R E B I R T H

IRAS SHORT TITLE: RALPP versus PVE for induction of liver hypertrophy

SHORT TITLE:

REGENERATION OF LIVER: PORTAL VEIN **E**M**B**OL**I**ZATION VERSUS **R**ADIOFREQUENCY ASSISTED LIGA**T**ION FOR LIVER **H**YPERTROPHY

FULL TITLE:

Liver Regeneration: a single-centre, prospective, randomised controlled trial comparing radiofrequency assisted liver partition with portal vein ligation (RALPP) with portal vein embolization (PVE) for preoperative induction of liver hypertrophy in patients with insufficient future liver remnant volume for major liver resection.

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Name & Role	Date	Signature

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Clinical Queries

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Sponsor

Imperial College London is the main research Sponsor for this study. For further information regarding the sponsorship conditions, please contact the Head of Regulatory Compliance at:

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Funder

This study is unfunded.

This protocol describes the study and provides information about procedures for entering participants. Every care was taken in its drafting, but corrections or amendments may be necessary. These will be circulated to investigators in the study. Problems relating to this study should be referred, in the first instance, to the Chief Investigator.

This study will adhere to the principles outlined in the NHS Research Governance Framework for Health and Social Care (2nd edition). It will be conducted in compliance with the protocol, the Data Protection Act and other regulatory requirements as appropriate.

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GLOSSARY OF ABBREVIATIONS

ALPPS	Associating liver partition and portal vein ligation with in situ liver splitting
CT	Computed tomography scan
FLRV	Functional liver remnant volume
PVE	Portal vein embolization
PI	Principal investigator
RALPP	Radiofrequency assisted liver partition with portal vein ligation
TLV	Total liver volume
WHO	World Health Organisation

KEYWORDS

Liver hypertrophy; liver resection; portal vein ligation; portal vein embolization; radiofrequency splitting

STUDY SUMMARY

TITLE	Liver Regeneration: a single-centre, prospective, randomised controlled trial comparing radiofrequency assisted liver partition with portal vein ligation (RALPP) with portal vein embolization (PVE) for preoperative induction of liver hypertrophy in patients with insufficient future liver remnant volume for major liver resection.
DESIGN	Single centre randomised controlled trial
AIMS	To ascertain whether radiofrequency in situ splitting with portal vein ligation is superior to the traditional portal vein embolization for liver hypertrophy.
OUTCOME MEASURES	Future liver remnant volume (primary) Postoperative liver function tests (secondary) Postoperative complication rate (secondary)
POPULATION	Hospital patients satisfying inclusion criteria
ELIGIBILITY	Adult patients requiring right or extended right hepatectomy and with insufficient future liver remnant volume on pre-operative scan
DURATION	18 months from randomisation; 2.5 years for total study

1. INTRODUCTION

1.1 BACKGROUND

Liver resection remains the gold standard treatment for patients with liver tumours providing them the only chance for long-term survival. In up to 45% of resectable cases, an extended hepatectomy is usually necessary to achieve a clear resection margin, a major determinant factor for long-term survival.[1-2] However, liver failure is usually common with this type of major resection due to insufficient remnant liver volume to support postoperative liver function, which itself is still the principal cause of postoperative death following a major liver resection. This leaves less than 20% patients with liver tumours suitable for this curative operation.[3] Furthermore, with increased use of neoadjuvant chemotherapy to downstage a tumour, liver function is inevitably affected by chemoagents which can induce cholestatic changes in liver making patients more prone to postoperative liver failure.

The liver consists of two major lobes: right and left which are made up from 8 segments based on the of Caunauid classification liver: segments I-IV of the left lobe and V-VIII of the right lobe (Figure 1). A major liver resection is defined as a removal of more than 3 segments of liver such as a right or left hepatectomy. An empirical estimate for a minimum volume of remnant liver required to maintain liver function following a major liver resection is around 25% in a healthy patient without any pre-existing liver disease. However, in patients with chronic liver disease or cholestasis following chemotherapy, it is impossible to estimate this. Volumetric analysis has been described as a tool to predict postoperative liver failure and death in patients with liver tumours.[3]

