CLINICAL STUDY / RESEARCH PLAN

Title:
BestFLR: Randomized controlled trial comparing preoperative portal vein embolization with polyvinyl alcohol (PVA) particles and coils *versus* N-butyl cyanoacrylate (NBCA).

Promoter:
Lisbon Central Hospital Centre, EPE (CHLC)

Research Team:
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Team of collaborators:
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Administrative support:
Susana Brigue and Pedro Pereira

Research Unit:
Hepato-Bilio-Pancreatic and Transplantation Center (CHBPT) at Curry Cabral Hospital, CHLC.

Epidemiological and Statistical Support and Consultancy:
Office of Epidemiological and Statistical Analysis of the CHLC Research Center.
Clinical Trials Unit of the CHLC Research Center.

Fundamentals of the Study:
One of the main challenges in contemporary liver cancer surgery[1] is to achieve an adequate future hepatic remnant (FLR) after extended liver resections. Postoperative FLR volume and function are directly associated with rates of complications and mortality after hepatic surgery[2-4]. In 1920 appeared the first publication that associated interruption of the portal flow (surgical portal vein ligation) with hepatic atrophy on the obstructed side and hepatic regeneration in the contralateral region, which remained with the free portal flow[5]. At that moment the liver´s ability to regenerate was demonstrated.
Preoperative portal vein embolization (PVE) to increase FLR volume was described by Makuuchi et al in 1982[6] and Kinoshita et al in 1986[6]. Over the decades, PVE gained solid foundations for its use and currently many

hepatobiliary and oncologic surgery units adopt this approach prior to extended liver resections (resections comprising 4 or more hepatic segments). Intraoperative portal vein ligation is also used for liver regeneration, but morbidity related to surgical dissection and increased susceptibility to hypertrophy failure favours the use of PVE[7].

There is considerable heterogeneity of the embolic materials adopted in the Interventional Radiology services to perform the PVE procedure. Several embolic agents for PVE have already been used, including gelfoam particles, absolute alcohol, polyvinyl alcohol (PVA) particles, calibrated microspheres, central vascular plugs or coils, N-butyl cyanoacrylate (NBCA) with lipiodol, fibrin glue and polydocanol[8]. Although a prospective controlled study comparing embolic materials has not yet been conducted, some clinical studies and a meta-analysis[7] suggest that the use of NBCA results in increased FLR volume[9]. PVE with NBCA has the potential to make these patients, more quickly and effectively, able to undergo the potentially curative treatment of liver resection. However, there is a lack of prospective quality evidence to make this the standard approach[9,10]. Thus, there is great interest in identifying the actual influence of the materials used for embolization on the hypertrophic response of the liver.

The objective of this randomized controlled trial is to prospectively compare the performance of two percutaneous portal embolization techniques in the promotion of FLR hypertrophy: PVA particles and coils *versus* NBCA. This study will involve patients who require extensive hepatic resections for treatment of primary or secondary liver cancer and who are considered to have an insufficient FLR. The procedures under evaluation correspond to the two percutaneous portal embolization techniques currently used in the CHBPT of CHLC.

Hypothesis in Study:

PVE with NBCA is no less effective but is more efficient than PVE with PVA particles and coils in the induction of hepatic hypertrophy in patients requiring extended liver resection for treatment of primary or secondary liver cancer and who are considered to have an insufficient FLR.

Study Design:

Randomized, controlled, prospective and open interventional study, to evaluate the efficacy of PVE in inducing hepatic hypertrophy.

Interventions in Study:

PVE with PVA particles and coils *versus* PVE with NBCA.

Primary Objective

To compare the degree of hepatic hypertrophy (liver growth), measured by computed tomography volumetry, at 14 and 28 days after PVE with both interventions.

Secondary Objectives

Comparative analysis of the two PVE methods:

a) Postoperative outcome (planned liver surgery achievement, causes of hepatectomy withdrawal, and postoperative course);
b) Efficiency (material costs, procedure execution time, volume of contrast used and radiation exposure).

