transducer. Chemotherapy, dextrose (5%), and albumin (20%) solutions can be prepared at this time.
5) Inflate all the balloon catheters, administer positive end expiratory pressure (PEEP) of 15-20 cmH_2O, and activate the timer.
6) Record the changes in the intrahepatic pressures over the next minute, then immediately disconnect the infusion catheter from the pressure transducer and connect it to the syringe with the dextrose solution.
7) Over the next 2 minutes, infuse enough of the dextrose to displace the blood volume of the liver segment/lobe to be infused.
8) Immediately disconnect the infusion catheter from the dextrose syringe and connect it to the chemotherapy syringe.
9) Over the next 5-7 minutes, infuse the chemotherapy dose using the syringe.
10) From the 20-minute mark, PEEP can be turned off, all balloon catheters can be deflated and all catheters/guidewires/sheaths can be removed. The AVAS can then be closed
11) The patient's sedation is stopped and the patient transferred to the recovery ward.
12) The patient must be assessed by a medical officer or an Investigator post-operatively but requires an Investigator's approval to be discharged.

The Clinical Trial Co-ordinator must be present during each infusion procedure to record the details of the procedure and collecting the DICOM files relevant to each procedure. They are also responsible in assisting the Investigator to report adverse events from when the patient is admitted to when they are discharged.

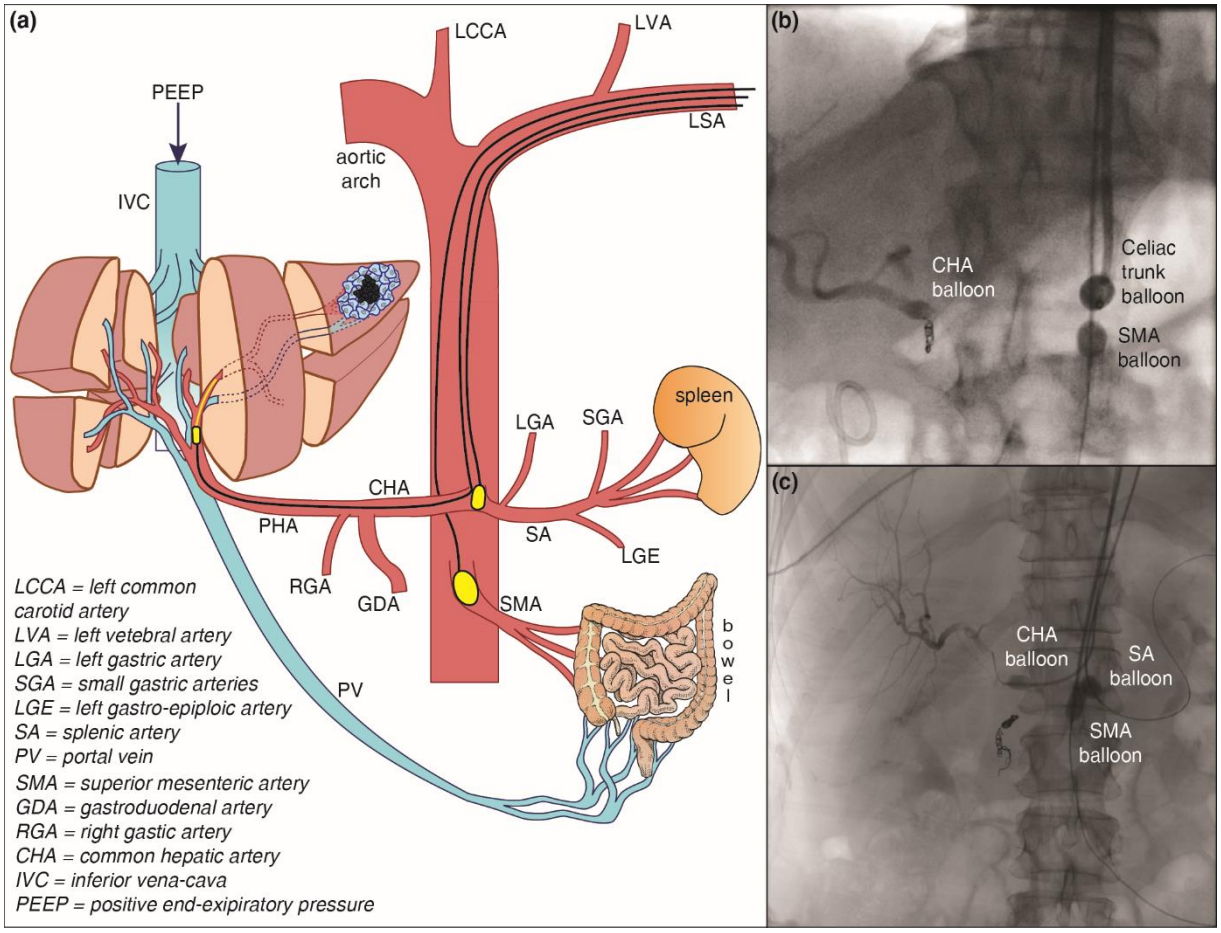


Figure 4 - Catheter schematic for intra-arterial hepatic isolation chemotherapy. The insets (b-c) show examples of the alternative setups (Lane et al [5]).

8.2.2.4 Dose Modification

The dose modification protocol for oxaliplatin has been appropriated from the guidance provided by the eviQ XELOX protocol [3] for applicability to this study. Alternatively, the dose modification for capecitabine has been kept identical to the eviQ XELOX protocol [3]. As per the dose modification requirements (Table 7), if DLTs arise due to the side effects of capecitabine but there is no need for a "discontinuation" of oxaliplatin, patients can be continued to be treated with oxaliplatin as per the timeline in Section 8.2.2 and until the end of the treatment as deemed appropriate by the patient's oncologist. Similarly, if there is no need for a "discontinuation" of capecitabine, patients should be prescribed capecitabine until the end of the second cycle as per the timeline in Section 8.2.2.

Table 7 – Dose modification protocol.

	Adverse Event	CTCAE Grading	Management
Oxaliplatin related	Peripheral neuropathy	Grade 2	Reduce oxaliplatin by 25%, if persists, reduce oxaliplatin by 50%
		Grade 3	Discontinue oxaliplatin infusions
		Grade 4	

Table 7 – Dose modification protocol.

	Adverse Event	CTCAE Grading	Management
		Acute laryngo-pharyngeal dysaesthesia	
Oxaliplatin AND capecitabine related	Neutropenia	Grade 2	Delay treatment until recovery
		Grade 3	
		Grade 4	Delay treatment until recovery and consider reducing oxaliplatin and capecitabine by 25% for subsequent cycles
		Febrile neutropenia	
	Thrombocytopenia	Grade 2	Delay treatment until recovery
		Grade 3	Delay treatment until recovery and consider reducing oxaliplatin and capecitabine by 25% for subsequent cycles
		Grade 4	
	Mucositis & stomatitis	Grade 2	Delay treatment until toxicity has resolved to Grade 1 or less and reduce the dose for subsequent cycles as follow: - 1st occurrence: No dose reduction - 2nd occurrence: Reduce oxaliplatin and capecitabine by 25% - 3rd occurrence: Reduce oxaliplatin and capecitabine by 50% - 4th occurrence: Discontinue chemotherapy
		Grade 3 or 4	Delay treatment until toxicity has resolved to Grade 1 or less and reduce the dose for subsequent cycles as follow: - 1st occurrence: Reduce oxaliplatin and capecitabine by 50% - 2nd occurrence: Discontinue chemotherapy
	Diarrhoea	Grade 2	Delay treatment until toxicity has resolved to Grade 1 or less and reduce the dose for subsequent cycles as follow: - 1st occurrence: No dose reduction - 2nd occurrence: Reduce oxaliplatin and capecitabine by 25% - 3rd occurrence: Reduce oxaliplatin and capecitabine by 50% - 4th occurrence: Discontinue chemotherapy
		Grade 3 or 4	Delay treatment until toxicity has resolved to Grade 1 or less and reduce the dose for subsequent cycles as follow: - 1st occurrence: Reduce oxaliplatin and capecitabine by 50% - 2nd occurrence: Discontinue chemotherapy
	Renal impairment [a]	Moderate	Reduce capecitabine by 25%
		Severe	Discontinue oxaliplatin AND capecitabine
Cap	Hepatic dysfunction [b]	Moderate	Reduce capecitabine by 25%
		Severe	Reduce capecitabine by 50%

Table 7 – Dose modification protocol.

	Adverse Event	CTCAE Grading	Management
	Palmar-plantar erythrodysesthesia syndrome	Grade 2	Delay treatment until toxicity has resolved to Grade 1 or less and reduce the dose for subsequent cycles as follow: - 1st occurrence: No dose reduction - 2nd occurrence: Reduce capecitabine 25% - 3rd occurrence: Reduce capecitabine by 50% - 4th occurrence: Discontinue capecitabine
		Grade 3	Delay treatment until toxicity has resolved to Grade 1 or less and reduce the dose for subsequent cycles as follow: - 1st occurrence: Reduce capecitabine by 50% - 2nd occurrence: Discontinue capecitabine

[a] *eviQ classification adapted from the National Kidney Foundation (NKF) and National Cancer Institute Organ Dysfunction Working Group (NCI OWG) definitions; moderate = 30-50 mL/min and severe = < 30 mL/min in creatinine clearance*

[b] *National Cancer Institute– sponsored Organ Dysfunction Working Group criteria; moderate = 1.5-3 × ULN and severe = > 3 x ULN bilirubin*

8.2.3 Explantation

Explantation of the AVAS is carried out in the OR under GA after the patient's last infusion as determined by the patient's oncologist. The device is surgically removed in accordance with the manufacturer's IFU. The Clinical Trial Co-ordinator should be present at the explantation procedure and assist the vascular surgeon in recording the procedure details.

Postoperatively, the patient is taken to the recovery unit and monitored overnight. A discharge follow-up will be carried out by an Investigator the following day. The patient will be assessed and may be prescribed prophylactic antibiotics. The implant/device exit wounds will be dressed and the patient will be educated on wound care/dressing management by trained nursing staff or an Investigator prior to being discharged. The Clinical Trial Co-ordinator may also assist the Investigator with this discharge follow-up.

8.2.4 Capecitabine Completion (Days 21-35)

Unless there is a need for the patient to "discontinue" their capecitabine treatment as per the dose modification requirements (Table 7), the patient is to complete their second cycle regardless of when the AVAS device is explanted.

The Clinical Trial Co-ordinator should collect the information on the dosage, frequency, and treatment plan for the capecitabine regimen throughout the patient's participation in the study.

8.3 Follow-up

All patients who were enrolled, received at least one chemotherapy infusion session, and did not withdraw from the study will be followed up by the study team for two years from the date of device explantation. A summary of the scheduled follow-up activities, personnel responsible, and data collected is provided below in Table 8.

It should be noted that after the follow-up CT scan and follow-up visit at 4-5 weeks after the AVAS explantation, the patient is free to undergo other therapies for the underlying disease at the discretion of the patient's managing oncologist. At 3, 6, 9, 12, 18 and 24-months, the patient's post-treatment status will be checked. This will provide information on whether the patient has been administered alternative treatments and, if yes, which treatment he/she has received. For these patients who are administered a second treatment, only the data that is available and closest to the scheduled follow-up time point is to be collected. However, general follow-up must be made at 2-year time point, regardless of the schedule of the second treatment, to obtain information on patient survival.

For patients who do not undergo a subsequent treatment after the study treatment, follow-up activities will be conducted as per the schedule summarised in Table 8.

Table 8 – Summary of data to be collected during follow-up.

Data	Follow-up schedule (post-explantation)		Study Personnel	
	4-5 weeks	3, 6, 9, 12, 18, 24 months	Principal Investigator	Radiologist
Follow-up visit	X	X*	Conduct	
QoL data (EORTC QLQ-C30 and QLQ-LMC21)	X	X*	Conduct	
Adverse event monitoring (CTCAE 4.03)	X	X*	Conduct	
Haematology (FBC, EUC, LFT, CEA)	X	X*	Refer, collect	
CT scan	X	X*	Refer, send to Rad	Review
Post treatment status (RECIST assessment)	X	X*	Collect	Conduct, send to PI
Adverse event monitoring	X	X**	Conduct	

** can exit the specified follow-up schedule once the patient commences another treatment regimen. Data must still be collected but as per the new treatment schedule.*

*** adverse event data does not need to be collected (apart from those leading to death) once the patient commences another treatment regimen*

8.4 Concomitant Medication

The following concomitant medicines, summarised in Table 9, may be prescribed/administered throughout the study period for the indications listed.

Table 9 – Summary of concomitant drugs

Indication	Drug	Dose & Frequency	Route	Details
Antiemetic	Dexamethasone	8mg o.d.	IV (bolus) and PO	- Taken with or after food (or in divided doses) - Taken on day of oxaliplatin and up to 3 days after
	Palonosetron	0.25mg	IV (bolus)	30 minutes before oxaliplatin
	Metoclopramide	10mg t.d.s.	PO	Max 30mg/24hr up to 5 days

Table 9 – Summary of concomitant drugs

Indication	Drug	Dose & Frequency	Route	Details
Antiemetic (breakthrough emesis)	OR Prochlorperazine	 10 mg/6 hr 12.5mg/6hr	 PO IV	None
Patients with prior episode of chemotherapy induced nausea or vomiting	Aprepitant	165mg	PO	Taken on day of oxaliplatin
	5-HT_3 antagonists	-	PO or IV(bolus)	Prior oxaliplatin infusion
	Dexamethasone	8-12mg o.d.	PO	- 8mg on day of oxaliplatin - 12mg up to 4 days after - Taken with or after food (or in divided doses)
Colorectal metastatic cancer	Capecitabine	Up to 1000mg/m^2 b.d.s.	PO	- Systemic therapy - Taken with or after food (or in divided doses)
Thrombosis	Enoxaparin	40mg	SC or IV (bolus)	- Prophylactic - Upon hospital admission on day of oxaliplatin
	Heparin	5000-7500 units	IV (bolus)	- Prophylactic - Under GA and prior to and or after oxaliplatin infusion
	Rivaroxaban	PRN	PO	- Prophylactic
Infection	Cephalosporin	1g	IV (bolus)	- Prophylactic antibiotic - Under GA and prior to oxaliplatin infusion
Vasospasm	Papaverine and other nitrates	PRN	Intra-arterial	- Under GA during cannulation
Pain	Paracetamol, fentanyl, morphine, and other opiates	PRN	PO or SC	- Post-operative pain management

During pre-enrolment and screening, a list of all of the patient's concomitant medication will be documented. Once admitted to the study site, the list of the patient's concomitant medication will be reviewed by a Principal Investigator every time it is updated to assess whether the medication is likely to have an outcome on the hepatic isolation chemotherapy treatment for the specific patient.

Patients participating in the study will be prescribed anticoagulants and antibiotics as prophylactic management of infection and thrombosis. They will also be prescribed analgesics for pain management. Apart from anti-inflammatory medications, there are no medications (including rescue medication) patients will not be permitted before and or during the trial.

8.5 Drug Interactions

Any possible interactions between oxaliplatin capecitabine and other medication that could possibly be used in concomitance is summarised below in Table 10.

Table 10 – Summary of drug interactions as listed in the eviQ XELOX protocol [3].

	Medicine	Interaction	Clinical Management
Oxaliplatin	Nephrotoxic drugs (e.g. aminoglycosides, amphotericin, cisplatin, contrast dye, frusemide, NSAIDs)	Additive nephrotoxicity	Avoid combination or monitor renal function closely
	Neurotoxic drugs (e.g. vincristine, paclitaxel)	Additive nephrotoxicity	Monitor closely for neuropathy if combination used
Capecitabine	Sorivudine* and analogues (e.g. brivudine*) *not currently marketed in Australia	Potentially fatal increased toxicity of fluorouracil, the active metabolite of capecitabine, due to reduced clearance	Combination contraindicated and at least 4 weeks must elapse between the end of treatment with sorivudine (or analogues, such as brivudine) and the start of capecitabine therapy
	Warfarin and other drugs metabolised by CYP2C9 (e.g. phenytoin etc.	Increased effects/toxicity of these drugs possible due to inhibition of CYP2C9 by capecitabine and/or its metabolites resulting in reduced clearance	Avoid combination or monitor for increased effect/toxicity. (e.g. INR can be increased by 91% in patients on warfarin)
	CYP inducers, inhibitors and substrates	Link to table of CYP inducers, inhibitors and substrates (http://medicine.iupui.edu/clinpharm/ddis/main-table)	
General Interactions	Warfarin	Antineoplastic agents may alter the anticoagulant effect of warfarin	Monitor INR regularly and adjust warfarin dosage as appropriate; consider alternative anticoagulant (e.g. LMWH or unfractionated heparin)
	Digoxin	Antineoplastic agents can damage the lining of the intestine; affecting the absorption of digoxin	Monitor digoxin serum levels; adjust digoxin dosage as appropriate
	Antiepileptics	Both altered antiepileptic and antineoplastic levels may occur, possibly leading to loss of efficacy or toxicity.	Where concurrent use of an enzyme-inducing antiepileptic cannot be avoided, monitor antiepileptic serum levels for toxicity, as well as seizure frequency for efficacy; adjust dosage as appropriate Also monitor closely for efficacy of the antineoplastic therapy
	Antiplatelet agents and NSAIDs	Increased risk of bleeding due to treatment related thrombocytopenia	Avoid or minimise combination If combination deemed essential, (e.g. low dose aspirin for ischaemic heart disease) monitor for signs of bleeding
	Serotonergic drugs, including selective serotonin reuptake inhibitors (SSRIs e.g. paroxetine) and serotonin noradrenaline reuptake inhibitors (SNRIs e.g. venlafaxine)	Increased risk of serotonin syndrome with concurrent use of 5-HT3 receptor antagonists (e.g. palonosetron, ondansetron, granisetron, tropisetron, dolasetron, etc.)	Avoid combination. If combination is clinically warranted, monitor for signs and symptoms of serotonin syndrome (e.g. confusion, agitation, tachycardia, hyperreflexia) For more information link to TGA Medicines Safety Update (http://www.tga.gov.au/alert/serotonin-blocking-medicines-used-treat-nausea-and-vomiting).
	Vaccines	Diminished response to vaccines and increased	Live vaccines (e.g. BCG, MMR, zoster and varicella) are contraindicated

Table 10 – Summary of drug interactions as listed in the eviQ XELOX protocol [3].

