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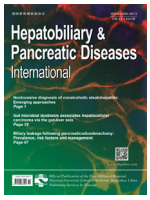

Original Article/Transplantation

Loco-regional hepatocellular carcinoma treatment services as a bridge to liver transplantation

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ABSTRACT

Background: Liver transplantation remains the main curative treatment option for hepatocellular carcinoma (HCC) patients. In the Eurotransplant area Milan criteria are used to assign priority extra points (exceptional MELD, exMELD) for patients on the waiting list. To prevent patients from tumor progression, loco-regional (neoadjuvant) treatment (LRT) is used. For patients unlikely to timely receive an organ via primary allocation, "extended critera donor (ECD) organs" are used. The present study aimed to investigate the survival after LT with a strategy of minimizing waiting list dropouts by using LRT for bridging and transplanting ECD organs if possible and necessary.

Methods: Between October 2010 and May 2015, 50 liver transplants for HCC were included in this retrospective study. Of those, 42 (84%) met the Milan criteria according to the preoperative radiological examination. Forty-one patients (82%) received LRT. The waiting time was analyzed according to LRT. Kaplan-Meier curves with log-rank statistics were used for survival analyses.

Results: One- and five-year overall survival within Milan criteria was 94.3% and 83.7% compared with 91.7% and 67.9% beyond Milan criteria, though statistical significance was not reached ($P=0.487$). LRT had no impact on overall survival ($P=0.629$). Median waiting time was shorter if no LRT was performed (4.6 months vs. 1.5 months, $P=0.006$) and there were no cases of waiting list dropouts. Using ECD organs had no impact on overall survival ($P=0.663$).

Conclusions: Patients with an expected waiting time to transplantation of >6 months could be successfully treated with LRT as a bridge to transplant. Overall and disease-free survival for patients within and beyond Milan criteria was comparable and the use of ECD organs in this cohort of HCC patients proved to be a safe option.

Introduction

Hepatocellular carcinoma (HCC) is the second leading indication for liver transplantation (LT) in Western countries [1]. LT is the only therapeutic option curing both the cancer and the underlying disease and thus accounts for the main treatment option for very early and early HCC (BCLC stage 0 and 1) in cirrhosis [2–4]. While surgical resection can be proposed in patients with solitary HCC and preserved liver function, LT is the best treating options for patients with multiple HCC or severely impaired liver function [3]. Best survival has been reported previously for patients with limited HCC (up to 3 tumors smaller than 3 cm or single tumor smaller than 5 cm without vascular invasion or extrahepatic metastases), defining Milan criteria, and recurrence is the main reason for post-transplant death [5,6]. While in times of organ shortage, the organ cannot be supplied for every potential candidate of LT. LT for HCC is reserved for the patients with the best outcome after LT [7,8]. In the Eurotransplant area, the Model for End-stage Liver Disease (MELD) is used for allocation, thus applying the "sickest-first-policy". Sicker patients with higher MELD scores are given priority [9]. Cancer patients often present with a comparably better liver function than other candidates for transplantation while cancer progression may lead to losing opportunity. Consequently priority extra points are assigned to patients fulfilling the Milan criteria via the exceptional MELD score (exMELD) to equal their risk of dying from disease progression [1,9]. To control the HCC

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progression during waiting, loco-regional treatment (LRT) is necessary if suspected waiting time exceeds 6 months [2,7,10,11]. While waiting list dropout rates have been reported to be as high as 30% during one year without neoadjuvant LRT, centers using LRT as a bridge to transplant report few to no cases of waiting list dropouts [3,12]. Furthermore, the potential role of LRT for downstaging patients initially beyond Milan criteria before transplantation has gained attention [11,13,14]. Nevertheless, the impact of LRT prior to transplantation on survival has rarely been noticed [3,11,15].

Tumor response to neoadjuvant therapy can be measured by Response Evaluation Criteria In Solid Tumors (RECIST) and specifically for LRT in HCC by modified RECIST (mRECIST) criteria [16]. Tumor response is categorized into complete remission (CR), partial response (PR), stable disease (SD) and progressive disease (PD). Response to LRT has been suggested as an outcome predictor for patients transplanted beyond Milan criteria [13,14,17,18].

In recent years, an expansion of indication for transplantation for HCC has been claimed and the University of California San Francisco (UCSF) criteria have been proposed (solitary tumor smaller than 6.5 cm, up to 3 tumors up to 4.5 cm or total tumor size smaller than 8.5 cm) [19]. In large retrospective analyses patients transplanted within Milan criteria showed a similar outcome to patients transplanted within UCSF criteria [19–21]. While the number of potential beneficiaries from LT is rising, the number of available organs for transplantation, particularly in Germany, is steadily declining [22]. Thus, the use of marginal (extended criteria donor, ECD) organs has been promoted. In a German retrospective single-center study a rise of the labMELD score of the transplanted patients has been described over the last fifteen years with a simultaneous rise of marginal organs for transplantation, reflecting the dilemma of transplanting lower quality organs to sicker recipients [23]. The question which patient benefits most from transplantation of an ECD organ is still to be answered. For HCC, LT of ECD organs has been described as feasible with comparable long-term graft survival [23]. The present study aimed to provide the outcome of a single-center multidisciplinary approach of minimizing waiting-list dropout rates by using LRT and transplanting ECD organs when necessary.

Methods

All patients transplanted for HCC in our center between October 2010 and May 2015 were included in this retrospective study ($n=59$). Diagnosis of HCC was made by typical appearance in two different imaging modalities (e.g. MRI, ultrasonography, CT-scan) and optional alpha fetoprotein (AFP) elevation. Patients with lesions within the Milan criteria were listed for transplantation with priority points (exMELD). Patients with HCC beyond Milan criteria were selected carefully and only listed if there were no suspect lymph nodes and no vascular invasion. These patients received an organ via rescue allocation, i.e. organs that had been rejected in 3 different centers due to medical reasons or when an allocation was not possible due to logistic reasons. Allocation was performed according to the Eurotransplant allocation protocol [9]. All patients with an expected waiting time >6 months were suggested for LRT. Decision about patient's individual plan was made in our center's multidisciplinary liver tumor board and LRT was favored if feasible. For all patients LRT prior to transplantation was recorded. ECDs were determined according to the guidelines by the German Medical Council [24]. Waiting time from listing to transplantation was recorded, as well as disease-free and overall survival after transplantation. Median waiting time was analyzed according to LRT and non-LRT by Mann-Whitney Rank Sum Test. Kaplan-Meier curves with log-rank statistics were used for survival analyses. Causes of deaths were worked out as well as sites of recurrences.

