



Liver transplantation as a lifesaving procedure for posthepatectomy liver failure and iatrogenic liver injuries

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Abstract

Background Iatrogenic injuries to vital structures of the liver and posthepatectomy liver failure are associated with high mortality. The current donor situation in Norway allows liver transplantation of patients beyond conventional criteria.

Methods From 1984 to 2017, a total of 1510 liver transplantations were performed. In this retrospective study, we report the results of 13 patients undergoing liver transplantation due to iatrogenic injuries to the liver vasculature or posthepatectomy liver failure.

Results Twelve men and one woman with a median age of 55 years (range 22–69) were included. Seven patients underwent radical surgery for cancer prior to transplantation. The median follow-up time was 70.5 months (range 2.2–177). Three of the patients with malignant disease did not experience disease recurrence, whereas four patients had cancer recurrence and died 7, 24, 45, and 78 months after transplantation. Five of six patients with non-malignant disease fully recovered, but one patient died after 9 months due to infectious complications.

Conclusions Liver transplantation for liver failure due to portal vein and hepatic artery injury in patients with non-malignant disease seems justified. However, it may be questioned whether patients with malignant disease beyond established criteria should be offered liver transplantation.

Keywords Liver transplantation · Rescue · Iatrogenic injuries · Posthepatectomy liver failure

Introduction

Liver transplantation (LT) is the only curative treatment for a wide range of diseases resulting in end-stage liver disease. LT is also offered to patients with hepatocellular carcinoma (HCC) within established criteria for disease stage. However, few studies have evaluated urgent rescue LT as a lifesaving treatment for patients suffering from acute liver failure (ALF) after liver resection or severe injuries to vital structures of the liver. Previous studies have mainly examined

LT after fatal bile duct injuries acquired during cholecystectomy [1–8], while other indications such as iatrogenic injuries to the portal vein during bariatric surgery [9], bleeding-complications related to insertion of transjugular intrahepatic portosystemic shunt [10], and ALF after coiling of the hepatic artery [11] have been reported in smaller case series or single cases. Emergent LT as treatment after fatal injuries to the portal vein and hepatic artery during open adrenalectomy [4, 12], and LT as a bailout solution after uncontrollable bleeding in relation to resection surgery [11, 13] have also been described.

The donation rates in Norway have varied between 20.4 and 21.8 per million of the population during the last 5 years and the wait list mortality has been below 3%. Our hospital is the only transplant center in Norway, and performs around 100 LTs per year. The current situation with short waiting list and good access to organs has allowed us to explore expanded indications for LT, giving rise to the SECA-study [14–16], the RAPID concept [17] and extended criteria for LT in patients with HCC beyond those established internationally [18]. The aim of the study was to report our institutional experience with rescue LT in patients suffering from ALF due to injuries to the portal vein and hepatic artery or following liver resection.

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Methods

Between 1984 and 2017, 1510 LTs were performed in our institution. Thirteen LTs were done as urgent procedures due to iatrogenic injuries of vital hepatic vasculature or ALF after prior liver resections. Complete medical files of all patients were available for data-extraction. Data on the corresponding donors were collected from our local registry. The study was approved by the institutional review board according to the general guidelines provided by the regional ethics committee (2015/1442).

All patients received standard triple immunosuppression (IS) with tacrolimus in combination with steroids and mycophenolate mofetil, and except patient no. 12 all received induction therapy with anti-IL-2 receptor antibody (basiliximab) with delayed introduction of tacrolimus due to kidney dysfunction at the time of transplantation. Due to ABO-incompatibility, patient no. 10 received 45 g intravenous immunoglobulins for 4 days and a single dose of 850 mg anti-CD20 antibody (rituximab) in addition to standard IS. Due to changes in our IS-protocol during the study period, patient no. 4 and 11 did not receive IVIG/rituximab despite ABO-incompatible LT. All operations were performed using piggy-back technique without use of veno-venous bypass, and only full liver grafts were used. The severity of liver failure was categorized according to MELD score [19].