	Medicine	Interaction	Clinical Management
		risk of infection with live vaccines	For more information; refer to the recommended schedule of vaccination for oncology patients, as outlined in the Australian Immunisation Handbook 10th Edition (updated 2015).

8.6 Subject Compliance

Since the chemotherapy is administered under GA, there are no opportunities for the patient to be non-compliant when receiving treatment. If the patient seeks to discontinue their treatment, they may withdraw from the study at any time (see Section 7.3).

9 Safety

AllVascular follows rigorous quality assurance and control procedures throughout the life of a product, from the business analysis phase through development, market release, and post market surveillance. The risk analysis process for the AVAS and the study treatment is being performed in accordance with ISO 14971, and will ensure that the level of risk is acceptable prior to starting the clinical study.

For market approved product(s) used in this study there are no known incremental risks associated to the subject as a result of participation in this study. However, there are potential risks and side effects associated with a device and follow-up procedures. These risks are documented in the product labelling. Only those risks associated with the AVAS and procedures in the study treatment and not the market released devices or chemotherapeutic agents have been discussed in the sections below. The full risk analysis report can be found attached to *Investigator's Brochure*.

9.1 Adverse Events

The safety issues associated with the study and its treatment will be assessed by monitoring all treatment related complications as well as adverse events. The study is performed in accordance with ISO 14155:2011, the TGA guidelines on Clinical Trials and in compliance with local and HREC requirements. Each of these authorities stipulates requirements for adverse event monitoring and reporting. The responsibilities of the investigators for recording and reporting adverse events are specified in Section 9.1.2. The timeframes in which these events must be reported to the Sponsor and the HREC(s) are also described in this section. Investigators should also use this reporting procedure in conjunction with the Sections 9.2 and 9.3 to determine whether an event is anticipated.

9.1.1 AE Terms & Definitions

The following terms and their definitions (Table 11), as per ISO 14155:2011, will be applied for defining and helping categorise adverse events (AEs).

Table 11 – Definition of terms for adverse event categorisation and reporting.

Term	Definition
Clinical Investigation Plan	Study protocol AV-LIVPIBII-01 Phase Ib/II Study of Intra-Arterial Liver Isolation Chemotherapy in Patients with Hepatic Metastases from Colorectal Cancer.
Investigational Device	Medical devices listed in this CIP that are currently not registered on the Australian Register of Therapeutic Goods of the Therapeutic Goods Administration for the indication/method of use as specified within the investigation plan.
Device Deficiency	Inadequacy of an investigational device(s) with respect to its identity, quality, durability, reliability, safety or performance. This includes malfunctions, use errors, and inadequate labelling.
Malfunction	Failure of an investigational medical device to perform in accordance with its intended purpose when used in accordance with the instructions for use or CIP.
Use Error	Act or omission of an act that results in a different medical device response than intended by the manufacturer or expected by the user. Use error includes slips, lapses, and mistakes. An unexpected physiological response of the subject does not in itself constitute a use error.
Adverse Event (AE)	Any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings): • in subjects whether or not related to the investigational device(s) or events related to the procedures involved. • In users or other persons from events related to the investigational medical device(s).
Serious Adverse Event (SAE)	Any AE that: • led to death, • led to serious deterioration in the health of the subject, that either resulted in: - a life-threatening illness or injury, or - a permanent impairment of a body structure or a body function, or - in-patient or prolonged hospitalization, or - medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function, • led to foetal distress, foetal death or a congenital abnormality or birth defect Note: planned hospitalization for a pre-existing condition, or for a procedure required by the study protocol, without serious deterioration in health, is not considered a serious adverse event.
Adverse Device Effect (ADE)	Adverse event related to the use of an investigational medical device and or the study procedure. This includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device. It also includes any event resulting from use error or from intentional misuse of the investigational medical device.
Serious Adverse Device Effect (SADE)	Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.
Anticipated Serious Adverse Device Effect (ASADE)	An effect which by its nature, incidence, severity or outcome has been identified in the current version of the risk analysis report and is described in this CIP or Investigator's Brochure.
Unanticipated Serious Adverse Device Effect (USADE)	An effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report and is not described in this CIP or Investigator's Brochure.
Serious Health Threat	Any SAE or AE which: • results in imminent risk to the study population of death, serious injury, or serious illness that requires prompt remedial action,. • may affect the conduct of the study, or • may affect the willingness of subjects to continue participation in the study.

Table 11 – Definition of terms for adverse event categorisation and reporting.

Term	Definition
	Note: this definition is a harmonized version from that of GHTF/SG2/N54:2006 and Clause 12.8.d of the NHMRC National Statement on Ethical Conduct in Research Involving Humans.

9.1.2 Reporting Procedure & Timelines

As a general rule, the investigator must report an event to the responsible bodies (Sponsor and HREC) if there is uncertainty as to whether an event is reportable or not. Events are to be recorded on the case report forms (CRF) provided by the Sponsor. Adverse Events are classified according to the Common Terminology Criteria for Adverse Events (CTCAE) (Version 4.03; June 14, 2010), U.S Department of Health and Human Services, National Institutes of Health, National Cancer Institute.

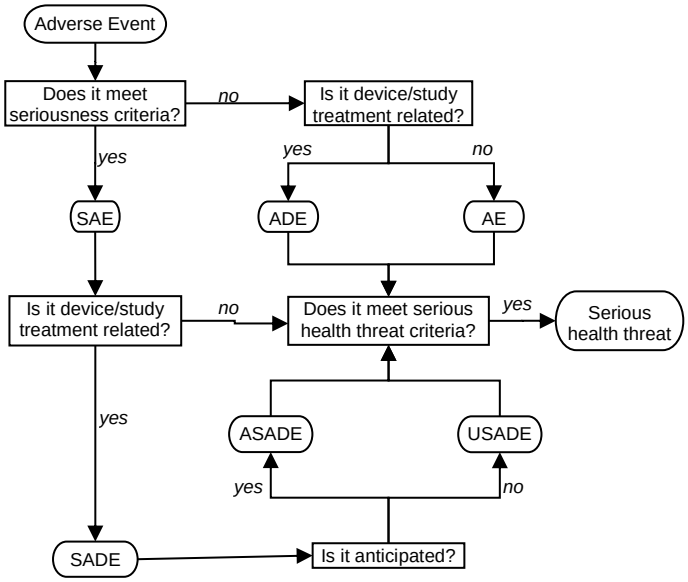


Figure 5 - AE categorisation algorithm.

The Investigator and Sponsor will independently assess every AE recorded as to whether it may constitute an SAE, ADE, ASADE, or USADE. A categorization chart is provided in Figure 5 as adapted from ISO 14155:2011.

If the Principal Investigator and the Sponsor cannot agree, both opinions should be reported to the HREC by the Investigator.

All AEs, SAEs, ADEs, SADEs (includes ASADEs and USADEs), device deficiencies, and serious health threats are to be reported provided they fall within the investigational period which is defined as the time from which the patient is enrolled (i.e. implanted with the AVAS) to whichever of the following timepoints is first reached:

- 2-year follow-up visit
- Death of the subject
- Patient commences another treatment regimen
- Subject withdraws from the study

Note: any SAE leading to a subject's death must *always* be reported if it is within the 2-year follow-up period regardless of whether they have withdrawn from the study or commenced another therapy.

A summary of the reporting timelines is provided in Table 12 and described in more detail in Sections 9.1.2.1 – 9.1.2.7.

Table 12 – Summary of reporting timelines.

Event or Event Type		Reported By	Reported To	Timeframe
Non-device/study treatment related	AE	Investigator	Sponsor	Quarterly
	SAE	Investigator	Sponsor	24 hours
			HREC	Per HREC requirements
		Sponsor	All PIs*	Quarterly
Device/study treatment related	ADE	Investigator	Sponsor	7 days
	ASADE	Investigator	Sponsor	24 hours
			HREC	Per HREC requirements
	USADE	Investigator	Sponsor	24 hours
			HREC	
		Sponsor	TGA	7 or 15 days
Device deficiency		Investigator	Sponsor	24 hours
Serious health threat		Investigator	Sponsor	Immediately
		Sponsor	HREC	2 days
			TGA	

** PI = Principal Investigator*

9.1.2.1 AEs and ADEs

The Investigator must provide a copy of all completed AE CRFs on a quarterly basis to the Sponsor. If an AE is categorized as an ADE, it must be reported to the Sponsor within 7 working days.

9.1.2.2 SAEs and SADEs

Using the form provided by the Sponsor, all SAEs and SADEs should be reported immediately by the Principal Investigator to the Sponsor within 24 hours of site staff becoming aware of the SAE.

SAEs and SADEs should be reported to the HREC committee in compliance with the approving HREC requirements.

The Principal Investigator must provide the HREC and or the Sponsor with any additional information requested related to the event in a timely manner.

9.1.2.3 ASADEs & USADEs

Investigators are to categorise all SADEs into either ASADEs or USADEs. Sections 9.2 - 9.3 of this CIP can be used to help with categorisation. The reporting requirements/timelines for ASADES and USADEs are already described in 9.1.2.2 as they are subsets of SADEs.

9.1.2.4 Serious Health Threats

Any event suspected of being a possible serious health threat must be reported by the site's Principal Investigator immediately to the Sponsor within 24 hours to assess whether the event is a serious health threat. Additional reporting requirements will be carried out by the Sponsor if the event is deemed as a serious health threat.

9.1.2.5 SAEs Leading to Death

For any reported deaths, the investigator should supply the Sponsor and HREC with any additional requested information (e.g., autopsy reports and terminal medical reports) in a timely manner.

9.1.2.6 Device Deficiencies

All device deficiencies are to be reported to the Sponsor using the CRF provided. Investigators must assess whether the device deficiencies could have led to USADES. The deficiency should be reported to the Sponsor within 24 hours of the investigator becoming aware of the deficiency.

9.1.2.7 Correspondences

The Investigator must provide copies of all correspondence between the site staff and the HREC regarding all AEs to the Sponsor upon request.

9.2 Potential Directly Related Anticipated Adverse Events

Adverse events associated with the proposed study treatment that can be reasonably anticipated include the following:

9.2.1 Toxicity and Tumour Progression

Systemic toxicity of the chemotherapy agents, deterioration of liver function, intestinal ischemia, anaemia and tumour progression are all anticipated events within the study. However, they are particular events of interest and thus will be regularly monitored from the patient's haematology and imaging. The safety parameters monitored, the monitoring method and schedule is summarised below in Table 13.

Table 13 - Summary of safety parameters for the treatment modality

Safety Parameter	Indicators	Monitoring Method	Schedule
Tumour progression/ response	CT	Imaging	***Prior Day 0:*** *at screening/pre-enrolment* ***CT:*** *4-5 weeks after the AVAS explantation* ***Follow-up:*** *conducted quarterly as per standard practice or at the discretion of the patient's oncologist.*
Systemic toxicity	FBC, EUC	Haematology	***Prior Day 0:*** at screening/pre-enrolment ***Day 0:*** on admission to study site on implantation day ***During study treatment:*** on admission to study site for <u>each</u> treatment session ***Follow-up:*** *conducted as per standard practice or at the discretion of the patient's oncologist.*
Tumour progression	CEA		
Liver function and intestinal ischemia	LFT		
Anaemia	FBC		
Peripheral neuropathy	Patient's feedback of	QoL (EORTC QLQ-C30	*QoL assessment taken after enrolment but prior to AVAS implantation, after three*

Table 13 - Summary of safety parameters for the treatment modality

Safety Parameter	Indicators	Monitoring Method	Schedule
Nausea, vomiting or diarrhoea	the symptoms	and QLQ-LMC21)	*cycles of Oxaliplatin infusion and 4-5weeks after the AVAS explantation.*
Allergic Reactions	-	Clinician/ nurse's observation of the patient	Constant monitoring required for signs of skin rash (urticarial), conjunctivitis or rhinitis.
Side effects of chemotherapy	Adverse Events	Clinician/ nurse's observation of the patient	Clinican/nurse's monitoring of the patient's status for the duration of the study treatment.

9.2.1.1 Liver Function and Intestinal Ischemia

The liver function is regularly monitored to study the toxic effects of oxaliplatin on the liver function, check the progress of the liver disease and compare the obtained data against some of the adverse events patients may experience during the treatment, such as abdominal pain, nausea, vomiting or jaundice. The biomarkers for the patient's liver function, which include bilirubin, ALP, GGT, AST, ALT, total protein, albumin and globulin, are withdrawn from routine haematological samples collected every time the patient is admitted to the study site to undergo a treatment session (i.e. up to twice a week during the treatment phase).

The extent of insufficient blood flow to the gastrointestinal tract is also assessed via routine collection of haematological samples. As aforementioned, these samples are collected prior to and 1 day after every treatment session. The biomarkers for intestinal ischemia include: LD and ALP. The results obtained will be assessed by an investigator who may consult with the Principal Investigator to evaluate the patient's deterioration/improvement.

9.2.1.2 Tumour/Disease Progression

Tumour/disease progression will also be monitored via routine haematological samples collected every time the patient is admitted to the study site to undergo a treatment session (i.e. up to twice a week during treatment phase). The tumour marker, CEA, will serve as an indicator of disease progression and will be reviewed by an investigator prior to each chemotherapy treatment session. In addition, disease progression/response will also be monitored via comparing the baseline CT scan taken at pre-enrolment/screening to the CT scan taken 4-5 weeks after the AVAS explantation.

9.2.1.3 Anaemia

The deficiency of oxygen level in blood due to decreased amount of haemoglobin will be monitored via FBCs. As well as revealing the absolute value of haemoglobin

concentration, the FBC data will also give haematocrit values which provide relative proportion of red blood cells in the patient's blood. Anaemia often involves symptoms such as tiredness, weakness, shortness of breath and poor ability to exercise. The haematological samples for the FBC data will be collected every time the patient is admitted to the study site to undergo a treatment session. If the patient presents more severe anaemic symptoms (> Grade 3; haemoglobin concentration < 4.9 mmol/L) and at the discretion of the Principal Investigator, a blood transfusion may be prescribed for the patient.

9.2.1.4 Peripheral Neuropathy

Peripheral neuropathy, which results from the damage done to the nerves around the body by the chemotherapeutic agents or the tumour's press against the nerves, can only be qualitatively assessed by the patient's feedback of the symptoms. Along with other assessments of the patient's quality of life, the patient's pain, sensitivity, numbness or weakness around his/her limbs are monitored via EORTC QLQ-C30 and QLQ-LMC21. These surveys will initially be conducted prior to the commencement of the treatment and repeated throughout the course of the patient's enrolment as scheduled under "Quality of Life" in Table 2 of Section 6.3.

9.2.2 Local Effects of Implant Device

The following AEs are to be anticipated as a direct result of using an implantable vascular access implant such as the AVAS:

- Haemorrhage
- Haematoma
- Infection
- Dissection/thrombus
- Anastomotic leak
- Pain

9.2.3 Effects of Hepatic Isolation/Endovascular Catheter Access

The following AEs are to be anticipated as a direct result of repeated cannulation/catheterisation and organ isolation:

- Permanent/semi-permanent ischaemic damage
- Sepsis
- Thrombus
- Infection
- Pseudo-aneurysm
- Haematoma
- Vessel wall damage/trauma

9.2.4 Effects of Chemotherapy (Oxaliplatin)

The following AEs are to be anticipated as a direct result of repeated local infusions of oxaliplatin:

Anticipated adverse effects of oxaliplatin.