Identification of eligible patients, selection, recruitment and randomization of participants:

Inclusion criteria:

1. Diagnosis of primary or secondary malignant tumours of the liver, documented by computed tomography or magnetic resonance imaging or biopsy of the tumor lesion;
2. Indication for resection of the hepatic tumor;
3. An estimated future liver remnant (FLR) less than[11, 12]:
    a. 25% in healthy liver.
    b. 40% in cirrhotic liver or with severe steatosis or previous chemotherapy.
4. Have not previously undergone liver surgical segmentectomy (resection of 2 or more hepatic segments).
5. Renal function suitable for the use of iodinated venous contrast medium:
    a. Serum creatinine ≤ 1.4 mg / dL
    b. Clearance of creatinine (GFR) ≥ 60 mL / min / 1.73m2
6. Age ≥ 18 years.

Exclusion criteria:

1. Uncorrectable coagulopathies.
2. Evidence of extensive extrahepatic neoplastic disease (eg, diffuse pulmonary metastases);
3. Sectorial portal thrombosis (eg, thrombosis of the right anterior sectorial branch).

The verification of the eligibility to participate in the trial and the nonexistence of any exclusion criteria is done when a clinical indication is given to perform the PVE. The evaluation and discussion of the patients proposed for liver tumor resection and the decision to propose PVE are made during the CHLC CHBPT multidisciplinary meeting, which takes place on Wednesdays starting at 3:00 p.m.

Recruitment of participants:

Patients considered eligible will be formally invited to participate in the clinical trial at the Intervention Radiology´s specialty consultation. However, the invitation will only be made once informed consent has been obtained to perform the extended hepatectomy, preceded by PVE, proposed by the liver surgeon assigned.
The patient is informed of the possibility of participating in the clinical trial, is given an information leaflet and verbally explained the purpose of the trial, the two procedures under study and the form of allocation to each arm of the study, the expected results and the fact that there is no different action for accepting or refusing to participate in the trial. After expressing the

willingness to answer any doubt or question, it is proposed to the patient to decide to consent to participate in the trial. The patient will be informed that at any moment, until the entrance in the room where the PVE will be carried out, he or she can change their decision. Consent shall be given in writing, in its own form, in accordance with the CHLC Multisectoral Procedure *INV-103*.

Estimated number of participants

The sample size was calculated in order to identify significant differences in the degree of FLR hypertrophy between groups, with a significance level of 0.05. The potency of the study (the probability of detecting a significant difference when it exists) was 80%. For the calculation, it was considered that the degree of FLR hypertrophy using PVE with NBCA will be 59.66% (corresponds to the estimate of the average percentage of increase expected for this technique, with an estimated standard deviation of 50.2) and of PVE with PVA particles plus coils will be 35.36% (corresponds to the estimated average percentage increase expected for this technique, with an estimated standard deviation of 11.37). These estimates used to calculate the sample size are in accordance with the systematic review and publications on the field[7, 9, 12-18]. Based on these requirements, it was estimated that each group would need 36 patients, resulting in a total of 72 patients participating in the study. Anticipating eventual losses and withdrawals from the study, we will add 14 patients (~ 19%), achieving a total endpoint of 86 patients. However, recruitment will be discontinued once the 36 participants with complete follow-up on both intervention arms of this trial have been reached.

CHBPT performs approximately 200 hepatectomies per year and 30% of these (60 patients) present insufficient FLR and are referred for PVE. It is estimated that two years will be enough to recruit the participants.

Randomization of participants by two interventions:

The 86 participating/patients will be randomized by the two interventions using a table obtained through a block randomization scheme, to be applied before entering the room of the Intervention Radiology Unit where the PVE will be performed. In order to ensure the balance of intervention groups in the event of an early interruption of the trial, participants will be randomized into 3 blocks of 20 patients and the last block of 26 patients (the randomization blocks are described at the end of this document).

Description of the Procedures and Interventions in the Trial:

PVE Protocol

This procedure follows the usual protocol established at Curry Cabral Hospital (internal document: Portal Vein Embolization Protocol of the Intervention Radiology Unit at Curry Cabral Hospital).

