Clinical Study Protocol

Associating Liver Partition with Portal Vein Ligation for Staged Hepatectomy (ALPPS) versus Two Stage-Hepatectomy for marginally resectable colorectal liver metastases – a randomized controlled trial

Short Title
ALPPS versus PVO (USZ-ZH-VIS-ALPPS)

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Protocol Version and Date:
USZ-ZH-VIS-ALPPS 5.2.
15.05.2013

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1 GENERAL INFORMATION

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Laboratory and other institutions involved in the trial:  
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Visceral- and Transplantation Surgery  
University Hospital Zurich  
CH-8091 Zurich, Switzerland
# STUDY SYNOPSIS

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<thead>
<tr>
<th>Principal Investigator:</th>
<th>Erik Schadde, MD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sponsor:</td>
<td>Pierre-Alain Clavien MD, PhD</td>
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<tr>
<td>Study Title:</td>
<td>ASSOCIATING LIVER PARTITION WITH PORTAL VEIN LIGATION FOR STAGED HEPATECTOMY (ALPPS) Versus Two-stage hepatectomy (TSH) For marginally resectable liver tumors – a randomized controlled trial</td>
</tr>
<tr>
<td>Short Title/Study ID:</td>
<td>ALLPS versus TSH – a randomized trial</td>
</tr>
<tr>
<td>Protocol Version and Date:</td>
<td>Version 5.2. 15.05.2014</td>
</tr>
<tr>
<td>Methodology:</td>
<td>Multiple Center Randomized Clinical study (Elements of the Protocol applicable in Zurich only are marked “Zurich only”)</td>
</tr>
<tr>
<td>Study Duration:</td>
<td>The planned duration of study participation for an individual subject from screening to follow-up is 12 months. The entire study duration is 2 years.</td>
</tr>
<tr>
<td>Study Center:</td>
<td>University Hospital Zürich</td>
</tr>
<tr>
<td>Investigator(s):</td>
<td>Erik Schadde MD, Henrik Petrowsky, Mickael Lesurtel MD, PhD, Michelle De Oliveira MD, Rolf Graf PhD, Thomas Frauenfelder MD, Bernhard Pestalozzi MD, Achim Weber MD, Milo Puhan PhD, Pierre-Alain Clavien MD, PhD</td>
</tr>
</tbody>
</table>
| Objective(s)/Outcome(s):| Primary endpoint: **Oncologic outcome: Patient alive and free of disease by PET CT 12 months after randomization**

Secondary endpoints:
1. Safety: Mortality
2. Safety: Complications by comprehensive complications score (CCI)
3. Feasibility of complete resection
4. Oncologic outcome: Incidence of R0 and R1 resection
5. Oncologic outcome: Overall survival
6. Quality of life
7. Liver volumetric changes (CT or MRI)

Translational part of the study (Zurich only):
Biopsies and blood samples
Physiology of changes in hepatic blood flow after portal vein ligation

Number of Subjects: 60 patients in each arm
<table>
<thead>
<tr>
<th><strong>Diagnosis and Main Inclusion Criteria:</strong></th>
<th>Patients with colorectal liver metastasis requiring liver resection, but are not resectable in one step because of future liver remnant to total liver volume &lt; 30 % OR future liver remnant to body weight ratio &lt; 0.5. Extrahepatic metastatic disease is not an exclusion criterion if they are resectable at a later time point (f.e. CRM pulmonary lesions)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Main Exclusion Criteria:</strong></td>
<td>Patients with</td>
</tr>
<tr>
<td></td>
<td>1. Liver tumors other than colorectal liver metastases</td>
</tr>
<tr>
<td></td>
<td>2. Patients with bilobar CRLM who have not received any chemotherapy</td>
</tr>
<tr>
<td></td>
<td>3. Patients with histological changes of fibrosis, cirrhosis, &gt;30% liver macrosteatosis</td>
</tr>
<tr>
<td></td>
<td>4. Significant comorbidity rendering subjects unsuitable for major surgery</td>
</tr>
<tr>
<td></td>
<td>5. Extrahepatic procedures performed simultaneously</td>
</tr>
<tr>
<td><strong>Study Schedule:</strong></td>
<td>Study duration 2 years</td>
</tr>
<tr>
<td></td>
<td>First-Subject-In is planned in Q 3 2014</td>
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<tr>
<td></td>
<td>Last-Subject-Out is planned for Q 2016</td>
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<tr>
<td><strong>Statistical Methodology:</strong></td>
<td>Randomized controlled clinical trial of two surgical methods to resect liver metastases</td>
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<tr>
<td><strong>Statement:</strong></td>
<td>This study will be conducted in compliance with the protocol, the current version of the Declaration of Helsinki, and ICH-GCP as well as all national legal and regulatory requirements. The study will also follow the respective SAMW Guideline regarding the collection of human biological material (Biobanking).</td>
</tr>
</tbody>
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## 3 STUDY FLOW CHART

<table>
<thead>
<tr>
<th>schedule</th>
<th>Enrollment visit</th>
<th>Preoperative Testing,</th>
<th>Stage One with postoperative Care Randomisation</th>
<th>Stage Two Surgery for</th>
<th>F/u visit 1</th>
<th>F/u visit 2</th>
<th>Later F/U visits</th>
<th>Study end visit</th>
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<tr>
<td>Visit Nr.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
<td>7</td>
<td>8</td>
</tr>
<tr>
<td>Day</td>
<td>minus 1 month</td>
<td>minus 1 week</td>
<td>Both arms: 0</td>
<td>ALPPS arm: week 1-2</td>
<td>TSH arm: week 4-8</td>
<td>Week 4 (+/− 5 days)</td>
<td>Week 8 (+/− 5 days)</td>
<td>Oncological follow-up month 3, month 6 month 9 (+/− 5 days)</td>
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<tr>
<td>Informed Consent</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
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<td>Demographics</td>
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<td>x</td>
<td>x</td>
<td>x</td>
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<td>Physical Examination</td>
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<td>xxx…</td>
<td>xxx…</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
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<tr>
<td>Registration</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
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<tr>
<td>Liver synthetic function</td>
<td>x</td>
<td>xxx…</td>
<td>xxx…</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
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<tr>
<td>ICG Green (Zurich only)</td>
<td>x</td>
<td>xxx</td>
<td>xxx</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
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<td>Renal function and myoglobin</td>
<td>x</td>
<td>xxx…</td>
<td>xxx…</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
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<td>Standard tumormarker&lt;sup&gt;3&lt;/sup&gt;</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
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<td>Circulating tumor cells (zurich only)</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
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<tr>
<td>Standard Dynamic MRI (abdomen) +volumetry (CRF 4) (Zurich only – in other centers CT volumetry might be used)</td>
<td>x (dynamic)</td>
<td>x (no contrast, not dynamic)</td>
<td>x (dynamic)</td>
<td>x (no contrast, not dynamic)</td>
<td>x</td>
<td>x</td>
<td>x</td>
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<tr>
<td>Intraoperative Flow and Pressure Measurement</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
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<tr>
<td>Tissue for standard H+E and KY-67 proliferation index of</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
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<tr>
<td>Procedure Description</td>
<td>Before and After</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>--------------------------------------------------------------------------------------</td>
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<tr>
<td>Blood Samples drawn from central line (Zurich only)</td>
<td>xx… preop, postop and every day postop</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td></td>
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<tr>
<td>Tissue for standard tumor histology and staging</td>
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<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
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<tr>
<td>Adverse Events/Complications</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td></td>
<td></td>
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<tr>
<td>Quality of life assessment, feeling thermometer</td>
<td>x</td>
<td>xx Before and after surgery</td>
<td>xx Before and after surgery</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td></td>
</tr>
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</table>
Screening marginally resectable CRLM

