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Sparrelid, Ernesto

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ORIGINAL ARTICLE

Liver transplantation in patients with post-hepatectomy liver failure – A Northern European multicenter cohort study

Ernesto Sparrelid[1], Trygve Thorsen[2,3], Christina Sauter[1], Carl Jorns[4], Per Stål[5], Arno Nordin[6], Marieke T. de Boer[7], Carlijn Buis[7], Sheraz Yaqub[3,8], Nicolai A. Schultz[9], Peter N. Larsen[9], Ville Sallinen[6], Pål-Dag Line[2,3] & Stefan Gilg[1]

[1]Department of Clinical Science, Intervention and Technology, Division of Surgery, Karolinska Institutet, Karolinska University Hospital, Stockholm, Sweden, [2]Department of Transplantation Medicine, Oslo University Hospital, [3]Institute of Clinical Medicine, University of Oslo, Norway, [4]Department of Clinical Science, Intervention and Technology, Division of Transplantation Surgery, [5]Department of Medicine, Division of Hepatology, Karolinska Institutet, Karolinska University Hospital, Stockholm, Sweden, [6]Department of Transplantation and Liver Surgery, Helsinki University Hospital and University of Helsinki, Helsinki, Finland, [7]Section of Hepatobiliary Surgery and Liver Transplantation, University of Groningen, Department of Surgery, University Medical Center Groningen, Groningen, the Netherlands, [8]Department of Hepato-Pancreato-Biliary Surgery, Oslo University Hospital, Oslo, Norway, and [9]Department of Surgical Gastroenterology and Transplantation, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark

Abstract

Background: Liver transplantation (LTX) has been described as a rescue treatment option in severe, intractable post-hepatectomy liver failure (PHLF), but is not considered to be indicated for this condition by many hepatobiliary and transplant surgeons. In this article we describe the clinical experience of five northern European tertiary centers in using LTX to treat selected patients with severe PHLF.

Methods: All patients subjected to LTX due to PHLF at the participating centers were identified from prospective clinical databases. Preoperative variables, surgical outcome (both resection surgery and LTX) and follow-up data were assessed.

Results: A total of 10 patients treated with LTX due to severe PHLF from September 2008 to May 2020 were identified and included in the study. All patients but one were male and the median age was 70 years (range 49–72). In all patients the indication for liver resection was suspected malignancy, but in six patients post-resection pathology revealed benign or pre-malignant disease. There was no 90-day mortality after LTX. Patients were followed for a median of 49 months (13–153) and eight patients were alive without recurrence at last follow-up.

Discussion: In selected patients with PHLF LTX can be a life-saving procedure with low short-term risk.

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Correspondence

Ernesto Sparrelid, Department of Clinical Science, Intervention and Technology, Division of Surgery, Karolinska Institutet, Karolinska University Hospital, Stockholm, Sweden. E-mail: Sweden.ernesto.sparrelid@ki.se

Introduction

Orthotopic liver transplantation (LTX) is an established procedure in the treatment of patients with acute or chronic liver failure.[1] Both short- and long-term results have improved over the past decades.[2] However, due to organ shortage LTX still is restricted to well established indications like acute liver failure due to for example paracetamol intoxication and chronic liver failure with complications from decompensated cirrhosis. Currently, the most common cancer diagnosis considered for LTX is hepatocellular cancer within strict inclusion criteria in terms of tumor size, number, biological markers and macrovascular invasion.[3] Selected patients with unresectable perihilar cholangiocarcinoma are also accepted for transplant after completing neo-adjuvant chemo-radiation in line with the Mayo protocol.[4,5] Recently, there has been a growing interest in LTX as treatment for unresectable colorectal cancer metastasis as some

trials have indicated a benefit, while more trials are currently running.[6–8]

A patient group with acute liver insufficiency, which does not belong to the established indications, is post-hepatectomy liver failure (PHLF). PHLF is the single most important complication contributing to 90-day mortality following major hepatectomy.[9,10] Once severe PHLF occurs there is no effective treatment available, and current clinical management consists of treating underlying infections and support vital organ functions.[11] For the most severe forms of PHLF, mortality rates at 60 and 90 days after liver resections were reported as high as 59% and 54% respectively for specific definitions of PHLF.[12,13] For this reason, LTX is occasionally considered also for this patient group, but mostly abandoned since most patients have been operated for primary or secondary hepatobiliary malignancies, which in many countries excludes them from being offered LTX. Despite this, LTX has been described in a limited number of scientific publications as a rescue option for PHLF patients.[14,15] However, several important questions remain unanswered.