Results

Twelve men and one woman were included in the study. The median age was 55 years (range 22–69). Patient characteristics, indications for liver transplantation and main outcome are presented in Table 1. Six patients (cases 1–6, Table 1) were transplanted due to complications after surgical procedures for non-malignant tumors or conditions.

Seven patients (cases 7–13, Table 1) had undergone radical surgery for various malignancies prior to transplantation.

Perioperative data are presented in Table 2. Median time from the primary procedure until LT was 17 days (range 0–37), and the median waiting-time after the patient was listed for LT was one day (range 0–7). Median MELD score was 33.5 (range 22–40). The median donor age was 56 years (range 18–83). Median cold ischemia time (CIT) was 423 min (range 210–642). The median intraoperative blood transfusion was 3000 ml (range 250–27,250).

There were three incidents of primary non-function (PNF) or dysfunction requiring early retransplantation after the rescue procedure. All these were related to marginal liver graft quality with no signs of technical issues as the cause of PNF. Two of the primary LTs (A → 0) and one retransplantation (AB → A) were ABO-incompatible transplantations. Median ICU-stay after LT was 10 days (range 1–97). Two patients

were treated for biopsy-proven rejection. Two patients were diagnosed with vascular complications (one with hepatic artery stenosis and one with portal vein thrombosis), and four patients had biliary complications (two patients with leakage from the cystic duct and two with leakage from the hepatico-jejunostomy). Eleven patients were in need of temporary renal replacement therapy after transplantation. Median follow-up time was 70.5 months (range 2.2–171).

Survival time was calculated from the day of LT until December 31, 2017, or to patient death. For the patients that were re-transplanted due to PNF, the calculation is based on the last liver graft. Five and ten-year Kaplan-Meier (KM) estimated survival for the whole cohort was 64.8% and 51.9%, respectively. The five and ten-year KM estimated survival for the patients were both 80.0%, whereas the corresponding results for the patients with malignant disease was 57.1% and 38.1%, respectively (Fig. 1a, b). Table 2 provides further details on MELD score, perioperative morbidity, waiting time, donor-data, and main postoperative complications. Table 3 presents details on the four patients transplanted due to CRLM.

Discussion

In this report, we present our experience with salvage LT for iatrogenic vascular injuries and for complications to cancer surgery beyond conventional criteria. The study shows that LT is a lifesaving procedure for patients with devastating iatrogenic injuries to the portal vein and hepatic artery and for patients experiencing posthepatectomy liver failure. Long-term survival was achieved for the majority of the patients. However, more than half of the patients with malignant disease died of cancer recurrence.

Salvage LT in case of iatrogenic injuries or posthepatectomy liver failure poses not only medical considerations, but also ethical concerns in the face of organ shortage [20–24]. The availability of organs for transplantation is a crucial limitation, which directs the prioritization at each center and complicates the establishment of generally accepted indications, criteria for acceptance, and allocation policies. ALF caused by iatrogenic injuries is a less controversial indication for LT compared to salvage LT for surgical complications after treatment for malignancies beyond the conventional criteria for transplantation. Our study demonstrates that it is difficult to predict the outcome in both circumstances. The cohort includes a heterogeneous group of patients in terms of primary diagnosis, operative procedures, mechanism of liver failure and the general clinical status. This is partly in line with the experiences with LT for ALF within conventional criteria such as toxic liver failure, acute viral hepatitis, and idiopathic acute and sub-acute liver failure [25, 26]. However, for these conditions,

Table 1 Patient characteristics, indications for liver transplantation, and main outcome

