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# Long-Term Results After Adult Ex Situ Split Liver Transplantation Since Its Introduction in 1987

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**Abstract**
*Background* Split liver transplantation is still discussed controversially. Utilization of split liver grafts has been declining since a change of allocation rules for the second graft abolished incentives for German centres to perform ex situ splits. We therefore analysed our long-term experiences with the first ex situ split liver transplant series worldwide.
*Methods* A total of 131 consecutive adult ex situ split liver transplants (01.12.1987–31.12.2010) were analysed retrospectively.
*Results* Thirty-day mortality rates and 1- and 3-year patient survival rates were 13, 76.3, and 66.4 %, respectively. One- and three-year graft survival rates were 63.4 and 54.2 %, respectively. The observed 10-year survival rate was 40.6 %. Continuous improvement of survival from era 1 to 3 was observed (each era: 8 years), indicating a learning curve over 24 years of experience. Patient and graft survival were not influenced by different combinations of transplanted segments or types of biliary reconstruction ($p > 0.05$; Cox regression). Patients transplanted for primary sclerosing cholangitis had better survival ($p = 0.021$; log-rank), whereas all other indications including acute liver failure (13.6 %), acute and chronic graft failure (9.1 %) had no significant influence on survival ($p > 0.05$; log-rank). Biliary complications (27.4 %) had no significant influence on patient or graft survival ($p > 0.05$; log-rank). Hepatic artery thrombosis (13.2 %) had a significant influence on graft survival but not on patient survival ($p = 0.002$, >0.05, respectively; log-rank).
*Conclusions* Split liver transplantation can be used safely and appears to be an underutilized resource that may benefit from liberal allocation of the second graft.

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**Abbreviations**

| | |
|---|---|
| ARDS | Acute respiratory distress syndrome |
| CIT | Cold ischemic time |
| CT | Computer tomography |
| ERC | Endoscopic retrograde cholangiography |
| GRWR | Graft-to-recipient body weight ratio |
| HAT | Hepatic artery thrombosis |
| HBSS | Hepatobiliary sequence scintigraphy |
| HBV | Hepatitis B virus |
| HCC | Hepatocellular carcinoma |
| HCV | Hepatitis C virus |
| HDV | Hepatitis D virus |
| HTK | Histidine–tryptophan–ketoglutarate organ preservation solution |
| ICU | Intensive care unit |

| | |
|---|---|
| labMELD | Model of end-stage liver disease based on laboratory results |
| MELD | Model of end-stage liver disease |
| MRCP | Magnetic resonance cholangiopancreatogram |
| PNF | Primary non-function of the graft |
| PSC | Primary sclerosing cholangitis |
| PTC | Percutaneous transhepatic cholangiography |
| PTCD | Percutaneous transhepatic cholangio-drainage |
| UNOS | United Network for Organ Sharing |
| UW | University of Wisconsin organ preservation solution |

## Introduction

The first description of a successful split liver transplantation using a left-lateral graft for a paediatric recipient and the remnant extended right graft for an adult recipient was reported by our institution in 1988 [1]. Before the introduction of split liver transplantation, reduced size liver transplantation had been used for paediatric liver transplantation, which resulted in the waste of liver segments 4–8 plus segment 1 [2]. Since 1988, with increasing experience and improvement of the surgical technique, the significant potential of split liver transplantation became apparent, and this modality soon became common practice [3–9]. Therefore, split liver transplantation from deceased donors still has a place in paediatric as well as adult liver transplantation [6–14]. More advanced developments include the full anatomical liver split procedure for transplantation in two smaller adult liver recipients [10–14]. Today, the splitting procedure can be done either in situ during liver procurement in the deceased heart-beating donor or ex situ [7–9]. Both methods are considered to increase the risk for biliary complications [7–9, 14–22]. Biliary complications belong to the most serious morbidities after all types of liver transplantation [18, 19]. Partial liver grafts have a higher incidence of biliary complications as a result of the risks of biliary leakage from the transected liver surface and as a result of the risks of surgical dissection in the hepatic hilum, which may cause injury to the intra- and extrahepatic bile ducts [3–17, 23, 24]. It could be demonstrated that the in situ split of the liver graft in the deceased donor is associated with significantly shorter cold ischemic times compared with the ex situ split procedure [6–9]. Unfortunately, the in situ split approach often is restrained by logistical and technical efforts and lack of expertise as well as financial expenditures, all of which are necessary for its ultimate success [4–11]. In practice, about half of all split liver transplantation procedures in Europe and the United States are done after ex situ split of the liver graft [7–9, 25–28]. Split liver transplantation is still discussed controversially for high-urgency and retransplant cases and some transplant centres still hesitate to use split liver grafts in adults [7–9, 17]. Our goal is to evaluate the long-term results of ex situ split liver transplantation and the influences of complications and their management.

## Patients and methods

This is a retrospective, single-centre analysis with ongoing data collection from a university hospital within the Eurotransplant community. Included were all consecutive ex situ split liver transplants performed in adult recipients. Excluded were all combined organ, living-related organ donor, and reduced size liver transplants. We investigated 131 consecutive split liver transplants, including seven acute retransplants (retransplantation within 30 days) and five chronic retransplants in a total of 131 patients [median age 43.8 (range 18–66) years; males $n = 52$, 39.7 %; females $n = 79$, 60.3 %]. All transplants were performed between the 01.12.1987 and the 31.12.2010. The post-transplant observational period ended on the 31.12.2012.

