ORIGINAL ARTICLE

Combined liver–thoracic transplantation: single-center experience with introduction of the *'Liver-first'* principle

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SUMMARY

Combined liver/thoracic transplantation (cLiThTx) is a complex procedure for end-stage/advanced liver and heart(H)/lung(Lu) disease. To avoid futile use of multiple organs in single recipients, results should be scrutinously analyzed. Single-center cLiThTx (04/2000–12/2015) were reviewed for the following: demographics, indications, surgical technique, complications, rejection, and five-year patient survival. Results are reported as median (range). Fourteen consecutive patients underwent cLiThTx: 3 cLiHTx, 10 cLiLuTx, and 1 cLiHLuTx. Recipient age was 42 years (17–63 years). Most frequent indications were cystic fibrosis ($n = 5$), hepatopulmonary fibrosis ($n = 2$), amyloidosis ($n = 2$), and epithelioid hemangio-endothelioma ($n = 2$). Thoracic organs were transplanted first, except in three where LiTx preceded LuTx. In the latter, lungs were preserved by normothermic *ex vivo* lung perfusion. Stenting was performed for stenosis of bile duct ($n = 4$), hepatic artery ($n = 2$), and bronchus ($n = 2$). Abdominal interventions were required for bleeding ($n = 3$), evisceration ($n = 1$), and adhesiolysis ($n = 1$). One liver (cLiLuTx) was lost to hepatic artery thrombosis 3 months post-transplant and successfully retransplanted. One patient (cLiHTx) died 4 months post-transplant (myocardial infarction). Follow-up was 4 years (2 months–16 years). One liver and 5 pulmonary rejections occurred, all mild and reversible. Two patients developed bronchiolitis obliterans, one is clinically well 16 years post-transplant, and the other successfully retransplanted. Estimated 5-year patient survival is 90%. CLiThTx is safe with excellent short-/long-term surgical and immunological results.

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Key words
combined liver–thoracic transplantation, *ex vivo* lung perfusion, heart transplantation, liver transplantation, lung transplantation

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Introduction

Transplantation of more than one organ in a single recipient remains controversial but offers the possibility of successful treatment for patients who would be unlikely to survive transplantation of an isolated organ [1]. Combined liver and thoracic transplantation (cLiThTx) is a rarely performed and complex procedure with variability in indications, surgical techniques, and reported outcome. Most common indications are familial amyloidosis in case of combined liver–heart transplantation (cLiHTx), cystic fibrosis for combined liver–lung transplantation (cLiLuTx), and cirrhosis with portopulmonary hypertension for combined liver–heart–lung transplantation (cLiHLuTx) [2–5]. To avoid futile use of multiple scarce life-saving organs in single recipients and to gain a better understanding of the outcome after cLiThTx, the activity, indications, surgical techniques, and results should be analyzed with scrutiny. Herein, we analyze our short- and long-term single-center experience with cLiThTx and provide a detailed overview of the published experience.

Patients and methods

Single-center analysis

Fourteen consecutive patients who underwent simultaneous cLiThTx in our center between April 2000 and December 2015 were retrospectively reviewed using data prospectively collected in an *ad hoc* database. Three patients underwent cLiHTx, 10 cLiLuTx, and 1 cLiHLuTx.

Recipient and donor demographics

Recipients and donors were analyzed for the following: age, gender, blood group, cytomegalovirus (CMV) status, human leukocyte antigen (HLA)-A/B/DR mismatches, and crossmatch. For the recipient, the presence of cytotoxic antibodies and waiting time before transplantation were analyzed. The donors′ causes of death were reviewed.

Indication for transplantation

The severity of liver disease was assessed by the model for end-stage liver disease (lab-MELD) score. Parameters for heart failure included: cardiac output (CO), left ventricular ejection fraction (LVEF), mean pulmonary artery pressure (mPAP), pulmonary capillary wedge pressure (PCWP), pulmonary vascular resistance (PVR), and cardiac index (CI). Pulmonary function was evaluated by forced expiratory volume in one second (FEV_1).

Procurement and transplantation

Organs were procured by standardized techniques and preserved by static cold storage except in three cases (cLiLuTx) where the lungs were normothermically perfused and oxygenated *ex vivo* (organ care system (OCS)™ portable Lung device, TransMedics®, Andover, MA, USA). Thoracic organs were transplanted prior to the liver, with exception of the latter three, where the LiTx was performed first (Fig. 1). In the first of these three cases, this was due to a severe acute liver failure-induced coagulation disorder. To decrease the risk of bleeding during LuTx, the liver was transplanted first. Due to an anticipated longer lung preservation time, the lungs were normothermically perfused and oxygenated as previously reported [6]. Based on this successful clinical experience, and the potential benefits of this *liver-first principle*, we opted for the same transplant sequence (liver first, lung second) in two other cLiLuTx.

