ORIGINAL ARTICLE

Liver transplantation versus watchful waiting in hepatocellular carcinoma patients with complete response to bridging therapy – a retrospective observational study

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SUMMARY

Bridging therapy to prevent progression on the waiting list can result in a sustained complete response (sCR). In some patients, the liver transplantation (LT) risk might exceed those of tumor recurrence. We thus evaluated whether a watchful waiting (CR-WW) strategy could be a feasible alternative to transplantation (CR-LT). We performed a retrospective analysis of overall survival (OS) and recurrence-free survival (RFS) of patients with a sCR (CR > 6 months). Permitted bridging included thermoablation, resection, and combinations of either with transarterial chemoembolization. Patients were divided into the intended treatment strategies CR-WW and CR-LT. 39 (18.40%) sCR patients from 212 were investigated. 22 patients were treated with a CR-LT and 17 patients a CR-WW strategy. Five-year RFS was lower in the CR-WW than in the CR-LT group [53.3% (22.1%; 77.0%) and 84.0% (57.6%; 94.7%)]. 29.4% (5/17) CR-WW patients received salvage transplantation because of recurrence. OS (5-year) was 83.9% [56.8%; 94.7%] after LT and 75.4% [39.8%; 91.7%] after WW. Our analysis shows that the intuitive decision made by our patients in agreement with their treating physicians for a watchful waiting strategy in sCR can be justified. Applied on a larger scale, this strategy could help to reduce the pressure on the donor pool.

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Introduction

Although liver transplantation remains the most aggressive and effective treatment strategy for treatment of early-stage hepatocellular carcinoma (HCC), the shortage of liver donors and the steadily increasing incidence of this tumor worldwide represent an growing challenge for patients with HCC on a waiting list for liver transplantation. Bridging therapy is highly effective in tumor control in patients with a long expected waiting time [1–4]. Frequently, bridging therapy results in significant downstaging of tumors. In some cases, even, bridging results in long-lasting complete tumor response, which can be considered as curative. Data from uncontrolled observational studies suggest that CR can be achieved in 30–90%, depending on inclusion criteria and treatment modalities used. Some of these responses are stable over an observational period of more than 6 months [1,2].

In these cases, attending physicians have to balance the risk of liver failure and untreatable tumor progression against the risk of morbidity and mortality of liver transplantation. In particular, in countries with low donor rates surgeons might be forced to utilize grafts from suboptimal donors, increasing the risk of transplantation significantly [5].

Approaches for a more detailed assessment of the need for liver transplantation based on treatment response exist [6,7]. However at present, transplantation is still recommended for all patients including patients with sustained CR [6]. This might result in possible overtreatment and a waste of organs at the same time.

Therefore, this observational study examines whether HCC patients with preserved liver function and sustained CR after bridging therapy should be transplanted or can safely be managed by a watchful waiting strategy.

Patients and methods

In this retrospective observational study, the patient data and disease progressions of patients on the joint liver waiting list of the Transplantation Center Munich of the Ludwig-Maximilian University and the Technical University of Munich were analyzed. The analysis was approved by the ethics committees of both collaborating Munich universities (# EK-LMU-19-395 and EK-TUM-410/19s) and is reported following the STROBE recommendations [8]. Additionally, this analysis is in accordance with the reporting criteria for downstaging studies formulated by Parikh *et al.* [9].

The diagnosis of HCC was confirmed by contrast-enhanced cross-section imaging according to the current national allocation guidelines [10]. Bridging therapy modalities were discussed in the respective interdisciplinary tumor boards. The decision on listing of suitable candidates for liver transplantation was made at the interdisciplinary liver transplant conference. Locoregional therapies used are detailed in Table 2. Tumor growth (response to therapy) and the AFP values were monitored every 3 months. Response to therapy was (re)evaluated according to the mRECIST criteria [11,12]. Patients who received liver resection as a bridge to transplant were evaluated as CR in case of R0 postresection status. In this study, a complete remission of more than 6 months was rated as sustained CR (sCR).

Treatment allocation

As mentioned above, therapy modalities were discussed in the respective interdisciplinary tumor boards. The decision on bridging therapy was guided by the condition, the functional state of the candidate, severity of cirrhosis, and localization of the tumor. Permitted bridging included thermoablation, resection, and combinations of either with transarterial chemoembolization (TACE). TACE alone was not included in this study, since it is not regarded as having a curative intend. Patients within the Milan criteria are eligible for "Standard Exception Points" (SE Points). This includes patients that received liver resection as a bridging-to-transplant treatment. Patients with nonresectable HCC and/or simultaneously poor liver function were primarily advised to undergo liver transplantation, even when sCR was achieved after bridging therapy. After counseling, some patients decided to be placed on the waiting list as not transplantable (NT) until a tumor recurrence might develop. All listed patients are discussed at every interdisciplinary liver transplant conference.

Immunosuppression

After transplantation, patients received a standard triple therapy with tacrolimus (trough levels 8–10 ng/ml; m0–m3), mycophenolate 1.5 g/day, and steroids. In the majority of patients, steroids were withdrawn by month 3 and patients were switched from tacrolimus to a mTOR inhibitor in maintenance therapy [13].