### Surgical technique

The details of the surgical technique in this series were described previously [1, 17]. The veno/veno bypass was used routinely in all liver transplants until December 1996 and then completely abandoned without any measurable negative effect on outcome. Severe graft congestion and caval outflow complications during the postoperative course were observed in two early cases after reconstruction of the middle hepatic vein. The middle hepatic vein was preserved in all full right grafts and reconstructed in all full left grafts with an autologous venous patch, harvested either from the graft itself or from an iliac vein of the donor ($n = 10$; segments 1–4 or segments 2–4). The venous outflow was preserved in all cases for segments 5–8 in the presence of large accessory hepatic veins (V6, V7, V8), because right split grafts were always transplanted with the complete vena cava.

### Organ preservation

Euro-Collins solution was only used for the first three adult ex situ split liver transplants in era 1 and abandoned completely afterwards.

### Immunosuppression

The immunosuppressant regimen changed over time. Cyclosporine, tacrolimus, mycophenolate mofetil, and

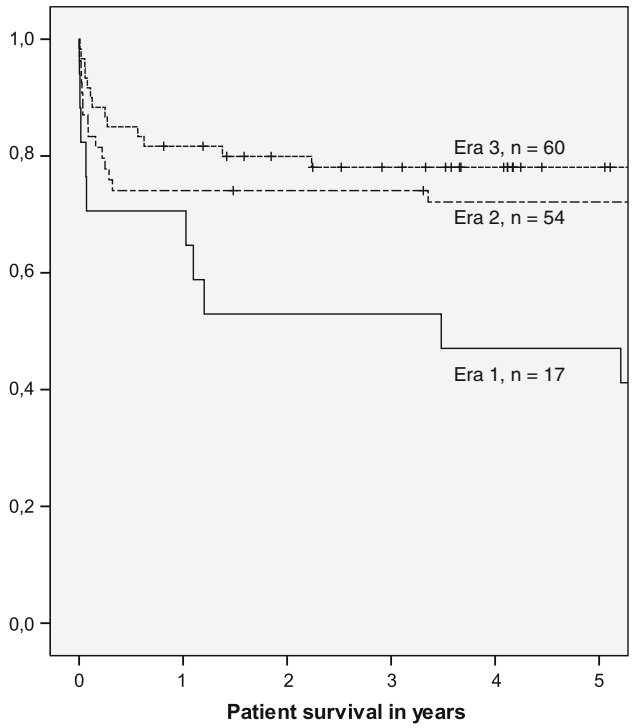


**Fig. 1** Influence of the era on patient survival ($p = 0.054$; Kaplan–Meier analysis, log-rank test) (era 1 = 01.01.1987–31.12.1994, era 2 = 01.01.1995–31.12.2002, era 3 = 01.01.2003–31.12.2010). It is interesting to note that the survival has improved continuously from era to era with a growing number of performed transplants

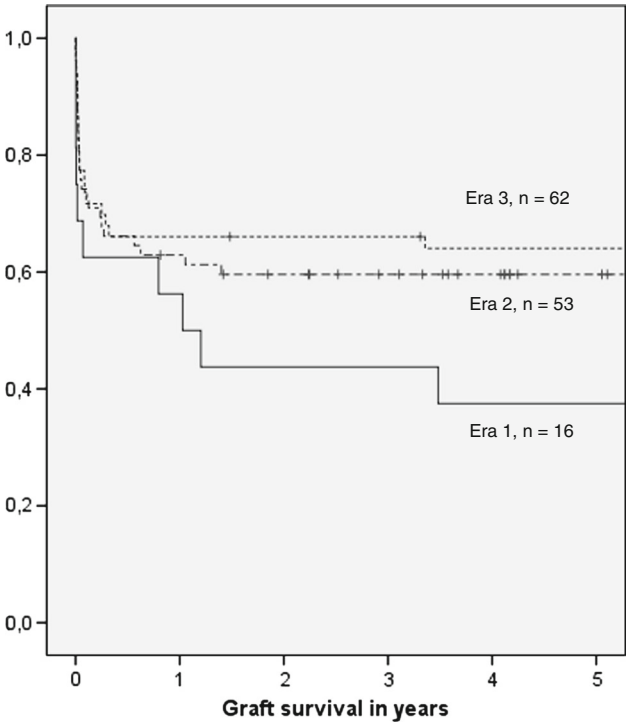


**Fig. 2** Influence of the era on graft survival ($p = 0.097$; Kaplan–Meier analysis, log-rank test) (era 1 = 01.01.1987–31.12.1994, era 2 = 01.01.1995–31.12.2002, era 3 = 01.01.2003–31.12.2010). It is interesting to note that graft survival has improved continuously from era to era with a growing number of performed transplants without reaching statistical significance

sirolimus were introduced very early in our centre due to participation in the respective phase I and II clinical trials. Immunosuppression was the same as for whole organ transplantation.

### Statistical analysis

Kaplan–Meier analysis, log-rank tests, Cox regression, logistic regression, Mann–Whitney *U* tests, and the Chi square tests were used where appropriate. For all statistical tests a $p < 0.05$ was defined as significant. The PASW statistics software version 20.0 (IBM, Somers, NY) was used for statistical analysis.

## Results

### Patient and graft survival

Mean observed patient survival was 5.7 years [median 5.6 (range 0–19.0) years], and the mean observed graft survival was 4.7 years [median 3.6 (range 0–16.6) years]. The 30-day mortality rate and the 1- and 3-year patient survival rates were 13, 76.3, and 66.4 %, respectively. The 1- and 3-year graft survival rates were 63.4 and 54.2 %, respectively. Thirty patients were retransplanted (retransplant rate 22.9 %). Sixty-four adult ex situ split liver transplants were performed before 31.12.2001 and resulted in an observed long-term patient survival of more than 10 years for 26 patients (observed 10-year survival rate: 40.6 %; mean: 12.9 years; median: 12.6 years; range 10–19 years). Patient and graft survival have improved continuously from era to era (each era: 8 years; $p = 0.054$, 0.097, respectively; Kaplan–Meier analysis, log-rank test; Figs. 1, 2).