In all cases, the organs were transplanted orthotopically. LiTx was performed with assistance of a veno-venous and portovenous bypass. Biliary anastomosis was routinely accomplished with an end-to-end choledocho-choledochostomy. All LuTx consisted of bilateral lung allografts and were transplanted sequentially through bilateral anterior thoracotomy. Cardiopulmonary bypass was only used in case of HTx. Once the heart or heart–lung graft was transplanted, the patient was draped again and a classic LiTx was performed. In case of cLiHLuTx, a domino HTx was considered but canceled due to poor ventricular function of the native heart. In one case (lung–liver Tx sequence), veno-venous extra-corporeal membrane oxygenation (VV-ECMO) was used as bridge to transplant for hypoxic deterioration. After completion of the LuTx, VV-ECMO was weaned successfully and the LiTx could be performed without complications. In all cases, the thoracic or abdominal transplant was completely finished with closure of the skin before the second transplant was initiated.

Ischemic and *ex vivo* perfusion time

For the three lung allografts which were preserved by *ex vivo* lung perfusion (EVLP), both ischemic times and EVLP time were analyzed. For all other organs, cold and warm ischemic times were reported.

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Immunosuppression

In case of combined LuTx, immunosuppression (IS) was administered according to the LuTx protocol. Induction IS consisted of 1000 mg intravenous mycophenolate mofetil, 3 days of rATG (3 mg/kg/day) and 3 × 125 mg methylprednisolone during the first postoperative day. Maintenance IS consisted of tacrolimus with a target trough level of 12–15 ng/ml, mycophenolate mofetil (1000 mg; 2*/d), and a steroid taper (starting at 0.4 mg/kg/day from day two). In case of simultaneous HTx, IS therapy was similar except for an additional induction bolus of 1000 mg methylprednisolone during reperfusion and a maintenance steroid taper starting at 0.25 mg/kg/day. Mycophenolate mofetil was switched to azathioprine in 2 cases and stopped in 6 due to leucopenia and/or gastrointestinal disorders. One patient was switched from tacrolimus to everolimus.

Follow-up

Initial intensive care unit (ICU) and hospital stay were analyzed. Complications requiring surgical re-interventions were reviewed. Early (<3 months post-Tx) and late (>3 months post-Tx) acute and chronic rejection (biopsy-proven) were analyzed. Lung allograft rejection was specified into three different types: acute vascular rejection (type A), acute bronchial inflammation (type B), and chronic airway rejection (bronchiolitis obliterans syndrome (BOS)). BOS was determined by the decrease in FEV_1 according to the International Society for Heart and Lung Transplantation guidelines [7]. These endpoints were compared with single-organ transplantations (liver, lung, and heart) performed at our center during the same time period.

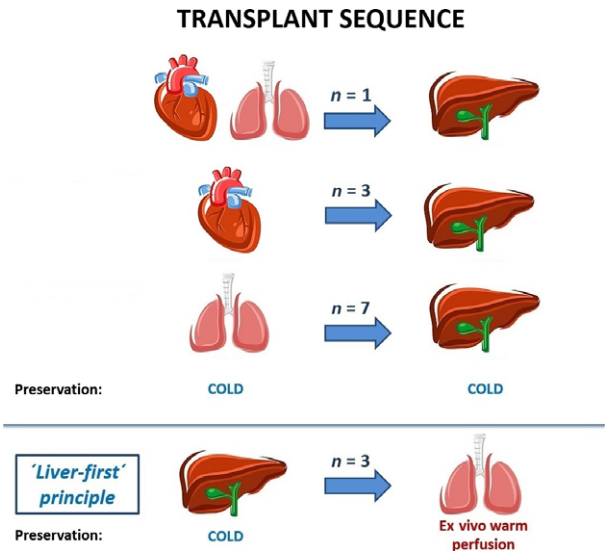

Figure 1 Single-center transplant sequence: 11 heart/lung prior to liver (all organs preserved on ice); 3 livers prior to lung (liver on ice, lungs preserved with *ex vivo* lung perfusion).

Statistics

For assessment of data and statistical analysis, Microsoft Excel 2013 and GraphPad Prism 5 (GraphPad Software Inc., La Jolla, CA, USA) were used. Five-year patient survival was estimated with the Kaplan–Meier method. Results are reported as median (range).

Results

The main findings of our fourteen patients are summarized in Table 1.

