DRAGON 2 - An international multicenter randomized controlled trial to compare combined Portal and Hepatic Vein Embolization (PVE/HVE) with PVE alone in patients with Colorectal Liver Cancer Metastases (CRLM) and a small Future Liver Remnant (FLR).

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Ethical review	Approved WMO
Status	Recruiting
Health condition type	Hepatobiliary neoplasms malignant and unspecified
Study type	Interventional

Summary

ID

NL-OMON51713

Source
ToetsingOnline

Brief title
The Randomized Controlled DRAGON 2 Trial

Condition

- Hepatobiliary neoplasms malignant and unspecified
- Hepatobiliary neoplasms malignant and unspecified
- Hepatobiliary therapeutic procedures

Synonym
Colorectal Cancer Liver Metastases (CRLM)

Research involving
Human

Sponsors and support

Primary sponsor: Medisch Universitair Ziekenhuis Maastricht
Source(s) of monetary or material Support: Abbott,Guerbet,KWF;daarnaast zijn wij in overleg met Abbott laboratories;Guerbet en de NIHR.

Intervention

Keyword: Colorectal liver cancer metastases (CRLM), Combined Portal and Hepatic Vein Embolization (PVE/HVE), Future Liver Remnant (FLR), Hypertrophy

Outcome measures

Primary outcome

• 5-year overall survival

• Future Liver Remnant sufficient for resection in week 3 (based on liver

volume)

Secondary outcome

• Kinetic growth and volume of the FLR (efficacy assessment)

• FLR function increase (LiMax, ICG clearance, Hepatobiliary scintigraphy,

MRI-function)

• VAS (post embolization and resection)

• Time to sufficient FLR volume

• Success rate of IR procedure Embolization performed as scheduled /

achievement of hemostasis

• Time from intervention to resection

• Postembolization complications prior to surgery

• Operation duration

• Postoperative complications at 90 days

• Mortality at 90 days

• Survival at 1 year

• Disease-free survival at 1 year

• Number of oncological co-interventions (for example: resections, ablations,

SIRT, Systemic theraphy, etcetera) during survival.

• Quality of life

• Economic evaluation

• Etcetera*

Study description

Background summary

The current standard treatment for patients at risk of developing PHLF is performing a PVE prior to the (major) liver resection. In cases where tumors are located in the FLR, a two-stage hepatectomy may be the best option to prevent tumor growth due to possible growth stimulus in the FLR after PVE. In the first stage, tumors in the FLR are removed (the FLR is *cleaned*). Afterwards, PVE is performed and after 4 weeks, the volume growth of the FLR is assessed by volumetry. Once the volume of the FLR is sufficient (>30% of total liver volume, or >40%in case of a chemotherapy damaged liver), a second stage resection can be scheduled. This technique is well established in many liver surgery centers.
This protocol proposes to study superiority of combined PVE/HVE over PVE alone in an international multicenter randomized controlled trial (1:1). The novel combined PVE/HVE technique has the potential to replace the current standard PVE. For the reason that PVE/HVE is more efficient, ALPPS will be less of a treatment option to consider and there will perhaps be no need for two staged hepatectomies because the time in which potential tumor progression can take place will be reduced. Participating centers in the DRAGON trials collaborative who safely performed 3 cases of combined PVE/HVE within a year in the DRAGON trial 1 or DRAGON registry are eligible for the DRAGON trial 2.

Study objective

The primary objective of DRAGON 2 is to demonstrate the superiority of combined PVE/HVE over PVE alone in either the resectability of the patients within 3 weeks after intervention defined as FLR sufficient for resection on week 3 and the 5-year overall survival.

Secondary Objectives
Secondary objectives of the study are volume and function changes of the FLR, complications, time to surgery/ waiting time, surgical details (e.g. bloodloss, operation duration), number of oncological co-interventions, quality of life, economical evaluation, etc.