Pat Age/ sex	Disease	Primary procedure	Primary procedure performed at OUS	Cancer	Reason for LT	Time from primary procedure to LT (days)	Follow-up (months)	Alive	Outcome
1 46/M	Gallstones. HCV	Laparoscopic cholecystectomy	No	No	Iatrogenic injury to PV and HA	2	121	Yes	Recurrence of HCV, otherwise well
2 22/M	Knife stab injury to abdomen	Abdominal packing for hemorrhage	No	No	Liver failure after hypovolemia and abdominal packing	4	71	Yes	Recovered
3 42/F	Suspected renal carcinoma (benign)	Laparoscopic nephrectomy	No	No	Iatrogenic injury to PV and HA	17	97	Yes	Recovered. Stented HAS. Repeated episodes of cholangitis due to stenotic biliary tracts in segment 5/8, successfully treated with partial PV embolization
4 62/M	Suspected duodenal cancer (high grade dysplasia)	Pancreatoduodenectomy	Yes	No	Liver failure after occlusion of stented HA-pseudoaneurysm	37	7	No	Death due to pneumonia and sepsis
5 63/M	Suspected HCC (regeneration nodules)	Right hepatectomy	Yes	No	Remnant liver failure	27	13	Yes	Recovered
6 52/M	Suspected CCA (benign IgG4 inflammation)	Right hepatectomy	Yes	No	Remnant liver failure	17	2	Yes	Recovered
7 49/M	HCC 2.1 cm/Child A cirrhosis	Local liver resection	No	Yes	Remnant liver failure	22	110	Yes	No signs of recurrence, doing well
8 69/M	CRLM	Right hepatectomy	Yes	Yes	Remnant liver failure (PV thrombosis)	9	78	No	Death due to recurrence of cancer
9 69/M	CRLM	Right hepatectomy	No	Yes	Remnant liver failure	20	72	Yes	Recovered, no signs of recurrence
10 67/M	CRLM	Planned right hepatectomy	Yes	Yes	Iatrogenic injury to left branches of PV and HA	6	45	No	Death due to recurrence of cancer
11 63/M	CRLM	Resection and auto-transplantation liver	Yes	Yes	Remnant liver failure due to intraoperatively massive bleeding	0	9	No	Death due to recurrence of cancer
12 42/M	PNET/liver metastasis	Planned distal pancreatic resection	Yes	Yes	Iatrogenic injury to PV and HA	1	177	Yes	Recovered, no signs of recurrence
13 55/M	Duodenal cancer	Pancreatoduodenectomy	Yes	Yes	Liver failure after HA-pseudoaneurysm and HAT	22	24	No	Death due to recurrence of cancer

OUS, Oslo University Hospital; LT, liver transplantation; PNET, pancreatic neuroendocrine tumor; PV, portal vein; HA, hepatic artery; HCV, hepatitis C virus; HCC, hepatocellular carcinoma; HAS, hepatic artery stenosis; CRLM, colorectal liver metastasis; HAT, hepatic artery thrombosis

Table 2 Details on patients, procedures, and results

Pat	MELD score	AKF w/ dialysis at time of listing	WT for LT (days)	Donor age (years)	Blood type donor → recipient (LT1/LT2)	CIT (min)	Blood transfusion perop (ml)	ICU-stay (days)	ACR within 30 days	Graft-loss re-tx	Cause of AKF postop	Vasc. compl	Biliary compl	Alive DWFG
1	40	Yes	0	62	0 → 0	642	250	10	No		Yes	No	No	Yes
2	38	No	2	83/69	A → A/0 → A	380/334	250/2000	19	No	Yes	PNF	No	No	Yes
3	34	Yes	4	46/58	0 → 0/0 → 0	514/202	3750/500	78	No	Yes	PNF	Yes	Yes	Yes
4	32	Yes	1	56/62	A → A/AB → A	531/651	3000/750	97	No	Yes	PNF	Yes	Yes	No
5	40	Yes	0	26	0 → A	492	7500	9	No		Yes	No	Yes	Yes
6	22	No	7	54	0 → A	350	2000	3	Yes		No	No	No	Yes
7	27	No	1	31	0 → 0	210	5400	20	No		No	No	No	Yes
8	39	Yes	1	55	A → A	423	3500	14	No		Yes	No	No	No
9	40	Yes	2	62	0 → 0	459	1250	5	No		Yes	No	No	Yes
10	29	Yes	2	69	A → 0	413	1000	1	No		Yes	No	No	No
11	22	No	0	70	A → 0	380	27,250	67	Yes		Yes	No	No	No
12	N/A	Yes	1	59	0 → 0	275	3000	9	No		Yes	No	Yes	Yes
13	33	Yes	2	18	A → A	703	3250	8	No		Yes	No	No	No