For all explanted livers histopathological examination was assessed. Comparison was made between latest pre-transplant imaging and histopathological findings. Linear regression analyses were used to compare pathological findings in the explanted liver and radiological imaging pre-transplant. Patients without histologic verification of HCC in final pathological examination were excluded from further analyses and classified as misdiagnosed ($n=9$).

For statistical analyses, Excel (Microsoft Excel) and SPSS (IBM SPSS statistics 21) were used. The level of significance used was $P<0.05$.

Results

Patients

Fifty-nine HCC patients were transplanted. Patients who were transplanted due to suspected HCC in imaging +/− AFP-elevation but did not show HCC or post LRT residuals in the explanted liver ($n=9$) were classified as misdiagnosed and excluded from further analyses, resulting in a total number of 50 patients for further analyses (Fig. 1).

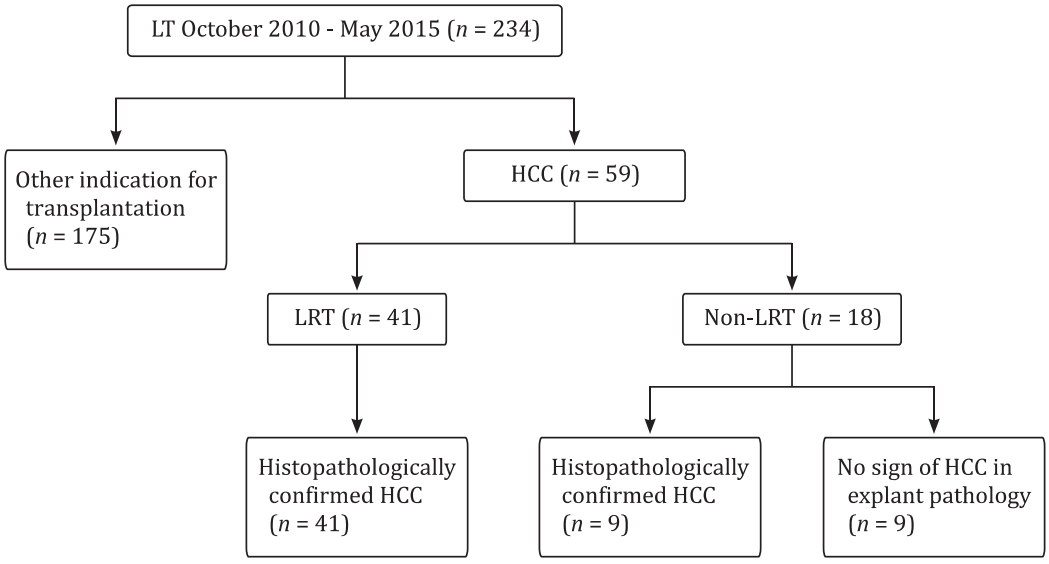

Fig. 1. Flow chart describing study cohort. LT: Liver transplantation; HCC: Hepatocellular carcinoma; LRT: Loco-regional therapy.

Table 1
Patient characteristics.

Variables	Value
Age (yr, mean ± SD)	59.1 ± 7.4
labMELD (median, range)	9 (6–30)
exMELD (median, range)	25 (22–33)
Sex	
Male	40 (80%)
Female	10 (20%)
Child-Pugh score	
No cirrhosis	1 (2%)
A	30 (60%)
B	13 (26%)
C	6 (12%)
Underlying disease*	
HCV	17 (34%)
HBV	6 (12%)
Alcoholic cirrhosis	9 (18%)
Cryptogenic	10 (20%)
Other	7 (14%)
Milan criteria according to radiological examination	
Within	42 (84%)
Beyond	8 (16%)
Milan criteria after pathological examination	
Within	38 (76%)
Beyond	12 (24%)
UCSF criteria according to radiological examination	
Within	46 (92%)
Beyond	4 (8%)
UCSF criteria after pathological examination	
Within	44 (88%)
Beyond	6 (12%)
ECD-critera	
3 or more	9 (18%)
1–2	27 (54%)
0	14 (28%)

* The underlying disease was assessed in the cirrhotic patients ($n = 49$). MELD: Model for end-stage liver disease; labMELD: Calculated MELD score; exMELD: Exceptional MELD score; HCV: Hepatitis C infection; HBV: Hepatitis B infection; UCSF: criteria proposed by University of California San Francisco; ECD: Extended criteria donor.

Forty recipients (80%) were male and 10 (20%) were female. The follow-up period was 2.99 ± 1.81 years (range 0.1–6.33 years). Forty-one recipients (82%) received LRT therapy prior to LT. Most common underlying disease was HCV-infection in 17 cases (34%), followed by cryptogenic cirrhosis in 10 cases (20%), alcoholic cirrhosis in 9 cases (18%) and HBV-infection in 6 cases (12%). Other causes include primary biliary cirrhosis (PBC), alpha-1-antitrypsin-deficieny and multiple causes.

Thirty-six HCC patients (72%) received an organ with positive ECD. Twelve (24%) patients were transplanted beyond Milan criteria including four patients (8%) transplanted beyond UCSF criteria. Those patients received an organ via rescue allocation (without priority extra points) and three quarters of them ($n = 9$) received ECD organs and one a living donor liver transplantation (LDLT). Further characteristics are listed in Table 1.

Waiting time

Median waiting time from listing to transplantation for all HCC patients was 3.8 months (range 0–15.0 months). In patients who received LRT, median waiting time was 4.6 months (range 0–15.0 months). For recipients who did not receive LRT, median waiting time was 1.5 months (range 0–6.0 months). The difference in waiting time was statistically significant ($P = 0.006$) (Fig. 2).

