Project title: Is there a difference in disease-free survival comparing ALPPS and two-stage hepatectomy in patients with colorectal liver metastases? (Short: ALPPS vs. TSH)

Authors:

Erik Schadde (Zurich), Mickael Lesurtel (Zurich), Rene Adam (Paris), Pierre-Alain Clavien (Zurich)

Largest 5 contributors to the ALPPS-registry and of LiverMetSurveyStatisticians: Milo Puhan, (Zurich), David Delvart (Paris)

other authors and contributors to be discussed

Background:

ALPPS is a new two-stage hepatectomy for colorectal liver metastases (CRLM) and reduces the drop-out rate of 30% that has been associated with conventional two-stage hepatectomies using portal vein embolization (PVE) and portal vein ligation (PVL). In a recent analysis of the ALPPS registry based in Zurich, ALPPS in CLRM had a 97% feasibility of resection, a 59% disease-free survival at 1 year and a perioperative mortality of 8%. LiverMET survey is a world-wide registry of patients undergoing liver resection for CRLM based in Paris and includes an estimated 1200 patients with conventional two-stage hepatectomies.

Hypothesis:

is that one of the two methods (ALPPS or conv TSH) achieves better disease-free survival than the other after correction for possible confounders. Null-Hypothesis is that both techniques achieve similar disease-free survival.

Objective:

To compare disease-free survival after ALPPS vs. conventional two-stage hepatectomy using PVE and PVL for colorectal cancer.

Methods:

We are planning to compare 220 patients who underwent ALPPS recorded in the ALPPS registry with an estimated 700 patients who underwent conventional Two-stage-hepatectomies during the same period in the LiverMet Survey database using the primary endpoint disease-free survival. Patients undergoing ALPPS recorded in the LiverMet Survey database will be carefully excluded. Only patients with completely recorded follow-up and confirmed survival and disease recurrence status will be included. It will be essential to also include those patients who did not proceed to the second stage. By fusing both databases using a common coding system that our groups will develop, the patients will be compared in patient demographics including age, gender, race, in biometrics like weight, height, BMI, BSA and liver remnant size; in disease characteristics like tumor type, tumor load, imaging characteristics, CEA, composite scores like the Fung score and others, exposure to chemotherapy and comorbidities and histological liver

characteristics (fibrosis, chemotherapy related liver injury); in procedure characteristics like, center volume, time between stages, transfusions and technical details as available in both databases; in perioperative endpoints like complications, mortality and postoperative liver failure. Based on a directed acyclic graph developed by the clinicians in the group, we will discuss the confounders we need to to adjust for in the analysis. Missing variables will be added through mulitple imputation to allow a maximum of patients to be analyzed. Due to the fact that both data collections are international registries with voluntary data entry, known biases of registries will apply to both cohorts. A Cox logistic regression model will be used to compare cohorts with regards to disease-free survival using dichotomization of continuous data. In parallel a case match between both cohorts will be performed using propensity scoring.

Intent

The intent is to publish the data from this analysis regardless of whether the null hypothesis is rejected or not.

Ethics approval for the analysis of both databases in Zurich will be sought by the Kantonal Ethics committee, Zurich. Respective approval will be sought in Paris, if necessary according to French law.