1. Dynamic MRI/CT
2. Transjugular biopsy
3. Consent
4. Registration
5. Randomization day 0

ALPPS arm (portal vein ligation and parenchymal transection)

Stage One
One week after stage 1
CT Volumetry

Step Two
If volume not sufficient:
CT volumetry

Discharge

f/u Visit # 1

f/u Visit # 2

Oncologic follow-up with screening for recurrence per: US or CT/MRI (per center preference)

TSH arm (portal vein ligation during stage 1 or embolization within one week)

Stage One
One week after ligation/embol
CT volumetry

Discharge

f/u Visit #1

Step Two

f/u Visit #2

If volume not sufficient
MRI/CT volumetry

Discharge

Oncologic follow-up with screening for recurrence per: US or CT/MRI (per center preference)

Week 0

Week 1

Week 2

Week 4

Week 8

Month 03

Month 06

Month 09

Month 12

Study termination: PET CT

Study termination: PET CT
# LIST OF ABBREVIATIONS

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Description</th>
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<tbody>
<tr>
<td>AE</td>
<td>Adverse Event</td>
</tr>
<tr>
<td>ALT</td>
<td>Alanine aminotransferase</td>
</tr>
<tr>
<td>ALPPS</td>
<td>Associating Liver Partition with Portal vein Ligation for Staged Hepatectomy</td>
</tr>
<tr>
<td>CEA</td>
<td>Carcinoemryonic antigen</td>
</tr>
<tr>
<td>CCC</td>
<td>Cholangiocarcinoma</td>
</tr>
<tr>
<td>CRM</td>
<td>Colorectal Cancer Metastasis</td>
</tr>
<tr>
<td>CRF</td>
<td>Case report form</td>
</tr>
<tr>
<td>CT</td>
<td>Computed tomography</td>
</tr>
<tr>
<td>CTCAE</td>
<td>Common terminology criteria for adverse events</td>
</tr>
<tr>
<td>CRC</td>
<td>Colorectal cancer</td>
</tr>
<tr>
<td>CR</td>
<td>Complete response</td>
</tr>
<tr>
<td>CTP</td>
<td>Child-Turcotte-Pugh Score</td>
</tr>
<tr>
<td>DPL</td>
<td>Deportalized Lobe</td>
</tr>
<tr>
<td>FDA</td>
<td>Federal food and drug administration (US)</td>
</tr>
<tr>
<td>FLR</td>
<td>Future liver remnant</td>
</tr>
<tr>
<td>FLR/BW</td>
<td>Future liver remnant to body weight ratio</td>
</tr>
<tr>
<td>FLR/TLV</td>
<td>Future liver remnant to total liver volume ratio</td>
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<tr>
<td>F/U</td>
<td>Follow-up</td>
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<tr>
<td>HCC</td>
<td>Hepatocellular carcinoma</td>
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<td>HCRM</td>
<td>Hepatic colorectal metastasis</td>
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<td>ICF</td>
<td>Informed consent form</td>
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<td>ICG</td>
<td>Indocyanine Green Test</td>
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<tr>
<td>IHC</td>
<td>Immunohistochemistry</td>
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<tr>
<td>ISSH</td>
<td>In-situ split staged hepatectomy</td>
</tr>
<tr>
<td>KEK</td>
<td>Kantonale Ethikkommission</td>
</tr>
<tr>
<td>LISH</td>
<td>Long interval staged hepatectomy</td>
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<tr>
<td>MRI</td>
<td>Magnetic resonance imaging</td>
</tr>
<tr>
<td>OS</td>
<td>Overall survival</td>
</tr>
<tr>
<td>PET</td>
<td>Positron emission tomography</td>
</tr>
<tr>
<td>PFS</td>
<td>Progression free survival</td>
</tr>
<tr>
<td>PT/INR</td>
<td>Prothromin time/International normalized ratio</td>
</tr>
<tr>
<td>PR</td>
<td>Partial response</td>
</tr>
<tr>
<td>PVE</td>
<td>Portal vein embolization</td>
</tr>
<tr>
<td>PVL</td>
<td>Portal vein ligation</td>
</tr>
<tr>
<td>PVO</td>
<td>Portal vein occlusion</td>
</tr>
<tr>
<td>RECIST</td>
<td>Response evaluation criteria in solid tumors</td>
</tr>
<tr>
<td>SAE</td>
<td>Serious adverse event</td>
</tr>
<tr>
<td>WBC</td>
<td>White blood count</td>
</tr>
</tbody>
</table>
5.1 Background: Treatment of marginally resectable CRLM

5.1.1. Portal vein manipulation to induce hepatic hypertrophy

Surgical resection has offered the best option for prolonged survival in patients with CLRM. Over the past 20 years significant progress has been made to expand the criteria for defining “resectability” in patients with primary or metastatic hepatic malignancy. The emphasis in the assessment of “resectability” – a term not clearly defined and varying depending on the experience of the individual surgeon – is preservation of hepatic inflow and outflow of the future liver remnant (FLR) as well as the volume of the FLR after resection that will remain to support the patient metabolically. In an attempt to further increase “resectability” criteria for patients with too small liver remnants, surgical and interventional maneuvers such as portal vein embolization (PVE), portal vein ligation (PVL) in Two-stage hepatectomies have been implemented.

![Algorithm](image)

**Figure 1**: Algorithm demonstrating the central role of the size of the future liver remnant for major liver resections

Limiting factor for major liver resections is the size of the FLR. In case of normal liver function 30% of the total liver volume is considered to be sufficient to maintain a
adequate liver function after resection. This algorithm is represented in figure 1. In patients with underlying liver disease or earlier stages of hepatic dysfunction (steatosis, steatohepatitis, chemotherapy) the FLR-cutoff ought to be higher at 40%. To avoid operating on patients with a low-volume FLR, occlusion of the portal vein in the tumor bearing lobe with subsequent volumetric increase of the contralateral lobe may be necessary. The rationale behind this approach is a portal flow diversion into the FLR.. Makuuchi et al. were the first to introduce PVE as a preoperative intervention to induce compensatory liver hypertrophy of the contralateral side [2]. The concept of PVE emerged from the recognition that tumor invasion of the portal vein causes contralateral lobar hypertrophy with ipsilateral atrophy. Nowadays, PVE is regarded as a safe intervention with a moderate complication rate of 5-8% bearing adequate volumetric FLR increase of 30-40% [3, 4]. In general, portal vein occlusion (PVO) can be achieved by portal vein embolization (PVE) performed by interventional radiologists.