In order to decrease the complications and improve the safety of extensive liver surgery in patients with insufficient future liver remnant volume (FLRV), preoperative portal vein embolization (PVE) has been used in patients with or without chronic liver disease prior to liver resection to stimulate liver regeneration on the opposite side of the PVE. A meta—analysis of published human studies on PVE has recently demonstrated that preoperative PVE results in an increase in liver volume independent of techniques used for PVE by 12% on average.[4] In 2012, Schnitzbauer et al. proposed an alternative method known as associating liver partition and portal vein ligation (ALPPS).[5] They compared this technique to PVE in 25 patients requiring a right hepatectomy. During the first procedure, the right portal vein was identified, divided and oversewn. In situ splitting (ISS) was subsequently undertaken whereby total or nearly total parenchymal dissection was performed. The second

stage to complete the extended right hepatectomy was performed after a median interval of 9 days. The mean hypertrophy rate of the FLRV was 74% with a median volume for the left lateral liver lobe of 310mls and 536mls prior to and after the ALPPS procedure respectively. Using uptake of 99mTcHIDA, De Santibanes et al. found that the diseased liver lobe, with a ligated portal vein, remained functional following ALPPS and represented up to 60% of total liver function.[6] Thus, the risk of liver failure is far less likely in these patients in the first week after ALPPS. Furthermore, the rapid regeneration response also ensures that tumour progression is unlikely within 9 days of the second definitive operation prior to the onset of adhesions. Although the reported volume increase of FLRV after ALPPS was far greater than that achieved with PVE (74% vs. 12%), there would seem to be a high postoperative morbidity rate associated with it ranging from 33% to 58%.[7-9]

In our centre, a novel technique has been described to achieve a rapid increase in FLRV within a short period of time as seen in ALPPS without the increased morbidity rates attributed to ALPPS. This technique uses in-line radiofrequency to create a virtual liver partition with portal vein ligation - Radiofrequency Assisted Liver Partition with Portal Vein Ligation (RALPP).[10] It has been shown that it is a feasible and safe alternative to ALPPS to achieve a rapid liver regeneration in the contralateral lobe of the liver without increased morbidity and mortality related to ALPPS.[10]

1.2 RATIONALE FOR CURRENT STUDY

CLINICAL ISSUES:

Hepatobiliary surgeons are seeing an increased number of referrals for liver resection of patients with primary and secondary liver cancer. A sizeable proportion of these referrals would traditionally have been deemed inoperable due to insufficient remnant liver volume following hepatectomy. While the technique of portal vein embolization (PVE) has enabled liver hypertrophy and subsequent hepatectomy for many previously inoperable patients, there is still significant scope for improvement. Specifically, both the final volume of liver hypertrophy induced and the time taken to develop such hypertrophy are important factors.
The more recent technique of associating liver partition and portal vein ligation (ALPPS) developed by Schnitzbauer et al. has demonstrated faster and greater volume hypertrophy. Unfortunately this technique has a high morbidity rate.

There is therefore a clinically important need to assess whether the technique of radiofrequency assisted liver partition with portal vein ligation (RALPP) can demonstrate the superior efficacy of ALPPS as compared to PVE without the increased morbidity profile. This method uses the same principle as ALPPS but achieves the in situ liver splitting with radiofrequency energy thus reducing the risk of potential visceral damage and bleeding.

RADIOFREQUENCY ASSISTED LIVER PARTITION WITH PORTAL VEIN LIGATION (RALPP):

RALPP is performed laparoscopically when possible. A five port (2 x 10mm working ports on each side of abdomen) technique is used. Following resection of tumour from the left lobe for those requiring staged liver resection with bilobar disease, as previously described by our group,[11] attention is paid to hilar dissection for identification and ligation of the right portal vein. The portal vein is carefully separated from the common hepatic duct behind the right hepatic artery. Whenever possible, the right hepatic artery is isolated and slung with a non-absorbable suture (2/0 Prolene) to aid identification and ligation of this at the second stage liver resection. The right portal vein is isolated using blunt dissection and ligated using two Hem-o-loks (Teleflex, NC, USA).

Following ligation of the right portal vein, the demarcation between the left and right lobe of the liver is clearly visible. Then, radiofrequency ablation with either cool tip RFA (Covidien, Hampshire, UK) or laparoscopic Habib Sealer (LH4X, Rita, USA) is performed for completion of RALPP along the line of the demarcation to segment VIII of the liver above the right hepatic vein superiorly and to segment V above the hilus on the left side of the gallbladder. For the open approach, the procedure is performed in a similar manner. To aid the identification of the right hepatic artery and portal vein, cholecystectomy is often performed first and the cystic duct stump ligated and divided. This can then be retracted medially to expose the hilus for dissection of the right hepatic artery and portal vein. The portal vein is then ligated with a 2/0 Vicryl tie and clipped with 2 ligaclips (10mm, Ethicon, Berkshire, UK). All patients have a restaging CT scan with contrast to assess the liver volume 2 weeks after RALPP prior to right hepatectomy.