Type	Description	Likelihood
Gastrointestinal	Diarrhoea, nausea, vomiting, stomatitis, anorexia, abdominal pain, mucositis, dehydration, ileus, intestinal obstruction, hypokalemia, metabolic acidosis, constipation	Very common
	Gastrointestinal haemorrhage	Common
	Colitis	Rare
Haematological	Anaemia, neutropenia, thrombocytopenia	Very common
Hepatobiliary	Elevated transaminases, elevated alkaline phosphatases	Very common
Hypersensitivity	Skin rash (urticarial), conjunctivitis, rhinitis	Very common
Immune system	Infections, fever, rigors, fatigue, asthenia	Very common
	Febrile neutropenia	Very common
	Autoimmune haemolytic anaemia and thrombocytopenia	Rare
Musculoskeletal	Back pain, arthralgia	Very common
Neurological	Sensory peripheral neuropathy, dysgeusia	Very common
	Pharyngolaryngeal dysaesthesia, jaw spasm, abnormal tongue sensation, feeling of chest pressure	Common
	Dysarthria, reversible posterior, leukoencephalopathy syndrome (RPLS), epistaxis	Rare
Renal	Altered renal function	Common
	Renal tubular necrosis	Very rare
Respiratory	Coughing	Very common
	Hiccups	Common
	Acute intestinal lung disease, pulmonary	Rare
	Fibrosis	Very rare
Sensory	Ototoxicity	Uncommon
	Deafness, optic neuritis, loss of visual activity, visual field disturbances, transient vision loss	Rare
Skin	Alopecia, rash	Common
Vascular	Epistaxis	Very common
	Deep vein thrombosis, thromboembolic event, hypertension, hypotension	Common

9.3 Potential Non-directly Related Anticipated Adverse Events

These are events that are not expected to be directly related to study treatment. Note that these are general conditions and are also expected in patients that are not participating in this study. These conditions that will be monitored are (and could include):

9.3.1 Effects of Chemotherapy (Capecitabine)

The following AEs are to be anticipated as a direct result of the capecitabine prescribed to the patient from enrolment to the primary endpoint follow-up. It should be noted that

the capecitabine is being used in its approved indication/route/dose and hence its side effects should not be considered to be a result of the experimental study treatment or the devices being used. However, since some side effects overlap with that of the side effects of oxaliplatin (9.2.4), discretion will be given to the investigator on assigning causality.

Anticipated adverse effects of capecitabine.

Type	Description	Likelihood
Gastrointestinal	Diarrhoea, nausea, vomiting, abdominal pain, stomatitis	Very common
	Constipation, dyspepsia, upper abdominal pain, dry mouth, flatulence, loose stools	Common
	Events related to inflammation/ulceration of mucous membranes such as esophagitis, gastritis, duodenitis, colitis, and gastrointestinal hemorrhage	Rare
Cutaneous	Hand-foot syndrome or palmar-plantar erythrodysesthesia, dermatitis	Very common
	Alopecia, dry skin, rash erythematous, skin hyperpigmentation, pruritus, nail disorders, localised exfoliation	Common
	Photosensitivity reactions, radiation recall syndrome, onycholysis, brittle nails, nail discoloration, nail dystrophy, and skin fissures	Rare
General undesirable side effects	Fatigue	Ver common
	Pyrexia, weakness, asthenia, lethargy, pain in limb	Common
Neurologic	Headache, paraesthesia, taste disturbance, dizziness, insomnia, hyperesthesia	Common
	Encephalopathy, confusion and cerebellar signs such as ataxia, dysarthria, impaired balance and abnormal co-ordination	Rare
Cardiovascular	Lower limb oedema	Common
	Chest pain, angina pectoris, myocardial infarction	Uncommon
	Cardiac failure, cardiac arrest, cardiomyopathy, sudden death, tachycardia, atrial arrhythmias including atrial fibrillation, and ventricular extrasystoles	Rare
Hepatobiliary	Abnormal liver function tests, jaundice	Rare
	hepatic failure, cholestatic hepatitis	Very rare
	Grade 3 or 4 (according to NCIC/CTC) bilirubin increases	Very common
Haematologic	Hyperglycemia, Grade 3 or 4 laboratory abnormalities (according to NCIC/CTC), decrease in hemoglobin and neutropenia. Grade 3 or 4 alkaline phosphatase.	Common
	Thrombocytopenia	Uncommon

Anticipated adverse effects of capecitabine.

Type	Description	Likelihood
	Bone marrow depression and pancytopenia. Events related to bone marrow depression, immune system compromise, and/or disruption of mucous membranes such as local and fatal systemic infections (including bacterial, viral, fungal etiologies) and sepsis.	Rare
Others	Anorexia	Very common
	Dehydration, dyspnea, increased lacrimation, conjunctivitis, decreased appetite, epistaxis, weight decrease, back pain, arthralgia, depression	Common
	Chest pain, myalgias, eye irritation and cough	Rare

9.3.2 Natural progression of the treated disease

The following adverse effects that are associated with the natural progression of the carcinoma/metastatic disease should be anticipated.

Advanced Hepatic Disease	
• Abdominal pain • Anorexia • Early satiety • Weight loss • Cachexia • Fatigue • Fever • Jaundice • Pancreatitis	• Back pain • Ascites • Intestinal effects (nausea, vomiting and diarrhoea) • Sweats • Biliary obstruction/blockage • Local pain (pancreatic and device) • Anaemia • Liver failure • Metastatic spread to other organs

NOTE: If any of these potential adverse effects ***triggered or exacerbated*** as a result of the study/treatment, it will no longer be considered as the "natural progression" of the treated disease and hence will be considered as an unanticipated directly related adverse event.

9.3.3 Natural progression of pre-existing conditions

The study is aimed at treating advanced unresectable CRC-LM patients only. Therefore, the potential adverse effects associated with the natural progression of any other pre-existing condition should be anticipated. All adverse events stemming from pre-existing conditions in the following systems should be anticipated:

- cardiovascular system
- circulatory and lymphatic systems
- respiratory system
- nervous system
- renal system
- endocrine system

- digestive system
- immune system
- musculoskeletal system
- reproductive system

NOTE: If any of these potential adverse effects ***triggered or exacerbated*** as a result of the study/treatment, it will no longer be considered as the "natural progression" of the treated disease and hence will be considered as an unanticipated directly related adverse event.

9.3.4 Adverse reactions to medication

Medication/drug regimen after the patient has completed either of the treatments and during the follow-up period is not stipulated by the study as the patient is under the care of their physician/oncologist. Thus all potential adverse reactions to any medications/drugs post explantation and not prescribed by a study investigator are not directly related to the study. Alternatively, adverse reactions to any medication/drugs between implantation and explantation will be considered as directly related to the study.

9.3.5 Unforeseeable injuries

These are adverse events that are a direct result of unforeseeable or natural occurrences that are beyond clinical control inclusive but not limited to:

- natural disasters (e.g. flood, bushfire, tsunami etc.)
- endemics/epidemics
- accidents (e.g. falls, burns, vehicular etc.)

NOTE: accidents ***resulting from the patient's physical or psychological state being compromised from the treatment*** will be classified as being directly related to the treatment.

9.4 Safety Reviews

There will be two review committees tasked with reviewing the safety/progress of this study.

9.4.1 Steering Committee Meeting

The following personnel must be present at a Steering Committee review meeting:

- a Principal Investigator
- at least one interventional radiologist who is a co-investigator
- at least one interventional radiologist who is not an investigator
- at least one oncologist who is not an investigator
- the Study Monitor and or a Sponsor representative

A meeting is to be held after the primary endpoint has been reached for every 10th patient. During the meeting, all recorded adverse events will be reviewed, as well as the progress of the trial and any other aspects of the trial that needs to be reviewed.

In the event that one or more of the above personnel is absent for the meeting, the minutes and outcomes must be forwarded to them for review and approval. All minutes and correspondences must be filed and available upon request for the Sponsor and the HREC.

9.4.2 Data & Safety Monitoring Board (DSMB)

The DSMB is responsible for assessing the progress of the trial, safety data, critical efficacy endpoints and to recommend whether to continue, modify or cease the trial.

DSMB membership will consist of 4 to 6 representatives, including experts in the fields of hepatobiliary surgery, oncology, interventional radiology, and clinical trial monitoring. DSMB members will be restricted to individuals without financial interest who would be substantially affected by the outcome of the trial. Investigators in any trial being assessed by a DSMB will not be considered for membership on the DSMB for that trial.

The DSMB is to convene at the following time points:

- after the Phase Ib part of the study is complete,
- after Stage 1 of the Phase II study is complete, and
- after Stage 2 of the Phase II study is complete.

The role of the Study Monitor is to present all data requested by the DSMB such as AEs, SAEs, haematology, patient progress, patient outcomes, protocol deviations and all other data that may be of interest to the DSMB.

10 Assessment of Efficacy

The efficacy of the treatment will be assessed by the primary and secondary endpoints (see Section 6.1 and 6.2). The liver specific response rate will be assessed using a CT scan to measure the tumour/disease progression via the RECIST 1.1 criteria 4-5 weeks after the device explantation. Liver and overall progression of the disease will be monitored via additional routine CT scans during the follow-up stage. The two-year survival will be monitored by follow-up visits. Organ isolation capability will be assessed by the intrahepatic pressures (see Section 8.2.2.3). Systemic side effects will be assessed by monitoring all adverse events that were a result of the patient participating in this study. Finally, the quality of life will be assessed by comparing the QoL surveys completed by the patient prior to the study treatment, after the first week of treatment or second infusion, and at the end of the treatment (end of the capecitabine regimen). These primary and secondary endpoints will be compared to the existing data available for those patients with a similar prognosis treated under standard FOLFOX chemotherapy.

11 Statistical Analysis

The safety and efficacy of this study will be assessed as described previously in Section 9 and 10 respectively. The clinical data that can be analysed for the primary endpoint of RR will be assessed quantitatively while the data for the secondary end points will be analysed qualitatively. The Phase Ib aspect of the study will only be used

to establish a recommended Phase II dose (RP2D) and the patient results from this stage of the study will not be included in the final data analysis described below.

11.1 Hypotheses & Statistical Power

As a single arm study, the results of the Phase II component of the study will be compared to historical information of comparable populations to provide binary endpoints (H_0: non-clinically significant improvement in RR; H_1: clinically significant improvement in RR). Based on the known RR of approximately 50% (P_0 = 0.50) for comparable patient cohorts, it was decided that the study treatment needed to yield a RR of at least 70% (P_1 = 0.70) with a statistical power of 80% and a significance level of 0.05 to be considered as a "clinically significant" improved RR. The null hypothesis must be rejected for the study treatment to be considered being tested in a larger Phase III study.

11.2 Sample Size & Stage Design

For ethical and safety reasons, the Phase II study will be split into two stages. Stage 1 will be completed once the primary endpoint (tumour response 5-6 weeks post-explantation) for first 23 patients (not including those in the Phase Ib component) have been assessed. A minimum of 13 patients must been deemed as responsive to continue the study and proceed to Stage 2. If the number of responsive patients at the end of Stage 1 is less than 13, patient enrolment will be ceased, the study shall be terminated, and the null hypothesis cannot be rejected. Stage 2 is complete once the primary endpoint for a total of 37 patients (not including those in the Phase Ib component) has been assessed. A minimum of 24 patients must be deemed as responsive for the null hypothesis to be rejected.

12 Source Data/Documents

All investigators are required under regulatory compliance to allow access to all source data related to the trial for a period of 15 years after the study is closed out. This access is required to be given to the Sponsor's nominated monitor(s), and the Sponsor's appointed auditors, the HREC and the TGA or any other regulatory inspectors. All information from the source data must be transcribed, de-identified and verified before being sent to the Sponsor.

12.1 Record Retention

Study records and source data shall be retained by the Principal Investigator for a minimum period of 15 years after the completion of the clinical trial.

13 Quality Control and Quality Assurance

Data collected for this trial shall be handled in such a way that quality and integrity of the data are maintained throughout all stages of the study. The following points are to be followed:

1. Data should be compliant with ALCOA-C requirements of GCP (Attribuatable, Legible, Contemporaneous, Original, Accurate and Complete).
2. Data shall be recorded in blue or black ink ONLY

3. Dates shall be recorded as DD/MMM/YY or DD/MMM/YYYY where DD = day, MMM = month and YYYY = year
4. Recorded time as XX:XX in 24 hour time format.
5. Each page of data collection forms shall be marked with the subject's Study ID
6. All forms are to be signed and dated only by authorised study personnel
7. Incorrect entries must be corrected by the following:
   a. Draw a single line through the incorrect entry
   b. Write correct entry next to incorrect entry
   c. Sign (or initial) and date the correction
8. Where queries regarding recorded data arise, clarification shall be sought from the authorised person(s) responsible for recording the data
9. When data transcribed into electronic format, the following shall be noted:
   a. When transcribing numbers, the correct number of decimal places shall be maintained
   b. Once the data is entered, it shall be verified against source data and the source data retained.

Any deviation to the investigation plan must be recorded on the Deviation from Investigation Plan form. A justification shall be recorded for the deviation. The Sponsor and the Co-ordinating Investigator shall determine the relevance of each deviation, its impact on the results of the trial and subsequent action necessary. If required, the deviations will also be reported to the HREC by the investigator.

13.1 Procedure for CRF System

The clinical trial will be administered using a paper based data capture system; specifically Case Report Forms (CRFs). Data from source documents will be transcribed onto CRFs by an Investigator or a Clinical Trial Co-ordinator and signed by an Investigator to verify accuracy and completeness. The completed CRF will be verified by the Clinical Trial Monitor against the source records. Original signed copies of the CRF will be filed at the Sponsor's address and photocopies will be filed at the Site.

13.2 Monitoring Plan

The trial will be monitored by a sponsor appointed monitor. The monitor will perform tasks as defined by *CT-04 Monitoring Plan*.

13.3 Modification of Investigation Plan

The Investigator will not modify or alter this investigation plan without first obtaining the concurrence of the Sponsor. All modifications will be documented as a formal amendment. Approval by the Investigator's HREC must also be obtained prior to implementation of the change, with two exceptions:

1. When necessary to eliminate apparent immediate hazard to the subject; or
2. When the modification does not involve the subject's participation in the trial.

An amendment may also require modification of the informed consent form. The Investigator will provide the Sponsor with an approval letter from the HREC for the amendment once obtained, and revised informed consent form, if applicable, to the

Sponsor. An amendment must be in writing and it must be dated and signed by both the Sponsor and the Investigator. If necessary, the Sponsor will notify the TGA of the amendment by varying the Clinical Trial Notification.

13.4 Reporting Clinical Investigation Deviations

The Investigator is obligated to follow the investigation plan without departure from the requirements written in the investigation plan. If the Investigator deviates from the investigation plan, the Sponsor will make the determination as to whether the subject will continue in the study. The Sponsor also has the right to discontinue the subject for protocol violations. The HREC may also have to be contacted if safety to the subject or if the scientific soundness of the study is involved. All deviations must be documented in the CRFs and reported to the Sponsor as soon as possible. The sponsor then must ensure that the deviations from the investigation plan are reported by the Investigator to the HREC in accordance with their requirements.

14 Ethics and Regulatory Requirements

This study is to be conducted in accordance with the specifications of this investigation plan and in accordance with principles consistent with Declaration of Helsinki, Good Clinical Practice (GCP) for the ethical treatment of human subjects involved in medical research, and the Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95). Furthermore, the trial is conducted under the monitoring of the Human Research Ethics Committee (HREC) responsible for overseeing ethical research for the testing centres listed in Section 1.1 and shall comply with all regulatory requirements of the local authorities. The conduct of the trial shall also conform to the requirements of NHMRC National Statement on Ethical Conduct in Human Research (2007), and ISO 14155:2011 - Clinical investigation of medical devices for human subjects - Good clinical practice. No changes in the investigation plan will be implemented without the prior review and approval of the IRB, except where it may be necessary to eliminate an immediate hazard to a research subject. In such a case, the change will be reported to the IRB as soon as possible, according to IRB regulations. Additionally, all study products used in this study are manufactured, handled, and stored in accordance with applicable Good Manufacturing Practices (GMP) and the products provided for this study will be used only in accordance with this investigational plan.

14.1 Human Research Ethics Committee

The Principal Investigator will provide the HREC with all appropriate materials as required, including but not limited to the clinical investigation plan, informed consent form, and any advertising materials. The study will not be initiated until the HREC provides written approval of the aforementioned documents and until approval documents have been obtained by the Principal Investigator and Sponsor or Sponsor designee. The Investigator will not participate in the decision. If the Investigator is an HREC member, documentation must be provided indicating recusal from the approval process. Appropriate reports on the progress of this study by the Principal Investigator will be made to the HREC as required by local and applicable government regulations and in agreement with policy established by the Sponsor. The Investigator is required to maintain an accurate and complete record of all written correspondence to and received from the HREC, and must agree to share all such documents and reports with the Sponsor.

No changes from the final approved clinical investigation plan will be initiated without the HRECs prior written approval or favourable opinion of a written amendment, except when necessary to eliminate immediate hazards to the subjects or when the change involves only logistics or administration.

14.2 Investigator's Responsibilities

The Investigators are responsible for performing the study in full accordance with the clinical investigation plan and the current revision of the Declaration of Helsinki, ICH/CP, the Good Clinical Practice: Consolidated Guideline, approved by the ISO 14155:2011 and any applicable national and local laws and regulations. Information regarding any study centres participating in this study that cannot comply with these standards will be documented.

14.3 Subject Informed Consent Requirements

Written and oral information about the study in a language understandable by the subject will be given to all subjects or their legal representative by the Investigator and/or designee. Written informed consent will be obtained from each subject before any procedures or assessments that would not otherwise be required for the care of the subject are done and after the aims, methods, anticipated benefits, potential hazards, and insurance arrangements in force are explained and the subject has been given sufficient time to ask questions and consider participation in the study. It will also be explained to the subjects that they are free to refuse entry into the study and free to withdraw from the study at any time without prejudice to future treatment. It is permissible for a third person (e.g., a family member) to be present during the explanation of the study.