Neoadjuvant treatment

Forty-one recipients (82%) received LRT therapy prior to LT: 36 patients (72%) received transarterial chemoembolization (TACE) alone, two (4%) received radiofrequency ablation (RFA) and TACE, two (4%) were treated by RFA alone and one (2%) was treated with selective intra-arterial radio-therapy (SIRT) combined with TACE. Twelve patients (24%) received two TACE sessions, two patients (4%) received three sessions and two patients (4%) received more than three TACE treatments (one received four and one received six). The response categories according to mRECIST and RECIST are presented in Table 2.

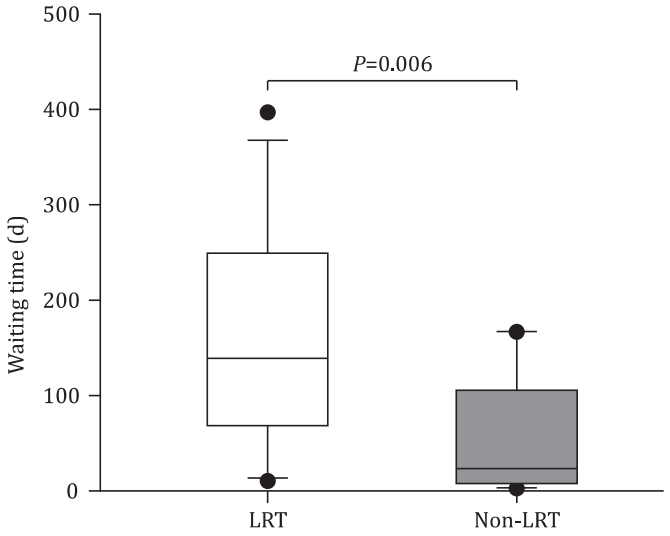

Fig. 2. Waiting time to liver transplantation according to loco-regional therapy (LRT).

Table 2
Neoadjuvant therapy and tumor response.

LRT	Value
TACE	36 (72%)
RFA	2 (4%)
SIRT + TACE	1 (2%)
RFA + TACE	2 (4%)
mRECIST*	
CR	3 (11.5%)
PR	16 (61.5%)
SD	7 (26.9%)
PD	0
RECIST*	
CR	0
PR	3 (11.5%)
SD	22 (84.6)
PD	1 (3.8%)

* Post-LRT control-images available ($n = 26$). TACE: Transarterial chemoembolization; RFA: Radiofrequency ablation; SIRT: Selective intraarterial radiotherapy; mRECIST: Modified response evaluation criteria in solid tumors; CR: Complete remission; PR: Partial response; SD: Stable disease; PD: Progressive disease; LRT: Loco-regional therapy.

Explant pathology

Of all 59 HCC patients listed, 50 (84.7%) were histologically proven HCC or had necrotic areas after LRT at the locations HCC was previously seen in radiological imaging, while in nine patients no HCC was found, but regenerative nodules ($n = 5$), adenoma ($n = 2$), hemangioma ($n = 1$) or dysplastic nodules ($n = 1$).

Compared to radiological staging prior to LT, accuracy concerning Milan criteria was 84% ($n = 42$). Two patients (4%) were radiologically overstaged and proved to be within Milan criteria in final pathological examination whereas 6 patients (12%) were radiologically diagnosed within Milan criteria but proved to be beyond Milan criteria after pathological examination.

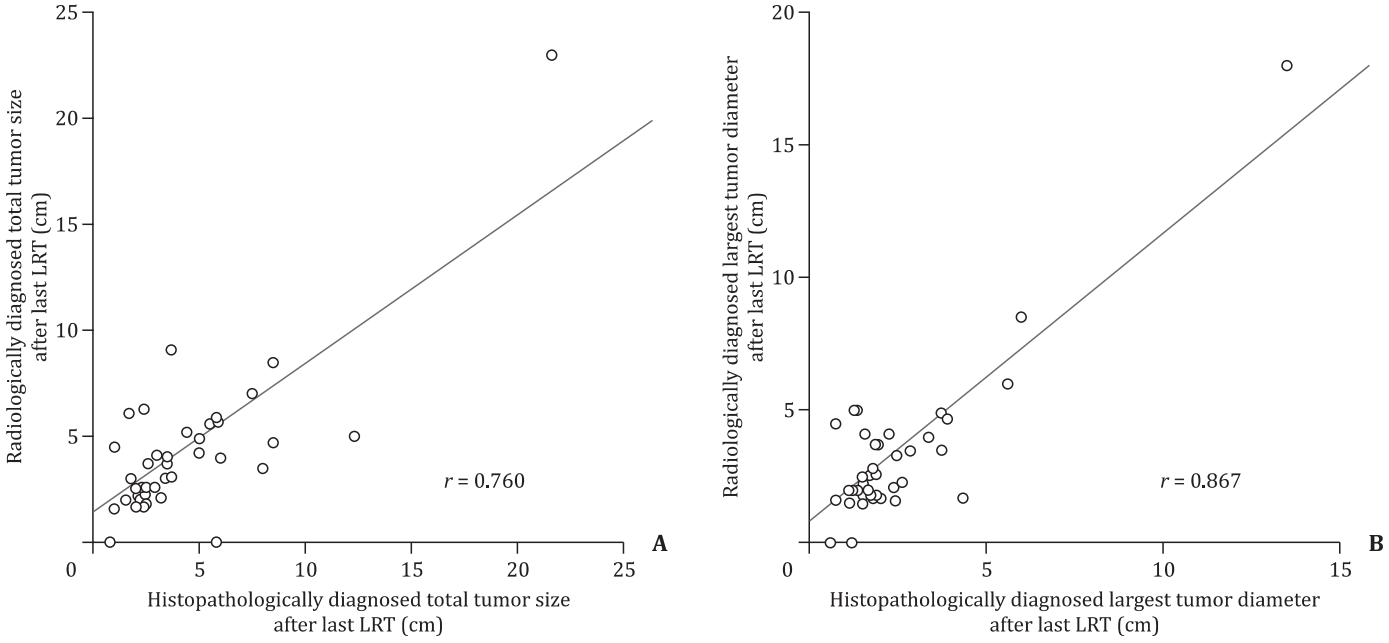

Fig. 3. **A**: Correlation of radiologically diagnosed total tumor size after TACE and histopathologically diagnosed total tumor size. **B**: Correlation of radiologically diagnosed largest tumor diameter and histopathologically diagnosed largest tumor diameter.