In this study we aim to present a northern European multicenter experience with the selective use of LTX to treat patients with severe PHLF. Secondly, we want to raise the question and discuss whether this treatment should be more readily used for this indication.

Methods

This study was reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement by using the checklist for cohort studies.[16] The study was approved by an ethical review board or a data protection officer in each country of all participating centers.

Study design and study population

This was a retrospective observational multicenter cohort study where the prospectively held transplant registries of five tertiary hepato-pancreato-biliary and transplant centers were screened to identify patients subjected to LTX due to PHLF. Participating centers were Karolinska University Hospital, Stockholm, Sweden, Oslo University Hospital, Norway, Rigshospitalet, Copenhagen, Denmark, Helsinki University Hospital, Finland and the University Hospital of Groningen, The Netherlands. Inclusion criteria was liver transplantation due to PHLF based on the criteria stated by the International Study Group for Liver Surgery (ISGLS)[13] within 3 months following hepatectomy. The study period was set to the date of the first identified patient in September 2008 until the last patient when screening of the transplant registries was performed in December 2020. Last follow-up was set to July 1st 2021. Patient data were collected retrospectively from electronic medical charts at each center.

For the patients with PHLF there were no uniform criteria for deciding to proceed to LTX, since this was a retrospective study collecting all procedures performed at the five participating centers during a 12-year period. Generally, malignant disease with tumors outside conventional transplantation criteria were not considered for rescue LTX in this setting. However, Oslo was an exception in also accepting patients with colorectal liver metastases within criteria setup locally and presented in various publications.[17–19]

Study variables

The collected baseline characteristics before liver resection were: age, gender, length, weight, co-morbidity according to the American Society of Anesthesiologists physical status classification system,[20] relevant tumor markers depending on preoperative diagnosis (alpha-fetoprotein, carcinoembryonic antigen and carbohydrate antigen 19-9), blood samples (bilirubin, international normalized ratio, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, albumin, platelets, creatinine and C-reactive protein), preoperative portal vein embolization, future liver remnant size both in absolute (ml) and relative (% of total liver) numbers, preoperative bile duct drainage including method, extrahepatic tumor manifestations and the indication for liver resection.

Intraoperative and post-hepatectomy variables were: date of resection, type of resection according to the Brisbane classification,[21] resection of extrahepatic bile ducts, duration of operation, intraoperative blood loss, intra-operative blood transfusion, use of Pringles maneuver, specific intraoperative complications by type, blood samples (same as preoperative) at postoperative day five and before liver transplantation, complications graded according to Clavien-Dindo classification[22] and also stated by type of complication, liver failure ISGLS grade, final pathology report, days from liver resection to liver transplant listing and days on waiting list before LTX.

Intraoperative and post-operative LTX variables were: donor age, donor gender, graft weight, donor-recipient blood groups, type of LTX, anhepatic time, blood loss, intraoperative complications by type, postoperative complications, blood samples (same as above) at postoperative day five and 90, clinical rejection, used immunosuppression, 30- and 90-day mortality, date of last follow-up or death and recurrence of primary disease.

Data collection and statistical analysis

Baseline patient characteristics, procedural data and complications were collected from prospective local databases at each center. Descriptive results for numerical variables were presented as median with range. Frequency distributions and percentages were used to summarize categorical variables. Missing values are reported in the tables for each presented variable. Follow-up in months was recorded with the liver resection as starting date. Collected data was treated as non-normally distributed due to the limited size of the cohort, and hence the Wilcoxon signed-rank test was used to compare differences in continuous variables before and after liver transplantation. A probability of less than 5% was considered statistically significant. All statistical

tests were performed with the statistical programs SPSS® version 25 (SPSS, Chicago, Illinois, USA) and GraphPad Prism version 7 (GraphPad Software, San Diego, California, USA).

Results

Patients

From September 2008 to May 2020 a total of 10 patients with severe PHLF were subjected to LTX within 90 days of the liver resection at the participating centers (Oslo n = 5, Stockholm n = 2, Helsinki, Groningen and Copenhagen n = 1 each). All patients but one were male and the median age was 70 years (range 49–72). Pre-resection bilirubin and international normalized ratio (INR) were essentially normal in all patients but one, with median bilirubin levels of 19 micro mol/L (range 4–257) and INR of 1.1 (range 1–3.3). Further baseline characteristics are displayed in Table 1.