Recipient and donor demographics

Recipient age was 42 years (17–63 years). Six patients were male and 8 were female. In none of the patients, cytotoxic antibodies were detected pretransplant. Time on the waiting list was 3 months (24 days–1.5 years). Ten patients were at home and 4 hospitalized at time of transplantation. Organs were recovered from the same donor with a median age of 43 years (27–67 years). Male/female ratio was 4/10, resulting in 2 donor–recipient gender mismatches. All donors were brain dead, due to craniocerebral trauma in 7, a cerebrovascular accident in 6 and anoxia in 1. Donor–recipient ABO blood group match was identical in 8 and compatible in 6. Seven donor–recipients had a CMV mismatch; crossmatch was negative in all; mean HLA-A/B/DR mismatches were 1/2/2.

Indication

Liver indications were cystic fibrosis-related cirrhosis with portal hypertension (n = 5), familial amyloidosis (n = 2), epithelioid hemangio-endothelioma (n = 2), cardiac-induced cirrhosis (n = 1), hepatitis C virus-induced cirrhosis (n = 1), postethyl cirrhosis (n = 1), nonalcoholic steatohepatitis (NASH) cirrhosis (n = 1), and tuberculostatics-induced liver failure (n = 1). Lab-MELD was 12 (6–32). Cardiac indications were familial amyloidosis (n = 2) and restrictive cardiomyopathy (n = 1). The CO was 2.6 l/min (2.4–3.2 l/min; normal: 4.9–5.6 l/min); LVEF was 48% (32–75%; normal: 55–70%); mPAP was 30 mmHg (28–30 mmHg; normal: 15–24 mmHg); PVR was 216 dyn*s/cm^2 (200–236 dyn*s/cm^2; normal:

<240 dyn*s/cm^2); and the CI was 1.6 (1.5–1.7). Pulmonary indications included cystic fibrosis (n = 5), epithelioid hemangio-endothelioma (n = 2), hepatopulmonary fibrosis (n = 2), and chronic obstructive pulmonary disease (COPD) stage IV (n = 1). Predicted FEV_1 was 35% (12–113%). Indication for combined pulmonary and cardiac replacement was hepatitis C virus-induced cirrhosis and portopulmonary hypertension (n = 1) with a mPAP exceeding 50 mmHg (normal: 15–24 mmHg), a mPCWP of 5 mmHg (normal: 15 mmHg), and PVR reaching 502 dyn*s/cm^2 (normal: < 240 dyn*s/cm^2).

Ischemic and operative time

In the three cases of liver-first transplantation, cold and warm ischemic times for the liver were 320 (240–438) and 40 (32–50) min, for the first lung 150 (80–324) and 70 (57–99) min, and for the second lung 330 (227–497) and 64 (58–67) min; EVLP time for the lung grafts was 668 (492–675) min. In the other cases (n = 11), cold and warm ischemic times for the liver were 632 (552–757) and 44 (24–57) min, for the first lung 178 (93–230) and 62 (51–75) min, for the second lung 352 (224–460) and 67 (45–119) min, and for the heart 100 (30–135) and 33 (30–40) min, respectively.

Follow-up

Initial ICU and hospital stay was 24 (6–92) days and 60 (21–114) days, respectively. Stenting was required for bile duct stenosis (n = 4, of which 2 had cystic fibrosis), hepatic artery stenosis (n = 2), and bronchial stenosis (n = 2). Abdominal surgical re-interventions were required for bleeding (n = 3), evisceration (n = 1), and adhesiolysis for obstruction (n = 1).

Follow-up was 4 years (2 months -16 years). So far, one mild acute liver, five late mild pulmonary rejections (4*A1 and 1*B1), and no acute heart rejection have occurred. No chronic liver or heart rejection was diagnosed. The cLiHLuTx recipient developed BOS but is clinically well almost 16 years post-transplant. One cLiLuTx developed BOS with acute deterioration 4.5 years post-Tx, requiring re-LuTx. The patient is clinically well 1 year later. One liver (cLiLuTx) was lost to hepatic artery thrombosis and successfully retransplanted 3 months post-Tx. One patient (cLiHTx) died to acute myocardial infarction 4 months post-Tx. Estimated 5-year patient survival was 90%. Subanalysis of these endpoints for each organ combination and comparison to single-organ experience is summarized in Table 2.

Discussion

A low incidence of rejection (1 mild in liver, 5 mild in lung) and graft loss (1 liver and 1 lung) and a 5-year patient survival of 90% in our cohort of fourteen patients who received a cLiThTx confirm that cLiThTx is a feasible and life-saving procedure in selected patients. Indications for cLiThTx and experience have grown over the last decade, which is confirmed by the European and United States registries. For the Eurotransplant activity from 2000 till 2015, we obtained following data from the Eurotransplant data registry: 17 cLiHTx, 44 cLiLuTx, and 5 cLiHLuTx [8]. Our fourteen procedures represent 21.2% of this Eurotransplant activity (Fig. 2). The United States Organization for Procurement and Transplantation (OPTN) reported following experience from 2000 till 2015: 173 cLiHTx, 67 cLiLuTx, and 10 cLiHLuTx [9]. Although multiorgan transplantation has gained acceptance, the procedure still faces many challenges. With an increase in cLiThTx indications and activity, but a severely limited availability of suitable donor organs, the allocation of two or more vital organs to a single recipient confronts us with many ethical questions [1]. Therefore, it is of utmost importance to report the outcome of these complex procedures.