Table 3
Comparison of pretransplant imaging and explant pathology.

Variables	Pretransplant imaging	Explant pathology	*r*	*P* value
Total tumor size (cm)	4.08 ± 3.46	3.76 ± 3.73	0.760	**0.01**
Largest tumor diameter (cm)	3.11 ± 2.70	2.78 ± 2.80	0.867	**0.01**

In post-LRT control-images (available for $n=26$), 3 cases (11.5%) were diagnosed as CR, 16 (61.5%) as PR and 7 (26.9%) as SD according to mRECIST. In all other cases ($n=15$) LT was performed prior to the four weeks control-imaging after LRT.

If there were histopathologically proven viable tumor cells in the explanted liver, the histopathologically diagnosed tumor size was highly correlated with radiologically diagnosed tumor size in the last available imaging ($r=0.760$, $P=0.01$ for total tumor size; $r=0.867$, $P=0.01$ for largest tumor diameter, Table 3, Fig. 3). All HCC classified as CR ($n=3$, 1.2%) according to mRECIST had no viable tumor cells in the explanted liver. Fig. 4 presented an example of CR after TACE.

Overall survival and disease-free survival

One- and five-year overall survival (OS) and disease-free survival (DFS) of all patients transplanted for HCC were 93.7% and 79.3% (OS) and 91.5% and 72.1% (DFS) respectively. One- and five-year survival in patients beyond Milan criteria according to pathological examination was 91.7% and 67.9% (OS) and 91.7% and 54.7% (DFS) compared to 94.3% and 83.7% (OS) and 91.4% and 79.8% (DFS) in recipients within the Milan criteria. The difference in OS and DFS was not statistically significant ($P=0.487$ and $P=0.311$, respectively). Fig. 5 presented the survival charts of patients transplanted within and beyond Milan criteria. With only 6 patients transplanted beyond UCSF criteria, Kaplan-Meier curves revealed no difference in OS nor DFS for patients within and beyond UCSF criteria (Fig. 6).

One- and five-year survival was 92.2% and 78.0% (OS) and 89.5% and 76.1% (DFS) in patients receiving neoadjuvant LRT while there were no deaths observed after one year and OS after five years was 83.3% in patients receiving no LRT. Additionally, there was no recurrence observed after one year and DFS after five years was and 65.4% in recipients who were transplanted without LRT. Kaplan-Meier analyses (log-rank) revealed no significant difference between LRT and non-LRT individuals concerning OS ($P=0.629$) and DFS ($P=0.997$), respectively (Fig. 7). Subgroups according to RECIST and mRECIST revealed no influence on OS and DFS (Data not shown).

There was no impact either on OS ($P=0.663$) or on DFS ($P=0.550$) if an ECD organ was used (Fig. 8).

Recurrent disease and causes of death

Five patients (10%) suffered from recurrence, and 3 of them died during follow-up. The other one underwent radiotherapy for bone metastases and one underwent palliative therapy and were alive at the time of the last follow-up (Table 4).

The mortality rate was 16% (8/50). Two out of the eight deceased patients had to undergo re-transplantation during follow-up. One was due to primary non-function (PNF) and one because of re-cirrhosis of the primary transplant. The patient with PNF underwent a re-transplantation two days after the primary transplant and showed a humoral rejection in explant. Plasmapheresis and modulation of immunosuppression were performed. Nevertheless severe liver injury was detected histologically in the re-transplant and the patient died in pulmonary sepsis under heavy immunosuppression. The other patient developed a re-cirrhosis of the transplanted liver 16 months after primary transplantation due to hepatitis C-reinfection and underwent re-transplantation. This patient suffered from cardiopulmonary reanimation with subsequent bleeding and arterial occlusion during LT leading to hepatic failure and requiring re-re-LT. In this clinically severe setting the patient developed an acute pancreatitis and pneumocystis pneumonia leading to sepsis and multiorgan failure. In the other six patients causes of death were severe septic complications ($n=2$), recurrence with palliative therapy ($n=3$) and late severe acute