### Influence of the MELD-score

At the time of transplant, the intensive care unit statements of both the donor and recipient were taken into account before transplantation. Retrospective model of end-stage liver disease based on laboratory results (labMELD) was available for 52 of 131 patients (labMELD: mean 14.2, median 12, range 6–40 points). Four of these 52 patients had a labMELD >30 at the time of transplantation with 75 % overall survival versus 79.2 % in patients transplanted with a labMELD <30 ($p = 0.867$, log-rank).

**Table 1** Indications for liver transplantation in the study population and the leading causes of death following split liver transplantation

| Indications for split liver transplantation ($n = 131$ patients) | $n$ | % |
|---|---|---|
| Acute liver failure | 18 | 13.6 |
| Alcoholic cirrhosis | 3 | 2.4 |
| Autoimmune hepatitis | 2 | 1.6 |
| Budd Chiari syndrome | 2 | 1.6 |
| Cryptogenic cirrhosis | 6 | 4.5 |
| Hemangioendothelioma | 1 | 0.8 |
| Metabolic diseases | 3 | 2.4 |
| HBV-related cirrhosis | 11 | 5.3 |
| HCV-related cirrhosis | 7 | 8.3 |
| Hepatocellular carcinoma | 19 | 14.4 |
| Klatskin tumour | 1 | 0.8 |
| Liver adenoma | 3 | 2.4 |
| M. Osler/hemangioma | 1 | 0.8 |
| Neuroendocrine metastases | 2 | 1.6 |
| Primary/secondary biliary cirrhosis | 13 | 9.9 |
| Primary sclerosing cholangitis | 25 | 18.9 |
| Polycystic disease | 2 | 1.6 |
| Retransplantation due to chronic graft failure | 5 | 3.8 |
| Retransplantation due to acute graft failure | 7 | 5.3 |
| Total | 131 | 100 |
| **Causes of death ($n = 44$ fatal long-term outcomes)** | **$n$** | **%** |
| Cardiovascular event | 3 | 2.3 |
| Cerebral: ischemia | 3 | 2.3 |
| De novo malignancy | 2 | 1.6 |
| Gastrointestinal: bleeding | 1 | 0.8 |
| Gastrointestinal: perforation | 1 | 0.8 |
| Infection: fungal | 2 | 1.6 |
| Infection: sepsis | 11 | 8.3 |
| Intraabdominal bleeding | 3 | 2.3 |
| Liver graft: biliary tract complications | 3 | 2.3 |
| Liver graft: HCV reinfection | 1 | 0.8 |
| Liver graft: PNF | 2 | 1.6 |
| Lung: ARDS | 1 | 0.8 |
| Lung: embolism | 1 | 0.8 |
| Lung: pneumonia | 1 | 0.8 |
| Tumour recurrence | 6 | 4.5 |
| Data not available | 3 | 2.3 |
| Survivors, no death | 87 | 66 |
| Total | 131 | 100 |

*HBV* hepatitis B, *HCV* hepatitis C, *PNF* primary nonfunction, *ARDS* acute respiratory distress syndrome

**Table 2** Transplanted segments, types of biliary reconstruction used, and T-drain usage frequency in this study

| Transplanted segments | $n$ | % |
|---|---|---|
| Not specified | 2 | 1.5 |
| Segments 1–4 | 2 | 1.5 |
| Segments 2–4 | 8 | 6.1 |
| Segments 2+3 | 5 | 3.8 |
| Segments 4–8 | 9 | 6.9 |
| Segments 4–8+1 | 62 | 47.3 |
| Segments 5–8 | 34 | 26 |
| Segments 5–8+1 | 9 | 6.9 |
| Total | 131 | 100 |
| **Biliary tract reconstruction** | **$n$** | **%** |
| Roux-en-Y choledochojejunostomy | 2 | 1.5 |
| End-to-end choledochocholedochostomy | 46 | 35.1 |
| End-to-side choledochocholedochostomy | 2 | 1.5 |
| Side-to-side choledochocholedochostomy | 9 | 6.9 |
| Hepaticocholedochostomy | 9 | 6.9 |
| Hepaticohepaticostomy | 8 | 6.1 |
| Roux-en-Y hepaticojejunostomy | 40 | 30.5 |
| Temporary biliary reconstruction | 8 | 6.1 |
| Secondary biliary reconstruction | 1 | 0.8 |
| Data not available | 6 | 4.6 |
| Total | 131 | 100 |
| **T-drain usage** | **$n$** | **%** |
| Yes | 9 | 6.9 |
| No | 116 | 88.5 |
| Data not available | 6 | 4.5 |
| Total | 131 | 100 |

## Influence of the underlying liver disease

Indications for transplantation and causes of death are summarized in Table 1. Patients with acute liver failure as compared to all other indications had no significantly different patient ($p = 0.491$; Kaplan–Meier, log-rank) or graft survival ($p = 0.3$; Kaplan–Meier, log-rank). The same was observed for patients with hepatocellular carcinoma, hepatitis B virus-related cirrhosis, and primary or secondary biliary cirrhosis (patient survival $p > 0.05$, log-rank; graft survival $p > 0.05$, log-rank). Cases with primary sclerosing cholangitis (PSC) had significantly better patient survival ($p = 0.021$; Kaplan–Meier, log-rank) compared with all other indications reaching 88 and 80 % patient survival after 1 and 3 years, and 68 and 52 % graft survival after 1 and 3 years, respectively.

