LIVERT(W)OHEAL

Living Donor Liver Transplantation With Two Stage Hepatectomy for Patients With Isolated, Irresectable Colorectal Liver Metastases

NCT-Nummer:
NCT03488953

Studienbeginn:
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Wirkstoff:
-

Indikation (Clinical Trials):
Neoplasm Metastasis, Liver Neoplasms

Geschlecht:
Alle

Altersgruppe:
Erwachsene (18+)

Phase:
-

Sponsor:
Jena University Hospital

Collaborator:
University Hospital Tuebingen

Studien-Informationen

Detailed Description:

Purpose

The purpose of the present study is to evaluate a two-stage hepatectomy with a left-lateral living donor liver transplantation and right portal vein ligation for treatment of otherwise irresectable liver metastases of colorectal carcinoma in curative intent.

Study setting

The study is an investigator-initiated, bi-institutional, one-arm trial. For ethical reasons, it was decided to perform no control group since the superiority of the liver transplantation procedure is to be expected. Therefore, it was decided to compare the transplantation cohort with a historic control group who has received the actual gold-standard of chemotherapy.

Endpoints Primary endpoint The primary endpoint is the overall patient survival 36 months after the 2nd step of liver transplantation in a two stage procedure.

This time point was chosen since the patient has to be regarded as "free of tumor" from this last step of tumor operation.

Secondary endpoints

Secondary endpoints are:

- the recurrence-free survival of the patients 36 months after second stage of hepatectomy.

- the morbidity of both donor and recipient, defined as complications ≥ IIIb according to the Clavien-Dindo classification.

Patient selection

All patients with irresectable colorectal liver metastases and no extrahepatic tumor burden (except resectable lung metastases) are potential candidates for study inclusion, if:

- the tumor burden is at least a "stable disease", according to the RECIST criteria at least after eight weeks of systemic chemotherapy

- an external, independent review board, composed of a surgeon, an oncologist and a radiologist, checked and approved the criteria for study inclusion.

Exclusion criteria

Patients are ineligible for study participation, if:

- there is an extrahepatic tumor burden, except resectable lung metastases

- no suitable donor available

- significant comorbidities that preclude transplantation

- there is a tumor progression during chemotherapy.

Treatment methods If the potential recipient fulfills the in- and exclusion criteria and has a potential suitable living donor, the patient will be admitted to a special transplantation ward, where the evaluation process for liver transplantation in this special setting begins according to the standard evaluation protocol of the specific centre. The procedure includes a PET-CT scan for tumor burden additional to the standard evaluation for liver transplantation.

If contraindications for liver transplantation are excluded, the potential recipient will be discussed in the transplantation board and subsequently listed as organ recipient at Eurotransplant waiting list.

Furthermore, the patient's history and all available imaging will be sent to an external review board, consisting of an experienced hepatobiliary surgeon, an oncologist and a radiologist, who will assess the individual case from their specialized field. Only if all three reviewer approve the study inclusion of the patient, the following steps are performed.

Now the potential donor will be evaluated for the living donation process. This includes an ultrasound, an MR scan for the visualization of the biliary tract and a CT scan. The latter ones will be analyzed with exact volumetric analyses of the donated and remaining liver parenchyma. Furthermore, the evaluation process includes a cardiologic examination and the premedication visit as well as a LiMAX test. Both, donor and recipient, will be interviewed by a clinical psychologist.

At the end of the evaluation procedure, the individual patient case will be judged by an independent living donation committee of the respective State Chamber of Physicians.

Operative procedure - Step 1 The transplantation procedure starts with an extensive exploration of the abdominal cavity of the recipient to exclude an extrahepatic tumor manifestation. If there is no extrahepatic tumor burden, a left hemihepatectomy is performed (the liver resection itself is undertaken using an appropriate device, e.g. Cavitron Ultrasound Aspirator), whereby the resection plane depends on the localization of the metastases and might vary between individual patients. For the subsequent reconstruction of the arterial inflow of the left lateral graft, a venous interposition graft (usually saphenous vein of the recipient) is established from the common hepatic artery.

Parallel, the donor procedure is started, whereby a left-lateral hepatectomy (resection of the segments II and III) is performed (also using standard devices for parenchymal transsection, e.g. Cavitron Ultrasound Aspirator).