Five patients requiring extended liver resection were operated on using the new radiofrequency ALPPS technique (RALPP). Their outcomes were compared to 5 historical patients who were matched for age, sex, initial liver function and pathology. RALPP demonstrated superior efficacy to PVE. There was no difference in liver function between the

two groups on day 15 post hepatectomy. No patients developed a postoperative bile leak (a common source of morbidity post ALPPS) in either group and there was no mortality at 90 days.[10]

PORTAL VEIN EMBOLISATIOM (PVE):

PVE was first demonstrated in the 1920s in a rabbit model. Rous and Larimore showed compensatory hypertrophy in the contralateral hepatic lobe following portal vein occlusion.[12] The first preoperative PVE in patients was undertaken in 1986 following which there have been numerous reports.[13] Large case series of PVE have demonstrated an increase in the FLRV from 8.0%-49.9%.[14, 15]

A meta-analysis from our group, including 1,088 patients who underwent PVE prior to hepatic resection, showed a mean hypertrophy rate of the FLRV after PVE of only 11.9% after an average of 29 days.[4] Transient liver failure following resection was seen in 2.5% and 0.8% of patients developed acute renal failure and died. Major morbidity from PVE was seen in 2.2% with no mortality. After liver resection the morbidity rate was 16.0% with a 1.7% mortality rate.

ETHICAL ISSUES:

Although RALPP has been demonstrated as superior to PVE, the full comparative efficacy profile in the medium and long term between RALPP and PVE remains unknown. A randomised controlled trial is required to assess this aspect in a more controlled and unbiased manner. Clinical equipoise between RALPP and PVE remains.

2. STUDY OBJECTIVES

Primary endpoint:

- Future liver remnant volume (FLRV)

Secondary endpoints:

- Postoperative liver function tests

- Postoperative complication rate

3. STUDY DESIGN

This study is a two arm, prospective, single centre randomised control trial of RALPP compared with PVE in patients with inadequate FLRV (<25%) prior to elective right or extended right hepatectomy.

There will be two groups in this study with 13 subjects in each group, for a total of 26 subjects. Each patient will give informed consent. Below are descriptions of operative technique, recruitment, and outcome measures.

MEASUREMENT OF LIVER VOLUME

Total liver volume (TLV), FLRV and tumour volume are measured by a single trial coordinator (MS). These volumes are assessed from the CTs carried out before and after RALPP, PVE and liver resection. Liver volumes are calculated using ImageJ (Image Processing and Analysis in Java, National Institute of Health) as previously described.[16] The FLRV is measured as the left lobe of the liver, to the left of Cantlie's line.

RECRUITMENT

Patients will be approached in the hepatobiliary clinic at Hammersmith Hospital. An experienced member of the clinical team will discuss the details of the trial and explain the possible risks and benefits of participation. The patient will then be given up to two weeks to decide if they wish to participate. During this time, they will have the phone number for a senior member of the clinical team should they wish to discuss any points in further detail.

RANDOMISATION

Those patients fulfilling the inclusion criteria and providing informed consent will be randomised. The randomisation sequence will be generated independently by http://www.sealedenvelope.com. This service handles both sequence generation and allocation concealment and will employ minimisation techniques to ensure that both

treatment groups are well balanced on baseline characteristics. These methods of sequence generation and allocation concealment ensure that the two groups are truly random and thus minimises selection bias and confounding. In other words, it increases the reliability of the final results.

PRE-INTERVENTION INVESTIGATIONS

Both groups will then receive pre-intervention blood tests and a contrast enhanced CT scan of the abdomen (this is routine clinical practice).

GROUP 1 - PVE GROUP

Patients allocated to the PVE group will have their portal vein embolized radiologically once their pre-intervention investigations have been completed and reviewed by the clinical team. The patient will be admitted to the ward before and after the procedure for routine monitoring post-procedure. Discharge will be at the discretion of a senior member of the clinical team once the patient is mobilising, passing urine and pain free with no evidence of procedural complication.

They will then receive a further post-intervention set of investigations (again consisting of blood tests and CT scan as described above) 4 weeks after the completion of the PVE. At this point, they will be listed to receive their definitive surgical hepatectomy.