The patient is admitted to the surgery ward A or B of the Curry Cabral Hospital on the day before PVE and blood samples for laboratory analysis (glucose, urea, creatinine, AST, ALT, GGT, FA, bilirubin and bilirubin

fractions, total proteins and main fractions, TAP, PTT, INR and complete blood count) are collected. On the second day of hospitalization, the patient is referred to the Intervention Radiology department where the PVE is performed, with 8 hours fasting. The laboratory blood results are reviewed by the interventional radiologist to confirm patient's eligibility.
In the Intervention Radiology room the patient is submitted to the following preparatory procedures for PVE:
1. Peripheral venous access
2. Noninvasive monitoring of heart rate, blood pressure and pulse oximetry
3. Venous sedation and analgesia according to the patient's need (the discomfort and pain generated by the PVE procedure is usually low and intravenous medication requirements vary from patient to patient) is administrated by the room nurse at the request of the executing physician.
After the PVE, the patient returns to the ward for general nursing care. The following day, after medical consulting, the patient is discharged to his residence.

Protocol of PVE procedure with PVA particles and coils - technical detail
This procedure follows the usual protocol established at Curry Cabral Hospital (internal document: Portal Embolization Protocol of the Intervention Radiology Unit of the Curry Cabral Hospital).
In addition its technical aspects will be described here:
This technique is performed in similarity to previous descriptions[19,20]. Briefly, the right portal branch is accessed through an ultrasound guided ipsilateral approach (by the puncture of the tumoral liver portal vein branch). Initial portal angiography is performed to evaluate the anatomical pattern of the portal vein. Next, the catheterization and embolization of the segmental portal branches with PVA particles until flow stasis is obtained. In these same branches coils are deposited to achieve complete venous occlusion. A control portography is performed to confirm right portal vein occlusion. Embolization of the transhepatic pathway is performed to avoid hematoma formation from the puncture access liver entrance. The embolization of segment IV branches will not be performed. PVE with particles of PVA and coils is the current standard approach in the Department of Interventional Radiology, with more than 15 years of experience with this technique.

Protocol of the PVE procedure with NBCA - technical detail
This procedure follows the usual protocol established at Curry Cabral Hospital (internal document: Portal Embolization Protocol of the Intervention Radiology Unit of the Curry Cabral Hospital).
In addition its technical aspects will be described here:
This technique will also be performed in accordance with previous descriptions[21-23]. Briefly, the left portal branch is accessed through an ultrasound guided contralateral approach (by the puncture of the non-tumoral liver portal vein branch). Portal angiography is performed to evaluate the anatomical pattern of the portal vein and variations of the anatomy. Catheterization and embolization of the segmental right portal branches are then performed with a mixture of Lipiodol and NBCA (3: 1 ratio)

until stasis. The proportion may be adequate and modified according to the identified portal flow. Control and embolization of the transhepatic pathway is performed. The embolization of segment IV branches will not be performed.

Evaluation of hepatic hypertrophy - Primary objective

This evaluation will be performed through computed tomography (CT) hepatic volumetry before and 14 and 28 days after PVE[24].
Variation in the FLR volume (hepatic segments that will remain after hepatectomy) and in the tumour bearing liver (hepatic segments that will be removed at hepatectomy) will be measured 14 and 28 days after PVE. This analysis will be done through measurements of hepatic volumes by computed tomography volumetric software from the Curry Cabral Hospital (Volume Tracing in Advanced Vessel Analysis, Philips Healthcare). The magnitude of the hypertrophy - volumetric increase of the FLR after the PVE - will be calculated as the percentage of increase relative to the initial volume {eg, a FLR which shows an increase in volume from 250g (before PVE) to 500g (28 days after PVE) will be interpreted as a 100% increase in FLR volume at 28 days after PVE}.