5.1.1. The concept of Two-Stage Hepatectomies

This portal vein manipulation strategy for patients with marginally resectable CLRM is generally used in the context of Two-stage hepatecomies introduced by Adam et al. in 2000 [5]. In their initial report the authors described a two-staged approach with the highest possible number of liver metastases removed during the first operation [5]. In a postoperative waiting interval the FLR was allowed to hypertrophy for a period of 2-14 months, sometimes combined with chemotherapy to limit cancer growth, before the remaining tumor was safely removed in a second stage. In the initial manuscript 6 out of 13 patients underwent PVE in the interval between the two stages to promote compensatory hypertrophy. A recent follow-up paper by the same group, presenting long-term results until 2008, reported that second stage resections have become possible in 41 out of 59 patients (69%) patients [6]. The patients who ultimately failed this approach, developed tumor recurrence in the interval between these two stages. Nevertheless, two-staged hepatectomies have become increasingly popular in many centers around the world with numerous groups reporting favourable clinical outcome in comparison to conventional surgical approaches. The concept is illustrated in figure
2. E.g. Jaeck et al. published a study of 33 patients following a systematic approach of resection of lesions from the FLR followed by PVE as illustrated in figure 3. Interestingly, 76 % of all patients enrolled achieved a second hepatectomy with sufficient FLR in 31 patients and a significantly reduced time interval between the two stages (8 to 13 weeks) [7].

![Portal vein embolization followed by resection of the right lobe](image)

**Figure 2:** Portal vein embolization followed by resection of the right lobe

### 4.1.1 Two-stage hepatectomy with portal vein ligation

In 2003 Belghiti et al. introduced a novel staged hepatectomy technique for patients with marginally resectable CRLM. This multistep multimodality therapy comprised the concept of primary tumor removal of the colorectal of neuroendocrine malignancy with left liver limited metastasectomies and right PVL, followed by right hepatectomy in a second stage operation (as illustrated in figure 4), with or without the use of percutaneous ablative therapy or systemic therapy. In this study a total of 20 patients were included (12 patients with CRC and 8 patients with neuroendocrine tumors) and due to the absence of recurrent disease 15 out of 20 patients (75%) were eligible for a definitive second step operation. Most importantly this approach proved to be a safe and feasible procedure as no major complications were reported (REF). In a follow-up study by the same group the authors compared two different ways of PVO and compensatory liver hypertrophy in the setting of two-step hepatectomies (REF) Compensatory liver hypertrophy as assessed by CT volumetry was comparable between the two groups (PVE: 35%+/-38%; PVL 38%+/-26%). Furthermore, two-
staged liver resections with PVL have the additional advantage of sparing the patient an intervention after the first stage of liver resection.

![Image](image.png)

**Figure 3:** Two stage hepatectomy with portal vein ligation

Based on the relative equivalence of data for PVE and PVL at the time of the first hepatectomy we have routinely performed two-stage hepatectomies with PVL at the University Hospital in Zurich since 2000, a strategy described in detail in 2007 [8]. Tsai et al. reported clinical results with this approach in a total of 45 patients from Johns Hopkins University. Here 32 of 45 patients underwent staged liver resection with PVL with 28 further receiving an alcohol sclerosant to prevent re-canalisation of the portal venous system [9]. The authors concluded that two-stage liver surgery can be performed with acceptable morbidity and mortality. Two-stage hepatectomies in patients with bilobar hepatic disease have by now become the standard in many centers around the world. However a major issue remains the non-progression of 20-30 % of patients to step 2, generally due to tumor progression in the interval. Table 1 summarizes the results to date.
Table 1: Safety data of two-stage hepatectomies in published series, compared with ALPPS

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>N° patients</th>
<th>Morbidity (major)</th>
<th>Liver Failure</th>
<th>90-day Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lam <em>et al</em> (Systematic review)¹</td>
<td>2013</td>
<td>459</td>
<td>40%</td>
<td>-</td>
<td>3%</td>
</tr>
<tr>
<td>Cardona <em>et al</em> (MSKCC)²</td>
<td>2013</td>
<td>40</td>
<td>45%</td>
<td>-</td>
<td>0%</td>
</tr>
<tr>
<td>Brouquet <em>et al</em> (MD Anderson)³</td>
<td>2011</td>
<td>65</td>
<td>29%</td>
<td>5%</td>
<td>6.4%</td>
</tr>
<tr>
<td>Tsai <em>et al</em> (J Hopkins)⁴</td>
<td>2010</td>
<td>45</td>
<td>28%</td>
<td>8.6%</td>
<td>8.8%</td>
</tr>
<tr>
<td>Belghiti J (Beaujon)⁵</td>
<td>2008</td>
<td>35</td>
<td>46%</td>
<td>15%</td>
<td>0%</td>
</tr>
<tr>
<td>Adam <em>et al</em> (Paul Brousse)⁶</td>
<td>2008</td>
<td>59</td>
<td>59%</td>
<td>22%</td>
<td>7%</td>
</tr>
<tr>
<td><strong>ALPPS Registry (CRLM)</strong></td>
<td></td>
<td>141</td>
<td>38%</td>
<td>6%</td>
<td>8%</td>
</tr>
</tbody>
</table>

5.2.1. Associating Liver Partition with Portal Vein Ligation for Staged Hepatectomy (ALPPS)

Baumgart *et al.* introduced a new surgical two-step technique, ALPPS, for obtaining adequate but rapid parenchymal hypertrophy in oncologic patients requiring extended right hepatic resection with limited functional reserve[10] Santibanes *et al.* published several case reports along the same lines[11, 12]. In a German pilot study, including 25 patients undergoing ALPPS, the authors developed a novel two-stage hepatectomy technique with employment of combined right PVL and in-situ splitting of the hepatic
parenchyma along the falciform ligament with subsequent extended right hepatectomy in a second step operation (REF): The approach is demonstrated in figure 5.

Interestingly the authors demonstrated that after a median postoperative waiting period of 9 days the volume of segments II and III increased to 536 ml representing a median volume increase of 74 % and a median left lateral lobe body weight ratio increase from 0.38 % to 0.61 % as assessed by CT-volumetry. Three out of the 25 study patients died due to complications related to surgery putting the mortality at 12 %.

Another 36 % developed mild complications (Grade I-IIIa) and 28 % developed severe complications according to the Zurich score for surgical complications (Grade IIIb-V).