Prioritization of multiple organ candidates on the waiting list

Although the goal should be to treat those patients with the highest medical urgency and restrict the overall waiting list mortality, the severity of illness for patients with multiple organ failure may not be accurately described in current single-organ allocation models. Our data show that the lab-MELD at time of simultaneous Tx is relatively low (median of 12); however, waiting list mortality for these patients would undoubtedly be higher than patients with isolated hepatic failure and a similar lab-MELD score. Wolf and Schaffer clearly demonstrated that patients listed for cLiThTx have a higher risk to die on the waiting list than candidates awaiting a single organ, and once transplanted, cLiThTx recipients have a significant survival benefit [1,10]. Criteria for prioritizing cLiThTx candidates may need to be considered to reduce disparity in waiting list survival. Eurotransplant (to which Belgium participates) adapted its regulations for listing of cLiThTx candidates to this inequality [11]. In order to be able to allocate two or more organs to one patient, every case has to be presented to an auditing

Table 1. Single-center combined liver–thoracic transplantation: demographics, indications, and clinical outcome

Patient	Transplant date	Graft type	Transplant sequence	Indication		Recipient age/ gender	Donor age/ gender	Indication for re-interventions	Rejection	Graft loss	Alive/dead *Follow-up*
				Liver	Heart/Lung						
1	04/2000	LiHLu	H/Lu > Li	HCV cirrhosis	Secondary PPHT with RV failure	41, M	30, M	Bleeding, bile duct stenosis	Lung	–	Alive *15 y 8 mo*
2	01/2001	LiLu	Lu > Li	Cystic fibrosis-induced cirrhosis with PHT	Cystic fibrosis	20, M	47, F	Hepatic artery and bronchus stenosis	Lung	–	Alive *14 y 11 mo*
3	01/2003	LiH	H > Li	Familial amyloidosis	Familial amyloidosis	43, F	40, F	Evisceration	–	–	Dead, myocardial infarction *4 mo*
4	11/2005	LiLu	Lu > Li	Cystic fibrosis-induced cirrhosis with PHT	Cystic fibrosis	29, M	27, M	Intestinal obstruction, bile duct stenosis	Lung	–	Alive *10 y 1 mo*
5	01/2008	LiH	H > Li	Familial amyloidosis	Familial amyloidosis	48, M	53, F	–	–	–	Alive *8 y*
6	12/2008	LiLu	Lu > Li	Epithelioid hemangio-endothelioma	Epithelioid hemangio-endothelioma	25, F	24, F	Hepatic artery thrombosis	Liver Lung	Liver	Alive *7 y*
7	06/2010	LiLu	Lu > Li	Cystic fibrosis-induced cirrhosis with PHT	Cystic fibrosis	21, F	27, F	Bleeding, bronchus and bile duct stenosis	Lung	Lung	Alive *5 y 5 mo*
8	02/2011	LiH	H > Li	Cardiac cirrhosis	Congenital cardiomyopathy	53, F	47, F	Hepatic artery stenosis	–	–	Alive *4 y 10 mo*
9	07/2013	LiLu	Li > Lu (EVLP)	Acute liver failure (drug-induced)	COPD stage IV	62, F	40, F	Bile duct stenosis	–	–	Alive *2 y 5 mo*
10	05/2014	LiLu	Li > Lu (EVLP)	Epithelioid hemangio-endothelioma	Epithelioid hemangio-endothelioma	51, F	43, F	–	–	–	Alive *1 y 7 mo*
11	09/2015	LiLu	Lu > Li	Ethyl cirrhosis	Hepatopulmonary fibrosis	57, F	67, F	–	–	–	Alive *3 mo*
12	10/2015	LiLu	Li > Lu (EVLP)	Cystic fibrosis-induced cirrhosis with PHT	Cystic fibrosis	17, F	47, F	–	–	–	Alive *2 mo*
13	11/2015	LiLu	Lu > Li	Cystic fibrosis-induced cirrhosis with PHT	Cystic fibrosis	34, M	44, M	Bleeding	–	–	Alive *1.5 mo*
14	11/2015	LiLu	Lu > Li	NASH cirrhosis	Hepatopulmonary fibrosis	54, M	61, M	–	–	–	Alive *1.5 mo*

Li, Liver; H: Heart; Lu, Lung; EVLP, *ex vivo* lung perfusion; HCV, hepatitis C virus; PHT, portal hypertension; PPHT, portopulmonary hypertension; COPD, chronic obstructive pulmonary disease; NASH, nonalcoholic steatohepatitis; M, male, F, female; y, years; mo, months.