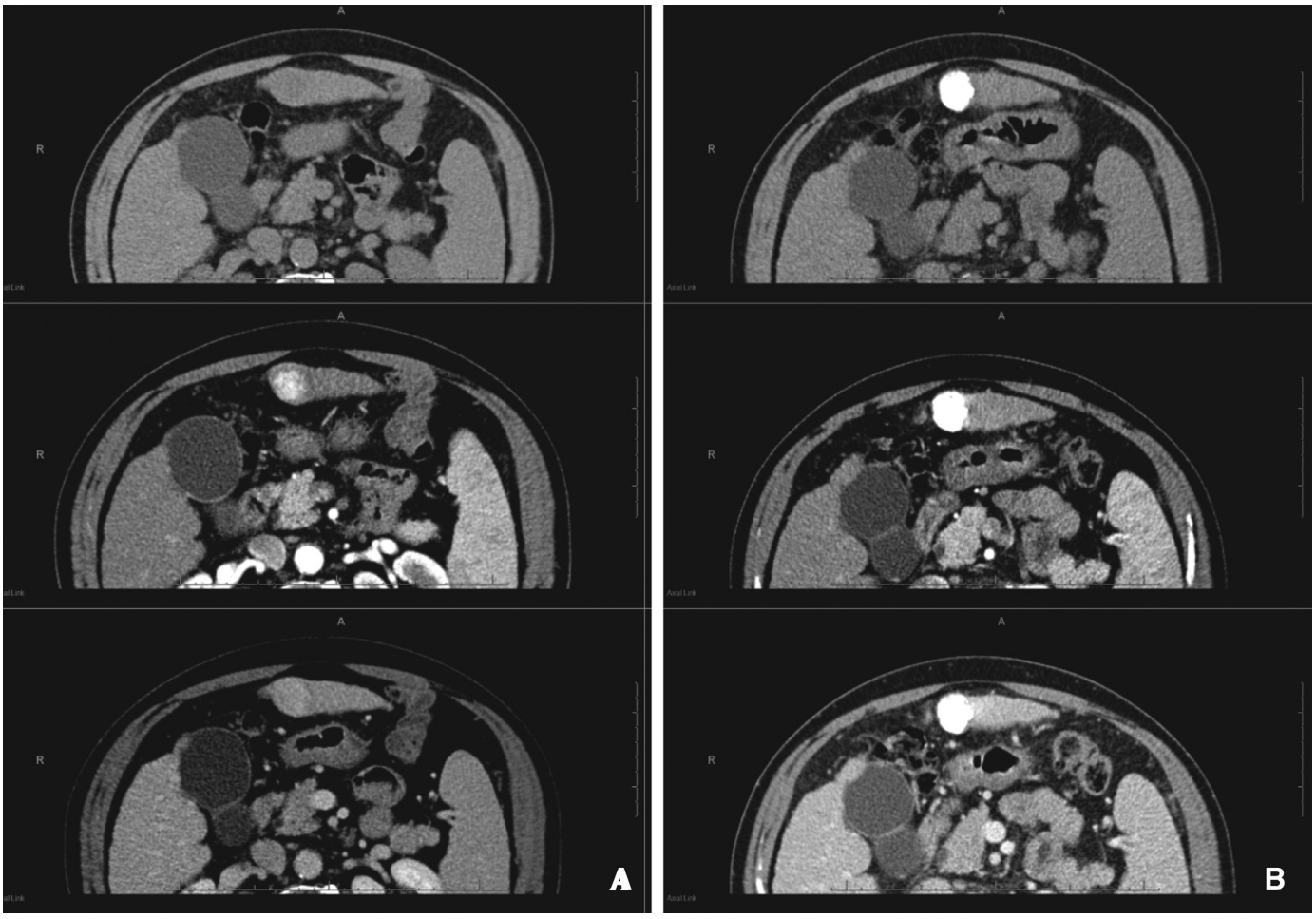

Fig. 4. **A**: Pre-TACE images in unenhanced, arterial and portalvenous phase of a patient with HCC classified as CR. **B**: Post-TACE images in unenhanced, arterial and portalvenous phase of a patient with HCC classified as CR.

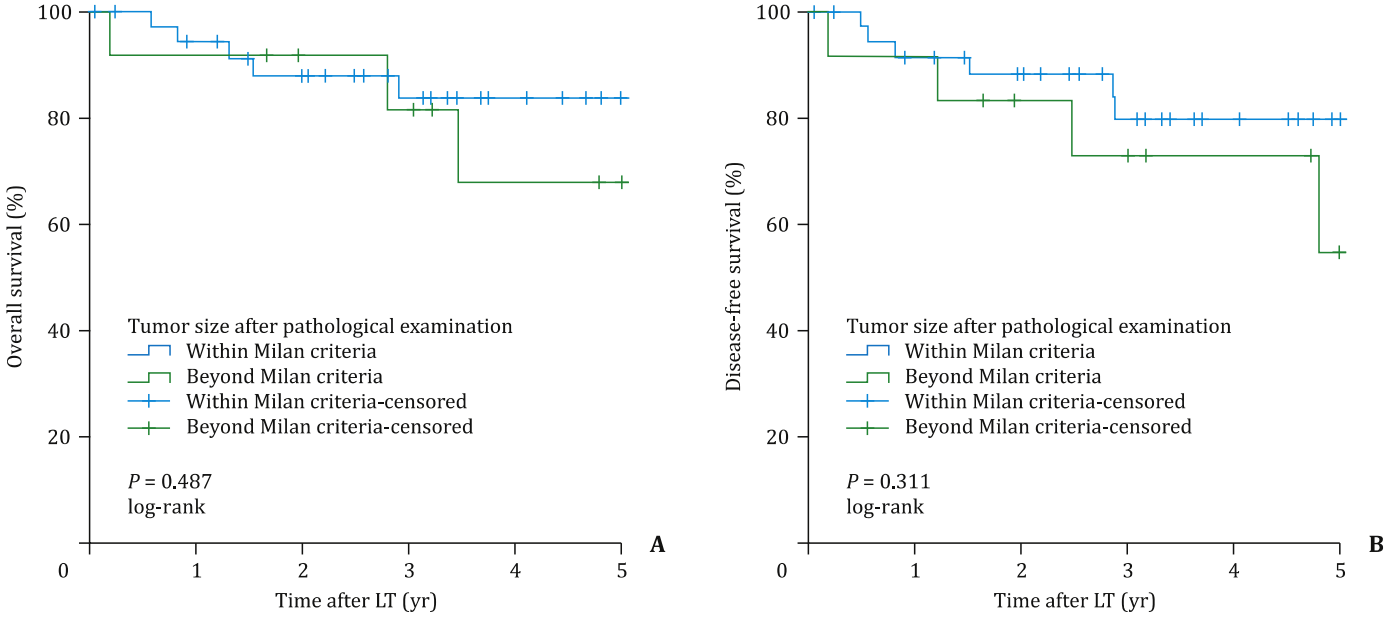

Fig. 5. **A**: Kaplan-Meier chart describing overall survival of patients after liver transplantation according to Milan criteria. **B**: Kaplan-Meier chart describing disease-free survival after liver transplantation according to Milan criteria.