The written PICF is to be in compliance with the *National Statement on Ethical Conduct in Human Research (2007)* and the *CPMP/ICH Note for Guidance on Good Clinical Practice*. The Sponsor will approve the PICF and all amendments to the PICF prior to submission to the IRB/IEC. A copy of the PICF to be used will be submitted by the Investigator to the HREC for review and approval prior to the start of the study. Each study site must provide the Sponsor with an unsigned copy of HREC-approved PICF along with applicable documentation to support this approval. The original signed PICF is retained in the subject's study records, and a copy is provided to the subject. A second copy may be filed in the subject's medical record, if allowed by institutional policy.

15 Financing and Insurance

The AVAS is manufactured, and supplied by the Sponsor; AllVascular Pty Ltd. The Sponsor will apply for insurance once the trial has been approved by the institutional HREC and prior to the commencement of the study.

16 Publication Plan

Manuscripts and abstracts will be prepared by both the Investigator(s) and the Sponsor. Publication of the study results in scientific journals will be pursued after completion of the final study report and submission of the report to the appropriate

regulatory authorities. It is the intent of the Sponsor to publish or present the study results together with the other sites, unless specific permission is obtained in advance from the Sponsor to publish separate results. Co-authorship with the Sponsor will be discussed and mutually accepted upon submission of a manuscript or publication.

All information concerning the Sponsor's operations (such as patent applications, formulae, manufacturing processes, basic scientific data, or formulation information supplied to the Investigator and not previously published) is considered confidential and shall remain the sole property of the Sponsor. The Investigator(s) agrees not to use it for other purposes without written consent.

It is understood by the Investigator that the Sponsor will use the information developed in this clinical trial in connection with an application for the devices used in this study for their inclusion on the Prostheses List to the Australian Government Department of Health and Ageing. Therefore, this information may be disclosed as required to other Investigators or appropriate regulatory authorities, and publication may be delayed due to regulatory commitments. By agreeing to participate in this clinical trial, the Investigator understands that he/she has an obligation to provide the Sponsor with complete test results and all data developed during this trial.

16.1 Publication and Disclosure

Because this is a multi-centre trial, site and Investigator(s) shall not independently publish, publicly disclose, present or discuss any results of or information pertaining to site's and Investigator's activities conducted under this agreement until such a multi-centre publication is released under Sponsor's direction; provided, however, that if a publication is not released within eighteen (18) months after completion of analysis of all study data from all studies conducted within the multi-centre trial, site and Investigator shall have the right to publish the results of and information pertaining to site's and Investigator's activities conducted under this investigational plan and the clinical trial agreement. Site and Investigator agree to submit any proposed manuscript, presentation or other public disclosure regarding the study to Sponsor for review at least thirty (30) days prior to submitting such proposed manuscript to a publisher or delivering or making such presentation or other public disclosure to any third party. Within thirty (30) days of its receipt, Sponsor shall advise site and/or Investigator, as the case may be, in writing of any information contained therein that is confidential information (other than research results included in a proposed manuscript) or that may impair sponsor's ability to obtain patent protection. Sponsor shall have the right to require site and/or Investigator, as applicable, to remove specifically identified confidential information (but may not require removal of research results from a proposed manuscript) and/or to delay the proposed submission or delivery of the proposed manuscript or presentation, or other public disclosure, for an additional sixty (60) days to enable Sponsor to seek patent protection. Site and Investigator shall not publish, publicly disclose, present, or discuss any results of or information pertaining to site's and Investigator's activities prior to completion of the trial, even if the multicentre trial or the study is terminated before its completion and the final clinical study report is signed off, or with respect to any endpoints or analyses other than those specified in this investigational plan.

17 Conflicts of Interest

Professor Rodney Lane is one of the managing directors for the Sponsor which manufactures the investigational device for the study. He may be involved in initially implanting/explanting the device for the purposes of proctoring and training other co-investigators in the study.

Nyan Khin is a PhD candidate at Macquarie University and is the Project Manager for the Sponsor. Data collected from this study may be used for his doctorate thesis.

18 References

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[5] Lane RJ., Safety and feasibility of repeatable hepatic vascular isolation chemotherapy: a pilot study, Annals of Surgical Oncology; DOI 10.1245/s10434-016-5198-z, 2016.

19 Revision History

Version	Changes/Meeting/ Report Reference	Date	Author
1.0	Initial submission to MUH	09NOV2016	NK
1.1	AE procedure modified to suit ISO 14155	06FEB2017	NK
1.2	AE procedure integrated into protocol	27MAR2017	NK
1.3	Addressing MUH CRE feedback	05MAY2017	NK
2.0	PET not required (CT is sufficient), eviQ assessment omitted	07AUG2017	NK

APPENDIX H – NATIONAL TRIALS REGISTRY: PIb/II OIC TRIAL

Trial Review

VIEW TRIAL AT REGISTRATION VIEW HISTORY

< BACK

Trial registered on ANZCTR

Trial ID	ACTRN12617001268336p
Ethics application status	Submitted, not yet approved
Date submitted	24/08/2017
Date registered	1/09/2017
Date last updated	1/09/2017
Type of registration	Prospectively registered

Titles & IDs

Public title	Direct Isolation Chemotherapy for Liver Metastases
Scientific title	Phase Ib/II Study of Intra-Arterial Liver Isolation Chemotherapy in Patients with Hepatic Metastases from Colorectal Cancer
Secondary ID [1]	None
Universal Trial Number (UTN)	
Trial acronym	
Linked study record	

Health condition

Health condition(s) or problem(s) studied:

Liver Cancer

Condition category	Condition code
Cancer	Liver
Cancer	Bowel - Back passage (rectum) or large bowel (colon)
Cancer	Bowel - Anal

Intervention/exposure

Study type	Interventional
Description of intervention(s) / exposure	Description of Intervention/Exposure The treatment proposed in this clinical investigation plan is to repeatedly administer intra-arterial chemotherapy to hepatic metastases from colorectal cancer when the blood flow to and from the liver has been isolated via balloon catheters. The objective of this study is to evaluate the tumour response, progression-free survival, morbidity and mortality of repeated and isolated intra-arterial hepatic infusion of oxaliplatin compared with the gold standard 5-FU/leucovorin/oxaliplatin (FOLFOX) treatment. The treatment proposed in this study is based on the hypothesis that direct arterial infusion of chemotherapy to metastatic tumours of the liver whilst the blood flow to the organ is isolated could potentially yield benefits that cannot be achieved with existing treatment regimens. There are three treatment stages; implantation of a vascular access device (known as the AVAS), intra-arterial chemotherapy infusions, and explantation of the AVAS.

Implantation: the participant is admitted to hospital and the AVAS is surgically implanted under general anaesthetic. The AVAS is an implantable large bore cannula with one end that can be anastomosed directly onto a peripheral vessel and the opposite end exiting the patient's skin. The device can be opened to access the patient's vasculature when required and closed when the device is not in use. In accordance with the manufacturer's Instructions-For-Use (IFU), the AVAS will be implanted in the axillary artery (i.e. the upper pectoral area) or in the common femoral artery (upper thigh) by a trained vascular surgeon. The implantation procedure takes around 2 hours. After implantation, the participant is monitored overnight.

Intra-arterial chemotherapy infusions: the participant is admitted to the angiography suite and under general anaesthetic or conscious sedation, intra-arterial hepatic isolation chemotherapy infusion is administered by an interventional radiologist. The first infusion can be administered 2 days after device implantation and infusions are spread out over an 8-week period at a maximum such that the patient receives 5 to 7 infusions in total, has at least 2 full calendar days between each infusion, and there are no more than 2 infusions over any 7 consecutive days. Each infusion can take between 2-3 hours during the first few infusions but should only take 1-2 hours for the remaining infusions as the radiologist becomes familiarised with the patient's vascular anatomy. During the Phase Ib stage, the starting dose of the oxaliplatin infused will be 50mg/m^2 and this dose will be escalated by 5mg with each patient until an optimal dose is established. The optimal dose will be used for all patients enrolled during the Phase II stage.

Explantation: the final infusion session is followed by the device explantation immediately, or at a later time depending on the availability of operating rooms and the condition of the participant. The surgical removal of the device takes approximately 1-2 hours, the participant is monitored overnight and discharged the next day.

In addition, capecitabine will be administered orally as per standard care (1000 mg/m^2 twice daily in 2 week cycles) throughout the study treatment period (from enrolment to 4-5 weeks after the AVAS explantation) as a form of systemic disease management. The oncologist may modify the capecitabine dose/frequency based on the patient's response to the medication.

Intervention code [1]	Treatment: Drugs
Intervention code [2]	Treatment: Devices
Comparator / control treatment	No control group
Control group	Uncontrolled

Outcomes

Primary outcome [1]	Response rate of tumours in liver as assessed via CT scans (RECIST criteria)
Timepoint [1]	4-5 weeks after explantation of the AVAS
Secondary outcome [1]	Two-year survival assessed via follow-up visits.
Timepoint [1]	Quarterly for the first year and six-monthly for the second year after AVAS explantation,
Secondary outcome [2]	Overall progression free survival assessed via routine CT scans (RECIST criteria).
Timepoint [2]	As per standard of care schedule (typically quarterly scans) for 2 years after AVAS explantation.
Secondary outcome [3]	Liver progression-free-survival assessed via routine CT scans (RECIST criteria).
Timepoint [3]	As per standard of care schedule (typically quarterly scans) for 2 years after AVAS explantation.
Secondary outcome [4]	Systemic side effects to chemotherapy assessed by collection of adverse events using Common Terminology Criteria for Adverse Events 4.03.
Timepoint [4]	From enrolment until primary outcome is assessed (4-5 weeks after explanation of the AVAS).
Secondary outcome [5]	Organ isolation capability as determined by pressure readings on catheters during infusions procedures.
Timepoint [5]	At the completion of each infusion procedure.
Secondary outcome [6]	Rate of conversion to resection assessed via follow-up visits.
Timepoint [6]	Quarterly for the first year and six-monthly for the second year after AVAS explantation.
Secondary outcome [7]	Quality of life assessed via a combined questionnaire (EORTC QLQ-C30 and QLQ-LMC21).
Timepoint [7]	Prior enrolment, after 2 infusions, and 4-5 weeks after AVAS explantation.

Eligibility

Key inclusion criteria	1. Patients with hepatic metastases from histologically proven adenocarcinoma of the colon/rectum 2. Patients with limited extrahepatic metastases in the lung or lymph nodes (fewer than 5 nodules less than or equal to 1 cm diameter or a single nodule less than or equal to 1.7cm diameter in the lung, and lymph node involvement in a single anatomical area less than 2 cm diameter) 3. Patients in whom CT at screening has confirmed non-progressive disease, as per RECIST v1.1, after the first 6 cycles of FOLFOX ± bevacizumab 4. Patients who have had no more than 7 cycles of FOLFOX ± bevacizumab or other chemotherapy 5. Patients with Genotype: RAS mutant 6. Estimated time between last monoclonal antibody treatment and anticipated date of first infusion will be

	at least 6 weeks 7. Patients must be fit for repeated general anaesthesia 8. Patients with World Health Organization performance status < 3 9. Patients with haemoglobin greater than or equal to 100 g/L, ANC greater than or equal to 1.5×10^9/L, platelet count greater than or equal to 100×10^9/L 10. Patients with adequate renal function (serum creatinine less than 1.5 × Upper Limit of Normal) 11. Patients with adequate liver function (bilirubin 1.0 - 2.0 × Upper Limit of Normal, AST less than 5 × Upper Limit of Normal) 12. Patients with normal coagulation (INR less than 1.5) 13. Patient over 18 years of age 14. Patients who are able to understand the risks and benefits of the study and give written informed consent to participate 15. Patients who are available for follow-up at the study sites for the length of the study
Minimum age	18 Years
Maximum age	No limit
Gender	Both males and females
Can healthy volunteers participate?	No
Key exclusion criteria	1. CT-angiogram confirms unsuitable vascular anatomy 2. All lesions in the liver are not measurable (RECIST v1.1) in the CT scan prior to FOLFOX commencement 3. All lesions in the liver are not measurable (RECIST v1.1) in the CT scan between the 6th and 7th FOLFOX cycles 4. Evidence of ascites, cirrhosis, portal hypertension, main portal venous tumour involvement or main portal venous thrombosis 5. Allergies to contrast agents 6. Previous hypersensitivity or laryngo-pharyngeal dysaesthesia associated with oxaliplatin 7. Previous allergies associated with 5-FU or oxaliplatin 8. Grade 2 or higher peripheral neuropathy 9. Significant co-morbidities (i.e. life expectancy less than or equal to 3 months) 10. Pregnant or breastfeeding women, or women of child bearing potential and who are not on a reliable form of birth control 11. Patients who are enrolled or intend to participate in another clinical trial (of an investigational drug or device, new indication for an approved drug or device, or requirement of additional testing beyond standard clinical practice) during this clinical study 12. Patients with medical conditions that preclude the testing required by the protocol, or limit study participation

Study design

Purpose of the study	Treatment
Allocation to intervention	Non-randomised trial
Procedure for enrolling a subject and allocating the treatment (allocation concealment procedures)	Not applicable
Methods used to generate the sequence in which subjects will be randomised (sequence generation)	Not applicable
Masking / blinding	Open (masking not used)
Who is / are masked / blinded?	
Intervention assignment	Single group
Other design features	
Phase	Phase 1 / Phase 2
Type of endpoint(s)	Safety/efficacy
Statistical methods / analysis	The study is a PhaseIb/II study. The Phase Ib study is a dose escalation study to establish a safe and recommended dose that will be used in the Phase II stage of the study. This stage is comprised of an accelerated stage and a confirmation stage. During the accelerated stage, patients will be treated one-by-one and the dose escalated after each patient until dose limiting symptoms are observed. From here the confirmation stage is initiated and patients can be treated with the same dose in groups of 3 until the dose limit is confirmed. The last dose used prior to the observed dose limit will be the dose used for the Phase II stage of the study. The number of patients required for the Phase Ib stage of the study cannot be reliably estimated. The Phase II study will assess the study treatment against historical information of comparable populations to provide binary endpoints (H0: non-clinically significant improvement in response rate; H1: clinically significant improvement in response rate). Based on the known response rate of approximately 50% (P0 = 0.50) for comparable patient cohorts, it was decided that the study treatment needed to yield a

response rate of at least 70% (P1 = 0.70) with a statistical power of 80% and a significance level of 0.05 to be considered as a "clinically significant" improved response rate. The null hypothesis must be rejected for the study treatment to be considered successful.

Sample Size & Stage Design - For ethical and safety reasons, the Phase II study will be split into two stages. Stage 1 will be completed once the primary endpoint (tumour response 4-5 weeks post-explantation) for the first 23 patients (not including those in the Phase Ib component) have been assessed. A minimum of 13 patients must respond to the treatment for the study to continue. If the number of responsive patients at the end of Stage 1 is less than 13, patient enrolment will be ceased, the study shall be terminated, and the null hypothesis cannot be rejected. Stage 2 is complete once the primary endpoint for a total of 37 patients (not including those in the Phase Ib component) has been assessed. A minimum of 24 patients must respond for the null hypothesis to be rejected.

Recruitment

Recruitment status Not yet recruiting

Date of first participant enrolment

Anticipated 1/11/2017 **Actual**

Date of last participant enrolment

Anticipated 1/11/2018 **Actual**

Date of last data collection

Anticipated 1/11/2020 **Actual**

Sample size

Target 37 **Accrual to date** **Final**

Recruitment in Australia

Recruitment state(s) NSW

Recruitment hospital [1] Macquarie University Hospital - Macquarie Park

Recruitment postcode(s) [1] 2109 - Macquarie Park

Funding & Sponsors

Funding source category [1] Government body

Name [1] NSW Health Medical Device Fund

Address [1] Office for Health and Medical Research
73 Miller Street
North Sydney
NSW 2060

Country [1] Australia

Primary sponsor type Commercial sector/Industry

Name AllVascular Pty Ltd

Address Suite 13
130-134 Pacific Highway
St Leonards
NSW 2065

Country Australia

Secondary sponsor category [1] None

Name [1]

Address [1]

Country [1]

Ethics approval

Ethics application status Submitted, not yet approved

Ethics committee name [1] Macquarie University Human Research Ethics Committee (Medical Sciences)

Ethics committee address [1] Research Office
Research Hub, Building C5C East
Macquarie University
NSW 2109

Ethics committee country [1]	Australia
Date submitted for ethics approval [1]	09/08/2017
Approval date [1]	
Ethics approval number [1]	

Summary

Brief summary

The aim of this study is to assess the efficacy of delivering chemotherapy treatment through the arteries directly to the liver, bypassing the main blood supply throughout the body.

Who is it for?
You may be eligible for this study if you are aged over 18 years, have hepatic metastases from histologically proven adenocarcinoma of the colon/rectum, and have had some systemic chemotherapy.

Study details
Once enrolled, patients will have baseline scans and will have the AVAS device implanted. The patient will be admitted to hospital up to twice a week to be treated with the liver directed therapy until they have received 5-7 treatments of oxaliplatin, after which the device will be explanted. Oxaliplatin is approved in Australia as chemotherapy treatment for liver metastases from colorectal cancer (via IV infusion), but has not previously been approved when delivered to through the arteries to the liver using the AVAS study device. All patients will also receive Capecitabine from enrolment to 4-5 weeks after the AVAS explantation as a form of systemic disease management. The patient's tumour will be scanned 4-5 weeks after explant of the device, and the patient will be followed up for two years.