Table 2. Single-center experience with rejection, morbidity, ICU/hospitalization stay, and survival in the combined organ versus the isolated organ transplants

	Combined organs				Isolated organ		
Morbidity	Total Liver–thoracic	Liver–lung	Liver–heart	Liver–heart–lung	Liver	Lung	Heart
Number	14	10	3	1	879	795	341
Acute Rejection	Liver 7% Lung 36% Heart 0%	Liver 10% Lung 40% *(mild)*	Liver 0% Heart 0%	Liver 0% Lung 100% Heart 0%	27%	46%	15%
Chronic Rejection	Liver 0% Lung 14%	Liver 10% Lung 10%	Liver 0%	Liver 0% Lung 100%	1%	26%	/
HAT	7%	10%*	0%	0%	2.6%	/	/
HAS	14%	10% (stent)	33% (stent)	0%	0.3%	/	/
Biliary stricture with intervention	29%	30%† (stent)	0%	100% (stent)	22%	/	/
Bronchial stenosis with intervention	14%	20%	0%	0%	/	11%	/
Surgical re-intervention	36%	30% Bleeding (abd) Bleeding (thor) Obstruction	33% Evisceration	100% Bleeding (thor)	31%	NA	NA
ICU (days)	24 (6–92‡)	24 (9–63)	8 (6–92‡)	33	7 (1–91)	11 (2–97)	10 (1–198)
Hospitalization (days)	63 (21–100‡)	63 (24–114)	30 (21–100‡)	64	28 (8–388)	30 (8–252)	27 (14–196)
1 year patient survival	90%	100%	67%	100%	91%	91%	92%
5 year patient survival	90%	100%	67%	100%	87%	73%	88%

*Leading to ischemic cholangitis and re-liver transplant.
†1 in liver–lung (stent), 2 in lung–liver (both stent).
‡1 patient died due to myocardial infarction.
HAT, Hepatic artery thrombosis; HAS, hepatic artery stenosis; ICU, intensive care unit.

committee of Eurotransplant. If permission is granted, the patient is listed immediately following the high-urgency candidates. Allocation of thoracic organs precedes the liver, intestine, pancreas, and kidneys. This implicates that for cLiThTx the heart and lung allocation rules will be followed (center-oriented allocation of heart or lungs from local donors within the hospital network). On the other hand, one may argue that isolated transplant candidates could be disadvantaged by prioritization of combined organ transplant candidates. However, based on the OPTN data of 2007–2013, Goldberg concluded that single-organ candidates — who were bypassed on the waiting list by cLiThTx candidates — did not experience an increased waitlist mortality compared with matched controls [12].

Indications

Indications and results of the largest reported series on cLiThTx are summarized in Table 3 [3–5,13–25]. As in our experience, the most frequently reported indication for cLiThTx is a systemic disease, like familial amyloidosis involving both cardiopulmonary and hepatic systems for cLiHTx; and cystic fibrosis or alpha-1-antitrypsin deficiency for cLiLuTx. A second group of patients suffers from a primary organ disease with a subsequent failure of another organ. The most common example for cLiHTx is cardiomyopathy leading to cardiac cirrhosis, and for cLiLu(H)Tx, the most frequent condition is hepatic cirrhosis evolving to portopulmonary hypertension. A third option is a primary

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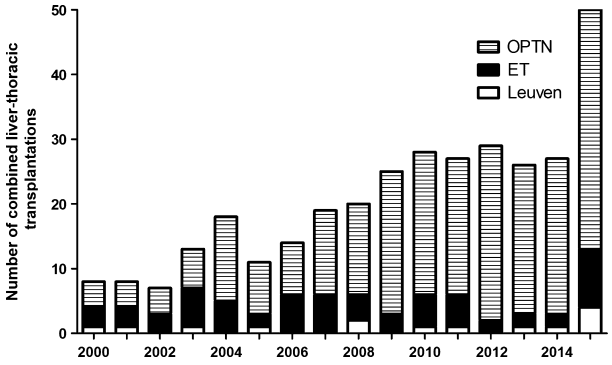

Figure 2 Worldwide combined liver–thoracic transplant experience (2000–2015): The United States Organization for Procurement and Transplantation (OPTN): 173 cLiHTx, 67 cLiLuTx, and 10 cLiHLuTx. The Eurotransplant data registry: 17 cLiHTx, 44 cLiLuTx, and 5 cLiHLuTx. The Leuven experience: 3 cLiHTx, 10 cLiLuTx, and 1 cLiHLuTx. CLiHLuTx: combined liver/heart/lung transplantation.

disease of both organs, like the patient in our series who was listed for end-stage lung failure (COPD) and developed drug-induced acute liver failure [6], as well as the two cases of epithelioid hemangio-endothelioma previously reported by our group for the first time [26].