MELD, model for end-stage liver disease; AKF, acute kidney failure; WT, waiting time; LT, liver transplantation; CIT, cold ischemia time; ICU, intensive care unit; ACR, acute cellular rejection; Re-tx, retransplantation; DWFG, dead with functioning graft; N/A, not applicable; PNF, primary non-function

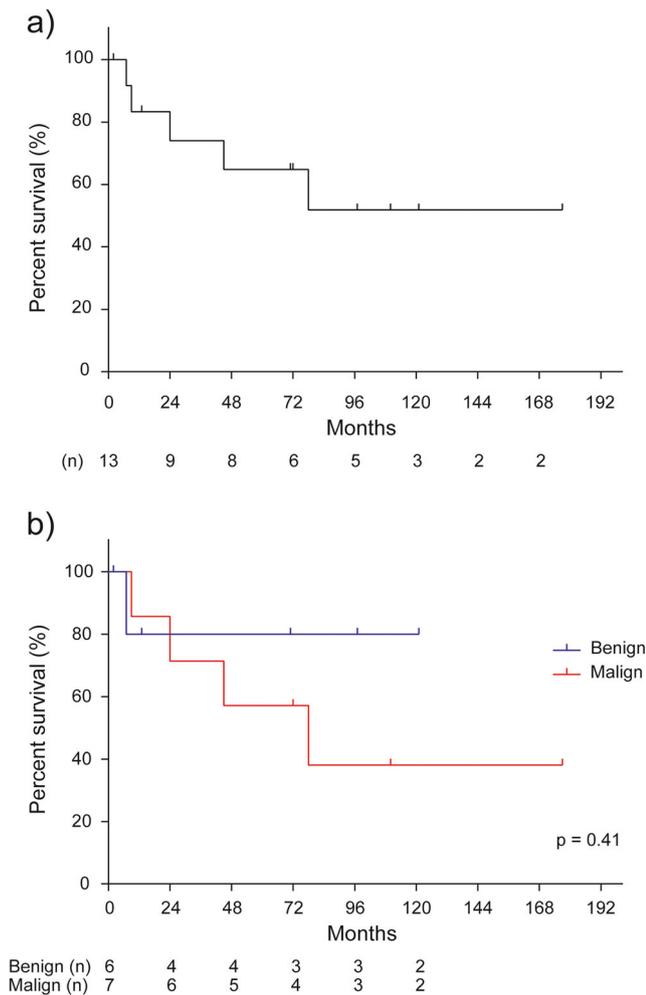


Fig. 1 **a** Kaplan-Meier plot of patient and graft survival for the whole rescue group. For the three patients that were re-transplanted due to primary non-function, the calculation is based on the last liver graft. **b**. Kaplan-Meier plots of patient and graft survival in the benign group vs malignant group. For the three patients that were re-transplanted due to primary non-function, the calculation is based on the last liver graft. Curves were compared using the log-rank test

there are well-established recommendations such as the King’s college guidelines [27]. For iatrogenic injuries, the reported experiences are scarce [11]. Patient 1 and 2 in our cohort underwent LT after vascular injuries, and the