Study design

An international multicenter randomized controlled trial (approximately 40 centers) in which patients will be randomized (1:1) in center-stratified blocks into two arms: combined PVE/HVE and PVE alone. In total 348 patients will be included (n=174 patients per arm)

Intervention

Combined PVE/HVE is the occlusion of the portal vein branch of one side of the liver complemented by the embolization of the hepatic veins draining the same area, to induce hypertrophy on the contralateral side.

In most cases, the embolization of the portal vein branch is achieved by PVE. A micro-puncture set either from the side that will be embolized or from the contralateral side (both techniques are used by interventional radiologists). PVE is a standard interventional radiology technique that is performed in most medical centers. Technical modifications are common between centers, but in this trial, PVE involves filling the portal vein system with glue consisting of a mixture of iodized oil (Lipiodol), cyanoacrylate and sometimes additional particles like coils or plugs can be placed centrally. We advise, if possible, to always embolize segment 4 during the PVE procedures. After the procedure, the access sheath is pulled back and the track occluded. The used technique is recorded, and the report with blacked identifiers is uploaded onto the electronic case report form (CRF). In the Work Instruction *PVE and PVE/HVE procedure* the PVE procedure is explained in more detail.

Subsequently, HVE is performed in the same session. Only in exceptional cases a staged procedure with up to 48 hours between PVE and HVE is accepted, but the reason must be filled out in the CRF. In HVE the right or left hepatic vein is accessed through a trans jugular approach. Through a sheath, an appropriately sized Amplatzer Vascular Plug device is introduced into the hepatic vein. Injection of contrast is then used to confirm placement of the vascular plug.

Additional embolization of small vessels with glue is not allowed in the DRAGON 2 trial. If applicable the middle hepatic vein is plugged as well. The HVE procedure is displayed in more detail in the WI *PVE an PVE/HVE*.

The decision on how many hepatic veins should be embolized is also left to the judgement of the local principal investigators, since it depends on the individual anatomy of the liver. We do advise to plug as much separate vein branches as possible. If required, cases can always be discussed upfront within the DRAGON trial study collaborative.

Study burden and risks

Based on the currently available literature, the performance of PVE/HVE is completely safe with no complications occurring more frequently compared to the gold standard PVE. Theoretically, because of the HVE in PVE/HVE, there is a risk of local bleeding (at the puncture site in the neck or groin), inflammation or plug migration into the hepatic vein, however, this has not yet been described in the literature and we have never seen this either.
The PVE/HVE procedure takes twice as long as the PVE procedure. Radiation is used during the procedures. Compared to PVE, the radiation exposure by PVE/HVE is twice as high (32mSv compared to 16 mSv). However, this has been approved by the radiation protection committee of the MUMC+.

With regard to the burden:
The regular care is followed in this trial, however, in the first year the patient is asked to fill out 5x a quality of life form.

Benefits of the interventional proccedure (PVE/HVE) could be more and faster Futurel Liver Remnant hypertrophy, which could lead to a higher resection rate in this arm. this could also improve the oncological outcomes in these patients.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

• Patients with primarily unresectable/ potentially resectable CRLM with a FLR <30% (<40% in chemotheraphy demaged livers)
• Patients with non-resected primary CRC may be included if there is an intention to resect the CRC after the liver treatment (liver first approach) or simultaneously during one of the liver procedures.
• Patients with resectable or ablatable lung or brain metastases can be included (statement about the resectability of these extrahepatic metastases by a tumor board needs to be available)
• 18 Years and older
• Men and women
• Able to understand the trial and provide informed consent.

Exclusion criteria

• Pregnant or lactating women
• Premenopausal females not willing to commit to oral contraception
• Patients with prohibitive comorbidities, decision made by local team
• Any patient with non-resectable or non-ablatable extrahepatic disease
• Patients with hepatic malignancies other than CRLM
• Progression of disease by RECIST criteria after cytoreduction chemotherapy
• Complete response after conversion chemotherapy
• Staging CT and (if indicated) CT/MRI brain that demonstrates non-resectable

extrahepatic disease

Study design

Design

Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	19-04-2023
Enrollment:	75
Type:	Actual

Ethics review

Approved WMO Date:	06-09-2022
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	14-05-2025
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
CCMO	NL80303.068.22