Combined liver and heart transplantation

In 1984, Starzl reported the first successful cLiHTx in a 6-year-old girl with severe familial hypercholesterolemia and heart failure secondary to coronary artery disease [27]. But only over the last years, several single-center experiences with cLiHTx were published, of which the largest are those reported by Atluri (Stanford; $n = 26$) and Barbara (Mayo clinic; $n = 27$) [3,18,20,22,23,25]. These data and a review of the OPTN experience in 2012 by Cannon, including 97 cLiHTx, confirmed the feasibility of this procedure and revealed excellent 1- and 5-year graft and patient survival (85–100% and 73–83%) similar to isolated heart transplantation (84% and 70% according to the most recent report of the International Society for Heart and Lung Transplantation) [2,16,28].

Combined liver and lung transplantation

Experience with cLiLuTx has rarely been reported. The largest published single-center cohort is by Grannas (Hannover; $n = 13$) [17]. One- and 5-year patient survival in this cohort was limited to 69% and 49%, respectively. Five recipients (38%) from the Hannover group developed pneumonia within 3 months post-Tx leading to death in 3 of them. The largest cLiLuTx experience within the United States was published by Arnon who identified 7 children and 8 adults (suffering from CF) in the OPTN database till 2008 [5]. One- and 5-year patient survival was 80% which seemed similar to patient survival after isolated LuTx for CF (84 and 76%) [5]. Although the Paris group probably has the largest experience, detailed results from the last decade have not been reported [13].

Combined liver, heart, and lung transplantation

Although cLiHTx and cLiLuTx activities are increasing, experience with cLiHLuTx remains limited [5 cases registered in Eurotransplant; 10 in the United States (2000–2015)]. The first cLiHLuTx was performed by Sir Roy Calne in 1986 [29]. A 35-year-old woman suffering from end-stage primary biliary cirrhosis and severe PPHT underwent transplantation of an en bloc heart–lung and sequential liver graft. After this first case, Calne modified the technique to an en bloc double-lung–heart–liver transplant and applied this in 7 cases for CF and 1 for alpha-1-antitrypsin deficiency where the native heart was used for a domino transplant [14]. A domino procedure was also foreseen in our cLiHLuTx patient, but was aborted due to largely dilated right native ventricle and poor contractile function at the time of transplantation [4].

Surgical techniques

Cardiopulmonary and veno-venous bypass

Various methods have been described for the application of cardiopulmonary and veno-venous bypass. In our experience, veno-venous bypass (porto-femoro-axillary) was used during LiTx in all cases as it might support hemodynamic stability and reduce portal or retroperitoneal venous hypertension during caval and portal vein occlusion. The same reason was advocated in the series of Yi, Barabara, and Atluri [22–24]. In contrast to our and Yi′s experience where cardiopulmonary bypass was not used for cLiLuTx, it was applied in this setting by several other centers: the group of Couetil described completion of the thoracic organ implantation with the use of cardiopulmonary bypass, after which the bypass was stopped, heparinization was reversed and LiTx could safely be performed [13]. Barshes and Grannas mentioned the same technique in some of their patients [15,17].

Bile duct anastomosis

One of the most debated questions is whether or not to perform a biliary reconstruction with an end-to-end

Table 3. Overview of the published reports on indications and outcome of combined liver–thoracic transplantation