## Combinations of transplanted segments and types of biliary reconstruction

The combinations of transplanted segments, the types of biliary reconstructions and T-drain usage in this series are summarized in Table 2. It is interesting that the

**Table 3** Biliary complications, diagnostic methods used to detect them, as well as the time intervals between transplantation and the detection of the complication, the treatment modalities of biliary complications, and the time intervals between liver transplantation and the treatment of biliary complications within the study cohort

| Types of biliary complications ($n = 35$) | Diagnostic methods used to detect biliary complications | Median days from Tx to diagnosis | Treatment modality for biliary complications | Median days from Tx to treatment of biliary complication |
|---|---|---|---|---|
| Dehiscence of biliary anastomosis ($n = 5$) | Intraoperative ($n = 2$)<br>HBSS ($n = 2$)<br>ERC ($n = 1$) | 18 (3–37) | Reanastomosis of biliary duct ($n = 3$)<br>ERC with stent ($n = 1$)<br>Re-LTx ($n = 1$) | 18 (4–37) |
| Anastomotic stenosis ($n = 5$) | Sono ($n = 1$)<br>ERC/PTCD ($n = 4$) | 211 (20–522) | Reanastomosis of biliary duct ($n = 1$)<br>ERC with stent ($n = 3$)<br>PTC with stent ($n = 1$) | 211 (20–522) |
| Biliary leakage from the resection plane ($n = 13$) | Intraoperative ($n = 6$)<br>CT ($n = 3$)<br>HBSS ($n = 2$)<br>Sono ($n = 1$)<br>MRCP ($n = 1$) | 6 (0–30) | Suture at the resection plane ($n = 8$)<br>No specific treatment ($n = 2$)<br>Interventional drainage ($n = 3$) | 6 (0–30) |
| Biliary leakage from a central bile duct ($n = 3$) | Intraoperative ($n = 2$)<br>CT ($n = 1$) | 18 (2–19) | Suture at the central bile duct followed by reanastomosis of biliary duct ($n = 1$)<br>Suture at the central bile duct followed by ERC with stent ($n = 1$)<br>Interventional drainage (CT-guided) followed by Reanastomosis of biliary duct ($n = 1$) | Primary treatment<br>18 (2–19)<br>Secondary treatment<br>23 (9–40) |
| Progressive ischaemic cholangiopathy ($n = 5$) | ERC/PTCD ($n = 3$)<br>Biopsy ($n = 2$) | 260 (78–3,436) | Re-LTx ($n = 2$)<br>PTC/ERC with stent ($n = 2$)<br>No specific treatment ($n = 1$) | 456 (107–3,436) |
| Combined biliary complications: biliary leakage and anastomotic stenosis ($n = 4$) | CT ($n = 1$)<br>HBSS ($n = 1$)<br>Sono ($n = 1$)<br>ERC ($n = 1$) | Primary diagnosis<br>15 (6–22)<br>Secondary diagnosis:<br>1,851 (28–1,869) | Interventional drainage followed by ERC/PTC with stent ($n = 2$)<br>Suture at the resection plane followed by reanastomosis of biliary duct ($n = 1$)<br>Reanastomosis of biliary duct ($n = 1$) | Primary treatment<br>16 (6–22)<br>Secondary treatment<br>963 (28–1,869) |

Five cases with progressive ischaemic cholangiopathy comprised two cases with ischemic-type biliary lesions (ITBL), two cases with secondary sclerosing cholangitis, and one case with CMV-associated chronic biliary tract destruction

*HBSS* hepatobiliary sequence scintigraphy, *CT* computed tomography, *ERC* endoscopic retrograde cholangiography, *PTC* percutaneous transhepatic cholangiography, *PTCD* percutaneous transhepatic cholangio-drainage, *MRCP* magnetic resonance cholangiopancreatogram

combinations of transplanted segments had no significant influence on patient and graft survival and also not on the later occurrence of biliary complications. The usage of a hepaticojejunostomy ($n = 41$; 31.3 %) had no statistically significant influence on patient survival ($p = 0.26$; Kaplan–Meier; log-rank) or graft survival ($p = 0.489$; Kaplan–Meier; log-rank). The types of biliary reconstruction used (Table 2) had no statistically significant influence on patient survival ($p = 0.396$; Cox regression analysis), on graft survival ($p = 0.138$; Cox regression analysis), and the later occurrence of biliary complications ($p = 0.251$, Chi square). Patient and graft survival were not significantly different for adults who received a full left graft compared with adults who received a full right or an extended right graft ($p > 0.05$; Cox regression). In nine patients, segment 1 was sacrificed for technical reasons and not retrieved together with segments 4–8.

## Biliary complications

Following split-liver transplantation biliary complications occurred in 35 of 128 patients (27.4 %). Late biliary

**Table 4** Types of biliary complications and their treatment as well as their respective statistical influence on patient and graft survival (Kaplan–Meier analysis with log-rank test)

| Types of biliary complications ($n = 35$) | No specific treatment ($n = 3$ in 3 patients) | Interventional treatment ($n = 16$ in 14 patients) | Surgical treatment ($n = 22$ in 20 patients) | Influence of the type of biliary complication on patient survival | Influence of the type of biliary complication on graft survival |
|---|---|---|---|---|---|
| Biliary leakage ($n = 21$) | 2 | 6 | 16 | 0.109 | 0.244 |
| Anastomotic stenosis ($n = 5$) | – | 4 | 1 | 0.257 | 0.137 |
| Progressive ischaemic cholangiopathy ($n = 5$) | 1 | 2 | 2 | 0.838 | 0.245 |
| Biliary leakage and anastomotic stenosis ($n = 4$) | – | 4 | 3 | 0.309 | 0.186 |
| Patients ($n$) | 3 (9 %) | 14 (40 %) | 20 (57.1 %) | | |
| Influence of the treatment modality on patient survival | 0.935 | 0.776 | 0.284 | n.a. | n.a. |
| Influence of the treatment modality on graft survival | 0.636 | 0.859 | 0.162 | n.a. | n.a. |

Two patients received both interventional and surgical treatment modalities for biliary complications

complications were primarily characterised as late anastomotic stenosis alone ($n = 4$) or combined with early biliary leakage ($n = 2$) or as progressive ischaemic cholangiopathy ($n = 5$). Early biliary complications were primarily detected as leakage from the biliary anastomosis ($n = 5$), biliary leakage from the resection plane ($n = 13$), biliary leakage from open previously unrecognized central bile ducts ($n = 3$), or as anastomotic stenosis either alone ($n = 1$) or combined with biliary leakage ($n = 2$; Table 3).