Figure 4: Associating Liver Partition with Portal Vein Ligation for Staged Hepatectomy (ALPPS)

5.1.1. ALPPS versus PVE/PVL – Comparative study

We performed a retrospective review of patients undergoing PVE/PVL or ALPPS at 4 high volume HPB centers between 2013 and 2012 (REF). Primary endpoint was liver free of tumor at three months and secondary endpoints included 90-day mortality, complications, FLR increase and tumor recurrence. 48 patients with ALPPS were compared with 83 patients with PVE/PVL. Eighty-three per cent (40/48) of ALPPS patients achieved complete resection compared with 66% (55/83 patients) in PVE/PVL.
(OR 3.34, \( p=0.027 \)). Ninety-day mortality in ALPPS and PVE/PVL was 15% and 6% respectively \( (p=0.20) \). This study provided evidence that ALPPS offers a better chance of complete resection in patients with primarily unresectable liver tumors at the cost of a relevant mortality. It supported the concept to further analyze the registry for safety.

**Comparative study of ALPPS vs. TSH**

![Comparative study of ALPPS vs. TSH](image)

**Figure 5:** Results of the comparative study ALPPS vs TSH using Portal vein ligation or embolization [13]

### 5.1.2. Study of 202 patients in the ALPPS registry

In January 2014 we performed an analysis to assess safety and outcomes of ALPPS more thoroughly using an international registry due to the relevant morbidity and mortality reported by many case series including our comparative study. A web-based data entry system was created with password access and data pseudoencryption [NCT01924741]. All patients with complete 90-day data were included. Multivariate logistic regression analysis was performed to identify
independent risk factors for severe complications and mortality, and volume growth of the FRL. Complete data were available in 202 patients. 141(70%) had colorectal metastases (CRLM). Median starting standardized future liver remnants (sFLR) of 21% increased by 80% within a median of 7 days. 90-day mortality was 19/202 (9%). Severe complications including mortalities (Clavien-Dindo ≥IIIb) occurred in 27% of patients. Independent factors for severe complications were red blood cell transfusion (OR 5.2), ALLPS stage I operating time > 300 min (OR 4.4), age > 60 years (OR 3.8) and non-CRLM (OR 2.7) Age, use of Pringle maneuver and histologic changes led to less volume growth. In patients younger than 60 years with CRLM, 90-day mortality was similar to conventional two-stage hepatectomies for CRLM. This first analysis of the ALPPS registry showed that ALPPS shows increased perioperative morbidity and mortality in older patients, but better outcomes in patients with CRLM (Figure 5). We concluded that it was time to perform a randomized study but to only include patients, who we could presume would be candidates with a perioperative risk comparable to the published literature on two-stage hepatectomies[14].
5.1.3. Experience from the first randomized study

After obtaining approval from the KEK Zurich and registration (clinicaltrials.gov-identifier: NCT01775267) we started a first randomized study with inclusion criteria of all types of liver tumors in november 2012 (approved protocol 5.0). We included perihilar cholangiocarcinoma as well as any other tumor etiology and allowed PVE and PVL in the control arm. We randomized 7 patients until november 2013. Because we observed 3 mortalities, one in the ALPPS arm and two in the control arm, we decided to hold the study in november 2013. An interim analysis and submitted it to the data safety monitoring board (DSMB – Patrick Bossuyt, Amsterdam, Peter Friend, Oxford, and Eberhard Renner, Toronto, with the request for guidance on november
th 2013. Recommendations of the DSMB in their answer from january 2014 were in summary (1) to extend the study endpoint to 6 months, (2) to introduce an age cut-off at 60 or 65 years, (3) to limit the study to patients with CRLM, (4) to exclude patients with any relevant histological abnormality (like steatosis, fibrosis) (5) very small FLRs and to perform another power analysis based on the recent experience.

5.2 Rationale for the current study

5.2.1 Endpoints

Primary endpoint

The goal of this new amendment of the study is to incorporate the recommendations of the DMSB into a amended protocol (USZ-ZH-VIS 5.2). The ALPPS procedure is now compared to conventional two-stage liver resections only in marginally resectable CLRM. The primary endpoint of this amendment is disease-free survival at 1 year. This is a relevant endpoint because currently the goal of aggressive surgical therapy in these patients is both to prolong survival as well as the render them disease free. We have evidence to hypothesize that due higher feasibility to achieve complete resection ALPPS may achieve a higher proportion of disease-free survival at 1 year (Figure 7).

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>N° patients</th>
<th>DFS 1yr</th>
<th>DFS 2yr</th>
<th>DFS 3yr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lam et al. (Systematic review)</td>
<td>2013</td>
<td>459</td>
<td>-</td>
<td>-</td>
<td>20%</td>
</tr>
<tr>
<td>Tsai et al (J Hopkins)</td>
<td>2010</td>
<td>45</td>
<td>85%</td>
<td>68%</td>
<td>45%</td>
</tr>
<tr>
<td>Brouquet et al (MD Anderson)</td>
<td>2011</td>
<td>65</td>
<td>39%</td>
<td>-</td>
<td>20%</td>
</tr>
<tr>
<td>Adam et al (Paul Brousse)</td>
<td>2008</td>
<td>41</td>
<td>60%</td>
<td>40%</td>
<td>26%</td>
</tr>
<tr>
<td>ALPPS Registry (CRLM)</td>
<td>2013</td>
<td>141</td>
<td>59%</td>
<td>41%</td>
<td>-</td>
</tr>
</tbody>
</table>
Figure 7: Disease-free survival after ALPPS and TSH in major series: evidence for 20% increased disease-free survival in intent to treat analysis.

Secondary endpoints

(A) Some secondary endpoints of the study determine downsides and benefits of the treatment:

(1) Mortality: All three metrics In-hospital mortality, 30-day mortality and 0-day mortality will be collected.
(2) All complications will be collected by Clavien-Dindo-score to collect all possible metrics including the comprehensive complications index, developed jointly by the Department of Surgery at the University of Zurich and the Bloomberg School of Public Health at Johns Hopkins University (REF). Overall survival and disease-free survival yearly up to 3 years (all centers)
(2) Feasibility of complete resection. Most prior studies on ALPPS have focused on feasibility endpoints[13]. In this study feasibility is just a secondary endpoint.
(3) Oncologic outcome: % of R0 resection clearly is a secondary endpoint. Its impact on disease free survival in two-stage hepatectomies has yet to be determined.
(4) Overall survival, especially when examined in long term follow-up analyses, has yet to be determined.
(5) Quality of life will be assessed by using the feeling thermometer.
(5) The difference of volumetric growth of the FLR between ALPPS patients and patients with TSH by MRI or CT volumetry at the same time points after portal vein occlusion (1 week, 2 weeks, 4 weeks, 8 weeks). Volumetry will be performed either by CT or MRI depending on the type of study that was used by the participating center. Volumetry will be performed locally by participating centers but may be reviewed for quality control by the study center in Zurich.

