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A comparative study between two materials in the promotion of liver growth before liver surgery

Submission date
02/07/2019

Recruitment status
No longer recruiting

Registration date
05/07/2019

Overall study status
Completed

Last Edited
17/08/2022

Condition category
Cancer

[_] Prospectively registered
[X] Protocol
[_] Statistical analysis plan
[X] Results
[_] Individual participant data

Plain English summary of protocol

Background and study aims
This study is dedicated to the topic of liver cancer, more specifically patients with liver cancer who might be candidates for surgical removal of this tumor. Unfortunately not all patients with liver tumours can undergo this surgery due to the small volume of healthy liver that will remain with the patient after surgery (the future liver remnant). The aim of this study is to evaluate a procedure that can increase healthy liver (called Portal Vein Embolization or simply PVE) before surgery and thus allow more patients to benefit from liver surgery. In this study two materials used to perform PVE are compared to evaluate which material produces the highest healthy liver growth.

Who can participate?
Patients aged 18 or over who have a liver tumor that was deemed resectable and has a small future liver remnant

What does the study involve?
Participants are randomly allocated to one of two groups. All undergo the same procedure, portal vein embolization (PVE). The difference is the materials used to perform PVE: one group undergo PVE using n-butyl-cyanoacrylate (medical glue) and the other group undergo PVE with micro-particles plus coils (small spherical particles associated with metallic spirals). 14 and 28 days after PVE participants are evaluated to calculate which material produced the highest healthy liver growth (in other words, which material produced the highest hypertrophy of the future liver remnant).

What are the possible benefits and risks of participating?
Patients undergo a procedure (Portal Vein Embolization – PVE) that might enable them to their liver tumor operated. This technique is intended to enable patients to undergo the potentially curative treatment of liver tumor resection. The side effects of PVE are few, namely local pain in the right upper abdominal quadrant, nauseas and fever. This symptoms usually last up to one to two days and are generally easily controlled with oral medication.

Where is the study run from?
Curry Cabral Hospital, Interventional Radiology Unit, Lisbon, Portugal

When is the study starting and how long is it expected to run for?
March 2017 to July 2020

Who is funding the study?
This is an investigator initiated and funded study. This means that the investigators developed the protocol, the study concept and design with no external influence or funding.

Who is the main contact?
Dr José Hugo Luz
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Additional identifiers

EudraCT/CTIS number
Nil known

IRAS number

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
CA1410

Study information

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

Acronym
BestFLR

Study objectives
Portal vein embolization with n-butyl-cyanoacrylate (NBCA) is more effective than portal vein embolization with polyvinyl alcohol 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.

Ethics approval required
Old ethics approval format

Ethics approval(s)

Approved 03/11/2017, Board of Directors of the Central Lisbon University Hospital Centre (Centro Hospitalar Universitário Lisboa Central, Rua José António Serrano. Zip code 1150-199. Lisbon. Portugal; Tel: +351 (0)218841000; Email: sec.ca@chlc.min-saude.pt), ref: CA1410

Study design
Interventional randomized single-centre trial

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Hospital

Study type(s)
Treatment

Participant information sheet

Health condition(s) or problem(s) studied
Liver cancer

Interventions
Method of randomization:
Randomization Method: RAR
The randomize R package of version 1.4 was used for generating the randomization list with the R version 3.4.0. This randomization was generated on August 27th 2017 at 22:31:05.

Methodology for each of the treatment arms:
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 field7, 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. It is estimated that two years will be enough to recruit the participants.

Randomization of participants by two interventions: The 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.

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 the 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 are 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. 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. Briefly, the left portal branch is accessed through an ultrasound-guided contralateral approach (by the puncture of the nontumoral 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.

Total duration of portal vein embolization: the procedure is performed only once (median procedure duration time is 90 minutes). Follow-up is up to 60 days after liver surgery.

Intervention Type
Procedure/Surgery

Primary outcome measure
Hepatic hypertrophy (liver volume growth) measured by computed tomography volumetry at 14 and 28 days

Secondary outcome measures
1. Fluoroscopy time (total minutes; e.g. 15 minutes of fluoroscopy), provided automatically by the Angiography machine at the end of each procedure (at the end of Portal Vein Embolization)
2. Contrast volume (millilitres), noted at the end of each procedure (at the end of Portal Vein Embolization)
3. Portal Vein Embolization execution total time (minutes), from the moment the Interventional Radiologist first punctures the liver up to the moment right after removing the liver access sheath
4. Postoperative outcome after liver surgery: this is a composite secondary endpoint:
4.1. Post-operative total hospitalization time (days) from the day of the liver surgery up to hospital discharge
4.2. Length of stay in the intensive care unit (days) from the day of the liver surgery up to intensive care unit discharge
4.3. Use of the "ISGLS" criteria (Rahbari et al Surgery 2011;149(5): 713–724) for liver failure evaluation
4.4. Occurrence of patient death up to 60 days after liver surgery (days) from liver surgery up to 60 days

Original secondary outcome measure at submission:
In the registry text, the "50-50" criteria was incorrectly attributed as the criteria to evaluate liver failure, being corrected to the "ISGLS" criteria, as in the original protocol (version 1.3).

Overall study start date
01/03/2017

Completion date
01/07/2020

Eligibility

Key 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:
3.1. 25% in healthy liver
3.2. 40% in cirrhotic liver or with severe steatosis or previous chemotherapy
4. Renal function suitable for the use of iodinated venous contrast medium:

4.1. Serum creatinine ≤ 1.4 mg/dL
4.2. Clearance of creatinine (GFR) ≥ 60 mL/min/1.73m2
5. Age ≥ 18 years

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Sex
Both

Target number of participants
72

Total final enrolment
60

Key exclusion criteria
1. Uncorrectable coagulopathies
2. Sectorial portal thrombosis (e.g., thrombosis of the right anterior sectorial branch)

Date of first enrolment
03/11/2017

Date of final enrolment
11/03/2020

Locations

Countries of recruitment
Portugal

Study participating centre
Curry Cabral Hospital
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Sponsor information

Organisation
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Sponsor type
Hospital/treatment centre

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ROR
https://ror.org/00k6r3f30

Funder(s)

Funder type
Other

Funder Name
Investigator initiated and funded

Results and Publications

Publication and dissemination plan
The intention is to publish this trial's results in a high-impact liver surgery or radiology journal in the second semester of 2020.

Intention to publish date
01/04/2021

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study are/will be available upon request from Dr José Hugo Luz (jose.luz@nms.unl.pt). Type of data: Database. When the data will become available and for how long: three months after the last recruited patient. Data will be available for 5 years. By what access criteria data will be shared: on request; including with whom: who might have specific interest in the data set, for what types of analyses: primary and secondary outcome (e.g. fluoroscopy time for each patient, volumetric results for each patient), and by what mechanism: this is an open issue, could be through post office or mail;

whether consent from participants was obtained: Yes; comments on data anonymisation: all patients are anonymised through codification (the study has the approval of the CNPD National Commission on Data Protection).

IPD sharing plan summary

Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article		06/04/2021	09/09/2021	Yes	No
Protocol file			17/08/2022	No	No