The occurrence of biliary complications had a significant influence on 30-day mortality ($p = 0.009$, Chi square test) but not on 1- and 3-year patient survival rates ($p > 0.05$, Chi square test), whereas the individual types of observed biliary complications failed to reach a significant influence on 30-day mortality and 1- and 3-year patient survival ($p > 0.05$, Chi square test). Central bile duct lesions at the biliary confluence lead to significantly worse long-term patient survival compared with all other types of biliary complications taken together ($p = 0.014$, log-rank; Table 3). The dissection along the biliary tract should not be close to the wall of the biliary duct so that the fine arterial plexus remains intact and is not damaged. We believe that central bile duct lesions may be the result of extensive dissection in the hepatic hilum, especially in full right and full left splits.

Biliary complications had a significant influence on 1- and 3-year graft survival ($p = 0.025$ and $p = 0.02$, respectively, Chi square test), whereas the individual types of observed biliary complications failed to have a statistically significant influence on 1- or 3-year graft survival ($p > 0.05$, Chi square test; Table 3). The type of biliary complications as well as the chosen treatment modality for biliary complications had no significant influence on patient and graft survival ($p > 0.05$; Kaplan–Meier, log-rank; Table 4). The majority of patients with biliary complications were treated surgically (57.1 %, $n = 20$) in all eras, whereas a significant increase in the percentage of interventional treatments for biliary complications was observed from era 1 to era 3 ($p = 0.048$, Chi square).

A large proportion of patients with biliary complications required interventional treatment (40 %, $n = 14$). A minority of patients with biliary complications, including chronic biliary tract destruction ($n = 1$) and biliary leakage from the liver resection plane ($n = 2$), did not receive any specific treatment during follow-up ($n = 3$; Tables 3, 4). Interestingly, the frequency of biliary complications did not change significantly between the three different eras.

## Use of adult ex situ split liver grafts for retransplantation

The 24-year experience with the use of ex situ split liver grafts for retransplantation is summarized in Table 5. A total of 12 retransplants (9.2 %) was performed with ex situ split liver grafts, including seven acute retransplants and five chronic retransplants.

**Table 5** Details of 12 adult split liver retransplants (reLTX) in this series with observed patient and graft survival as well as the indications for the primary liver transplant procedures (LTX) and the retransplant procedures (reLTX) and the time intervals between LTX and reLTX in days

| Recipient sex | Time between LTX and reLTX (days) | Indication for primary LTX | Indication for reLTX | Transplanted segments (reLTX) | Death during the observation period | Patient survival (year) | Graft survival (year) |
|---|---|---|---|---|---|---|---|
| F | 47 | Cryptogenic cirrhosis | Biliary tract complications | 5–8 | Yes | 1.1 | 0.8 |
| F | 37 | PBC | Initial graft non-function | 1–4 | Yes | 9.0 | 0.1 |
| M | 1,159 | HBV HCV-related cirrhosis | Biliary tract complications | 4–8 | Yes | 0.1 | 0.1 |
| F | 10 | PSC | Biliary tract complications | 5–8+1 | Yes | 0.0 | 0.0 |
| F | 7 | HCC | Acute rejection | 5–8+1 | Yes | 0.2 | 0.2 |
| M | 666 | PSC | Chronic graft failure | 4–8+1 | No | 12.1 | 12.1 |
| F | 4,122 | Bylers disease | Chronic graft failure | 4–8+1 | No | 7.5 | 7.5 |
| F | 253 | HBV HDV-related cirrhosis | Biliary tract complications | 5–8+1 | No | 7.2 | 7.2 |
| M | 20 | Budd Chiari syndrome | Hepatic Artery thrombosis | 4–8+1 | No | 7.1 | 7.1 |
| M | 3 | HCC | Hepatic Artery thrombosis | 4–8+1 | Yes | 0.1 | 0.1 |
| M | 5,058 | Caroli syndrome | Chronic graft failure | 5–8 | No | 1.4 | 1.4 |
| M | 2 | Alcoholic cirrhosis | Initial graft nonfunction | 4–8+1 | Yes | 3.5 | 3.5 |

All primary transplants were performed with whole organ grafts

*F* female, *M* male, *HCC* hepatocellular carcinoma, *HDV* hepatitis D virus, *PSC* primary sclerosing cholangitis

### Hepatic artery thrombosis after transplantation

Hepatic artery thrombosis occurred in a total of 17 of 129 (13.2 %) patients and in 4 of 35 (11.5 %) patients with biliary complications. This difference in frequency did not reach statistical significance (Chi square test: $p = 0.654$; logistic regression: $p = 0.654$; Exp(B) = 1.273, 95 % confidence interval 0.443–3.662; Table 6). Patients with biliary leakage demonstrated a lower frequency of hepatic artery thrombosis (2/25, 8 %) compared with the whole cohort (17/129, 13.2 %). Hepatic artery thrombosis was detected in one of eight patients with early or late anastomotic stenosis and in one of five patients with progressive ischemic cholangiopathy during long-term follow-up. The cold ischemic time had a significant influence on the development of hepatic artery thrombosis ($p = 0.02$; Mann–Whitney *U* test). This was not the case for the use of arterial interposition grafts ($n = 4$) as well as the number of intraoperatively transfused units of red blood cells and the number of intraoperatively transfused units fresh-frozen plasma ($p > 0.05$; Chi square and Mann–Whitney *U* tests). Hepatic artery thrombosis had a significant influence on graft survival ($p = 0.002$; Kaplan–Meier, log-rank) but not on patient survival ($p > 0.05$; Kaplan–Meier, log-rank; Table 6).