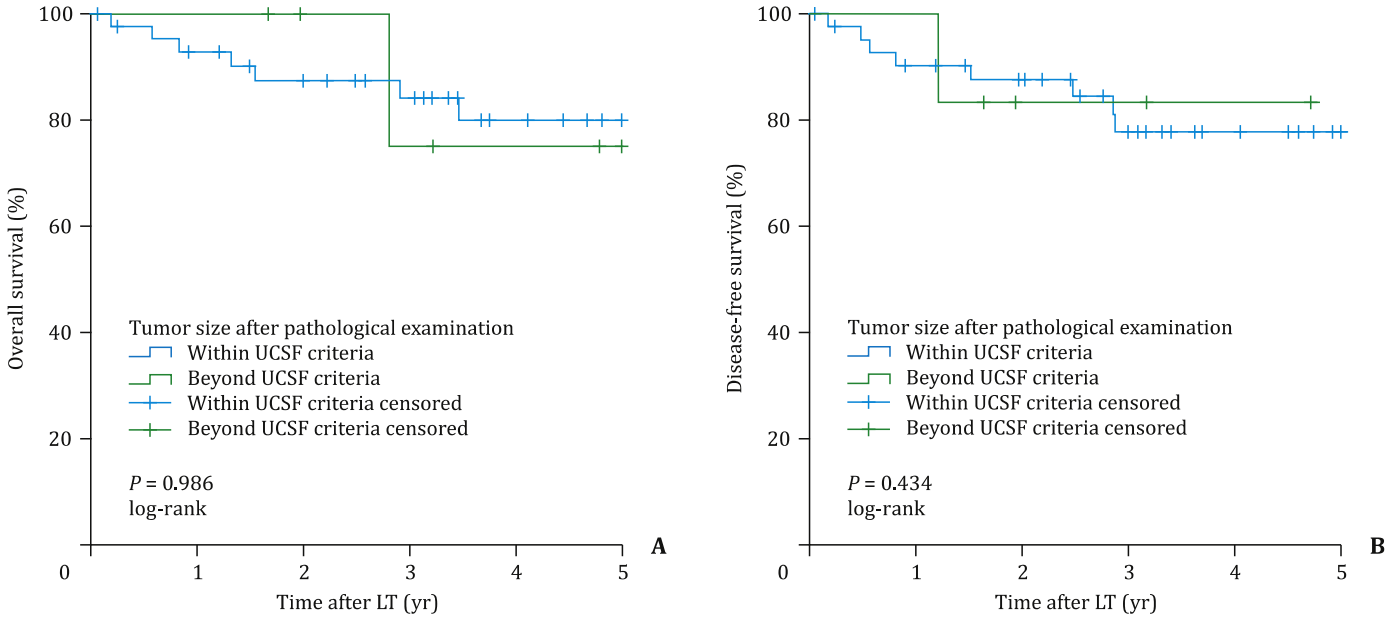

Fig. 6. **A**: Kaplan-Meier chart describing overall survival after liver transplantation according to UCSF criteria. **B**: Kaplan-Meier chart describing disease-free survival after liver transplantation according to UCSF criteria.

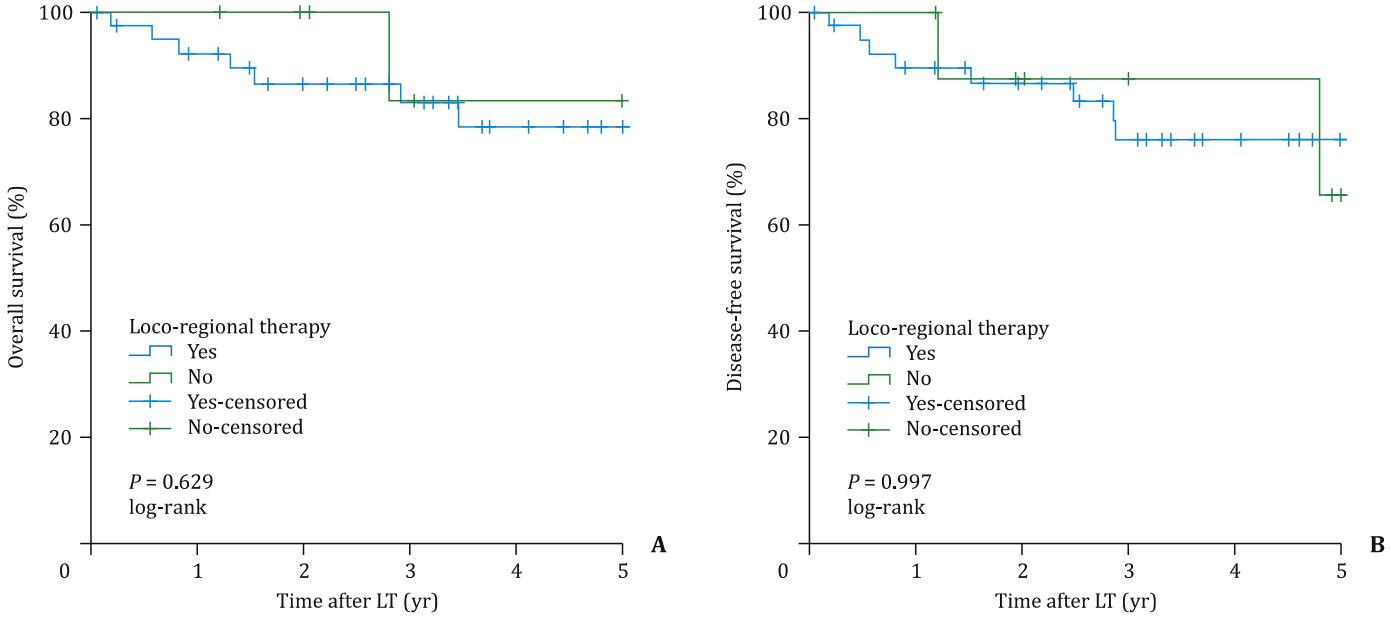

Fig. 7. **A**: Kaplan-Meier chart describing overall survival of patients after liver transplantation according to LRT. **B**: Kaplan-Meier chart describing disease-free survival of patients after liver transplantation according to LRT. LRT: Loco-regional treatment.

Table 4
Characteristics of patients with recurrence.

Age (yr)	Sex	Underlying disease	Milan criteria	Site of recurrence	Date of LT	Date of recurrence	End date of FU	Outcome	OS (year)	DFS (year)
52	M	Cryptogenic	Yes	Pulmonary, lymphatic, hepatic	07.10.2011	01.04.2012	21.01.2013	Deceased	1.20	0.48
69	M	Alcoholic cirrhosis	No	Adrenal, pulmonal, bone	10.05.2011	14.11.2013	08.10.2014	Deceased	3.41	2.51
62	M	Alcoholic cirrhosis	Yes	Abdominal wall	30.12.2012	15.11.2015	18.05.2017	Alive, palliative therapy	4.44	2.88
58	M	Alcoholic cirrhosis	Yes	Hepatic	29.07.2014	15.10.2015	04.05.2017	Deceased	2.81	1.21
71	M	HCV	No	Bone	13.06.2012	01.04.2017	30.06.2017	Alive, radiotherapy	5.00	4.80

LT: Liver transplantation; FU: Follow-up; OS: Overall survival; DFS: Disease-free survival.