The treatment proposed in this study is based on the hypothesis that direct arterial infusion of chemotherapy to metastatic tumours of the liver whilst the blood flow to the organ is isolated could potentially yield benefits that cannot be achieved with existing treatment regimens.

Trial website	
Trial related presentations / publications	
Public notes	

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APPENDIX I – OTHER PUBLICATIONS THROUHGOUT CANDIDATURE

Journal of
Vascular Surgery
Venous and Lymphatic Disorders™

Popliteal vein compression syndrome pathophysiology and correlation with popliteal compartment pressures

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North Ryde, St. Leonards, and Killara, New South Wales, Australia

Objective: **The link between obesity and popliteal vein compression syndrome (PVCS) has been documented, but the pathophysiological mechanism is unclear. The aim of this study is to understand the pathogenesis of PVCS by assessing popliteal compartment pressures (PCP).**
Methods: **Twenty-three limbs (15 patients) were included. Eleven limbs were ultrasonically diagnosed with PVCS and underwent popliteal vein decompression. The control group consisted of 12 limbs with functional popliteal artery entrapment. Perioperatively, PCP measurements were obtained. The body mass index (BMI) was calculated and the clinical symptoms were documented (CEAP).**
Results: **The median BMI for the PVCS group was 32 (range, 26-45.8) compared with 28 (range, 19-31) for the control group ($P = .05$). In PVCS, the popliteal vein internal diameter was 9.4 mm (range, 8.0-20.0 mm) upon knee flexion, compared with 0 mm (range, 0.0-0.1 mm) upon knee extension. Upon knee flexion, there was no difference in pressure (PVCS 10.0 [range, 4-20] vs control 11.5 [range, 3-22]; $P = .95$). Upon knee extension, the median PCP in the PVCS group was 53 cm H_2O (range, 38-76 cm H_2O) compared with 26 cm H_2O (range, 17-43 cm H_2O) in the control group ($P < .001$).**
Conclusions: **PVCS is associated with high popliteal compartment pressures compared with controls. The pathophysiology of popliteal obstruction, in the absence of anatomical abnormalities, is related to an increase in popliteal compartment pressure while standing due an increase of the popliteal fat pad, related to high BMI. (J Vasc Surg: Venous and Lym Dis 2013;1:181-6.)**

Obesity and venous disease are commonly encountered together.[1-3] Popliteal vein compression (PVC) has been encountered both on ultrasound as well as venographically. However, a clear etiology has not been established, and compression may be physiological.[4-9] Knee extension has been shown to compress the popliteal vein (POPV) in up to 43% of patients undergoing surgery in the supine position, with body mass index (BMI) being a predictive factor. Furthermore, in this subgroup, popliteal vein compression syndrome (PVCS) has been implicated as an etiological factor for deep venous thrombosis (DVT).[10-12] The recent comprehensive review on popliteal entrapment by Sinha et al shows there is a lack of prospective data, especially for venous compression, and it does not propose a pathophysiological mechanism.[13] PVCS typically presents with symptoms and signs typical of chronic venous hypertension (CVH) but without evidence of venous reflux, venous obstruction, or primary calf pump dysfunction. Alternatively, there may be a gross mismatch between standard objective noninvasive studies and the clinical picture. These patients are often of large frame or obese.[14] Another interesting problem is the group of patients who have received appropriate treatment for superficial venous disease only to return with acceleration of the venous disease process. These patients have usually had a faultlessly performed surgical stripping procedure or other ablative procedure with apparent immediate success. They then re-present with progression of their symptoms that are often worse than pretreatment, in some cases to the point of ulceration. These frustrating problems are reflected in the literature. Tong and Royle have shown that 30% of patients with ostensibly venous edema have no functional evidence of venous incompetence or obstruction on standard testing procedures.[15] Nicolaides suggested that there is often a discrepancy between clinical findings and the results of exhaustive investigations.[16]

Despite specific ultrasonic investigations targeted to PVCS, the diagnosis remains troublesome and is often delayed. An earlier study showed there is a correlation between PVCS and obesity. This study shows that the POPV normalizes following popliteal fasciotomy and popliteal fat pad removal. The preoperative internal diameters were 11.7 mm (±5 mm) with the knee flexed, compared with 1.0 mm (±2 mm) upon knee locking. Following surgical intervention, these patients showed no compression of the POPV on knee locking as determined by ultrasonography (9.0 ± 1.5 mm) and venous symptoms

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The editors and reviewers of this article have no relevant financial relationships to disclose per the Journal policy that requires reviewers to decline review of any manuscript for which they may have a conflict of interest.
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improved.[14] A common finding during surgery in these patients is a surplus of adipose tissue in the popliteal compartment. This led to the hypothesis of an increased pressure due to increased volume causing PVC, specifically upon knee locking when the popliteal fossa space is diminished and also emphasises the popliteal fasciotomy to be an integral part of the procedure. There is extensive research on fasciotomies in the relief of high compartmental pressures, although not directly in the popliteal fossa.[17] The aim of this study is to use direct pressure measurements of the popliteal compartment as a means to understanding the pathogenesis of PVCS. In addition, the study aims to relate ultrasonically determined popliteal cross-sectional areas with and without knee flexion to popliteal compartment pressures, BMI, and venous disease as independent variables.

METHODS

Patients. A prospective cohort study was designed to differentiate between PCP in PVCS compared with controls. Twenty-three limbs (in 15 patients) were included. Eleven limbs had sonographic evidence of PVCS, which was defined as greater than 90% reduction in the maximum internal diameter (ID) of the POPV with knee extension compared with the knee flexed. The typical presentation of PVCS with swelling, restless legs, lipodermatosclerosis, and ulcers with very mild varicose veins or deep venous symptomatology was present in all cases (C6 = 5, C5 = 2, C3 = 2, C2 = 2). Due to the presence of superficial disease, all patients' etiology was classified as primary disease (Ep n = 11). One patient showed deep venous insufficiency at the level of the femoral vein but not the POPV (Ad n = 1). Eight patients had incompetent perforators (Ap n = 8), and nine patients had superficial incompetence (As n = 9). All patients were classified as having obstruction as the main pathophysiologic mechanism (Po n = 11). Eight limbs in the PVCS group (73%) had previously underwent high ligation and stripping of the greater saphenous vein. The control group consisted of 12 consecutive limbs with angiographically proven functional popliteal artery entrapment syndrome without sonographic PVC or venous symptoms. Specifically, none of the patients in the control group showed POPV compression at rest and with full knee extension. Controls underwent compartment pressure measurements to exclude chronic exertional compartment syndrome.[17] The full diagnostic algorithm for PVCS is shown in Fig 1. The diagnostic algorithm for functional popliteal entrapment has been previously published.[18] Pressure measurements in all cases were obtained with full muscle relaxation. The clinical symptoms and signs were recorded according to international venous protocol.[19] The BMI of each group was calculated. After failed conservative treatment (weight loss, compression hosiery, and avoidance of prolonged standing if possible), all limbs (n = 23) underwent open popliteal decompression. The popliteal compartment pressures were measured in the prone position.

Color duplex ultrasound. Ultrasound imaging of the lower limb was performed using a GE Logic 700 Expert Series and a GE Logic 9 (General Electric Medical Systems, Milwaukee, Wisc) with wideband 5-10 and 6-13 MHz probes. During the exam, continuous care was taken not

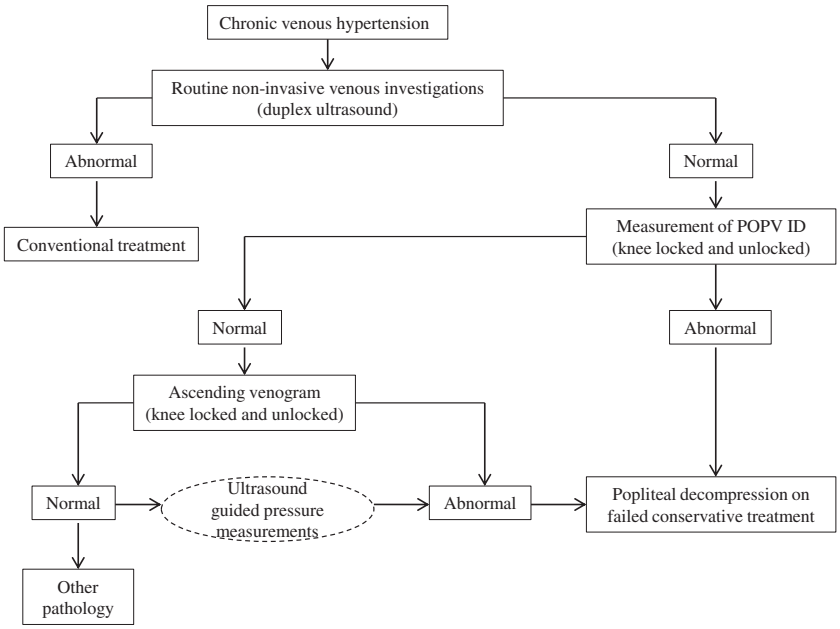

Fig 1. Diagnostic algorithm. Algorithm used in the management of patients presenting with suspected popliteal vein compression syndrome (PVCS). *POPV ID*, Popliteal vein internal diameter.

to compress the vein using the probe. The initial examination entailed a complete assessment of the deep and superficial veins of the lower limb.

The popliteal region was interrogated with brightness-mode (B-mode) to determine vascular and nonvascular anatomy and pathology. Specific examinations included measurements of the maximum ID of the POPV with knee flexion and knee extension (locking). The contralateral limb was similarly examined. A detailed description of the examinations was previously published.[14] Fig 2 shows a color duplex ultrasonic imaging of the popliteal compartment (a) at rest and (b) with knee extension. In this patient, full knee extension led to total compression of the POPV.

Popliteal compartment pressures. Pressures were measured in the popliteal compartment using a standard pressure transducer system (I.T.C, L 420). After skin incision, with the fascia still intact, a 15-gauge needle was introduced. The pressure was measured after skin incision in order to avoid puncturing the neurovascular bundle, and care was taken not to introduce the needle intravenously. In some of the very obese patients, it is uncertain where the tip of the needle is, if introduced percutaneously, and for the study purpose, it is important to be in the popliteal fossa. The pressure was then zeroed, and three separate measurements were performed for both knee flexion and knee extension. The mean of the three measurements was calculated and used for statistical analysis.

Surgical technique. A standard posterior popliteal approach using a lazy "s" skin or a transverse skin crease incision was used in all limbs. After pressure measurements, the popliteal fascia was divided over the medial head of the gastrocnemius (which was often hypertrophied), avoiding the short saphenous vein and sural nerve. The POPV was dissected and gently mobilized. During exploration of the popliteal fossa, functional POPV compression was excluded by hyperextension testing. In case of PVCS, the popliteal compartment was debulked of adipose tissue, and a posterior fasciotomy was performed extending two-thirds down the calf. The popliteal fascia was not resutured prior to closure of the skin. No wound drainage was used. Firm compression in the form of a self-adherent bandage was continued for 1 week followed by below-knee compression hosiery (class II) until the symptoms subsided.

The same approach was used in the control group. In these patients, both the tendon and muscle belly of the medial head of the gastrocnemial muscle were divided. A more detailed description of the surgical technique for arterial entrapment has previously been published.[18]

Statistical analysis. Data analysis was performed using SPSS statistics 17.0 (SPSS Inc, Chicago, Ill). Continuous variables are described as median and full range. Differences between continuous variables were tested using independent *t*-test and paired *t*-test or the Wilcoxon rank-sum test (if $n < 30$). Categorical variables were tested using Pearson χ^2 test or the Fisher exact test (if $n < 5$). Intervariable correlations were tested using logistical regression analysis. Two-sided *P* values $<.05$ were considered significant.

RESULTS

A total of 23 limbs (PVCS $n = 11$, control $n = 12$) in 15 patients underwent popliteal decompression. There is a significant difference in age between the PVCS and the control group ($P \leq .001$). Patients in the PVCS group have a higher BMI compared with the controls ($P = .05$). The demographics are shown in the Table.

A total of eight (73%) limbs in our study group had concomitant incompetent perforators as shown by ultrasonography.

The pressure during flexion does not differ between the PVCS and control group. Upon extension, there is a significant difference in pressure, with the pressure in the PVCS group being as high as 76 cm H_2O. The highest change in pressure (ΔP), which is the added pressure, measured was 60 cm H_2O. The POPV is routinely investigated in our

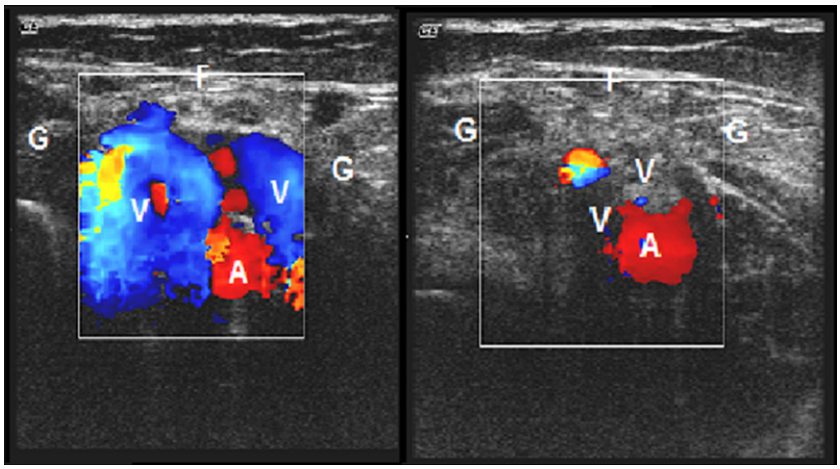

Fig 2. Ultrasound. Transverse color duplex imaging of the contents of the popliteal fossa with the popliteal artery (*A*) and the popliteal vein (*V*) and the gastrocnemial muscle (*G*) at knee flexion **(left)** and with knee extension **(right)**. Upon knee extension, there is a complete compression of the popliteal vein.

Table. Demographics, ultrasound findings, and pressure measurements

	PVCS (n = 11)	*Control (n = 12)*	P
Age, years (range)	54 (41-66)	25 (15-41)	<.05
BMI (range)	32 (26-45.8)	28 (19-31)	.05
C classification[a]			
C2	n = 2 (18%)		
C3	n = 2 (18%)		
C5	n = 2 (18%)		
C6	n = 5 (45%)		
Previous treatment			
Superficial venous incompetence	n = 8 (73%)		
POPV ID			
Knee flexed, mm (range)	9.4 (8.0-20.0)	[b]	
Knee locked, mm (range)	0 (0.0-0.1)	[b]	
PCP			
Knee flexed, mm (range)	10 (4-20)	11.5 (3-22)	.95
Knee locked, mm (range)	53 (38-76)	26 (17-43)	<.05
ΔP (range)	44 (29-60)	14 (5-32)	<.05

BMI, Body mass index; *PCP,* popliteal compartment pressure (cm H_2O); *POPV ID,* popliteal vein internal diameter on ultrasound in mm; *PVCS,* popliteal vein compression syndrome.
[a]For the full CEAP, see the Methods section.
[b]Specific ultrasound showed no change in diameter.

practice but only recorded for the control group if there was a difference in vein size (knee flexion vs knee extension). For the control group, only one patient showed a change in POPV ID (7.4 mm on knee flexion and 7.0 mm knee extension). In all others, there was no change in vein size. The Table shows the POPV ID as well as direct popliteal compartment pressure measurements. Logistical regression analysis shows a positive association between BMI and popliteal compartment pressures (r = 0.345).

The patients presenting with ulcers (C6, n = 5) responded well to the surgical intervention with healing of the ulcers. Functional outcome, clinical score, pain, edema, pigmentation, lipodermatosclerosis, disease score, and changes on ultrasound investigations have been previously published in a larger series.[14]

One patient in the study presented with venous symptoms and PVC but was not obese (BMI = 20.9). In this case, crowding of the popliteal compartment was caused by a large Baker's cyst. In another patient, measurements were performed after a previously performed popliteal decompression and fasciotomy for PVCS. This patient now presented with incompetence of the lesser saphenous vein. As expected, in this patient, there was no difference in pressure upon knee flexion and extension (both 20 cm H_2O upon flexion and extension). Both of these cases were excluded from the final statistical analysis.

DISCUSSION

The results show ultrasonically determined POPV compression is associated with increased popliteal fossa pressures with knee extension. A larger study from the same institution has shown that in patients with PVCS, surgical intervention significantly improves venous symptoms and POPV compression as determined by ultrasound. Furthermore, there is a positive association with cross-sectional areas, obesity, venous symptoms and signs, and PVCS.[9,14] This is confirmed in this small study with all ulcers having healed.

In this study, the control group consisted of patients undergoing popliteal decompression for functional arterial popliteal entrapment. These patients were selected to clarify the current confusion in the literature between arterial and venous entrapment.[13] Specifically, venous compression has been described together with arterial entrapment and is thought to be physiological.[4] In this study, none of the patients in the control group displayed any venous symptoms. Nor was there venous compression as determined by ultrasound upon knee extension (standing upright), at which time the muscles are relaxed. Therefore, it was deemed appropriate to use them as controls, even though they are younger and had a lower BMI.