### Portal vein thrombosis

Portal vein thrombosis was verified during 8 of 131 split liver transplant procedures leading to significantly worse survival ($p = 0.035$, log-rank).

### Risk factor analysis

Only the number of intraoperatively transfused packs of red blood cells ($p = 0.005$; Exp(B) = 0.851; 95 % confidence interval 0.761–0.951) and the number of intraoperatively transfused units of fresh-frozen plasma ($p = 0.005$; Exp(B) = 0.879; 95 % confidence interval 0.803–0.961; logistic regression) demonstrated a statistically significant influence on the occurrence of biliary complications during follow-up after transplantation (Table 6). These results could not be confirmed with the Chi square test. The number of intraoperatively transfused packs of red blood cells had a significant influence on 1-year patient survival ($p = 0.022$; Chi square), whereas the cold and warm ischemic times did not (Table 6).

### Hospital stay and intensive care stay

The absence or presence of biliary complications had no statistically significant influence on the duration of hospital stay ($p = 0.059$; Kaplan–Meier, log-rank) or the duration of intensive care unit stay ($p = 0.893$; Kaplan–Meier, log-rank; Fig. 3).

## Discussion

Reports using pooled registry data considered split liver transplantation as an independent predictor of poor patient outcomes for adults and children [29–31], whereas studies from specialised centres demonstrated survival outcomes

**Table 6** Variables, their frequencies in our series, and their statistical influence on the occurrence of biliary complications after split liver transplantation (univariate logistic regression analysis, Chi square test) and on graft and patient survival

| Variables | Influence on biliary complications | Graft survival | Patient survival |
|---|---|---|---|
| Cold ischemic time (min) | n.s.[a] | n.s.[a] | n.s.[a] |
| Mean 705 min, median 722 min | | | |
| Range 104–1,262 min | | | |
| Warm ischemic time (min) | n.s.[a] | n.s.[a] | n.s.[a] |
| Mean 40 min, median 38 min | | | |
| Range 18–112 min | | | |
| HTK preservation ($n = 77$) vs. UW preservation ($n = 51$) | n.s.[a] | n.s.[b] | n.s.[b] |
| Hepatic artery thrombosis yes ($n = 17$) or no ($n = 110$) | n.s.[a] | $p = 0.002$[b] | n.s.[b] |
| Left-lateral graft yes ($n = 5$) or no ($n = 126$) | n.s.[a] | n.s.[b] | n.s.[b] |
| Hepaticojejunostomy yes ($n = 41$) or no ($n = 84$) | n.s.[a] | n.s.[b] | n.s.[b] |
| Postoperative bleeding complication yes ($n = 27$) or no ($n = 102$) | n.s.[a] | n.s.[b] | n.s.[b] |
| Retransplant case yes ($n = 12$) or no ($n = 119$) | n.s.[a] | n.s.[a] | n.s.[a] |
| Units of intraoperatively transfused | $p = 0.005$[c] | n.s.[a] | $p = 0.022$[a] |
| Red blood cells; mean 7, median 6 | Exp(B) = 0.851 | | |
| range 0–45 | (95 % CI 0.761–0.951) | | |
| Units of intraoperatively transfused | $p = 0.005$[c] | n.s.[a] | n.s.[a] |
| Fresh-frozen plasma; mean 9, median 8 | Exp(B) = 0.879 | | |
| range 0–41 | (95 % CI 0.803–0.961) | | |

Postoperative portal venous thrombosis did not occur in this series

*n.s.* not significant, *HTK* histidine-tryptophan-ketoglutarate organ preservation solution, *UW* University of Wisconsin organ preservation solution

[a] 1-year survival Chi square test results

[b] Kaplan–Meier analysis with log-rank test results

[c] Logistic regression analysis

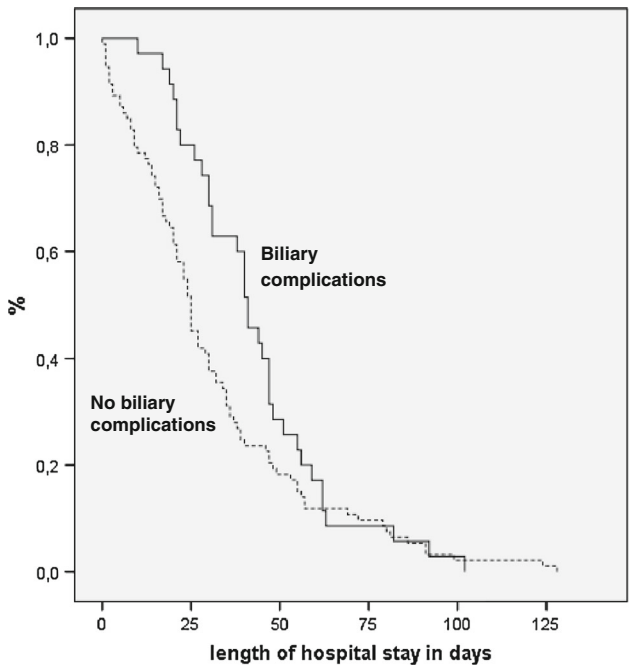


**Fig. 3** Influence of observed biliary complications after split liver transplantation on hospital stay in days ($p = 0.059$; Kaplan–Meier analysis, log-rank test)

comparable with whole organ liver transplantation [17, 22, 32–42]. We therefore consider that the long-term results of the first series of adult ex situ split liver transplantation since 1987 will be of interest in times of continued donor organ shortage and resulting deaths on the waiting lists.