Liver resection and development of PHLF

The indication for liver resection was suspected malignancy in all patients; more specifically perihilar cholangiocarcinoma (n = 5), hepatocellular carcinoma (n = 2), colorectal liver metastases (n = 2) and possibly malignant intraductal papillary mucinous neoplasia of the bile duct (n = 1). The extent of liver resection was major or extended hepatectomy in all but two patients where segmentectomies were performed. Concomitant resection of extrahepatic bile ducts was performed in 7 out of the total 10 patients. Additional data associated with the liver resection are shown in Table 2.

At day five after liver resection bilirubin and INR was elevated in all but one patient with a median bilirubin of 82 micro mol/L (range 16–243) and an INR of 1.6 (range 1.0–2.7). Bilirubin and INR values continued to rise after postoperative day five until LTX to median 257 micro mol/L (range 129–338) and 2.6 (range 1.4–3.7) respectively. In Fig. 1 perioperative values of bilirubin and INR are displayed. Since all patients had pathological bilirubin and INR on or after postoperative day five together with organ failure leading to intensive care treatment and rescue liver transplantation, they all were classified as grade C liver failure according to the ISGLS criteria of PHLF. In addition to liver failure, all patients but one suffered a postoperative complication grade 3 or higher. Out of the total 10 patients, six of them needed treatment at the intensive care unit during the time period that elapsed between the liver resection and LTX. All these patients suffered from multiorgan failure, with at least one other failing organ system besides the liver (treated with invasive treatment such as continuous renal dialysis, intubation on ventilator and in one patient extracorporeal liver support). The pathology report of the resected specimens revealed a benign or premalignant

Table 1 Baseline characteristics

Variable	All patients (n = 10)
Gender, n (%)	
Female	1 (10)
Male	9 (90)
Age in years, median (range)	70 (49–72)
Body mass index, kg/m2 median (range)	24.1 (20.9–29.1)
ASA class, n 1/2/3	3/3/4
Bilirubin preoperative, micro mol/L median (range)	19 (4–257)
INR preoperative, median (range)	1.1 (1–3.3)
Preoperative PVE, n (%)	2 (20)
sFLR %, median (range)	33 (30–48)
Preoperative bile duct drainage, n (%)	4 (40)
Indication for liver resection	
Perihilar cholangiocarcinoma	5
Hepatocellular carcinoma	2
Colorectal liver metastases	2
IPMN-B	1

ASA: American Society of Anesthesiologists physical status classification system, PVE: portal vein embolization, sFLR: standardized future liver remnant, IPMN-B: intraductal papillary mucinous neoplasia of the bile duct.

Table 2 Intraoperative and post-hepatectomy data

Variable	All patients (n = 10)
Type of resection	
Extended right hepatectomy	3
Right hepatectomy	4
Left hepatectomy	1
Other liver resection	2
Concomintant bile duct resection	7
Intraoperative blood loss, ml median (range)	1200 (500–21500)
Use of Pringles maneuver	3
Bilirubin at postoperative day 5, micro mol/L median (range)	82 (16–243)
INR at postoperative day 5, median (range)	1.6 (1–2.7)
Bilirubin prior to liver transplantation, micro mol/L median (range)	257 (129–338)
INR prior to liver transplantation, median (range)	2.6 (1.4–3.7)
PHLF ISGLS grade C, n (%)	10 (100)
CD complication grade >3, n (%)	9 (90)
Pathology report	
High-grade dysplasia or benign	6
Malignant tumor	4

INR: international normalized ratio, PHLF: post-hepatectomy liver failure, ISGLS: international study group for liver surgery, CD: Clavien-Dindo.