GROUP 2 - RALPP GROUP

Patients allocated to the RALPP group will have their right portal vein surgically ligated followed by radiofrequency ablation in situ splitting of the liver. Certain patients may additionally have a tumourectomy or wedge resection of the left liver lobe if clinically indicated. For analysis purposes, all patients within the RALPP group will be considered together and no formal a priori subgroup analysis is planned.

The RALPP procedure will occur once the patient's pre-intervention investigations have been completed and reviewed by the clinical team. The patient will be admitted to the ward before and after the procedure for routine monitoring post-procedure. Discharge will be at

the discretion of a senior member of the clinical team once the patient is mobilising, passing urine and pain free with no evidence of procedural complication.

They will then receive a further post-intervention set of investigations (again consisting of blood tests and CT scan as described above) 2 weeks after the completion of the RALPP. At this point, they will be listed to receive their definitive surgical hepatectomy.

DEFINITIVE SURGERY

At the time points described above, patients from both groups will be admitted to the ward for right or extended right hepatectomy as per their clinical indication. From the time of surgery onwards, both groups will be treated identically. In other words, the intervention period of the study lasts from admission for PVE or RALPP procedure to admission for definitive surgery. All interactions before and after this intervention period will be identical between groups.

Discharge will be at the discretion of a senior member of the clinical team once the patient is mobilising, passing urine and pain free with no evidence of procedural complication.

FOLLOW-UP CARE

See section 6 of this protocol.

3.1 STUDY OUTCOME MEASURES

Primary endpoint:

- Future liver remnant volume – as measured by volumetric analysis of CT scan

Secondary endpoints:

- Postoperative liver function tests – as measured by blood tests
- Postoperative complication rate – as defined by Dindo Clavien classification of surgical complications

4. PARTICIPANT ENTRY

4.1 PRE-REGISTRATION EVALUATIONS

After informed consent, participants will have routine blood tests taken (full blood count, renal profile, bone profile, liver function tests, C-reactive protein, clotting) and a CT scan with contrast of the abdomen and pelvis.

4.2 INCLUSION CRITERIA

- Age ≥ 18 years.
- Any patient requiring right or extended right hepatectomy with FLRV less than 25% on preoperative volumetric study.
- WHO performance status 0, 1 or 2.
- Patient able to comply with protocol requirements and deemed fit for surgical resection.
- Written informed consent.

4.3 EXCLUSION CRITERIA

- Inability to give informed consent
- Pregnancy.
- WHO status 3 or 4.
- New York Heart Association Classification Grade III or IV.

4.4 WITHDRAWAL CRITERIA

An interim analysis will be conducted after 16 patients have been recruited. The trial may be stopped at this point for futility or for overwhelming effect. All participants are free to withdraw at any time. Safety monitoring will be conducted by the clinical team with withdrawal of the patient from the trial under clinical grounds resting with the PI.

5. ADVERSE EVENTS

5.1 DEFINITIONS

Adverse Event (AE): any untoward medical occurrence in a patient or clinical study subject.

Serious Adverse Event (SAE): any untoward and unexpected medical occurrence or effect that:

- **Results in death**

- **Is life-threatening** – *refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe*

- **Requires hospitalisation, or prolongation of existing inpatients' hospitalisation**
- **Results in persistent or significant disability or incapacity**
- **Is a congenital anomaly or birth defect**

Medical judgement should be exercised in deciding whether an AE is serious in other situations. Important AEs that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above, should also be considered serious.

5.2 REPORTING PROCEDURES

All adverse events should be reported. Depending on the nature of the event the reporting procedures below should be followed. Any questions concerning adverse event reporting should be directed to the Chief Investigator in the first instance.

5.3.1 NON SERIOUS AEs

All such events, whether expected or not, should be recorded.

5.3.2 SERIOUS AEs

An SAE form should be completed and faxed to the Chief Investigator within 24 hours. However, relapse and death due to underlying cancer, and hospitalisations for elective treatment of a pre-existing condition do not need reporting as SAEs.

All SAEs should be reported to the Bloomsbury (London) REC where in the opinion of the Chief Investigator, the event was:

- 'related', i.e. resulted from the administration of any of the research procedures; and
- 'unexpected', i.e. an event that is not listed in the protocol as an expected occurrence

Reports of related and unexpected SAEs should be submitted within 15 days of the Chief Investigator becoming aware of the event, using the NRES SAE form for non-IMP studies. The Chief Investigator must also notify the Sponsor of all SAEs.