Thirty-day mortality in this series appears comparatively high and the overall 1- and 3-year patient survival rates appear comparatively low compared with today's expectations. As could be demonstrated in Fig. 1, these results were influenced by the era during which the transplants have been performed. In this context, it is very interesting to note that patient survival has improved continuously from era to era. It can be assumed that the development of our series reflects a learning curve since the introduction of split liver transplantation in 1987. The comparatively high retransplant rate (22.9 %) is a result of the very long observational period. Mean graft survival of split liver transplants that were followed by a retransplant procedure during follow-up was 533 (range 1–2,655) days. A significant improvement of graft survival from era 1 to 3 was observed ($p = 0.041$, log-rank). Taken together, we consider that our results are largely comparable to other recently published series of split liver transplantation from

specialised centres within comparable eras [17, 20, 21, 32–41]. It appears noteworthy that this retrospective long-term study is able to demonstrate a mean observed patient survival of 5.7 years (median 5.6 years; range 0–19.0 years) and a mean observed graft survival of 4.7 years (median 3.6 years; range 0–16.6 years) and an observed 10-year survival rate of 40.6 % (mean 12.9 years, median 12.6 years; range 10–19 years) after adult ex situ split liver transplantation. These results underline the long-term value of the concept of adult ex situ split liver transplantation.

We were able to demonstrate earlier with a matched-pair analysis that extended right liver grafts obtained by ex situ split can be used safely for primary and secondary liver transplantation with acceptable biliary morbidity [17]. The possibility that adult ex situ split liver transplantation can be used for retransplantation is important, but as shown in Table 5 long-term results seem quite disappointing. The results of full size liver retransplantation also are disappointing without being significantly better unfortunately.

The present study shows the value of all different segmental combinations in adult ex situ split liver transplantation since its inception. The type of biliary reconstruction, the usage of a hepaticojejunostomy, and the usage of a T-tube all had no significant statistical influence on patient and graft survival and also not on the later occurrence of biliary complications (Table 2). A recently published meta-analysis on the routine use of a T-tube in liver transplantation is in line with our findings [43]. In our experience T tubes can be omitted and are omitted in our current practice of split and full size liver transplantation even though the data presented in our paper does not seem to provide clear evidence that this is the right choice. There is no conclusive evidence available for the influence of different types of biliary tract reconstruction on biliary complications after split liver transplantation or on graft or patient survival due to a complete lack of randomized, controlled trials [15, 17–19, 44]. Interestingly, a recent study including all types of liver transplantation could demonstrate that hepaticojejunostomy was an independent risk factor for the development of hepatic artery thrombosis [45]. We also found a significant influence of hepaticojejunostomy on the development of hepatic artery thrombosis in this series. In our practice, Roux-en-Y biliary reconstruction is limited to cases transplanted for PSC and to cases with destructed central bile ducts (e.g., in retransplant cases) as is the case in full size liver transplantation. The current series contains many patients with primary sclerosing cholangitis because our hepatologists have a research focus and a special clinical interest in this disease.

We believe that it is a progress in surgical technique to abandon the veno/venous bypass. Due to improved surgical skills, the potential advantages of the veno/venous bypass were made redundant.

According to United Network for Organ Sharing (UNOS) data, of the hepatic retransplantations performed between 1996 and 2007, only 8.7 % were done using right or extended right grafts from deceased donors. A small series of five hepatic retransplants using right partial grafts was reported by Gruttadauria et al. [46] in 2009. In our series, the fact whether split liver transplantation was performed as a retransplant or as a primary procedure had no statistically significant influence on patient or graft survival (Table 6). We believe that the results of this study show that adult ex situ split liver transplantation can be used as an option for acute and chronic retransplant cases and can enable long-term survival (Table 5).

Biliary complications are frequently considered the technical "Achilles heel" of liver transplantation because of their high frequency, the need for long-term, repeated treatment, and the potential detrimental effects on graft and patient survival. The incidence of biliary complications in our series (27.4 %) was similar to other published series [15, 47]. The results of this series could not confirm a previous observation of significantly increased mortality caused by biliary complications after adult ex situ split liver transplantation [15].

The results of this study confirm an earlier observation that cold ischemia time is not a major determinant of biliary complications [48]. The use of the histidine-tryptophan-ketoglutarate organ preservation solution (HTK) versus the University of Wisconsin organ preservation solution did not have a significant influence on the occurrence of biliary complications and also not on patient and graft survival (Table 6).

The overall incidence of early and late hepatic artery thrombosis (13.2 %) was lower in our series compared with early reports on paediatric partial liver transplantation (15–25 %) [49] and comparatively higher than other series of all types of liver transplantation (4.9 %) [45] and also compared with more recent reports on paediatric liver transplantation (7.8 %) [50]. Hepatic artery thrombosis had a significant influence on graft survival but not on patient survival. It is interesting to note that the overall incidence of hepatic artery thrombosis after transplantation ($n = 17$; 13.2 %) was slightly more frequent compared with the incidence of hepatic artery thrombosis ($n = 4$; 11.8 %) in cases with biliary complications which may be a consequence of early retransplantation after hepatic artery thrombosis before biliary complications could manifest in some cases. It could be demonstrated in an earlier study on hepatic artery thrombosis after all kinds of liver transplantations that cold ischemic time, the use of blood and plasma, and the use of aortic conduits in arterial reconstruction were significantly associated with hepatic artery thrombosis [45]. This association could only be confirmed in this study for cold ischemic time. Although surgical

revision used to be the standard treatment for biliary complications after liver transplantation, nonoperative management of biliary complications has more and more become a standard alternative practice over the past two decades in this and other series [47, 51–54]. In this series, surgical and interventional methods were used alone or combined for the treatment of biliary complications, including operative reanastomosis or suture, retransplantation, endoscopic retrograde cholangiography, percutaneous transhepatic cholangiography, endoscopic stent placement, and either computed tomography or ultrasound-guided interventional drainage (Table 3). Interventional treatment versus surgical treatment and the type of biliary complications after adult ex situ split liver transplantation both had no significant influence on patient or graft survival (Table 4).