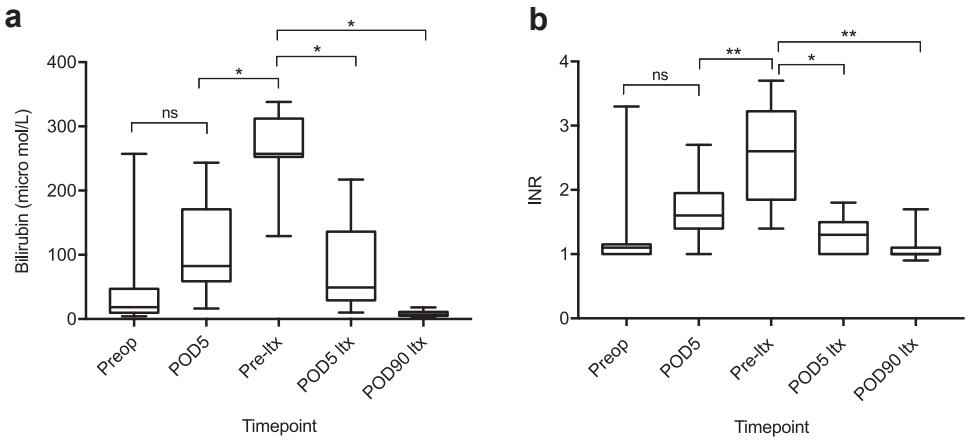

Figure 1 Levels of bilirubin and INR before and after liver resection and liver transplantation. a. Bilirubin levels before liver resection (preop), at postoperative day five (POD5), before liver transplantation (Pre-ltx), at day five after liver transplantation (POD5 ltx) and at day 90 after liver transplantation (POD90 ltx). b. International normalized ratio (INR) levels at same time points as bilirubin described above. Data are presented as median with range. Differences between time points are analyzed with Wilcoxon signed-rank test. *$p < 0.05$, **$p < 0.01$, *ns* not significant

condition in six out of 10 patients. The remaining four patients with malignant pathology consisted of two patients with colorectal liver metastases, one perihilar cholangiocarcinoma and one hepatocellular carcinoma (Table 4). The patient with perihilar cholangiocarcinoma had a two-centimeter lesion staged as a pT2N0M0, poorly differentiated and with a radical resection by a two-millimeter margin. The patient with hepatocellular carcinoma had a 21-mm tumor of fibrolamellar type that was radically resected. The first of the two patients with colorectal liver metastases had one 30-mm lesion with no lymph-node metastases and a radical resection, and the second patient had three metastases measuring 24, 4 and 2 mm that were also radically resected.

Table 3 Liver transplantation data

Variable	All patients (n = 10)
Liver transplantation decision on POD, days median (range)	14 (7–76)
Days on waiting list, median (range)	1 (0–10)
Type of liver transplantation	
Orthotopic whole graft	10
Anhepatic time, minutes median (range)	63 (59–120)
Intraoperative blood loss, ml median (range)	3000 (1100–7500)
Post liver transplantation complications, CD > 3 n (%)	5 (50)
Bilirubin post liver transplantation day 5, micro mol/L median (range)	49 (10–217)
INR post liver transplantation day 5, median (range)	1.3 (1–1.8)
Bilirubin post liver transplantation day 90, micro mol/L median (range)	7 (4–18)
INR post liver transplantation day 90, median (range)	1 (0.9–1.7)
90-day mortality post liver transplantation	0
Follow-up, months	49 (13–153)
Alive at last follow up, n (%)	8 (80%)

POD: postoperative day, INR: international normalized ratio, CD: Clavien-Dindo.

Liver transplantation and follow-up data

The decision to offer the patients rescue LTX was made in median 14 days (range 7–76) after liver resection and the patients were on the waiting list for in median 1 day (range 0–10). All patients were operated with orthotopic whole graft liver transplantation with an anhepatic time of in median 63 min (range 59–120) and with an intraoperative bleeding of 3000 ml (range 1100–7500). Post-transplant complications graded 3 or higher occurred in five patients. Further detailed data on the transplantations are given in Table 3.

At postoperative day 90 after LTX all patients had normalized bilirubin levels and only one patient had abnormal INR. There was no 90-day mortality after LTX. Patients were followed for a median of 49 months (13–153) and eight patients were alive without recurrence at last follow-up. One patient with colorectal liver metastases recurred after 59 months and died at 78 months and one patient with perihilar cholangiocarcinoma recurred after 21 months and died at 22 months. Final pathology report and follow-up data for all patients are shown in Table 4.