(B) Some secondary endpoints offer insights into how the treatment works:
Liver synthetic function: We will measure global synthetic liver function by determining PT/INR (all centers) and using Factor V, Indocyanine Green (ICG) (Zurich only) and HIDA scans.

Renal function: Renal function is an important predictor of morbidity and mortality after hepatic surgery. We have in the past analyzed factors impacting on renal outcome after major liver resection [16]. We have observed acute renal failure in both surgical strategies. A difference in renal function might provide an insight how one surgical strategy might result in better outcomes that the other. Renal function will be analyzed using the RIFLE system (all centers).

(C) Some secondary endpoints of the study will generate hypotheses for further studies. We will therefore

(7) Obtain biopsies from both liver lobes 60 minutes prior to and 60 minutes after the parenchymal transaction during step 1 and of the liver prior to the removal of the deportalized lobe at step 2 for further histological and molecular analysis for mechanisms of liver hypertrophy (DNA, RNA, proteomics). (Zurich only)

(8) Obtain blood samples from hepatic venous effluent 60 minutes prior to and before 60 minutes after the parenchymal transaction during step 1 and of the liver prior to the removal of the deportalized lobe at step 2 to analyze levels of blood components (platelets), hepatic growth factors and other factors which might prove important in future analysis. (Zurich only)

(11) Obtain blood samples for perioperative measurement of circulating tumor cells. (Zurich only)

(12) Intraoperative measurement of portal vein pressure, flow (Zurich only)

5.2.2 Both ALPPS and Traditional staged hepatectomy are safe and effective surgical strategies

As outlined above several centers have reported on two stage hepatectomies with portal vein occlusion to make extensive liver resections safe and effective procedures for patients with large and multifocal tumors of the liver. Most series are uncontrolled
cohort studies from single institutions and have included only few patients [5, 6, 9, 11, 12, 17, 18]. However recently a systematic review and metanalysis has been performed that demonstrates acceptable safety and efficacy to treat CRLM overall[14]. Nevertheless, substantial progress has been made and many tumors that were previously considered to be unresectable are now amenable to complete surgical resection. Innovative strategies that make manipulation of the FLR possible, such as PVE, PVL, and staged hepatectomies are now considered standard therapy in most specialized centers around the world.

The largest series on the ALPPS technique which demonstrates a overall complication rate of 40% and a mortality of 9%[15]. The largest contemporary series on TSH by Brouquet et al. cites a perioperative mortality of 6% and an overall complication rate of 49%[19].

5.2.3 ALPPS and conventional two-stage hepatectomy at the Swiss HPB Center

Both procedures have been successfully performed by the hepato-pancreatico-biliary (HPB) team of the Department of Visceral- and Transplantation Surgery of the University Hospital Zurich. The results of two-staged hepatectomy with both portal vein ligation and embolization as well as ALPPS have been published together with the HPB groups from Buenos Aires, Mainz and London, Ontario, Canada[13].

6. STUDY DESIGN

This is a multi-center randomized controlled clinical trial to evaluate a new surgical approach to bilobar liver malignancies.

Our sample size calculation included the following variables:

1. primary endpoint: disease free survival at 12 months (treatment success)
2. a-error = 0.05
3. equal n in both arms
4. medium power assumed = 0.6 (feasibility considerations)
(5) ALPPS: We observed a **disease-free survival at 1 year of 59%** in the registry study. [15]

(6) PVE/PVL: Brouquet et al. observed a **disease-free survival at 1 year of 39%** in an intent-to-treat analysis[19]

Based on a standard power calculation 60 patients will have to be enrolled in each arm. An interim analysis will be performed based on the periodic assessment a Data Safety Monitoring Board with 3 independent reviewers not involved in the conduct of this study. The interim analysis will be performed after each 20 patients enrolled. If mortality for one or both arms exceeds the expected mortality for two staged-hepatectomy the Board will take a decision and make a statement about early termination of the study for safety reasons. The chairman of the Data Safety Monitoring Board will report their decision to the sponsor and the PI in Zurich by mail.

Secondary endpoints will be evaluated based on the power available for the primary endpoint.

The study is only feasible as a multi-center study of more than 5 centers. Each center should be able to enrol alt least 10 patients per year. The duration of inclusion in the study for each patient will be 12 months and the estimated duration of the study to enrol patients will at least 3 years. Preconditions to participation are experience with major liver resections and documentation of having performed at least 5 ALLPS cases prior to participation due to the learning curve with this quite complex procedure.

The randomization will be performed in the week prior to the first step and cannot be performed the day of the first step, because portal vein embolization is performed in Interventional Radiology and requires some planning.

**6.1. STUDY OUTCOME MEASURES**
The primary outcome measure will be disease-free survival at 1 year by PET-CT. The primary outcome will be assessed by by two independent radiologists in Zurich who will blinded to which arm the patient was enrolled in. Patients who die, are lost to follow up or are too sick to undergo imaging are counted as failures to reach the primary endpoint. Patients may need resection of their primary tumor after the study intervention (liver first strategy). They may develop recurrence within the study period ablation, systemic or in the liver. In these patients, reoperation and chemotherapy are used as customary clinical routine. whether they achieved tumor free survival however depends only on the PET-CT at one year.

Secondary Outcome measures will be:

1. Safety Mortality: Mortality will be assessed both by assessing the CRF for complications, the AE reports, as well as the study end CRF filled out at 12 months. Every mortality will be confirmed with the centers

2. Complications will be assessed from the “complications” CRF and the AE CRF. All major complications (Clavien-Dindo > 3A) will be confirmed with the centers. CCI will be calculated by the study center in Zurich.

3. Feasibility of complete resection. On the CRF for stage two, “complete resection” will be assessed by the investigators. In case of incomplete data entry, investigation by the study center in Zurich will ensue.

4. Oncologic outcome: Investigators will have to enter a consensus between pathologists and surgeons on the R-status of the resection, judging both stages separately and together. Through re-resection R0 may be achieved overall even if there was a R1 resection after stage 1.

5. Oncologic outcome. Death of the patient will be reported with date on the study end CFR.

6. Liver volumetric changes. All volumetries are performed locally and reported into a respective volumetry CRF. There will be no central evaluation of volumetries.
7. SUBJECT SELECTION AND WITHDRAWAL

7.1. SUBJECT RECRUITING AND SCREENING

Subjects will be screened in the outpatient clinic of the Department of Visceral- and Transplantation Surgery at the University Hospital Zurich. Participation will be offered based on screening criteria and will be discussed in the interdisciplinary tumor board. No financial compensation will be offered to the patients for participation in the study.