The type of biliary complications and the chosen treatment modality for biliary complications had no statistically significant influence on patient and graft survival (Table 4). Although these latter statistical results should be interpreted with caution due to the relatively small numbers of patients with different biliary complications and different treatment modalities for these complications it should be noted that they are in line with most published observations on split liver transplantation [4, 6, 7, 9, 14, 16, 17, 20–22, 55].

Case by case evaluation in the present series of cases transplanted after the 01.12.2006 revealed that the survival of patients with a labMELD >30 at the time of split-liver transplantation is not worse as compared to recipients with a labMELD <30. This observation, although based on very small case numbers is in line with a recent study based on the American UNOS data base [33].

Our data is principally in line with the very encouraging results of a recent Italian study which found that split liver transplantation can be successfully performed for two adult recipients including full right and left grafts [56]. A prerequisite for a successful full left and right split liver transplant procedure for two small adults lies in the successful avoidance of a small-for-size liver syndrome. This may be achieved by a split and reconstruction of the middle hepatic vein either for the right lobe graft [56] or like in our series the left lobe graft.

There is a widespread consensus that only liver grafts without extended donor criteria and unquestionable donor organ quality should be considered as potential candidates for the splitting procedure to enable two liver transplants [3–17, 20, 21, 57]. Unfortunately, these organs appear to become rarer and rarer within the Eurotransplant community [58]. Several reports could demonstrate that split liver transplantation has potential equal to that of whole organ liver transplantation not only for adult but also for paediatric recipients [4, 6, 7, 9, 14, 16, 17, 20–22, 39–41, 55]. Merion et al. [29] found that split liver transplantation could provide enough organs to satisfy the entire current demand for paediatric donor livers in the United States and thus provide more aggregate years of life than whole organ transplantation and result in larger numbers of recipients. Encouraging results have been reported from Ghent for adult split liver transplantation with extended right lobe grafts from deceased donors that did not meet the Eurotransplant criteria for optimal donors [59].

It was reported that the quality of donor organs has seen a continuous deterioration in most Eurotransplant countries over the past 10–15 years: 63 % of organs are labelled "sub-optimal" with a donor risk index >1.5 [58].

The graft-to-recipient body weight ratio (GRWR) was not routinely calculated before the splitting procedure in this first series of split liver transplantation. The clinical role of the GRWR in split liver transplantation was only later recognized. Data on the GRWR was available retrospectively for 89 of 131 split liver transplants in this series. The mean GRWR was 1.73 (median 1.67; range 0.85–3.73). It was found previously that a GRWR less than 0.8 does not exclude adult-to-adult right lobe living donor transplantation [57].

Donor livers were selected for the ex situ split procedure on the basis of donor organ availability for paediatric and adult recipients, the clinical urgency of transplantation, and the clinical judgement of donor organ quality. A rationale for exact mathematical benefit calculations for optimal use of available donors is unfortunately not yet available.

During the observational period a total of 297 consecutive ex situ split liver transplants were performed at our centre, 131 adult and 166 paediatric transplants. In 36 of these 131 adult split liver transplants, the other graft was shared with other institutions, and in 95 cases, the other graft also was transplanted at our institution: 7 of these into another adult recipient and the remainder into paediatric recipients. Interestingly, estimated 3- and 10-year survival rates were better for paediatric split liver recipients (78 vs. 72.8 % and 71.8 vs. 56.5 %, Kaplan–Meier) without reaching statistical significance ($p = 0.201$, log-rank).

At the end of 2005, allocation policies in Germany were changed so that the optional use of the other graft by the same centre was no longer possible. Within the Eurotransplant community, the overall number of transplanted split liver grafts has decreased within recent years. The reasons for this observation may be partially explained by the reported deterioration of donor liver quality and a change in the allocation policy for split liver grafts without a direct incentive for the transplant centre that performs the splitting procedure and no incentive for transplant centres without a paediatric transplant programme.

The increased risk for biliary complications after transplantation of adult ex situ split liver grafts does not

render them as irresponsibly unsafe, especially in times of problematic donor organ shortage and resulting deaths on the waiting lists. Biliary complications and their treatment increase morbidity without significantly decreasing patient and graft survival. The low number of full left grafts in this series does not allow definitive conclusions on their influence on the risk of biliary complications or on survival after transplantation.

We are aware that split liver transplantation is limited by some obstacles due to a comparably high rate of biliary and arterial complications, the necessary technical expertise and the requirement of a good graft while a wider use of split liver transplantation would eliminate the shortage of liver grafts for small children. Split liver transplantation is increasingly important in times of decreasing altruistic organ donation in Germany after the recent transplant scandals [60]. Therefore, we believe that split liver transplantation appears to be an underutilized resource that may benefit from a more liberal allocation of the second lobe.

In our experience, the choice of the recipient for split liver transplantation needs to take into account the increased risk of biliary complications with increased posttransplant morbidity, whereas the choice of the graft for an ex situ splitting procedure needs to take into account the absence of macrovesicular steatosis >20 % and a sufficient graft volume with a GRWR that is ideally larger than 0.8. Sufficient technical expertise with split liver transplantation is mandatory for this procedure.

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