primary procedure was performed due to a non-malignant medical condition. Both patients recovered and, in our view, represent cases that should be offered transplantation whenever possible. Thus, these groups are now included in the conventional ALF-group considered for LT in our center. Iatrogenic injuries that occur during surgery for cancer or suspected malignant disease are more challenging. Patient 3 and 4 underwent surgery for suspected renal and duodenal cancer, respectively. However, malignancy was excluded by final histology prior to transplantation in patient 4. The liver failure in this patient was caused by thrombosis in a stent in the hepatic artery placed due to a pseudoaneurysm after a pancreatoduodenectomy. This may be considered as an iatrogenic vascular injury finally indicating LT. Hepatic artery pseudoaneurysm after pancreatoduodenectomy carries a high mortality rate. Radiological intervention with stent placement is the first-line treatment. However, with complex arterial pathologies, as were the case in the two patients in our study, surgical revascularization, or even LT, may be the only lifesaving option to avoid lethal liver failure. To the best of our knowledge, LT has not been reported as a treatment option in this setting. Patient 3 was transplanted at a time when malignant kidney tumor was still suspected, and the benign diagnosis was confirmed after transplantation. This case poses several questions as no definite diagnosis had been made at the time of transplantation. Our decision to offer this patient transplantation was partly based on the dramatic consequences of an iatrogenic injury that occurred during surgery of a potentially curable kidney tumor.

Eight patients in our cohort underwent a liver resection for suspected or verified malignancy and were transplanted due to remnant liver failure. Two of these patients (5 and 6) did not have cancer and one patient (7) had HCC in a cirrhotic liver where the tumor was within established criteria for LT. However, the fourth and the fifth patient (8, 9) developed liver remnant failure after right hepatectomy for CRLM. All these five patients (5–9) developed grade C posthepatectomy liver failure according to the classification suggested by the International Study Group of Liver Surgery [28]. The

Table 3 Details on patients undergoing liver transplantation for colorectal liver metastasis

Pat	Diameter of largest tumor (cm)	Number of tumors	Last CEA before LT (µg/l)	Preop. chemotherapy (Y/N)	Response to chemotherapy according to RECIST (Y/N/SD)	Time from primary diagnosis to LT (months)	Survival (months)	Alive (Y/N)
8	3.0	1	3.5	Y	Y	5.9	78	N
9	2.3	3	< 1.0	Y	Y	11.5	72	Y
10	14.0	4	189	Y	SD	7.3	45	N
11	5.5	2	137	Y	SD	24.5	9	N

CEA, carcinoembryonic antigen; LT, liver transplantation

remaining three patients with posthepatectomy liver failure were also transplanted after primary surgery for a malignancy outside established criteria for LT. Due to the study design and small study sample, it is not possible to draw any conclusions regarding LT for patients with malignancy beyond the conventional criteria based on this study, except that the patients survive the primary surgical procedure, and do not die of ALF. If salvage LT is considered after surgery for suspected malignant disease, a detailed histology report should be available to confirm the diagnosis, and to evaluate the tumor stage and prognosis before a final decision for LT is made. Two of the patients had CRLM (10 and 11), and one had liver metastases from a pancreatic neuroendocrine tumor (12). These indications for LT are certainly controversial in a situation with organ shortage, and three of the four patients with CRLM died due to recurrence of cancer. Our institution has explored the potential benefit of transplanting patients with CRLM without extrahepatic disease in the SECA-study with encouraging results [14]. According to the results from the SECA trial, two of these patients could be considered as low risk based on maximal tumor diameter < 5 cm, pre LT CEA level below 80 µg/L and objective response on chemotherapy (14). One of these patients died 78 months after transplantation, and the other patient has still not developed recurrence after 72 months follow-up. Since transplantation for CRLM is still experimental and definitive selection criteria has not been established, it is difficult to predict the potential outcome in the setting of postresection failure. This study show that some patients may have acceptable or even exceptional results. Prolonged disease-free and overall survival after LT for CRLM have also recently been published in a cohort from some European centers. Importantly, they found that compassionate transplantation as a salvage procedure was associated with poorer outcome with respect to disease-free survival than patients where LT was a planned procedure [29]. To further conclude

regarding the outcome of LT for patients with malignancy beyond the conventional criteria, further studies with larger sample size are needed.