7.2 INCLUSION CRITERIA

Patients fulfilling the following inclusion criteria may be enrolled in the study:

1. Male or female patients 18-99 years of age.
2. Patients with multifocal CRLM with a FLR/TLV< 30% OR a FLR/BW ratio of < 0.5.
3. Patient with primary colorectal malignancies not yet resected may be included into the study as long as the extrahepatic disease may surgically cured (Liver first strategy)
4. Patients with lung metastases may be included inot the study as long as the lung metastases are potenitally curable by resection by judgement of a thoracic surgery consultant.
5. Patient compliance and geographic proximity allow proper staging and follow-up.
6. Presentation of the case at the Multidisciplinary Meeting attended by hepatobiliary surgeons, oncologists, hepatologists and radiologists
7. Written informed consent given by the patient
8. Women who are not breastfeeding and are using effective contraception if sexually active, who are not pregnant and agree not to become pregnant during the 12 months thereafter. A negative pregnancy test before inclusion into the trial is required for women, who are not yet menopausal, had their last menses within less than 12 months, have not had uterus and or ovaries removed surgically or undergone tubal ligation.
9. Effective **contraception** may involve standard devices, techniques and methods used to prevent fertilization. Barrier contraceptives are devices which attempt to prevent pregnancy by physically preventing sperm from entering the uterus. Devices in common use include condoms, female condoms, cervical caps, and diaphragms. Hormonal contraceptives inhibit female ovulation or fertilization. These include oral contraceptives. The most common hormonal contraceptives are the combined oral contraceptive pill, commonly referred as "The Pill", which includes a combination of an estrogen and a progestin (progestogen).

### 7.3 EXCLUSION CRITERIA

The presence of any one of the following exclusion criteria will lead to the exclusion of the subject:

1. If the transjugular biopsy prior to enrollment shows cirrhosis, fibrosis or >30% macrosteatosis patients may not be enrolled.
2. Significant concomitant diseases making the patient unsuitable for major liver surgery by the judgement of the physicians involved, especially in the elderly.
3. Need for major extrahepatic surgery (e.g. pancreas resection, gastric resection, rectal surgery) that may not be delayed for 3 months until the study enrolment is finished.
4. Suspected non compliance (drug- and/or alcohol abuse)
5. Enrollment into a clinical trial within the last 4 weeks
6. If the intraperative biopsy shows cirrhosis, fibrosis or >30% macrosteatosis during stage, patients should not be randomized.
7. Peritoneal carcinomatosis or other extensive extrahepatic disease.

### 7.4 WITHDRAWAL CRITERIA
Only patients who fulfill inclusion/exclusion criteria will be invited to participate in the present study. The patient will be advised that he/she is free to withdraw from the study at any time. Also, the investigators may remove a patient if he/she feels this action is in the best interest of the patient. Patient removal may occur as the result of an adverse event (AE) that in the judgment of the investigator places an unacceptable consequence or risk for the patient. Patient removal might also occur because of a protocol violation. Notification of the discontinuation will be clearly documented on the patient’s case report form (CRF).

To allow intention to treat analyses, when a patient is withdrawn from the study all of the safety data normally required at the end of the study should be obtained if possible. All already collected data will be kept in the CRF of patients prematurely withdrawn from the study, unless the patient specifically refuses.

All tissue and blood specimen of patients withdrawn from the study will be destroyed.

8. EFFICACY AND SAFETY VARIABLES

8.1 EFFICACY VARIABLES

Primary Efficacy variable
The Primary Efficacy Variable is disease free survival at 12 months by PET CT as assessed by two blinded radiologists in Zurich. The Images will be transferred to Zurich as DICOM FILES.

Secondary efficacy variables include:

1. Safety: Mortality will be evaluated based on the data entered into the CRF on complications and the follow-up report forms.
2. **Complications** will be evaluated based on the entries on the complications form in the CRF according to the Clavien-Dindo complication score. The CCI will be automatically calculated by the SECUTRIAL CRF.

3. **Feasibility of complete resection** will be evaluated from the data entries on stage 2 resections in the CRF.

4. **Oncological outcome: RO or R1 (and rarely R2) resection status** will be evaluated from the electronic CRF entries under “pathology”.

5. **Oncological outcome: overall survival**. Long term survival and progression free survival will be assessed by performing following studies on patients after discontinuation of the study with a new ethics approval at 12 months, 18 months, 24 month, 3, 4 and 5 years and 10 years.

6. **Quality of life assessment** will be evaluated based on the entries in the CRF. The assessment will use the Feeling Thermometer (see Appendix), which is sensitive to change, easy to administer and also amenable to economic analysis. Our hypothesis is that there is advantage for patients to undergo staged hepatectomies in the time frame of 7 to 10 days rather than separating the procedures by 4 weeks. No data are currently available for quality of life after ALPPS or TSH.

7. **Liver volumetric changes** after portal vein ligation will be assessed at week 1, 2, 4, 8 and 12 after portal vein occlusion in stage 1. They will serve to establish a standardized growth assessment of livers after both methods, which is currently not available.

9.2 **SAFETY VARIABLES**

All adverse events observed by the investigator and/or reported by the subject must be reported in the CRF during the entire study period, i.e. the period of time from the first
AEs are coded with the NCI Common Terminology Criteria for Adverse Events (CTCAE) v.4.0 and assigned a grade (from 1 = mild to 5 = death related to AE) as well as a relationship to trial treatment. The NCI CTCAE v4.03 (as pdf) as well as instruction on how to use the criteria can be found on http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf

Postoperative complication will be in parallel assessed using the Clavien-Dindo-score.

9. COURSE OF STUDY AND FOLLOW-UP

9.1 ENROLLMENT VISIT (VISIT 1)

The patient will be seen at the outpatient clinic of the Department of Visceral Surgery and Transplantation and based on the extent of liver disease and general candidacy (able to undergo major liver resection, appropriate liver, renal and cardiovascular function) will be considered for candidacy of participation in the study. Patient will be informed by their surgeon about the possible candidacy and given the information leaflet about the study and a copy of the consent form for consideration. All patients have to undergo a transjugular liver biopsy prior to surgery. Imaging with liver CT or MRI and PET CT obtained outside of our institution will be entered into our imaging system and preliminary volumetry performed and volumetric inclusion criteria assessed. Routine chemistry, hematology tests and tumor markers (CEA) will be ordered (if not already available).

If cardiac optimization is necessary, the judgement about operability of the patient is up the consultant from cardiology. Renal dysfunction is no contraindication to undergo major liver surgery, however appropriate risk stratification and care by nephrology perioperatively have to be arranged.

The patient will have to be discussed in the multidisciplinary tumor board.
After candidacy has been agreed upon by the tumor board the patient will be seen by
the PI and the study will be discussed and any questions addressed. If the subject
agrees to participate the consent form will be signed.

Registration on a Screening Log in the electronic CRF will be performed.

Randomization will be performed by the PI using the Secutrial website
intraoperatively, after surgical exploration laparoscopically, or open.

Due to the limitation of the study to CRLM no prestratification will be necessary.