Discussion

In this retrospective multi-center cohort study from five Northern European high-volume HPB and transplant centers we demonstrate that in selected patients with severe PHLF, liver

Table 4 Indication, final pathology and follow-up

	Indication for liver resection	Pathology report	Recurrence	Alive at follow-up	Follow-up or death, months
Patient 1	pCCA	Bile duct high grade dysplasia	No, premalignant	Yes	35
Patient 2	IPMN-B	IPMN-B high grade dysplasia	No, premalignant	Yes	13
Patient 3	pCCA	pCCA	Yes, 21 months postop	No	22
Patient 4	pCCA	IgG4 autoimmune disease	Benign	Yes	80
Patient 5	pCCA	IgG4 autoimmune disease	Benign	Yes	30
Patient 6	HCC	Regeneration nodules	Benign	Yes	55
Patient 7	pCCA	IgG4 autoimmune disease	Benign	Yes	43
Patient 8	HCC	HCC	No	Yes	153
Patient 9	CRLM	CRLM	Yes, 59 months postop	No	78
Patient 10	CRLM	CRLM	No	Yes	114

pCAA: perihilar cholangiocarcinoma, IPMN-B: intraductal papillary mucinous neoplasia of the bile duct, HCC: hepatocellular carcinoma, CRLM: colorectal liver metastases.

transplantation can be a life-saving procedure with low short-term risk and good long-term survival in line with what can be achieved for other established indications. Although limited in size, this is to the best of our knowledge the largest published cohort of patients treated with LTX after liver resection leading to severe PHLF.

To date there is still no effective treatment once severe PHLF occurs and mortality remains high.[23] One suggested treatment option for PHLF is extracorporeal artificial liver support, but despite several attempts to treat PHLF with different liver support systems, there is still insufficient evidence for systematic use of any of them outside clinical trials.[24–26]

The use of LTX to treat uncommon conditions like severe traumatic and iatrogenic hepatobiliary injuries seem to be accepted by many transplant centers and a few selected cases have been reported previously.[27,28] However, the use of LTX to treat severe PHLF in the light of a previous liver resection for malignancy is more controversial due to organ shortage and the risk of recurrent malignant disease after LTX. In countries with short waiting list and good access to organs like in Norway, LTX in unresectable colorectal liver metastases has been explored successfully.[17–19] We argue that when severe irreversible PHLF occur, the first action is to ask for rapid pathological assessment of the resected specimen to evaluate a potential benign or pre-malignant condition. If this can be confirmed, as in six of the patients in the present cohort, the use of LTX is essentially comparable to in other causes of fulminant hepatic failure and would most likely be considered by most centers. If the pathology confirms malignant disease, a careful consideration must be undertaken with evaluation of the risk for recurrence if LTX is to be performed. In HCC, we would consider LTX if the tumor situation prior to liver resection was within the Milan or UCSF criteria, and extension of criteria could possibly be considered given that the explant does not show any signs of vascular invasion and that the AFP level prior to resection was within reasonable limits according to the French AFP model.[29]

For colorectal liver metastases the decision to proceed with LTX in this setting is more difficult, even with the promising results from the SECA trials from Oslo mentioned above. In transplant oncology, standard routine is to make an individualized assessment of each patient for transplant inclusion criteria. There are some more recent publications on transplant criteria for CRLM,[19] as well as scoring systems that can be utilized to predict long term survival after LTX for CRLM[30] that can be helpful when assessing a CRLM patient with fulminant PHLF. Furthermore, the International Hepato-Pancreato-Biliary Association recently published consensus guidelines for LTX in CRLM.[31]

If future trials show superiority of LTX for CRLM, and the survival outcome is comparable to established indications for liver transplantation, a wider acceptance for LTX for CRLM is likely. This could also lead to less reluctance to use LTX in selected cases of PHLF with CRLM as diagnosis. The availability of liver grafts may also be improved by the effective antiviral treatment against hepatitis C, donation after circulatory death and the use of extended criteria donors, thereby enabling more patients with malignant diseases to be considered for transplant.[32,33]

There are several limitations associated with this study. First, the retrospective design which carries an inherent risk for several forms of bias. Secondly, the small sample size which together with known selection bias reduce generalizability of the results (even if the multi-center setup gives some indication of possible external validity). Another observation is the gender issue with only one woman out of 10 patients offered LTX for PHLF in this series. We have no obvious explanation for this. In the series reported by Otsuka et al.,[14] five out of 7 patients were male and in the Oslo experience reported by Thorsen et al.[15] only one woman

out of 13 patients (five of which are included in the present study) were offered LTX for PHLF.

In conclusion, PHLF is not universally accepted as an indication for LTX. In selected patients with PHLF, LTX can be a lifesaving procedure with low short-term risk. Special attention must be paid to oncological long-term prognosis before proceeding with LTX in this setting.

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Conflicts of interest

None declared.

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