Pathophysiology. In the average patient, the hydrostatic column at the level of the POPV is approximately 59 mm Hg when standing passively (no muscle pump action). The respiratory cycle generates a negative pressure of up to -5 mm Hg. This results in the POPV pressure of 54 mm Hg in the 174-cm human and a considerably lower pressure in shorter persons. Pressures up to 76 cm H_2O, which correlates with 56 mm Hg, were detected in this series with complete obstruction of the POPV.[20]

Stasis due to hydrostatic pressure also occurs in the healthy population. But in contrast, in patients with PVCS in the standing position at which arterial inflow is unimpeded, venous volume continues to rise, and deep venous pressure also rises due to compression of the POPV. With PVCS, when the knee joint is locked, the medial and lateral heads of the gastrocnemius muscles in the relaxed state increase their muscle bulk. Secondly, obese patients have an increase in adipose tissue and, in most cases, hypertrophied calf muscles. In these patients, an increased pressure arises due to the diffuse transmission of pressure throughout the adipose tissue that is semi-liquid at body temperature (Pascal's Law). If patients with PVCS are exposed to prolonged standing or maintain postures that require the knee to remain in the locked position, symptoms and signs of CVH may develop. More specific, the greater volume of flow through to the superficial system via perforators produces dilation of existing venous trunks. As a result, some patients develop ascending venous incompetence, which may also be associated with perforator incompetence. This is confirmed by the high incidence of perforator incompetence in our study population (n = 8; 73%). There is no doubt two-way flow can occur through perforators. This can be seen ultrasonically. The perforators, however, are usually only indirectly connected to the popliteal fossa. The activation of the muscle pump, however, immediately decreases this pressure. In addition, high venous pressure can lead to axial venous

incompetence from the point of obstruction inferiorly, an observation also made by Raju et al.[4] Furthermore, in case of incompetent great or small saphenous systems, treatment by means of perfectly performed ablative procedures such as laser or stripping unwittingly accelerates CVH by removing the major collateral pathway.[14]

Ambulatory pressure measurements have been performed in order to select patients in which pathology was present with moderate success but have not gained wide acceptance, in part because this involves extensive invasive pressure measurements both at the level of the POPV as well as the ankle during ambulation. Also, the relation between a drop in pressure at the ankle level and the POPV pressure drop (or rise) is influenced by numerous factors and a clear correlation is debatable.[21]

Raju has suggested the diagnosis is by exclusion. Careful history and specific examinations, especially targeted ultrasonography, makes PVCS a diagnosable disease. Especially, PVCS should be considered if the patient presents after surgical treatment for incompetent superficial venous systems with swelling or worsening symptoms. In the absence of other pathology, direct pressure measurements might help to identify those patients in which POPV compression is part of the syndrome.

Based on this study sample, the finding of increased popliteal fossa pressure adds to the understanding of the pathophysiology of PVCS. Although the study shows pressures to be significantly higher compared with controls, the study design does not compare popliteal compartment pressures in otherwise asymptomatic obese patients to those patients suffering from PVCS. From an ethical point of view, performing invasive measurements in otherwise healthy patients is troublesome. Given the outcome of this study, a subsequent study comparing patients with PVCS to otherwise healthy obese patients will address this.

Possible ramifications of PVCS. Standard compression hosiery achieves venous return by external compression of the lower and upper leg. Given that the pressure of the popliteal compartment can be as high as 76 cm H_2O or 56 mm Hg, theoretically even class IV hosiery (pressure up to 50 mm Hg) may not be sufficient. Especially when combined with poor patient compliance for compression stockings, this may account for the poor treatment outcomes in these patients.[22]

Swelling following recurrent groin dissection for recurrent varicose veins has often been attributed to interruption of the lymphatics. An alternative suggestion is that the underlying problem may be the POPV obstruction, in which case the repeat surgery often removes the collateral flow channels.

During open below-knee phlebectomy, the surgeon is often confronted by surprisingly high venous pressures (bleeding). The usual explanation is the anesthetic positive pressure or respiration pressure and the abdominal fat pad in the obese. An alternative suggestion is PVCS. As well as elevating the feet, bending the knee may be appropriate.

In addition to standardized use of anti-thrombolytic agents during operative procedures, there has been an increase in the use of calf and thigh compression systems for the prevention of deep venous thrombosis and pulmonary embolism. These devices typically deliver pressures of 30 to 50 mm Hg at the calf level. In selected cases, these pressures may not be sufficient to overcome the popliteal compartment pressure.[23,24]

DVT is more common in obese patients, but a clear etiology has not been established.[25] In addition, orthopedic procedures and especially knee replacement surgery are associated with a high incidence of DVT.[26] Numerous risk factors have been proposed, among which is obesity. Also, in patients undergoing surgery in the supine position under general anesthesia, the incidence of PVC reported is as high as 64%. A recent study by Huber and colleagues showed a correlation between PVS and the risk of development of DVT.[27] Postoperatively, an increase in popliteal compartment volume could be caused by edema and hematoma, which in obese patients adds to a higher compartment pressure. PVCS, whether postoperative and transient or chronic in the obese, could be the final common pathway.

CONCLUSIONS

PVCS is associated with high popliteal compartment pressures compared with controls. In selected patients, standard compression hosiery may not be sufficient. The probable pathophysiology of popliteal obstruction, in the absence of anatomical abnormalities, is related to an increase in popliteal compartment pressure while standing due to an increase of the popliteal fat pad and hypertrophied muscles. Surgical decompression should be considered in selected patients depending on the severity of clinical symptoms.

AUTHOR CONTRIBUTIONS

Conception and design: MD, RL, NK
Analysis and interpretation: MD, RL
Data collection: MD, RL, ST
Writing the article: MD, RL
Critical revision of the article: MD, RL, ST, NK
Final approval of the article: MD, RL, ST, NK
Statistical analysis: MD, RL
Obtained funding: Not applicable
Overall responsibility: RJ

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Endovenous Valve Transfer for Chronic Deep Venous Insufficiency

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WHAT THIS PAPER ADDS

This paper offers a method for endovenous valve transfer for chronic deep venous insufficiency; a specific stent design to optimise and simplify the technique; and an assessment of patency, competence, safety, and efficacy in 16 sheep and a small human pilot study. It also highlights the challenges of venous valve transfer in chronic deep venous insufficiency.

Objectives: The aims of the study were to test the safety and efficacy of a custom-made endovenous valve transfer stent, and delivery system in animals and humans.

Methods: The internal jugular veins of 16 sheep, weighing 45—55 kg, were used. A segment of vein with venous valve was enclosed circumferentially with a barbed stent. This segment from the internal jugular vein was introduced and deployed remotely into the contralateral internal jugular vein. Harvesting occurred acutely (one sheep) and at 1, 3, and 6 months postoperatively (five sheep per group). Operative competence testing, histological and scanning electron microscopic (SEM) examinations were performed. Four males with recalcitrant ulcers (mean age of 22 years) had axillary veins transferred from the popliteal vein and were followed for a mean of 3.8 years.

Results: At harvest, all the transferred valves were competent, with no evidence of thrombosis, tilting, endoleak, or migration with normal macroscopic and SEM findings. Although only 50% of the ulcers completely healed in humans, the remainder were improved, with all valves being competent and patent.

Conclusions: Endovenous valve transfer with a custom-made circumferential stent produces near perfect results in sheep and encouraging results in a small pilot study.

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INTRODUCTION

Chronic deep venous insufficiency (CDVI) imposes an enormous clinical and financial burden on the community,[1,2] with current treatment modalities being unsatisfactory.[3] The syndrome relates to venous valve dysfunction or obstruction leading to venous reflux, outflow congestion, and venous hypertension.[4] It is well known that, in the long term, this may lead to varicose veins, chronic venous ulcers, and other related conditions. For patients with persistent deep venous symptoms in which other treatment modalities (compression therapy, ablative procedures) are exhausted, venous valves repaired directly or by venous valve transposition in the deep system have produced encouraging results in the short and long term.[5—12] However, these procedures require considerable surgical skill, are not commonly performed, and may be associated with potentially serious complications, specifically deep venous thrombosis and pulmonary embolism.[12] Additionally, there are also problems related to valve ring dilatation in the transposed vein and subsequent incompetence in the long term.[6] A venous valve delivered remotely and perhaps percutaneously may alleviate some of these logistical difficulties, hence the development of artificial (polymer, biosynthetic, and autogenous) venous valves with promising results in animals, although thrombosis (5—80%) and cusp thickening related to the use of a foreign body are to be addressed.[13—17]

An autologous endovenous valve transfer stent (EVTS) would appear to be a logical improvement, taking advantage of available vascular stent developments and deployment technology. There are encouraging results of stented autologous venous valve transfers in both goats[18] and dogs.[19—21] The present study uses a custom design in which a stent is placed around a native vein with a functional valve. The stent, with mounted valve, is then transferred

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and placed endovenously at the recipient site. This is performed using standard surgical techniques and readily available endovascular equipment. The results of this venous valve transfer system in animals and a small pilot study in humans are presented.

METHODS

Subjects

For the animal study, 16 sheep weighing between 45 to 55 kg were included. For the human pilot study, four men were included. The demographics are shown in Table 1. The CEAP classification was C_6 E_S A_D P_{RO} $n = 3$ and C_6 E_P A_D P_{RO} $n = 1$. The investigative protocols in both animals (NSCCH1039) and humans (Protocol EVTS AV005 [Clinical Trial Notification 0509-174M]) were approved by the local institutional review board of the Northern Sydney Central Coast Health service. The animal trial was conducted in accordance with good laboratory practice and international guidelines in animal research, and the human trials were performed in accordance with the ethical principles as described in the Declaration of Helsinki. Written consent was obtained from all patients in the human pilot trial.

Materials

The EVTS (9 × 24 mm, including barbs) (Fig. 1a) was made by AllVascular (St Leonards, NSW, Australia) and the introducing system produced by Cook (Bloomington, IN, USA). There are very specific characteristics of a venous valve transfer stent that would separate it from commercially available devices designed to expand a lumen rather than act as a carrier of a valve. The optimal design encompasses an exo-stent with a variable diameter, i.e., placed circumferentially around the valve-containing vein segment, usually in the axilla or contralateral profunda vein. The venous connections to the stent would need to be fluid sealed to prevent endoleak, and the stent itself have a minimal blood interface to minimise thrombogenicity as the barbs have blood contact. Additionally, the device, as well as being crimpable to minimise the diameter profile of the introductory system, would optimally be expandable to maximise adhesion to the recipient wall.

For optimal wall fixation, fine barbs (3 mm in length) were designed to penetrate the donor wall, as well as to impinge on the recipient wall. These also could be used as an easy way to connect the ends of the venous valve-containing segment onto the stent. In addition, the body of the stent had a zigzag pattern, which creates high frictional resistance between the external surface of the stent and the recipient vein wall. Furthermore, in the assessment of the recipient diameter, a 2-mm expansion coefficient was considered optimal, i.e., if the axillary vein required a 10-mm stent, an 8-mm recipient site was selected.

The length of the EVTS was 20 mm to avoid tilting within the recipient vein and to minimise endoleak, i.e., an artificial passage between the donor and recipient vein. In the clinical situation the device needs to be small enough to avoid crossing major tributaries, again precipitating endoleak, but also avoiding haemodynamic disturbances.

Animal pre-surgical protocol

Two portable, battery-powered duplex scanners (Sonosite, Bothell, WA, USA) and Terason 2000 (Terason Ultrasound, Burlington, MA, USA) were used to identify venous valves in the jugular system. A completely competent segment or a segment with very minimal reflux were acceptable.

Animal surgical procedure

The sheep were anaesthetised with intravenous thiopentone, following which they were intubated and ventilated. Both internal jugular veins were isolated and the valves identified (Fig. 1b). A nitinol stent was placed around the competent valve (Fig. 1c) and the length of the vein fixed with sutures to prevent longitudinal shortening. Further, 5.0 Prolene sutures were used to adjust the diameter of the EVTS. The vein was then harvested and, similarly, sutures were used to join the end of the EVTS to the contained vein segment. The EVTS and the venous valve segment (Fig. 1d) were then placed into the flared end of the introducing system and a pusher used to position the stented valve at the front end of the introducing system. After controlling the recipient vein with Vessiloops, a venotomy allowed remote deployment of the EVTS and valve segment. Competence was tested by leaving the venotomy open. The absence of back flow when the distal Vessiloop was released indicated competence (Fig. 2). Postoperatively, the sheep were returned to their pen and Clexane 40 mg (Sanofi-Avantis, Macquarie Park, NSW, Australia) given subcutaneously daily for 1 week. The veins

Table 1. Human patient results.

Initials	Sex	Age (y)	Previous treatment (A,B,C,D,E,F)[a]	Primary/secondary (1/2)[b]	Ulcer time (y)	Ulcer size (cm^2)	Postoperative Patent	Postoperative Competent	Ulcer follow up time (y)	Ulcer size (cm^2)
JM	M	67	ABCDEF	2	34	45	Yes	Yes	2.3	18
JG	M	75	ABCDEF	2	25	16	Yes	Yes	4	4
GW	M	46	ABCE	1	15	16	Yes	Yes	4.8	0
KP	M	58	ABCEF	2	9	Widespread superficial	Yes	Yes	4.2	0

Note. M = male.

[a] A = compression; B = stripping; C = perforator ligation; D = skin grafting; E = sclerotherapy; F = hyperbaric oxygen.

[b] 1 = primary venous disease; 2 = secondary venous disease.

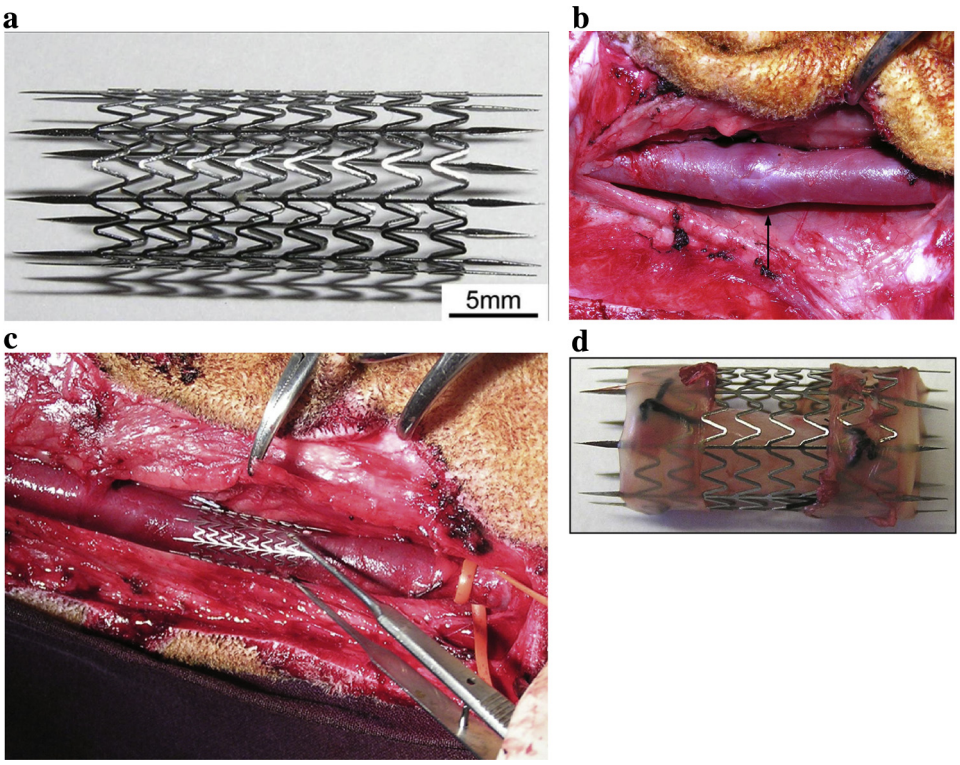

Figure 1. (a) The basic design of a venous valve transfer stent. The sharp barbs at each end penetrate the donor wall and impinge the recipient wall. (b) Identification of venous valves via external appearance with competence tested via the milking technique. (c) Stent placement around the valve. (d) Stent encasing a vein containing a competent valve.

were then harvested acutely in one sheep, and five sheep at 1 month, 3 months, and 6 months respectively. At these times the findings were recorded.

Human protocol

A pilot study in four humans was conducted to illustrate the modification of the animal method to humans. All patients had a long history of chronic leg ulceration due to CDVI. All standard treatment modalities had been exhausted (Table 1) and antibiotics were used if appropriate according to sensitivity. The pre-operative assessment included bacteriological swabs of the active ulcers and duplex ultrasound (Logic 9G; GE, Milwaukee, WI, USA) of the upper limbs (potential competent donor valves) and affected lower limbs (recipient site). The diameters of the donor valves were recorded and suitable open popliteal venous segments were identified. The venous function was assessed with infrared photoplethysmographs[22] with the waveform during exercise indicative of calf muscle pump. Ascending venography in the arms further correlates suitable valves with ascending and descending venography in the affected limb to further assess reflux and potential recipient sites. The optimal site is a long, smooth-walled popliteal venous segment without significant tributaries or entering collaterals. Under general anaesthetic the axillary veins containing the valve were externally stented and tested to be competent. The axillary veins were then ligated. The above-knee popliteal vein was dissected and controlled with Vessiloops, and through a small longitudinal incision in the above-knee popliteal the lower popliteal and tibial systems were manually dilated (using dilators) and the EVTS deployed proximal to the tibio peroneal trunk (approximately 15 cm from venotomy). In one limb an operative descending venogram (Fig. 3) demonstrated a small endoleak, as well as a patent and competent valve. All patients received anticoagulation therapy consisting of heparin and postoperative Warfarin starting on day 1 with a target range of 2.5—3.5. Daily Clexane 1.5 mg/kg was given until the international normalised ratio was sufficient.