9.2 PREOPERATIVE TESTING (VISIT 2)

All preoperative test should be performed within a month prior to surgery.
A research ICG Green and LiMAX test will be performed after randomization and
before the First Step Surgery (Zurich only). The ICG Green involves injected a dye
(ICG) that will be metabolized by the liver. The dye signal will be picked up by an
oximetry-like device. This test is routinely performed in Zurich prior to major liver
resections.

9.3 STAGE ONE WITH POSTOPERATIVE CARE (VISIT 3)

Randomization will be performed by the PI using the Secutrial website
intraoperatively, after surgical exploration and biopsy, laparoscopically or open.
Exclusion of patients is possible after biopsy.

In randomized patients stage 1 surgery will be performed according to the practice of
the respective center. Hilar occlusion will be performed as necessary and recorded.
Portal vein ligation should be performed at the end of parenchymal transection unless
indicated otherwise by the surgeon intraoperativey. To avoid formation of adhesions
only resorbable material should be used (like tachysil).

During the procedure, intraoperative biopsies, blood draws from the hepatic veins,
pressure and flow measurements will be performed (only in Zurich) Drains may be
inserted at the end of case according to the centers preference.

In the TSH the procedure consists in either a removal of tumors from the FLR with
simultaneous ligation of the portal vein of the contralateral lobe, or delayed catheter
based portal vein embolization to induce hypertrophy in the contralateral lobe performed in the interventional radiology department about 1 weeks after FLR resection.

9.4 STAGE TWO SURGERY FOR ALPPS GROUP (VISIT 4)

In the ALPPS arm Step 2 will be generally performed after appropriate hypertrophy has been obtained. The judgement of what is considered ‘appropriate hypertrophy’ will be left up to the centers. In Zurich a combined volumetric/functional assessment using cross sectional imaging and HIDA scan [20] will be performed. If hypertrophy is not enough, MRIs will be performed at the same intervals as for the conventional PVO group. The ALPPS step 2 consists in ligation of the hepatic artery, transection of the biliary pedicle with a vascular stapler, transection of the hepatic vein with a vascular stapler and removal of the liver lobe. In Zurich, intraoperative biopsies will be obtained, blood drawn from the hepatic veins and pressure and flow measurements will be taken, but the performance of biopsies is left up to centers. Pre- and postoperatively liver synthetic function, metabolic function and testing recording of complications will be performed. Repeat MRI volumetry will be performed at week 2, which in most cases should be one of the days prior to discharge. Patients enrolled in the conventional TSH arm will generally proceed to discharge without Step 2 performed during the same admission. They generally reach appropriate volumes at week 4 or 8, maybe later. These patients will be sent home with a follow-up 4 weeks after randomization. At 4 and 8 weeks a repeat dynamic MRI with volumetry will be performed. If hypertrophy is judged appropriate, in Zurich by volumetric/functional assessment, the second stage will be performed.

Chemotherapy may be performed in both arms either after step 2 or between steps as thought appropriate by the treatment team since chemotherapy might play a role avoiding recurrence after two-step liver resections. In our experience initiation of chemotherapy is possible early after randomization in ALPPS but also between steps in conventional TSH (“interval chemotherapy”).
9.5 STAGE TWO SURGERY FOR TSH (VISIT 4)

Stage two surgery in TSH arm will consist in reexploration through the previous bilateral subcostal incision, lysis of adhesions, ligation of the arterial inflow and then parenchymal transection and removal of the liver lobe. In Zurich, intraoperative biopsies will be obtained, blood samples, pressure and flow measurements will be taken. Pre- and postoperative liver synthetic function and cholestasis testing as well as recording of complications will be performed. In our experience stage 2 is generally performed during weeks 1-2 in ALPPS and during weeks 4-9 in TSH.

9.6 FOLLOW-UP 1 (VISIT 5)

Subjects in the TSH will be seen in the HPB Center at week 4 after randomization for follow-up. Patients in the ALPPS arm will be seen at week 4 after randomization for both steps surgeries. Routine physical examination will be performed, standard laboratory parameters obtained and perioperative adverse events will be recorded.

9.7 FOLLOW-UP 2 (VISIT 6)

Subjects in the TSH arm will be seen in the HPB Center 8 weeks after randomization for follow-up and discussion of the repeat MRI with volumetry. Patients in the ALPPS arm will be seen 8 weeks after randomization. Routine physical examination will be performed, standard laboratory parameters obtained and perioperative adverse events will be recorded.

9.8 LATER FOLLOW-UP (VISIT 7)

If patients cannot undergo resection at week 8, later follow-ups should be performed per decision of the treatment team in monthly intervals. It may be decided to proceed to resection at any time during the entire follow-up period one year after randomization. Very likely chemotherapy will be reinititated during that phase.
9.8 STUDY END  (VISIT 8)

Study participation will end after 12 months. At 12 months patients will be invited to undergo full laboratory exam including tumor makers and a PET-CT. The decision about which patients has achieved a state of “disease-free” will be based solely on the assessment of the PET-CT by two blinded radiologists in the study center in Zurich. Controversial cases will be shown to a third blinded radiologist for final decision. Elevation of tumor markers alone without PET evidence of disease will be classified as “disease free”. Repeat CT scans are allowed, if the centers wish to perform them in controversial situations. SAEs are not expected after study termination.

10. SAFETY

10.1 DEFINITIONS

**Adverse Event (AE):** any untoward medical occurrence in a subject to whom a medicinal intervention has been administered, including occurrences which are not necessarily caused by or related to that intervention.

**Serious Adverse Event (SAE):** any untoward and unexpected medical occurrence or effect that: results in death. It does not refer to an event which hypothetically might have caused death if it were more severe. It relates to events that Require hospitalization, or prolongation of existing inpatients’ hospitalization and to events that result in persistent or significant disability or incapacity.

Medical judgement should be exercised in deciding whether an AE is serious in other situations. Important AEs that are not immediately life-threatening or do not result in death or hospitalization but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above, should also be considered serious.
10.2 RECORDING OF (SERIOUS) ADVERSE EVENTS

All adverse events, serious or not, should be recorded in the CRF. Depending on the nature of the event the reporting procedure below should be followed.

10.3 REPORTING OF SERIOUS ADVERSE EVENTS

An SAE form should be completed for any occurring SAE during the study. All deaths of study participants have to be reported to the Sponsor of the Study (Dr. Clavien) and to the Kantonale Ethikkommission (KEK) immediately but at least within 7 days. All life-threatening SAEs related to the study have to be reported to the sponsor (Dr. Clavien) and the Kantonale Ethikkommission immediately or at least in 7 days. If SAEs related to the study are not life-threatening or fatal, they have to be reported within 15 days. Study related treatments in this study are the study-related blood sampling, imaging procedures and surgeries. The Principal Investigator will assess whether the event is ‘related’, i.e. resulted from any of the research procedures. The responsibility for reporting to sponsor and KEK rests with the Principal Investigator.