Evaluation of postoperative outcome:

The immediate postoperative outcome (up to 30 days after surgery) will be analysed through the following postoperative parameters[25]:
1. Post-operative total hospitalization time.
2. Length of stay in the intensive care unit in the postoperative period.
3. Need for transfusion of blood products.
4. Complications after liver surgery.
5. Occurrence of postoperative liver failure.
The comparison of the complication rates between the two intervention groups is not a main objective of the trial, due to the already available literature that demonstrates that both techniques are equally safe and are widely used in different specialized health centers[7, 22]. However, the occurrence of serious adverse events will be monitored continuously throughout the study.
Other reviews:
Age, gender, liver disease etiology (hepatitis B, hepatitis C, alcohol consumption, NASH), number of cycles of previous chemotherapy regimen, ECOG performance status, Child-Pugh class, tumor number / diameter, total bilirubin, AST and ALT.

Compliance with administrative, ethical and legal requirements
The internal CHLC procedures associated with the Research Policy will be followed:
- Participant Information Form for Consent (INV 103)
- Form for obtaining Informed Consent for Participation in Health Research Studies (INV 103)

- Opinion of those responsible for the Areas / Specialties / Units where the study is intended
- Authorization of the Board of Directors of CHLC, as the Institutional Promoter of the Trial.
National procedures for conducting clinical trials will be followed:
- Registration with the National Commission for Data Protection (CNPD),
- Request for the opinion of Infarmed and inclusion in the National Register of Clinical Trials
- Request for an opinion from the Committee on Ethics for Clinical Research (CEIC).
- Register at ClinicalTrials.gov.

It is further guaranteed that:
- All medication prescribed for the treatment of other conditions may be maintained throughout the study;
- Participation in the test does not entail additional costs for the participants;
- The personal and clinical data of each patient will be anonymised, guaranteeing the privacy and confidentiality of the information.

Secondary objectives:
Evaluation of the cost, time for PVE execution, volume of contrast used, radiation exposure and postoperative evolution
The material used to perform PVE (the material used for embolization - NBCA, coils, PVA, catheters - and the conventional material of the angiography room), total time for its execution (in minutes), radiation exposure and total volume of iodinated contrast used will be collected in both groups for comparison.

Information note on cost evaluation:
• Comparison of costs associated with treatment arms (hypothesis to be tested: PVE with NBCA has significantly lower costs):

- Current average cost (estimated through the weighted average of the last 10 procedures) of PVE with PVA particles and coils: € 1320.00 per procedure.
- Average cost (estimated by consulting the price of NBCA and lipiodol at Curry Cabral Hospital and its expected consumption) of PVE with NBCA: € 158.00 per procedure.
- If total procedure time (room occupancy time) for NBCA PVE is significantly lower, it might translate in total cost reduction.

After the conclusion of this study we might be able to demonstrate the lower cost of performing PVE with NBCA.

Data collection
For this Trial there will be gathering of patient´s clinical data (by direct access to the patient and also through his or her clinical process) and PVE related information. For each patient a study number will be created in order to

anonymise the personal information guaranteeing confidentiality (for each patient a number will be assigned in order of recruitment, so the first patient will be the number 1 and so on). A separate information collection sheet will be created to guarantee these requirements. The information collection sheets will be grouped into a specific dossier that will be stored securely in the Interventional Radiology department under the responsibility of the principal investigator.

Statistical analysis plan

To estimate the efficacy of PVE in the induction of hepatic hypertrophy, the FLR volume (hepatic segments that will remain after hepatectomy) and tumor bearing liver volume (hepatic segments that will be removed at hepatectomy) will be measured at 14 and 28 days after PVE. The degree of hypertrophy - volumetric increase of the FLR after the PVE - will be calculated by the percentage of increase relative to the initial volume. Comparison of hepatic volumes will be performed using the t-pairs or Wilcoxon non-parametric test, as appropriate. Generalized additive regression models will be used to identify the variables that explain the variability of the degree of FLR hypertrophy after PVE.

Note: Interim analyzes of the Trial´s results will be carried out every 6 months to evaluate the efficacy of both approaches (NBCA versus PVA plus Coils). If evidence of benefit from one approach to the other is identified, the study will be discontinued early.

Trial length and patient follow-up

Each participant will be followed from the recruitment up to 30 days after the surgery.