Patient survival in some of the previous reports on the use of urgent LT has not been encouraging, with short-term mortality up to 80% [7, 11]. Table 4 summarizes selected earlier reports on acute rescue LT. These results may partly be related to that the patients were in a dismal state at the time of transplantation such as suffering from infections, sepsis or multiorgan failure. These factors are predictors of poor survival in any candidate undergoing LT regardless of the underlying disease.

Certain limitations of this study must be acknowledged. First, this was a retrospective analysis of patients treated at a single institution with all the inherent biases associated with this study design. However, the clinical database used was prospectively maintained and provided complete follow-up data. Second, the sample size was small. However, despite the limitations of the small sample size, this is one of the largest series to date evaluating the outcome of salvage LT for posthepatectomy liver failure and iatrogenic injuries to vital structures of the liver. Last, and most important, the patients were highly selected and underwent LT without a study protocol and predefined criteria. As previously discussed, a fortunate donor situation and short waiting times has enabled LT to patients beyond conventional criteria. Thus, in case of organ shortage or other systems for allocation of available donor organs, the external validity of the study should be considered with caution.

In conclusion, LT can be a lifesaving procedure for patients suffering from iatrogenic liver injuries or posthepatectomy liver failure. LT for liver failure due to portal vein and hepatic artery injuries in patients with non-malignant disease seems justified. However, it is debatable whether patients with known malignant disease beyond accepted LT-criteria should be offered LT in a situation with organ scarcity.

Table 4 Selected studies on acute rescue liver transplantation

Author, year	No. pat. with acute LT*	Reason for performing LT	Outcome
Nordin et al., 2001 [1]	1	Transection of hilum during OC	Alive after 2 years follow-up
Fernandez et al., 2004 [3]	1	Ligation of PV and HA during LC	Death after 35 days
Zaydfudim et al., 2009 [4]	2	Transection of hilum during 1) open right adrenalectomy and 2) LC	Alive after 2 and 6 years follow-up
Parilla et al., 2013 [7]	5	Severe injury to hilum with BVI during LC	4 of 5 patients died within 30 days after LT
Leale et al., 2016 [8]	2	1) Acute-on-chronic liver failure after OC (Child C) 2) Massive liver-bleeding during LC	Alive after 2 and 8 years follow-up
Huerta et al., 2006 [9]	3	Severe injury to PV during bariatric surgery	Death after few days, 6 weeks and 8 weeks
Benedetto et al., 2010 [10]	2	Bleeding complications after TIPS	Long-term survival
Lauterio et al., 2017 [11]	2	1) Massive bleeding during liver resection 2) ALF after HA embolization due to bleeding	Long-term survival
Tessier et al., 2009 [12]	1	Transection of hilum during lap. adrenalectomy	Long-term survival

LT, liver transplantation; * defined as LT within 6 weeks after time of primary surgery; OC, open cholecystectomy; PV, portal vein; HA, hepatic artery; LC, laparoscopic cholecystectomy; BVI, bilio-vascular injury; TIPS, transjugular intrahepatic portosystemic shunt

Authors' contributions T.T: Study conception and design, acquisition of data, analysis and interpretation of data and drafting of manuscript. J.M.S.: Acquisition of data and drafting of manuscript. K.J.L.: Study conception and design, and critical revision of manuscript. P-D.L.: Study conception and design, and critical revision of manuscript. E.M.A.A.: Study conception and design, analysis and interpretation of data and drafting of manuscript. All authors have approved the final article.

Compliance with ethical standards

Disclosure The authors of this manuscript have no conflicts of interest to disclose.

Ethical standards The study was approved by the institutional review board according to the general guidelines provided by the regional ethics committee (2015/1442). For this type of study formal consent is not required (retrospective study).

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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