Author (year)	Center	Time span	Type of graft	Number of patients	Indication Liver	Indication Heart/Lung	Rejection (cases)	Survival (%)			
								1 y	3 y	5 y	10 y
Couetil (1995)	Broussais Hospital, Paris (France)	1990–1995	LiLu LiHLu	5 5	CF	CF	/	70	70	–	–
Praseedom (2001)	Papworth Hospital, Cambridge (UK)	1986–1999	LiHLu	9	CF (7), PBC (1), AATD (1)	CF (7), PPHT (1), AATD (1)	Li (1); Lu (3)	56	–	42	–
Pirenne (2002)	University of Illinois Chicago (USA)	1994	LiLu	1	HCV	PPHT	/	Died during operation			
	University Hospitals Leuven (Belgium)	2000	LiHLu	1	HCV	PPHT	Lu (1)	Alive (14 years later)			
Barshes (2005)	USA	1987–2004	LiLu	11	CF	CF	Lu (3)	79	63	63	–
Te (2008)	USA	1987–2007	LiH	46	FA (14), HCV (6), hemochromatosis (6), cardiac-(5), cryptogenic- (4), alcoholic cirrhosis (3), PBC (2), AATD (1), glycogen storage disease (1), AIH (1) Budd-Chiari (1), PSC (1), nodular hyperplasia (1)	FA (14), idiopathic- (9), congenital- (6), alcoholic- (3), viral CMP (2), hemochromatosis (5), coronary artery- (3), valvular- (2), glycogen storage disease (1), unknown (1)	Li (6); H (5)	85	80	76	–
Grannas (2008)	Hannover Medical School (Germany)	1999–2003	LiLu LiHLu	12 1	CF (5), AATD (2), sarcoidosis (1), PHT (5)	CF (5), AATD (2), sarcoidosis (1), PPHT (5)	Li (3); Lu (5)	69	62	49	–
Raichlin (2009)	Mayo Clinic, Rochester (USA)	1992–2007	LiH LiHLu	12 1	FA	FA	Li (2); H (2)	100	–	75	60
Scouras (2011)	Literature review + Pittsburgh (n = 1), Pennsylvania, USA	/	LiLu LiHLu	6 4	PHT	PPHT	NA	–	–	–	–
Arnon (2011)	USA	1987–2008	LiLu	15	CF	CF	NA	80	–	80	–
Nagpal (2013)	Cleveland Clinic, Ohio (USA)	2006–2012	LiH	5	HCV (4), FA (1)	Nonischemic CMP	None	100	100	–	–
Topilsky (2013)	Mayo Clinic, Rochester (USA)	2004–2009	LiH	10	NA	FA (8), ischemic CMP (1), idiopathic CMP (1)	NA	–	–	100	–

Table 3 continued

Author (year)	Center	Time span	Type of graft	Number of patients	Indication Liver	Indication Heart/Lung	Rejection (cases)	Survival (%) 1 y	3 y	5 y	10 y
Barbara (2014)	Mayo Clinic, Rochester (USA)	1999–2013	LiH	27	FA (21), congestive hepatopathy (6)	FA (21), congenital CMP (4), idiopathic CMP (2)	NA	–	–	–	–
Atluri (2014)	University of Pennsylvania (USA)	1997–2013	LiH	26	Cardiac cirrhosis (23), HCV (2), AATD (1)	Nonischemic- (18), congenital- (2), ischemic CMP (6)	H (4)	87	–	83	–
Yi (2014)	Methodist Hospital, Houston (USA)	2009–2012	LiLu LiHLu	7 1	CF (3), HCV (2), AATD (1), cryptogenic cirrhosis (1), congestive hepatopathy (1)	CF (3), IPF (2), AATD (1), PPHT (2)	Lu (1)	71,4	–	–	–
Careddu (2015)	University of Bologna (Italy)	1999–2012	LiH	14	FA (13), chronic hepatitis (1)	FA (13), nonischemic CMP (1)	Li (2); H (3)	93	–	82	–
Reich (2015)	Cedars-Sinai Medical Center, LA (USA)	1998–2014	LiH	7 (1 staged)	FA (3), cardiac cirrhosis (3), cholangiohepatitis (1)	FA (3), congenital- (1), hypertrophic- (1), idiopathic CMP (1), SLE (1)	Li (1)	83	83	83	83
Ceulemans (2016)	University Hospitals Leuven (Belgium)	2000–2015	LiH LiLu LiHLu	3 10 1	CF (5), FA (2), EHE (2), acute liver failure (1), cardiac cirrhosis (1), HCV (1), ethyl cirrhosis (1), NASH (1)	CF (5), FA (2), EHE (2), hepatopulmonary fibrosis (2), PPHT (1), congenital CMP (1), COPD (1)	Li (1); Lu (5)	90	90	90	90

Li, Liver; H, Heart; Lu, Lung; CF, cystic fibrosis; PBC, primary biliary cirrhosis; AATD, alpha-1-antitrypsin deficiency; HCV, hepatitis C virus; FA, familial amyloidosis; PSC, primary sclerosing cholangitis; P(P)HT, portal (pulmonary) hypertension; NA, not Available; EHE, epithelioid hemangioendothelioma; NASH, nonalcoholic steatohepatitis; CMP, cardiomyopathy; COPD, chronic obstructive pulmonary disease; SLE, systemic lupus erythematosus.

anastomosis or Roux-en-Y choledochojejunostomy; especially in case of CF, it is assumed that the condition could have a detrimental impact on the biliary duct anastomosis. This can be due to the fact that the gene encoding for the cystic fibrosis transmembrane conductance regulator (CFTR) that is expressed in the liver exclusively in the biliary epithelial cells, contributing to ductal bile excretion, is mutated in case of cystic fibrosis. Mutations in this channel will lead to bile thickening, stone formation, bile duct obstruction, biliary cell necrosis, and cholangitis [30,31].