The overall length of the Trial will be approximately 2 years:

- 12 months to total recruitment,
- 6 months to complete the execution of PVE procedures and liver surgeries;
- 6 months to complete the databases, epidemiological, statistical analysis, preparation of forms of disclosure of results (free communications and publication of results).

Resources required for the Study - Budget

The conduct of the clinical trial does not imposes additional costs for CHLC regarding materials and use of clinical services. There is rather time for the elements of the research team to be spent on the Trial.

Admission and complementary examinations during the study:

- According to the existing hospital protocol.

Execution of the PVE procedures:

- All procedures and materials to perform PVE, whether with PVA plus coils or with NBCA, will be those currently used in the Department of Interventional Radiology at Curry Cabral Hospital.

Study Schedule

	January 2019 to march 2019	April 2019 to April 2020	May to November 2020	December to June 2021
Elaboration of the project and submission to obtain authorization to conduct clinical studies	X			
Recruitment of patients, PVE execution and hepatectomies		X		
Statistical analysis, preparation of material for scientific dissemination			X	
Writing of scientific papers			X	
Publication of articles in high impact journals indexed in the area of liver surgery, oncology or radiology				X

Protocol changes
The current protocol is version 1.3 (February 27, 2018). Any change in protocol during the Trial that may affect its conduction, safety or benefit to patients will require a formal amendment to the protocol.

References:

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Randomization:
Block identifier, block size, sequence within block, treatment

1,20,1,Group B=GLUE

1,20,2,Group B=GLUE

1,20,3,Group A=PVA

1,20,4,Group B=GLUE

1,20,5,Group A=PVA

1,20,6,Group B=GLUE

1,20,7,Group A=PVA

1,20,8,Group A=PVA

1,20,9,Group A=PVA

1,20,10,Group A=PVA

1,20,11,Group B=GLUE

1,20,12,Group B=GLUE

1,20,13,Group A=PVA

1,20,14,Group B=GLUE

1,20,15,Group A=PVA

1,20,16,Group B=GLUE

1,20,17,Group B=GLUE

1,20,18,Group A=PVA

1,20,19,Group A=PVA

1,20,20,Group B=GLUE

2,20,1,Group A=PVA

2,20,2,Group B=GLUE

2,20,3,Group B=GLUE

2,20,4,Group B=GLUE

2,20,5,Group A=PVA

2,20,6,Group B=GLUE

2,20,7,Group A=PVA

2,20,8,Group B=GLUE

2,20,9,Group A=PVA

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2,20,14,Group B=GLUE

2,20,15,Group A=PVA

2,20,16,Group A=PVA

2,20,17,Group B=GLUE

2,20,18,Group B=GLUE

2,20,19,Group A=PVA

2,20,20,Group B=GLUE

3,20,1,Group B=GLUE

3,20,2,Group B=GLUE

3,20,3,Group A=PVA

3,20,4,Group A=PVA

3,20,5,Group B=GLUE

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3,20,7,Group B=GLUE

3,20,8,Group A=PVA

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3,20,15,Group B=GLUE

3,20,16,Group B=GLUE

3,20,17,Group A=PVA

3,20,18,Group A=PVA

3,20,19,Group B=GLUE

3,20,20,Group A=PVA

4,26,1,Group B=GLUE

4,26,2,Group A=PVA

4,26,3,Group B=GLUE

4,26,4,Group A=PVA

4,26,5,Group B=GLUE

4,26,6,Group A=PVA

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4,26,12,Group B=GLUE

4,26,13,Group A=PVA

4,26,14,Group A=PVA

4,26,15,Group B=GLUE

4,26,16,Group B=GLUE

4,26,17,Group A=PVA

4,26,18,Group A=PVA

4,26,19,Group A=PVA

4,26,20,Group B=GLUE

4,26,21,Group A=PVA

4,26,22,Group A=PVA

4,26,23,Group B=GLUE

4,26,24,Group B=GLUE

4,26,25,Group B=GLUE

4,26,26,Group B=PVA