11. STATISTICS AND DATA ANALYSIS

The number of patients enrolled is based on a power analysis with the two proportions disease-free survival based on the two largest studies on ALPPS and TSH (see above).

For descriptive statistics median and mean with standard deviation, Fischer exact and Mann-Whitney test will be used for quantitative variables and chi-square test for qualitative variables.

Progression free survival and overall survival will be evaluated in a Kaplan-Meier plot.
12. REGULATORY ISSUES

12.1. ETHICS APPROVAL AND ETHICAL CONDUCT OF THE STUDY

Before this study will be conducted, the protocol, the proposed subject information and consent form as well as other study-specific documents will be submitted to a properly constituted Independent Ethics Committee (IEC) in agreement with local legal requirements in each center. The decision of the local IEC concerning the conduct of the study will be made in writing to the Sponsor of the study in Zurich before initiation of this study. The study will be carried out in accordance with principles enunciated in the current version of the Declaration of Helsinki, the guidelines of Good Clinical Practice (GCP) issued by ICH, and, in Zurich, according to Swiss regulatory authority requirements.

A Data Safety Monitoring Board (DSMB) consisting of 3 experts in the field who are completely independent of the study will monitor the results after each 20 randomized patients and may stop the study due to safety reasons if they deem one arm to exceed the expected morbidity and mortality or lack clinical effectiveness. Data safety monitoring board will consist of the hepatologist Dr. Renner, from Toronto, Canada, the HPB surgeon: Dr. Friend from Oxford, U.K., and the epidemiologist Dr. Bossuyt from the Netherlands.

12.2 SUBJECT INFORMATION AND CONSENT

The investigator must explain to each subject the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits and any discomfort it may entail. Each subject must be informed that the participation in the study is voluntary and that he/she may withdraw from the study at any time and that withdrawal of consent will not affect his/her subsequent medical treatment. The subject must be informed that his/her medical records may be examined by authorized individuals other than their treating physician. All subjects for this study will be
provided a subject information sheet and a consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. The subject information sheet and the consent form will be submitted with the protocol for review and approval for the study by the IEC. The formal consent of a subject, using the approved consent form, must be obtained before that subject is submitted to any study procedure. The subject should read and consider the statement before signing and dating the informed consent form, and should be given a copy of the signed document. The consent form must also be signed and dated by the local principal investigator and it will be retained as part of the study records.

12.3 CONFIDENTIALITY

The investigators are liable to treat the entire information related to the study and the compiled data strictly confidentially. Any passing-on of information to persons that are not directly involved in the study must be approved by the owner of the information.

Data generation, transmission, archiving and analysis of personal data within this study, in Zurich strictly follows Swiss legal requirements according to the federal law on data security (DSG), as well as the regulation on professional secrecy in clinical research (VOBG). Prerequisite is the voluntary approval of the subject given by signing the informed consent prior to the start of participation of the clinical trial.

Individual subject medical information obtained as a result of this study is considered confidential and disclosure to third parties is prohibited. Subject confidentiality will be further ensured by utilising subject identification code numbers to correspond to treatment data in the computer files.

Such medical information may be given to the subjects personal physician or to other appropriate medical personnel responsible for the subject's welfare, if the patient has given his/her written consent to do so.
12.4 INSURANCE

Insurance is covered by “Haftpflichtversicherung für den Kanton Zürich betreffend das UniversitätsSpital Zürich“ (Policy No 1037, Vertragsnummer 9.730.682/14.970.888 Zurich Versicherungsgesellschaft AG). Any damage developed during the course of the study is covered by this insurance. So as not to forfeit their insurance cover, the subjects themselves must strictly follow the instructions of the study personell.

Medical emergency treatment must be reported immediately to the investigator. The investigator must also be informed instantly, in the event of health problems or other damages during or after the course of study treatment.

12.5 FUNDING

This study is funded by a Klinisches Schwerpunktgrant of the University of Zurich “Unresectable liver tumors – from palliation to cure” to the sponsor of the study, P.-A. Clavien.

12.6 AUDITS AND INSPECTIONS

The study may be subject to inspection and audit by regulatory bodies to ensure adherence to GCP, national law, and regulatory requirements. The quality assurance auditor/inspector will have access to all medical records, the investigator's study related files and correspondence, and the informed consent documentation that is relevant to this clinical study. The investigator will allow the persons being responsible for the audit or the inspection to have access to the source data/documents and to answer any questions arising. All involved parties will keep the patient data strictly confidential.

13. STUDY MANAGEMENT
The day-to-day management of the study in Zurich will be coordinated through Dr. Schadde, Dr. Tschuor and the study nurse Sabine Kern RN.

Principal investigators in other centers will be added in amendments to this protocol once other centers join in the trial.

Data management will be performed by Ksenja Slankamenac, and Erik Schadde and Henrik Petrowsky in Zurich.

Data will be stored in case report files in the respective CRF forms using the secutrial online data entry system (preliminarily submitted in text processing documents in the Appendix). Export of the data will be performed confidentially and, blinded for the Pis, only for DSMB reviews and after closure of the study by the clinical trials center in Zurich.

Sample preparation methods, sample storage

1. Blood will be drawn into heparinized test tubes for hematology analysis, serum will be separated from blood components and both stored at -80 degrees for further analysis (Zurich only (responsible coinvestigator Chris Tschuor)).

2. Two core biopsies on each liver side will be obtained at the the time of surgery during stage 1 and stage 2. Half of one core will be sent to routine pathology for diagnosis, the remaining specimen will go the research laboratory for translational research projects. Patient will receive the USZ biobank information form and sign the USZ biobank general consent form (“Generaleinwilligung”) together with the specific study consent form if they intend to participate in the study (Zurich only).

3. Tissue will be preserved from tumor and surrounding healthy tissue in frozen format for future study according to the guidelines of the USZ biobank, if diagnostic procedures are not compromised (Zurich only).

All serum and tissue samples will be stored at the Department of Surgery.
Erik Schadde, MD, Henrik Petrowsky and Mickael Lesurtel MD are responsible for the evaluation of the translational research project in Zurich. After completion of the translational research project the tissue and blood samples will be stored for an indefinite period and used for further investigations on cancer and treatment options.

14. PUBLICATION POLICY

After the statistical analysis of this trial the investigator will make every endeavour to publish the data in a medical journal.

15. SIGNATURES

Principal Investigator

This clinical trial protocol was subject to critical review and has been approved by the Principal Investigator. The information herein is consistent with
- the current risk/benefit evaluation of the investigational procedure(s)
- the moral, ethical and scientific principles governing clinical research as set out in the current version of the Declaration of Helsinki, Good Clinical Practice the SAMW biobanking guidelines.

Erik Schadde, MD

______________________________  
Zurich, 15.05.2014  Signature

Pierre-Alain Clavien, MD, PhD

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Zurich, 15.05.2014  Signature
16. REFERENCES