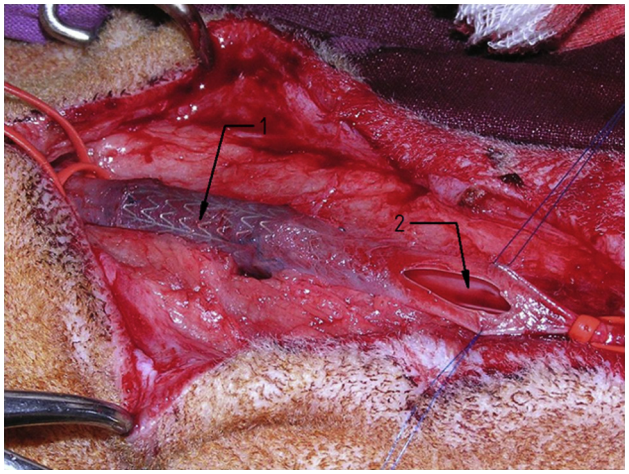

Figure 2. Testing the competence of the transferred valve (1) shows no backbleeding through the insertion site (2).

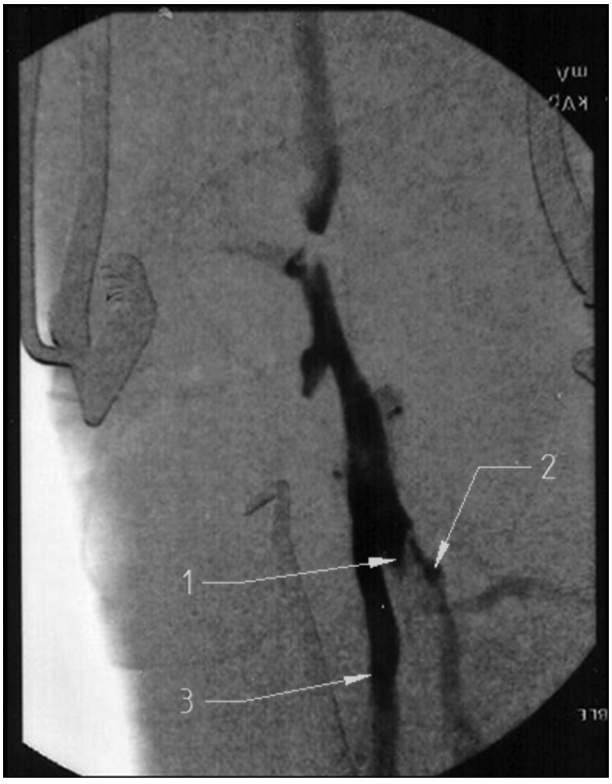

Figure 3. Operative descending venogram showing a patent and competent venous valve (1) with slight bulging and prolapse of the valve cusps. There is a type 1 venous endoleak (2) due to a tributary entering alongside the stent. There is a duplicated and insufficient popliteal vein (3) running alongside the stented vein.

Selection of deployment site

The aim of deployment site selection was to create a competent segment as close as feasible to the ulceration area without obstructing major tributaries. Both venography and duplex may fail to define tributary entry, which is often related to multiple smaller collaterals induced by proximal venous obstruction and hence the possibility of a minor endoleak,

End points

Animal study. An intra-operative and postoperative assessment were made of patency, competence, thrombosis, tilting of the valve, migration, endoleak, fixation, stent visibility, and untoward effects of the remote access venotomy. This had been 1.5-cm long and closed by direct suture. Scanning electron microscopy (SEM) and light microscopy were performed on a total of seven specimens—one at 1 month, two at 2 months, and four at 6 months.

Human study. End points included postoperative ultrasonic assessment of valve patency and competency. The clinical follow-up times were immediate postoperative, at 1 month, 3 months, and 6 months, and long term (>1 year). Ultrasonic examination was performed by an experienced vascular sonographer.

RESULTS

Animal study

All 16 sheep specimens had no macroscopic evidence of thrombosis, EVTS migration, or tilting, and no stents were visible (i.e., no nitinol protruding through the lumen). The pathology examination of multiple sections showed microscopically that there was no evidence of thrombosis, or inflammatory changes or evidence of intimal hyperplasia or cellular infiltrate (Fig. 4). The SEM showed no thrombosis, cusp changes, and normal endothelial cellular characteristics (Fig. 5).

Human study

On average, the procedure time was 2.5 hours. All human patients showed a decrease in ulcer size, with complete healing of the ulcer in two patients (50%). All valves remained patent and competent during follow up. Two valves showed signs of a “venous endoleak” due to a large tributary entering alongside the stented valve at operation, but were not detectable at any time postoperatively on duplex. The tributaries remained patent and there was no evidence of peri-graft haematoma. The results of the human pilot study are shown in Tables 1 and 2.

DISCUSSION

The results of both animal and initial human studies show that venous valves can be transferred from one site to another endovenously with safety. The transferred valves are durable with patency and competency maintained for up to 6 months in sheep and up to 4.8 years in humans. Fifty per cent of all ulcers completely healed with a 67% area reduction in the remainder. These experiments confirm similar experiments in goats and dogs using standard stents.[18,21,23] The basic techniques differ little from

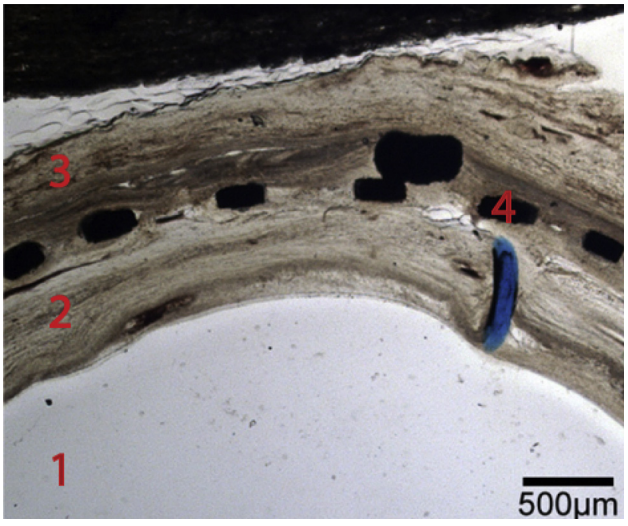

Figure 4. Light microscopic sections at 6 months of the sheep donor valve showing the vein lumen (1), transferred valve with endothelium (2), recipient wall with endothelium not discernible (3), and the stent struts (4).

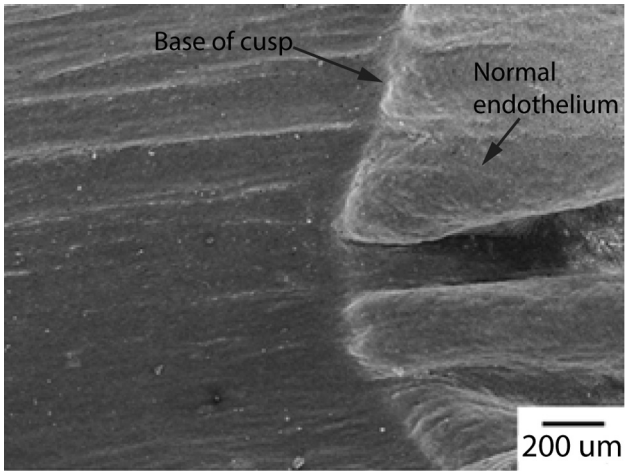

Figure 5. Scanning elctromicrographs of the endothelium showing normal healthy endothelium of the recipient valve.

standard endovascular concepts. However, the protocol was developed to test modification of standard stent morphology and function to facilitate venous valve harvesting and transfer.

Alternative approaches

There is ample experimental and clinical evidence that creating deep venous valvular competence significantly improves the sequelae of chronic venous hypertension.[5,6,10,12] A novel technique described by Maleti creates a neovalve by dissecting the vein wall to obtain flaps. Although a venotomy is required the technique offers an alternative in extensively affected post-thrombotic veins. The results are promising.[24] This technique may be possible to be used in unison with venous valve transfer as one competent valve transfer produced complete healing in 50% of limbs.

The greatest challenge for the post-phlebitic limb is to provide a minimally invasive procedure of widespread applicability and to avoid long-term deterioration following free valve transfer. Specifically, Taheri et al.[25] note a progressive dilatation of the valve ring with deterioration of valve function following brachial valve transfer to the femoral vein. Bry et al.[11] transferred axillary valves to the popliteal for better size matching as it was thought that the popliteal vein was the gatekeeper to the calf. Hence, the logic of this protocol of a stented transferred valve to the popliteal fossa.

The advantages of biosynthetic valves comprised of a stainless steel stent and barbs with a sheet of small intestinal submucosa introduced percutaneously[14] under local anaesthetic have wide applicability and, theoretically, it may be possible to implant an unlimited number of valves. There have been notable advances, as described by Pavcnik et al.[14] In practice, however, thickening of the cusps in these designs requires inertial forces to be much higher to open and close compared with native valves, and this may induce cusp wall adherence. This limits the number of valves being placed. Also, the compliance within the prosthetic valve is variable and dystrophic calcification is a further problem in the long term. In general, the durability of biological tissue after human implantation remains a significant problem, which has not improved over the past 30 years.[14]

There are logistical advantages of stented endovenous valve transfer. These are prevention of secondary valve ring dilatation, selectability of the recipient site, the capability to harvest smaller valves, and multiple valves can be inserted via the same system.

Selection of suitable patients with adequate valves for transfer, adequate muscle pump, and adequate landing zones are a prerequisite for success. The selection of site deployment may be particularly difficult as pre-operative duplex and venography may not define the entrance of multiple tributaries into the “optimal” site. Ulcers remaining recalcitrant after valve transfers could be due to extensive scar tissue formation with poor micro-circulation, relative calf muscle incompetence, or an insufficient number of valves to create sufficient deep venous competence. The significance of venous endoleaks remains uncertain, but must contribute to the degree of reflux and chronic venous hypertension. The fact that they were not detectable postoperatively indicated that they were of small size or that they had spontaneously closed.

Table 2. Human patient valve transfer details.

Initials	Harvest Ø (mm) (left axillary vein)	Target site	Target Ø (mm)
JM	7, 9	Right popliteal vein	8, 6
JG	7	Left popliteal vein	7
GW	8	Left popliteal vein	7
KP	7	Right popliteal vein	5.5

CONCLUSIONS

Endovenous valve transfer can be performed safely with 100% patency, with no loss of competence in 16 sheep for up to 6 months. The technique uses standard endovascular techniques and the surgical procedure in both animals and four human patients is straightforward. Further improvements in the introducing system may allow a less invasive deployment.

FUNDING

None.

CONFLICT OF INTEREST

Prof. Rodney Lane is the director of Allvascular Pty Ltd. AllVascular Pty Ltd is responsible for manufacturing of the stent.

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The effect of pregnancy on venous valve repair to the sapheno-femoral junction for varicose veins

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Abstract

Objectives: Pregnancy represents a special situation where both the mechanical and hormonal instigating factors of varicose veins are reversible with the venous valve cusps preserved. Exostent venous valve repairs are a physiological alternative which minimises stimulus to collateral growth (recurrence). The study purpose was to assess the effect of pregnancy on the durability of valve repairs.

Methods: In a prospective study of 36 limbs, 20 young females (30 ± 4.7 years) had an exostent implanted to the terminal valve of the saphenofemoral junction for varicose veins. At routine long-term follow up (9.7 ± 3.8 years), 38 pregnancies were completed (mean: 1.8, range: 1–4). The controls were a non-pregnant group of limbs ($n = 386$).

Results: At 9.7 years, the internal diameter of the greater saphenous vein (GSV) changed from 7.8 ± 2.8 mm preoperatively to 4.5 ± 1.4 mm postoperatively. Recurrence was associated with reflux, preoperative deep system and ovarian vein involvement. Pregnancy induced 33.3% recurrences compared with non-pregnant controls (4.7%) similarly treated or 22.8% compared with non-pregnant ablative controls. At 9.7 years, symptomatic improvement continued with significantly better CEAP status (described later) ($31C_SEAP$ preoperative to $6C_SEAP$) with no further truncal ablation (strip, laser) required.

Conclusions: Venous valve repairs can withstand the special stresses of pregnancy. There is no need to ablate the GSV. This approach is contrary to the traditional dictum; the treatment of varicose veins should be delayed until the family is completed.

Keywords

cardiovascular, multiple pregnancy

Introduction

Pregnancy, particularly multiple pregnancies, is a major factor in the development and exacerbation of varicose veins.[1–4] However, pregnancy represents a special and different vascular status: many of its effects are essentially reversible and yet cumulative. The contributing factors are a mechanical obstruction of the venous outflow in the pelvis, increased circulating blood volume and hormonal effects causing smooth muscle dilatation with an inhibition of normal contractility.[5–7] All of these factors summate to create dilatation of the venous valve rings rather than cusp degeneration which is a function of age.[8] The post-pregnant patient presents at an earlier age with tributary and perforator incompetence rather than truncal dilatation.[9] The perforating systems are often paravaginal and associated with new ovarian vein incompetence which also may be symptomatic in their own right.[9] These younger patients are more sensitive to the effects of varicose veins and tend to present earlier.

These differing, reversible etiological factors demand a different approach to simply destroying the greater saphenous system with radiofrequency, laser or stripping. A venous exostent is a simple valve support implant which decreases the internal diameter of the valve ring allowing apposition of the cusps with re-establishment of one way flow.[8,9] The development of high quality ultrasonic venous valve imaging has improved the selection criteria for venous valve repair of the greater saphenous vein (GSV) system.[10] As the Australian Medicare Database[11] indicates, over recent times 3372 devices have been implanted with repair of the terminal and/or sub terminal valves of the GSV. The aims of this communication are to compare the effect of pregnancy on varicose veins and their recurrence compared with a non-pregnant control group.[12] Further to this, to report the incidence of recurrence and reversal of truncal dilatation with stent repair, to define the effect of ovarian vein incompetence and to highlight the differing anatomical distribution of post-pregnant recurrent varicose veins which suggests a physiological form of treatment related to the special reversible effects of pregnancy.

In summary, to report the 10-year durability of stent repair to the sapheno femoral junction (SFJ) and or sub-terminal valves implanted prior to or in between pregnancies.

Methods

Patients

A total of 36 limbs (in 20 patients) were treated with venous valve exostents and subsequently these repairs were subjected to 38 pregnancies (mean: 1.8, range: 1–4). All patients presented with reflux at the SFJ. The demographics and CEAP international classification are summarised in Tables 1 and 2. The patients were prospectively followed up clinically and ultrasonically up to 17 years post valve repair. Table 3 shows the preoperative ultrasonic values and initial results.

Controls

From a database of a large venous clinic, 193 controls (121 females to 72 males with a mean age of 48.1 ± 7.2 years) were obtained. Controls were defined as patients with no recorded pregnancies with stripping on one side and a simultaneous stent repair to the SFJ of the other limb

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(386 limbs). These patients were enrolled as per Figure 1 and followed up clinically and ultrasonically for up to 12.7 years.

Materials

The Venocuff (Figure 2) is a Dacron reinforced variable diameter exostent manufactured by Allvascular, St Leonards, Australia. Figure 3 shows the basic concept of exostent venous valve repair. The left and right Venocuffs are designed specifically to externally plicate the SFJ. The un-notched version has been designed for the subterminal valves of the GSV or the deep venous system. There are three holes within the body of the stent indicating internal diameters (including the vein wall of 4.5, 5.5 and 6.5 mm). The smallest diameter is for a small woman (<160 cm) whilst the largest is for a large male (>180 cm).

The preoperative assessment

Ultrasonic assessment of the valve cusps intended for treatment is paramount. A typical sonographic worksheet is shown in Figure 4. The essential prerequisite is that there are two cusps that are present, mobile and incompetent (Figure 5). The degree of dilatation at the site of the subterminal valves is recorded. The distance from the SFJ is important to plan the site of the incision and also help recognition of the valves at operation. Ultrasound imaging delineates the degree of valve ring dilatation as well as how far the cusps are apart to estimate the degree of diameter reduction required by the external support. The contraindications of valve repair are cusp avulsion, fixation, extensive dilatation of the GSV >11 mm, excessive tortuosity of the remainder of the GSV and thrombophlebitis.

Operative method

The procedure can be performed under local or general anaesthetic depending on the concomitant proposed treatment of non-truncal veins (e.g. sclerotherapy, tributary avulsion or perforator ligation). A standard small groin incision (4 cm) is used to expose the SFJ and the tributaries of the termination of the GSV are ligated only for access of the stent. A vessiloop (Getz Bros, Chicago, IL, USA) is placed in the wound distally around the GSV. This is used to test the valve for reflux by obstructing upward flow. A right angle forceps is placed around the

Table 1. Demographics.

Patients (*n*)	20
Age (years ± SD)	30 ± 4.7
Pregnancies (*n*)	38 (1.8, 1 – 4)
Previous pregnancies	3 – P1 1 – P2
Legs (*n*)	36 (90.0%)

P1: para 1; P2: para 2.

Table 2. International CEAP classification (preoperative).

No.	C	E	A	P
28	C_S	E_P	A_S	P_R
6	C_A	E_P	A_S	P_R
2	C_S	E_P	A_D	P_R

C: clinical symptoms; clinically symptomatic (C_S) or asymptomatic (C_A); E: etiology; primary (E_P) or secondary (E_S); A: anatomy; superficial (A_S) or deep (A_D); P: pathophysiology; reflux (P_R) or no reflux (0).