Local investigators should report any SAEs as required by their Local Research Ethics Committee, Sponsor and/or Research & Development Office.

Contact details for reporting SAEs
Fax: +44 (0) 20 8383 3179, attention of Mr Mikael Sodergren
Please send SAE forms to: Mr Mikael Sodergren
Tel: +44 (0) 20 83833937
(Mon to Fri 09.00 – 17.00)

6. ASSESSMENT AND FOLLOW-UP

Patients from both groups will be reviewed in the HPB Clinic between 2 and 4 weeks post discharge. At all times after discharge, patients will have the contact details of a senior member of the clinical team should any problems or questions arise. A regular out-patient clinic appointment as per current standard of care will take place (so no change from normal clinical practice). Patients will remain under follow-up with the HPB clinic for a minimum of 18 months from the time of definitive surgery. This will involve only outpatient clinic appointments as clinically indicated.

The trial is deemed to have ended upon completion of 18 month follow-up of final recruited participant.

7. STATISTICS AND DATA ANALYSIS

Sample size was calculated based on the pilot data from our institution published in Annals of Surgery.[10] This is based on the mean rates of increase in FLRV on the assumption that a RCT should be able to detect a clinically meaningful increase in FLRV. The null hypothesis was that there was no difference between the intervention and standard treatment in the primary endpoint. The sample size calculation assumed two-sided testing.

The sample size of each arm was calculated using the equation designed for two proportions; α was set at 0.05 to control for type I error (false-positive result) and β at 0.10 to control for type II error (false-negative result). Based on these data a power calculation estimated a total sample size of 16 patients, however due to the relatively small sample size of the pilot data it was decided to aim to recruit 26 patients to the trial.

Following recruitment of 16 patients, an interim analysis comparing primary end-point outcomes in the two groups will be conducted. The trial will be halted at this point of a significant difference of $p<0.05$ is determined.

Data and all appropriate documentation will be stored for a minimum of 10 years after the completion of the study, including the follow-up period.

8. REGULATORY ISSUES

8.1 ETHICS APPROVAL

The Chief Investigator has obtained approval from the Imperial College Research Ethics Committee. The study must be submitted for Site Specific Assessment (SSA) at each participating NHS Trust. The Chief Investigator will require a copy of the Trust R&D approval letter before accepting participants into the study. The study will be conducted in accordance with the recommendations for physicians involved in research on human subjects adopted by the 18th World Medical Assembly, Helsinki 1964 and later revisions.

8.2 CONSENT

Consent to enter the study must be sought from each participant only after a full explanation has been given, an information leaflet offered and time allowed for consideration. Signed participant consent should be obtained. The right of the participant to refuse to participate without giving reasons must be respected. After the participant has entered the study the clinician remains free to give alternative treatment to that specified in the protocol at any stage if he/she feels it is in the participant's best interest, but the reasons for doing so should be recorded. In these cases the participants remain within the study for the purposes of follow-up and data analysis. All participants are free to withdraw at any time from the protocol treatment without giving reasons and without prejudicing further treatment.

8.3 CONFIDENTIALITY

The Chief Investigator will preserve the confidentiality of participants taking part in the study and is registered under the Data Protection Act.

8.4 INDEMNITY

Imperial College London holds negligent harm and non-negligent harm insurance policies which apply to this study.

8.5 SPONSOR

Imperial College London will act as the main Sponsor for this study. Delegated responsibilities will be assigned to the NHS trusts taking part in this study.

8.6 FUNDING

This study is unfunded. No payments will be made to participants, investigators or any other personnel associated with the study.

8.7 AUDITS

The study may be subject to inspection and audit by Imperial College London under their remit as sponsor and other regulatory bodies to ensure adherence to GCP and the NHS Research Governance Framework for Health and Social Care (2nd edition).

9. STUDY MANAGEMENT

The day-to-day management of the study will be co-ordinated through Imperial College London by Mr Mikael Sodergren.

10. PUBLICATION POLICY

We intend to report and disseminate our findings via conference presentations and peer-reviewed scientific journal articles. All data used in analysis and public reporting will be non-identifiable.

Patients will be asked if they wish to receive in writing the anonymised results of the research following publication in peer-review journals. If this is the case this will be sent to them by post at the appropriate time.

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Figure 1. Caunauid classification liver