The left-lateral graft is transplanted orthotopically. To induct a more rapid growth and regeneration of the graft, the right portal vein is ligated (according to an ALPPS procedure) while measuring the portal pressure. The reconstruction of the biliary tree of the graft is realized performing a bilio-enteric anastomosis. This allows an easier procurement of the right liver in step 2.

The immunosuppression is performed according to the following protocol:

- Intraoperative

500 mg Methylprednisolone i.v.

- Early postoperative phase

Tacrolimus Target level 5 - 10 ng/ml

Mycophenolat-Mofetil 1000 mg twice daily

Basiliximab 20 mg i.v. on the day of the transplantation and on POD 4

Prednisolone 0,5 mg/kgBW/d from POD 1 - 10 and reduction of 0,1 mg/kgBW/d every 10 days

* 3 months after the transplantation procedure

Everolimus in combination with Tacrolimus Both with a target level of around 5 ng/ml

Between both operative steps, continuous laboratory analyses as well as ultrasound investigations will be performed. Presumable after three weeks, a CT scan, a subsequent MEVIS analysis and a LiMAX test are performed. If a normal liver function is diagnosed, step 2 is scheduled for the following day.

Operative procedure - Step 2 In this operation, the remaining right liver will be removed. Hereby, additional parenchymal transsection is usually not necessary since both liver has been completely separated in Step 1.

Follow-up The follow-up is coordinated by the transplantation unit of the centers. It includes a CT scan of thorax and abdomen six, nine, 18 and 30 months after the finalization of the two-stage procedure (step 2). Furthermore, a PET-CT scan will be performed after three months and 1, 2 and three years after step 2. At these points in time, a LIMAX-test will also be performed to assess the liver function of the graft. Furthermore, the individual immunosuppressive regime is recorded. In case of an adjuvant chemotherapy, agents, duration and tolerance of the drug(s) will be registered.

Statistical methods The primary endpoint (overall survival) and the secondary endpoint "disease-free survival" are examined in a model using a Gray's test since they are competing events. For both events, the calculated hazard ratios are indicated with a confidence interval of 95 %.

All other secondary endpoints, reflecting the morbidity of donor or recipient, are compared using Fisher's exact test between the groups. The absolute and relative frequency of these adverse events per group will be reported.

The significance level for all tests is defined as $\alpha=0,05$. The analysis is performed according to an "intention-to-treat"-principle. Subgroup analysis are not planned.

Centralized monitoring and the Data and Safety Monitoring Committee The data monitoring will be performed by the Center of Clinical Studies in Jena and Tübingen.

Participating institutions The German Medical Association approved the study protocol for the liver transplantation centers in Jena and Tübingen. During this study, it is not provided to enable other transplantation centers the study participation.

Ein-/Ausschlusskriterien

Inclusion Criteria:

- Patients with irresectable colorectal liver metastases without extrahepatic tumor burden, except

resectable pulmonary metastases

- stable disease or regression after at least eight weeks of systemic chemotherapy

Exclusion Criteria:

- comorbidities precluding liver transplantation

- extrahepatic tumor spread, except resectable pulmonary metastases

- progression during chemotherapy

Studien-Rationale

Primary outcome:

1. Overall survival three years after 2nd-stage of hepatectomy (Time Frame - 3 years):
Overall survival three years after 2nd-stage of hepatectomy

Secondary outcome:

1. Disease-free survival three years after 2nd-stage of hepatectomy (Time Frame - 3 years):
Disease-free survival three years after 2nd-stage of hepatectomy

2. Morbidity of the recipient (Time Frame - 3 years):
all complications > grade IIIa according to the Clavien-Dindo classification

3. Morbidity of the donor (Time Frame - 3 years):
all complications > grade IIIa according to the Clavien-Dindo classification

Geprüfte Regime

- Living donor liver transplantation with two-staged hepatectomy.:
Two-stage hepatectomy combined with transplantation of left-lateral lobe from a living donor.

Kontakt

Falk Rauchfuss, M.D., M.Sc.
Kontakt:
Phone: 004936419322601
E-Mail: Falk.Rauchfuss@med.uni-jena.de

Ulrike McCaulley, Study Nurse
Kontakt:
Phone: 004936419322694
E-Mail: Ulrike.McCaulley@med.uni-jena.de

Studienlocations (2 von 2)

Jena University Hospital
07747 Jena
(Thüringen)
Germany

Status: Rekrutierend

University Hospital Tübingen
72076 Tübingen
(Baden-Württemberg)
Germany

Status: Rekrutierend

Quelle: ClinicalTrials.gov