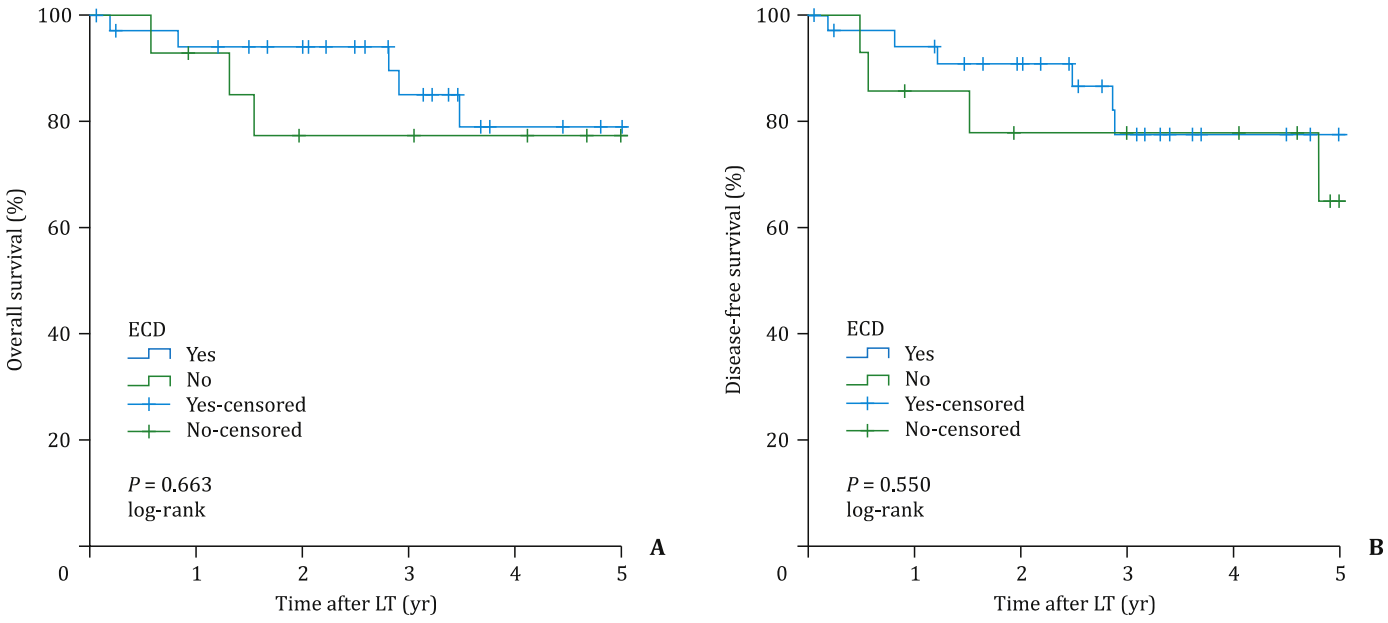

Fig. 8. **A**: Kaplan-Meier chart describing overall survival of patients after liver transplantation according to ECD. **B**: Kaplan-Meier chart describing disease-free survival of patients after liver transplantation according to ECD. ECD: Extended criteria donor.

Table 5
Deceased patients' characteristics.

Case	Age(yr)	Sex	Underlying disease	Milan criteria	Recurrence	OS (yr)	DFS (yr)	Re-transplantation	Cause of death
1	68	F	Alcoholic cirrhosis	No	No	0.19	0.19	Yes	Humoral rejection, pulmonary septic shock under intensive immunosuppression
2	52	M	Cryptogenic	Yes	Yes	1.20	0.48	No	Recurrence, death under palliative therapy
3	67	M	Alcoholic cirrhosis	Yes	No	2.86	2.86	No	Pulmonary sepsis, *de-novo* CCC in transplanted liver
4	59	M	Cryptogenic	No	No	0.81	0.81	No	Pulmonary septic shock with MOF
5	54	M	HBV/HCV	Yes	No	1.52	1.52	Yes	Occlusion of hepatic artery, abdominal and pulmonary sepsis, MOF
6	69	M	Alcoholic cirrhosis	No	Yes	3.41	2.51	No	Recurrence, death under palliative therapy
7	70	F	HCV	Yes	No	0.57	0.57	No	Late severe acute rejection
8	58	M	Alcoholic cirrhosis	Yes	Yes	2.81	1.21	No	Recurrence, death under palliative therapy

OS: Overall survival; DFS: Disease-free survival; CCC: Cholangiocellular carcinoma; HBV: Hepatitis B virus, HCV: Hepatitis C virus; MOF: Multi-organ failure.

rejection under insufficient immunosuppression ($n=1$). Table 5 shows an overview of the deceased patients' characteristics.

Discussion

In terms of long-term survival LT remains the gold standard for therapy of very early and early HCC (BCLC stage 0 and 1), being the only therapeutic option curing both the cancer and the underlying disease [25,26]. Due to organ shortage and consecutive waiting time, selection of patients on the waiting list for bridging therapy and potential bridging modality is an important question.

In our center 59 patients were transplanted for suspected HCC between October 2010 and May 2015, with 9 cases of misdiagnosis (15.3%). Already ten years ago Compagnon et al. published a series of patients transplanted for HCC with 19.6% false diagnosis (20 out of 102 patients, diagnoses after pathological examination including dysplastic nodules, regenerative nodules, cholangiocellular carcinoma, hemangioma and no lesion), while most false diagnoses were made in tumors <3 cm and low AFP levels [27]. Small lesions in imaging are likely to prove false positive, thus EASL guidelines recommend imaging control in lesions <1 cm [2]. Although a rate of 15.3% of misdiagnoses in our cohort seems lower in this context, it is still too high. In times of severe organ shortage one should reevaluate the necessity of biopsy proof accompanied by tumor grading and microvascular involvement or further molecular pathological analyses, when the decision is made to put the patient on the transplant waiting list. When it comes to Milan criteria, a recent publication stated that the rate of incorrectly applied Milan criteria in the Eurotransplant area is 50% [28]. In our cohort, incorrectly assessed Milan criteria when compared to final histological examination was far smaller (16%).