In their series of 10 consecutive cases of cLiLuTx for CF, Couetil opted for biliary reconstruction by end-to-end anastomosis with a T-tube in 2 cases, and Roux-en-Y choledochojejunostomy in 8 [13]. Biliary strictures developed only in the first 2 patients who needed reconversion to a Roux-en-Y choledochojejunostomy. In contrast to this, Grannas performed a duct-to-duct anastomosis in 12 of 13 cases (including 5 with CF) and a Roux-en-Y in the other [17]. Only 1 stenosis was observed in the patient who underwent the Roux-en-Y procedure. In our series, where biliary reconstruction was routinely accomplished with an end-to-end choledochostomy, we encountered 4 bile duct stenoses (of whom 2 underwent cLiLuTx for CF) who required endoscopic retrograde cholangiopancreatography and stenting.

Skin closure

Although we routinely decided to completely finish one transplant before initiating the other, most centers leave the chest open during LiTx to allow access for temporary porto-atrial shunting. Couetil argued that the thorax should be closed before the completion of the biliary anastomosis to reduce the risk of infection [13].

Liver-first principle

In accordance with the generally accepted tolerable cold ischemic period, which is shorter for the heart or lungs than for the liver, almost all cLiThTx reported so far were performed in the same sequence: H/LuTx prior to LiTx. Only few exceptions were described: *first*, en bloc double-lung–liver–heart transplantation was routinely performed at Papworth hospital, Cambridge [14]. *Second*, in two cases from the Mayo Clinic in Rochester, LiTx was conducted prior to HTx [22,32]. In this setting, it was hypothesized that the transplanted liver graft would be able to absorb high-titer donor-specific HLA antibodies. After transplantation crossmatch turned negative, anti-HLA antibody titers decreased significantly and no rejection occurred. *Finally*, our group described the first case of LiTx prior to LuTx in a patient with COPD and acute liver failure [6]. Following an abnormal coagulation status (INR >10), the decision was made to transplant the liver first to correct the coagulation status and render the subsequent LuTx safer. In anticipation of the longer lung preservation time, the lungs were normothermically perfused. No rejection occurred. Following this experience, we performed two additional successful cases reported herein.

Additional hypothetical incentives of this *liver-first principle* are as follows: (i) liver reperfusion–injury is captured by the native lungs instead of the new lungs, reducing lung edema; (ii) restoration of the coagulation status might reduce the need for transfusion during LuTx and thereby prevent edema of the new lungs; and (iii) shorter liver cold ischemia time results in less biliary strictures [33]. In our first two cases of liver-first sequence, the transplantation of both organs was performed without any hemodynamic or ventilation problems. However, in the third case (cystic fibrosis and cirrhosis), it might have been preferable to transplant the lung first, in retrospect, due to the very poor oxygen delivery during LiTx (pO2 23 mmHg, pCO2 59 mmHg, lactate 6.1 mmol/L). In the latter case, *the sickest-organ first principle* would have overcome the benefits of the *liver-first*. In all three liver-first sequences, the lungs were preserved with EVLP which could safely extend the *ex vivo* time of the lung grafts. Although follow-up is relatively short (3 months, 1.5 years, and 2.5 years), results are promising.

Immunoprotective effect in combined organ transplantation

This series and others confirm that patients receiving combined transplantation exhibit relatively low rates of rejection [34,35]. The liver in particular appears to provide a protective effect to other organs, confirming its "immunoprivileged" status [36]. Multiple mechanisms have been proposed to explain this protective effect of the liver: the liver ability to "absorb" and "neutralize" lymphocytotoxic antibodies (particularly class I) [37–39], the release of soluble human leukocyte antigens acting as blocking factors, expansion of regulatory cells, and deletion of cytotoxic cells. It has also been suggested that a higher antigen load (independent of the type of transplanted organ) may exert a beneficial effect on graft survival. Because of the overwhelming pressure

on the immune system, a state of immune paralysis is deployed in which the host becomes unable to mount any further immune response to foreign antigens. This phenomenon has been referred to as "Activation Induced Cell Death" [40]. This could implicate that patients undergoing cLiThTx may tolerate a reduced level of chronic immunosuppressive therapy compared with patients undergoing isolated organ transplantation.

Conclusion

Our single-center experience illustrates that cLiThTx is a feasible and life-saving procedure for selected patients with excellent long-term results and a low risk of rejection and graft loss. Transplanting the liver first might have several potential advantages that need further exploration.

Authorship

LJC, SS: designed the paper, reviewed the literature, collected and analyzed the data, contributed important ideas and wrote the paper. AN, DVR, JP: designed the paper, reviewed the literature, collected the data, contributed important ideas and revised the paper. SV, DR: collected the data, contributed important ideas and revised the paper. DM, PDL, JV, BM, FN, GV: designed the paper, collected the data, contributed important ideas and revised the paper.

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Conflict of interest

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