Table 3. Preoperative valve repair and short-term follow-up.

SFJ reflux preoperative (*n*)	36 (100%)
GSV internal diameter (mm ± SD)	7.8 ± 2.8
Deep vein reflux (*n*)	2 (5.6%)
SFJ reflux at three months	3 (8.3%)

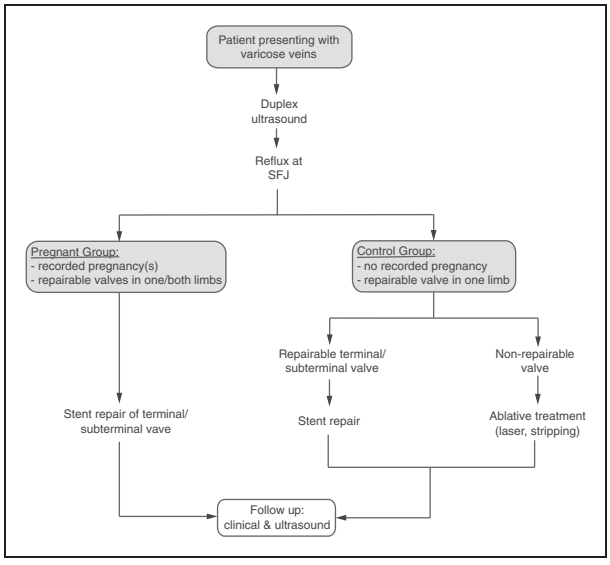

Figure 1. Enrolment process for pregnant and control patients.

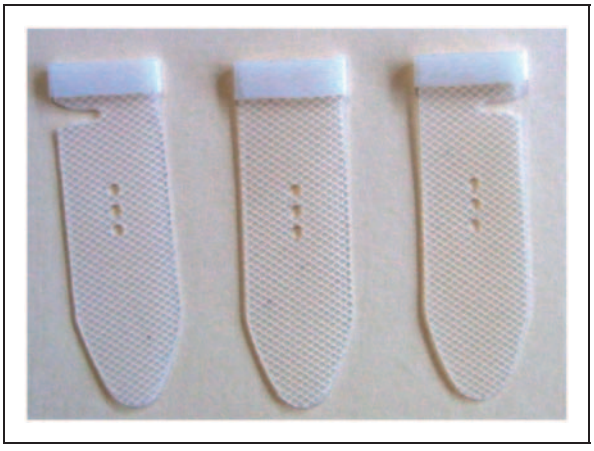

Figure 2. The three different exostents: Left and right ones are notched; the un-notched stent is for the subterminal valve or the deep system. The holes in the body of the exostent indicate diameters 4.5, 5.5, 6.5 mm for various increasingly large phenotypes.

valve after identification. The valve insertion into the vein wall appears as a white line circumventing the SFJ (Figure 6). The tail of the Venocuff is inserted through the buckle and tightened to the appropriate diameter. The notch of the Venocuff must fit snugly between the end of the femoral vein and the inferior margin of the SFJ (Figure 3). A 5.0 prolene suture is then used to fix the vein wall to the body of the stent and the buckle. This through and through suture stabilises the diameter. The excess tail of the Venocuff is then removed. Testing is performed with valsalva if local anaesthetic is employed or in case of a general anaesthetic positive end expiratory pressure with maximum depression of the legs to induce the highest venous pressure possible. Competence is visualised when the segment between the vessiloop and

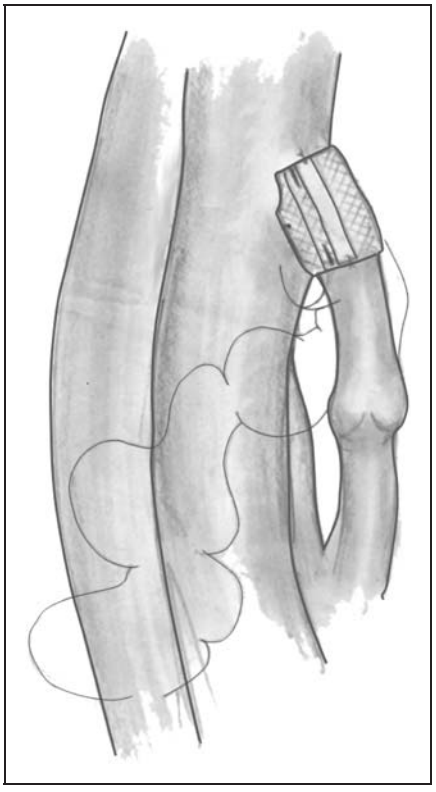

Figure 3. Schematic of the standard venous exostent with the notch fitting snuggly at the SFJ. The diameter is fixed by sutures through the buckle and body combined both superiorly and inferiorly. The subterminal valve is shown as competent. In this case, the grossly dilated varicose veins are the lateral accessory system. As the remainder of the GSV is often normal, the result is to return to physiological normalcy.

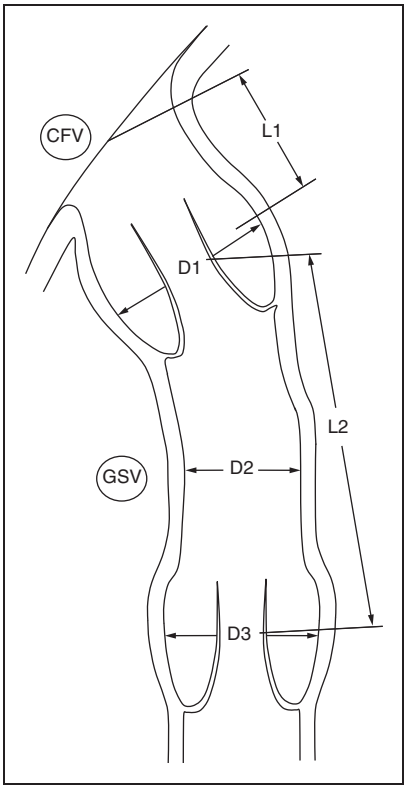

Figure 4. This is the ultrasonic worksheet. Important considerations are cusp, mobility and presence, and the dilatation of the valve ring. L1 is the distance of the SFJ to the terminal valve, D1 is the valve dilatation, D2 is the intervalvular diameter, L2 is the intervalvular distance and D3 is the intercommusural distance.

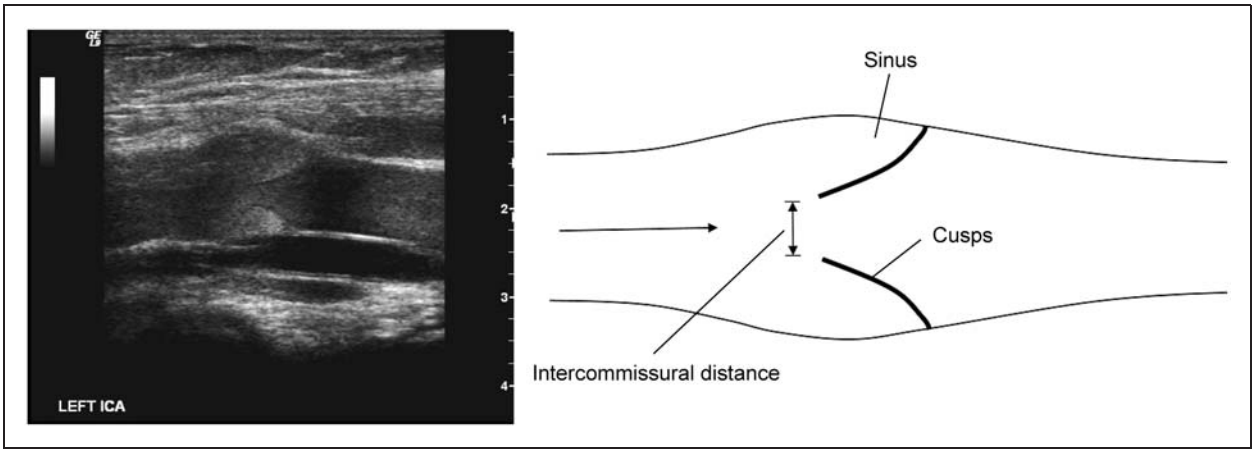

Figure 5. Ultrasonic image of a typical venous valve with cusps visible but non-opposing, incompetent and mobile.

the distal end of the stent remains completely flat after digital compression of the vein. An alternative test is to leave a tributary non-ligated so that blood can be seen emanating from the open vein, if incompetent. The wound is irrigated with antibiotic solution (first generation cephalosporin) and the wound closed in layers. Routine anticoagulation (heparin 2000 IV and enoxaparin 40–60 mg s.c.) and antibiotics (1 mg cefazolin) are given at the time of the procedure.

Results

The outcomes at the short-term follow up (three months) for the pregnant group are shown in Table 3. SFJ reflux was defined by a delayed valve enclosure at the SFJ junction. The mean long-term follow up of patients in the pregnant group and control group were 9.7 ± 3.8 years and 5.7 ± 3.2 years, respectively. The recurrence rates in these two groups are summarised in Figure 7. All recurrences in the pregnant group were treated satisfactorily with ultrasound guided sclerotherapy. None have required ablation of the GSV. There were no post-operative infective or thrombotic complications. A detailed breakdown of the recurrences in the pregnant group is summarised in Table 4 and the post-operative CEAP classification is shown in Table 5. Recurrence was associated with reflux at the SFJ ($P < 0.05$), concomitant ovarian vein reflux ($P < 0.05$) and pre-existing deep venous disease ($P < 0.05$).

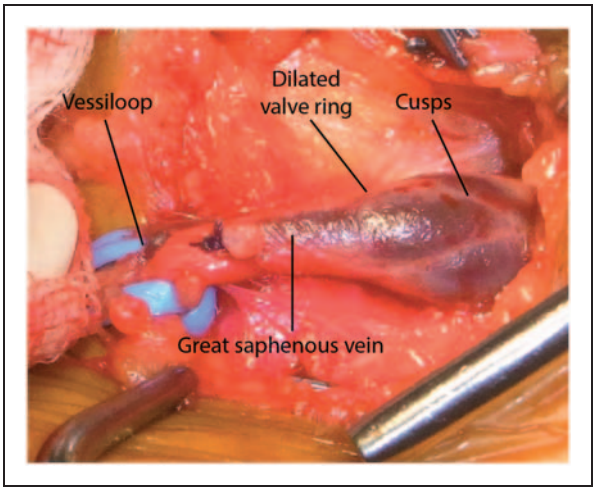

Figure 6. An operative photograph of the SFJ valve visible through the dilated vessel.

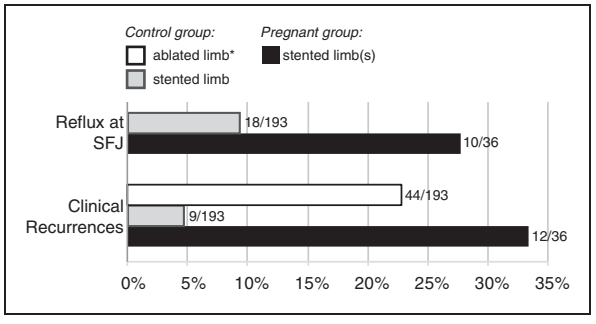

Figure 7. Recurrences in patients from the pregnant group and control group (*reflux at SFJ in ablated limbs not graphed due to neovascularisation).

Discussion

Subsequent pregnancy is associated with an increased incidence of long-term recurrence of varicose veins compared with similarly treated non-pregnant controls (33.3% at 9.7 years versus 4.7% at 5.7 years). This trend is significant when age adjusted. Similarly, when compared with a non-pregnant control group, ablative procedures were performed where the difference was 33.3% in the pregnant group versus 22.8% in the non-pregnant group. The striking effect of pregnancy post-stenting on varicose veins is the type of recurrence following treatment. These are mainly tributaries of a mildly incompetent GSV where the truncal diameter remains significantly smaller than preoperatively; 7.8 mm versus 5.5 mm at 9.7 years post-operatively. The diameter remains 1 mm greater than the competent GSV and all of these veins could be used for bypass for arterial re-vascularisation procedures if required in the future. Most importantly, further treatment is primarily tributary sclerotherapy in a mildly dilated truncal trunk rather than further expensive ablative procedures. The etiology of recurrences is multifactorial with 19.4% being associated with new ovarian vein reflux, 5.6% deep disease (femoral vein incompetence) and 27.8% reflux at the SFJ. These factors often occurred in combination, compounding each other.

Women of child bearing age present at a younger age (30 ± 4.7 years) compared to the general population (45 years)[2] as valve deterioration is a function of age and the valve cusps are often preserved.[13] The reparative physiological approach is theoretically optimal in young patients contemplating or in between pregnancies. The results suggest that the often quoted dictum 'that repair of varicose veins should be left until after all pregnancies have been completed' is essentially incorrect.[1,4] Valve repairs are almost always possible with a reduction in the risk of subsequent clinically significant varicose veins. A patient

Table 4. Valve repair long-term follow-up.

Follow up (year ± SD)	9.7 ± 3.8
SFJ reflux (*n*)	10 (27.8%)
Incompetent perforators (*n*)	2 (5.6%)
GSV internal diameter (mm ± SD)	7.8 ± 2.8
Preoperative	4.5 ± 1.4
Post-operative	4.0 ± 1.3
Without reflux	5.0 ± 1.4 ($P < 0.05$)
With reflux	
Ovarian vein reflux (*n*)	7 (19.4%)
Deep reflux	2 (5.6%)
Treatment (*n*) (Sclerotherapy)	5 (13.9%)

Table 5. International CEAP Classification at 9.7 years follow-up.

No.	C	E	A	P
2	C_A	E_P	A_S	0
26	C_A	E_P	A_S	0
3	C_A	E_P	A_D	P_R
3	C_S	E_P	A_D	P_R
2	C_S	E_P	A_S	R_R

with varicose veins intending to have further pregnancies should be actively treated to reduce morbidity in the future. The varices predating pregnancy are often exacerbated by further pregnancies.

In this study, venous valve repair resulted in a relative absence of symptoms at 10 years $31C_{Symptomatic}$ versus $6C_{Symptomatic,}$ pre and post-operative, respectively. The motivation for presentation with recurrence for these patients is cosmesis.

Pregnancy is associated with progression of varicose veins and it is occasionally impossible for valve repairs to be performed and an ablative procedure is the only alternative. A prospective controlled trial of patients with earlier disease who had cusp preservation showed long-term results at least as good as the ablative procedure.[12,14]

Mechanism of recurrence in pregnancy

As the implanted stents incur a fixed diameter to the SFJ (4–5 mm) and the cusps are normal preoperatively, the development of new reflux at the SFJ is logically related to new cusp degeneration. Unfortunately, post-operative ultrasound cannot define cusp morphology related to the inability of ultrasound to penetrate the stent itself. The preoperative association with deep reflux and new ovarian vein reflux suggests the underlying problem is in the matrix of the cusp itself[5,13] aggravated by the increased volume flow associated with pregnancy and the circular reflux pattern set up with ovarian vein incompetence and deep vein reflux.

Ovarian vein incompetence may produce a different mechanism of recurrence.[15,16] The labial and paravaginal perforators connect to the distal GSV creating a functional bypass to the valve repairs. If patients are wishing to proceed with further pregnancies, the strong association with new reflux suggests that ovarian vein embolisation should be considered. Specifically, both SFJ incompetence and ovarian vein incompetence should be treated to avoid these etiological factors compounding each other.

The natural history of varicose veins in pregnancy indicates inevitable deterioration and therefore earlier intervention is logically a better approach. Up to 20% of varicose veins develop during pregnancy.[16–19] Mullane showed an increasing severity with progressive numbers of pregnancies; 13% primiparous, 30% secundiparous and 57% multiparous.[20]

The advantages of exostent repair

As the GSV is preserved, there is very little post-operative discomfort compared with ablative procedures. The repair is physiological and minimises collateral stimulation and preserves the normal conduit in patients with concomitant deep disease. The long-term results are satisfactory.[9] The procedure is quick, can be performed under local anaesthetic and is inexpensive. Valve repair, however, is selective and requires mobile cusps with the prime pathology being dilatation of the valve ring.

Conclusion

Although stent repairs have shown to be better than conventional ablative procedures, pregnancy remains a major contributing factor to recurrences. However, the underlying etiology, distribution and vein type in these recurring cases are different from standard varicose veins and in general require a less aggressive remedy. Stent repairs to the SFJ and or sub-terminal valve produce a durable alternative for women contemplating initial or further pregnancies. The reparative physiological approach is a reflection of earlier age and hence cusp preservation in pre-pregnant females compared to the normal population. This approach is contrary to the usual dictum that treatment of varicose veins should be delayed until the family is completed.

Declarations of conflicting interests

RL is a director of the manufacturer AllVascular. MD, JC, SH have nothing to declare.

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Ethical approval

N/A – Government already approved procedure. All patients were consented as per the Royal Australasian College of Surgeons Informed Consent Policy.

Guarantor

Rodney James Lane

Contributorship

Conception and design: NK, RL; analysis and interpretation: MD, NK, SH, RL; data collection: MD, JC, SH, RL; writing the article: MD, NK, RL; critical revision of the article: JC, SH, RL; final approval of the article: NK, RL; statistical analysis: MD, RL; overall responsibility: RL.

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