Concerning all correctly diagnosed patients, relatively few patients suffered from recurrence (10%) or died (16%) in the time of follow-up. Out of the 8 patients who died during follow-up, 3 (37.5%) died because of recurrence under palliative therapy and 4 (50%) because of septic complications. Five-year OS rate in our center was 79.3% and DFS rate was 72.1%. We had no cases of waiting list dropout in the last years in our center while others reported one-year-dropout rates for patients listed for diagnosis of HCC overall reach as high as 17.7% [29].

Milan criteria have been established as a good predictor for long-term survival after LT [2,5]. After pathological examination, 76% of patients transplanted in our center proved to be within Milan criteria in comparison to 84% who were diagnosed within Milan criteria in radiological imaging. Kaplan-Meier-Charts revealed a better survival for patients transplanted within Milan criteria, though statistical significance could not be reached. This has to be interpreted with caution due to the low number of patients transplanted beyond Milan criteria. Clavien et al. claim that LT should be reserved for HCC patients whose 5-year survival is comparable to 5-year survival for other indications [7]. According to the European Liver Transplant Registry, 5-year survival rates from patients transplanted between 1998 and 2015 range from 63% for patients with an indication for transplantation due to cancer to 79% for patients transplanted for metabolic diseases [30]. The complex operation itself and the obligatory strong postoperative immunosuppression make LT a challenging scenario with potentially severe complications, which is reflected in severe septic complications in 50% of our deceased patients.

With only 5 cases of recurrence in total, recurrence rate resulted in 7.1% for patients within Milan criteria according to radiological examination ($n=3$) and 25% beyond Milan criteria according to radiological examination ($n=2$). DFS regarding within and beyond Milan criteria did not differ significantly. Duffy et al. found a similar survival rate for patients transplanted beyond Milan criteria but within UCSF criteria [20]. Only 6 of our patients (12%) were transplanted beyond UCSF criteria. Of these, only one suffered from recurrence in the time of follow-up. This has to be compared to the reported devastating natural course of untreated HCC reaching 1- and 3-year survival rates of only 54% and 28%, respectively [31]. In a recent review of 2184 exMELD applications not meeting Milan criteria in the United States, Bitterman et al. [21] compared survival after LT with survival after waiting list dropout. Survival after LT was similar for patients within and beyond Milan criteria, but waitlist mortality was significantly higher for patients beyond Milan criteria.

In this light, Volk et al. [8] advocate that with the lack of other comparably successful treatment options, LT for patients beyond Milan criteria can be justified as long as there's a balance in the benefit for HCC patients and the harm to other patients on the waiting list (prolonged waiting time). In Volks' publication a calculated Markov model weights these parameters against each other. According to that model, a 5-year survival rate of approximately 61% would be necessary to justify transplantation beyond Milan criteria. Our patients transplanted beyond Milan criteria reached a 5-year survival rate of 67.9%, thus justifying transplantation according to the Markov model by Volk et al. [8]. Furthermore, using solely organs located via rescue allocation and thus mainly ECD organs, waiting time is unlikely to be prolonged for other patients on the list, as these organs would otherwise rarely be used at all. Interestingly, OS and DFS rates for HCC patients who received an organ with positive ECD and those with negative ECD were not statistically different in our center. Thus, ECD organs could safely be used in HCC patients, as proposed before in a large single-center long-term outcome analysis [23].

Neoadjuvant LRT is recommended in T2 tumors if suspected waiting time is >6 months while evidence for bridging therapy in patients with T1 tumors and/or waiting time <6 months is weak [7,32]. There were 82% of our patients received LRT prior to transplantation. In our cohort waiting time appeared to be significantly longer in patients receiving LRT pre-transplantation with a median of 4.6 months compared to 1.5 months if no LRT was used. Five-year OS was comparable in patients receiving neoadjuvant LRT and those without neoadjuvant LRT (78.0% vs. 83.3%). In 2005 a multicenter retrospective case-control study of 100 cases with neoadjuvant TACE and 100 controls also found comparable 5-year OS of 59% in both groups [15]. So far, there has not been evidence for a positive impact on OS of LRT prior to transplantation from randomized controlled trials (RCTs) [11]. With the lack of alternatives for preventing HCC-spreading in patients waiting for transplantation, LRT is widely used as a gold standard and randomized controlled trials seem unfeasible [11]. In advanced disease, LRT appears to be significantly superior in OS if compared to best supportive care [33]. Most of our patients that received LRT were treated with TACE (95%, $n=39$), a safe procedure with mild side effects that usually resolve spontaneously [33].

Pre-transplant imaging and post-transplant explant pathology showed a high correlation in total tumor size and largest tumor diameter and all patients classified as CR in imaging had no viable tumor cells in the explant pathology. If LRT was conducted, control imaging was performed in 63% of patients. First control imaging was regularly scheduled 6 weeks after LRT. In all other patients, an organ became available before the scheduled control imaging. Percentage of total tumor necrosis after LRT appears to be essential for estimating long-term survival. Millonig et al. found a 5-year survival rate of 85.1% for patients with CR compared to 51.4% in patients who did not respond to therapy [34]. In our cohort, numbers of patients in the subgroups were too small to reach statistical significance.

In conclusion, patients with an expected waiting time to transplantation of >6 months could be successfully treated with LRT as a bridge to transplant. OS and DFS for patients within and beyond Milan criteria was comparable and the use of ECD organs in this cohort of HCC patients proved to be a feasible option.

Contributors

SS collected and analyzed data and wrote paper. LG, UF and NU performed transplants and revised paper. AA collected and analyzed data and revised paper. BP performed TACE and revised paper. SHM collected data and revised paper. SW designed the study, performed transplants, analyzed data and wrote paper. SW is the guarantor.

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Ethical approval

This study was approved by the Ethics Committee of RWTH Aachen University (EK 189–16).

Competing interest

No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this article.

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