

Study Protocol

Title of the study: Split-in-situ Resection With Radio-frequency Ablation Instead of Liver Partition on the First Stage (RALPPS) in Patients With Hilar and Intrahepatic Cholangiocarcinoma

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Background: Unsatisfactory immediate outcomes of Associating liver partition and portal vein ligation for staged hepatectomy (ALPPS) in surgery of cholangiocarcinoma suggested that patients with biliary cancer should not be treated by ALPPS. Short-term results of ALPPS variants with reduced surgical trauma on the first stage in patients with cholangiocarcinoma were not yet estimated.

Study design: retrospective observational case-control study.

The purpose of the study: comparison of short-term results of RALPPS and portal vein embolization (PVE) in patients with hilar (h-CCA) and intrahepatic (i-CCA) cholangiocarcinoma.

Material and Methods: two groups will be compared.

Group 1: patients with h-CCA and i-CCA underwent RALPPS.

Group 2: patients with h-CCA and i-CCA underwent PVE.

Inclusion Criteria: patients with h-CCA and i-CCA which are the candidates for radical treatment (intention to R0 resection) using major liver resection with volume of future liver remnant (FLR) less than 40%.

Indication for RALPPS/PVE.

- h-CCA, type II-IV, T1-3N0-1M0, volume of FLR<40%
- i-CCA, T1-3N0-1M0, volume of FLR<40%

Contraindication for RALPPS/PVE.

- h-CCA, stage IVA, B
- i-CCA, stage IVB
- i-CCA, T4N0-1M0
- i-CCA, h-CCA with volume of FLR >45%
- acute cholangitis and/or infected fluid collections, liver abscesses, other unresolved surgical complications of biliary draining procedures.
- jaundice with total bilirubin >50 μ mol/L
- prior anamnestic allergic reaction or any other sign of intolerance to iodinated contrast media

Inclusion Criteria

- Gender: both, male and female
- Minimum age 18 years
- Maximum age: 80 years

Exclusion Criteria

- Age under 18 years
- Age above 80 years
- Persons who are incapable of giving consent
- Pregnant or breast-feeding women

Preoperative examination:

1. Abdominal ultrasound examination,
2. Abdominal enhanced CT (with or without MRI and MRCP),
3. Direct cholangiography,
4. Chest CT,
5. The upper digestive tract endoscopic examination,
6. Colonoscopy (if it is absent over the past year),
7. Tumor markers (CEA and CA 19-9).

Comparative analysis should include following intraoperative and postoperative factors

Primary endpoint: rate of FLR hypertrophy (%).

The standard formula for calculation the rate of hypertrophy:

$$[(\text{Post-PVE FLR} - \text{Pre-PVE FLR}) / (\text{Pre-PVE FLR})] \times 100$$

Secondary endpoints:

1. Morbidity after stage 1 (according to Clavien-Dindo classification, [attachment 1](#))
2. Morbidity after stage 2
3. Blood loss (during stage 2)
4. Duration of hospital stay

Bile leakage will be classified in severity according to the international study group for liver surgery ([attachment 2](#)).

Posthepatectomy liver failure was estimated according to the international study group for liver surgery ([attachment 3](#)).

The number of patients for primary estimation of short-term results consist of 10 patients in RALPPS group and 20 patients in group of PVE. If preliminary results reveal tendency to better results of RALPPS in terms of FLR hypertrophy and confirm safety of RALPPS the number of patients will be increased to 60 (30 patients in each group).

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Attachments 1

CLAVIEN-DINDO GRADING SYSTEM FOR THE CLASSIFICATION OF SURGICAL COMPLICATIONS

Grades	Definition
Grade I:	Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic and radiological interventions. Allowed therapeutic regimens are: drugs as antiemetics, antipyretics, analgetics, diuretics and electrolytes and physiotherapy. This grade also includes wound infections opened at the bedside.
Grade II:	Requiring pharmacological treatment with drugs other than such allowed for grade I complications. Blood transfusions and total parenteral nutrition are also included.
Grade III:	Requiring surgical, endoscopic or radiological intervention
Grade III-a:	Intervention not under general anesthesia
Grade III-b:	Intervention under general anesthesia
Grade IV:	Life-threatening complication (including CNS complications: brain haemorrhage, ischaemic stroke, subarachnoid bleeding, but excluding transient ischaemic attacks) requiring IC/ICU management.
Grade IV-a:	Single organ dysfunction (including dialysis)
Grade IV-b:	Multi-organ dysfunction
Grade V:	Death of a patient
Suffix 'd':	If the patient suffers from a complication at the time of discharge, the suffix "d" (for 'disability') is added to the respective grade of complication. This label indicates the need for a follow-up to fully evaluate the complication.

Clavien PA, Barkun J, de Oliveira ML, et al. The Clavien-Dindo classification of surgical complications: five-year experience. Ann Surg. 2009 Aug;250(2):187-96. doi: 10.1097/SLA.0b013e3181b13ca2.

Attachments 2

Bile leakage

Bile leakage grade A: Grade A bile leakage has little or no impact on patients' clinical management.

Bile leakage grade B: A bile leakage requiring a change in patients' clinical management but can be treated without relaparotomy.

Bile leakage grade C: Patients with a Grade C bile leakage require relaparotomy to control this complication.

Koch M, Garden OJ, Padbury R, et al. Bile leakage after hepatobiliary and pancreatic surgery: a definition and grading of severity by the International Study Group of Liver Surgery. Surgery. 2011 May;149(5):680-8. doi: 10.1016/j.surg.2010.12.002. Epub 2011 Feb 12.

Attachments 3

Posthepatectomy liver failure

Grade A posthepatectomy liver failure: Grade A PHLF represents a postoperative deterioration of liver function that does not require a change in the patient's clinical management.

Grade B posthepatectomy liver failure: Patients are diagnosed with grade B PHLF if there is a deviation from the regular, postoperative clinical pathway, but they can be managed without invasive treatment.

Grade C posthepatectomy liver failure: Patients who develop PHLF requiring an invasive procedure are classified as having grade C PHLF.

Rahbari NN, Garden OJ, Padbury R, et al. Posthepatectomy liver failure: a definition and grading by the International Study Group of Liver Surgery (ISGLS). *Surgery*. 2011 May;149(5):713-24. doi: 10.1016/j.surg.2010.10.001. Epub 2011 Jan 14.