Statistical analysis

The data on demographics, liver disease, Child–Pugh–Turcotte (CTP) stage, $_{lab}$MELD (model of end-stage liver disease), AFP (α-fetoprotein) level, bridging-to-transplant therapy, response to therapy (mRECIST), tumor stage, and survival data were obtained [11].

Donor age, donor type, body mass index (BMI), and "Eurotransplant Donor Risk Index" (ET-DRI) were noted [14]. CR patients were grouped according to the intended treatment path:

- CR-WW (complete remission watchful waiting strategy): Transplantation was deferred or patient delisted.
- CR-LT (complete remission liver transplantation strategy): Patients were transplanted.

Complete remission watchful waiting strategy patients that experienced recurrence and received a salvage transplantation remained in the CR-WW group. Therefore, the intention to treat was analyzed. Overall survival and recurrence-free survival were calculated from the date of listing to the date of death or recurrence, respectively. CR-LT patients with residual tumor cells in the explant pathology were not considered to have tumor recurrence, since it cannot be determined whether they are residual tumor cells or recurrent after a complete pathological response (cPR) [4,15]. Comparison of data was performed using the *t*-test, Wilcoxon rank sum test and chi-square test where applicable. Survival was calculated using the Kaplan–Meier method. 95% confidence interval (CI) is reported next to the survival rates in square brackets. A *P*-value ≤ 0.05 was considered as statistically significant. All statistical analyses were performed using the "survival," "ggplot2," and "ggpubr" packages within the RStudio software (RStudio, Version 1.1.463; RStudio Inc., Boston, MA, USA) [16,17].

Results

Study cohort

This study investigates the results from a small subgroup ($n = 39$) of patients who achieved sCR after treatment of HCC. Altogether, between January 1, 2007, and December 31, 2017, 212 patients presenting with HCC without metastatic disease were treated and listed for liver transplantation. Figure 1 depicts the patient cohort analysis with exclusion criteria in accordance with the STROBE recommendations. Median follow-up for this selected group was 36 (26.4, 82.5) months. Wait time for CR-LT patients was 13 (10,24) months. Only 27.3% of patients were transplanted with marginal donors. All patients received organs from deceased donors. The donor age was relatively high [median: 65 (47.5,70)], and the BMI was 26 (25,29). The ET-DRI was 1.74 (1.36, 2.13).

Demographics and detailed descriptive analysis

Of all patients with a sCR ($n = 39$), 22 (56.4%) remained within the transplantation strategy (CR-LT). 17 (43.6%) patients had their transplantation either deferred ($n = 10$; 58.8%) or were delisted ($n = 7$; 41.2%) (CR-WW). CR-WW patients were older than CR-LT patients (64 (57.2, 67.2) vs. 57.5 (55,64) years, $P = 0.022$). This was the only significant difference in demographics comparing both groups. All other noted variables, including CTP score, cause of cirrhosis, number of tumors, largest tumor size, and type of a bridging therapy, showed no significant difference (Table 2).

Two (9.1%) patients died in-hospital after transplantation (CR-LT group). One (4.5%) of these patients died within 24 h because of intraoperative complications, and one (4.5%) died from multi-organ failure because of septic shock. Recurrence was observed in 2 (9.1%) CR-LT and 9 (52.9%) CR-WW patients. In the CR-LT group, the recurrence patients were treated palliatively, and one (4.5%) patient died 2 months after recurrence. One (4.5%) patient was still alive at last follow-up. In the CR-WW group, 4 (23.53%) patients received a salvage transplantation because of recurrence. Only one (5.88%) of these four patients developed metastases after salvage LT. Three (17.65%) CR-WW patients with a recurrence received LRT in a palliative setting. Since recurrence, these patients survived 13 and 36 months until last follow-up. One (5.9%) patient died after 31 months. Two patients (11.8%) were not treated after recurrence but received best supportive care. The patients were alive at last follow-up. When analyzing the location of recurrences, 39.7% of CR-WW patients had a local recurrence, only 2 (13.3%) patients developed extrahepatic metastases.

As mentioned above, 4 (23.53%) patients crossed over to transplantation because of recurrence. Additionally, 1 (5.88%) patient recommitted to transplantation after HCV treatment failed and liver function deteriorated. Therefore, altogether 5 (29.41%) patients eventually crossed over to receive a liver transplantation. Vital tumor cells were found in 9 of 26 explant pathologies (34.6%). Detailed data regarding each individual patient can be found in supplemental Tables 1 and 2.

Survival analysis for liver transplantation and watchful waiting strategy

As described above, we observed more recurrence in the CR-WW group. RFS after CR-LT was 90.5% [67.0%; 97.5%] after 1 year, 84.0% [57.6%; 94.7%] after 3 years, and 84.0% [57.6%; 94.7%] after 5 years of follow-up. After CR-WW, 94.1% [65.0%; 99.1%], 74.7% [45.5%; 89.7%], and 53.3% [22.1%; 77.0%] survived 1, 3, and 5 years of follow-up without recurrence. This difference was statistically significant ($P = 0.049$; Fig. 2).

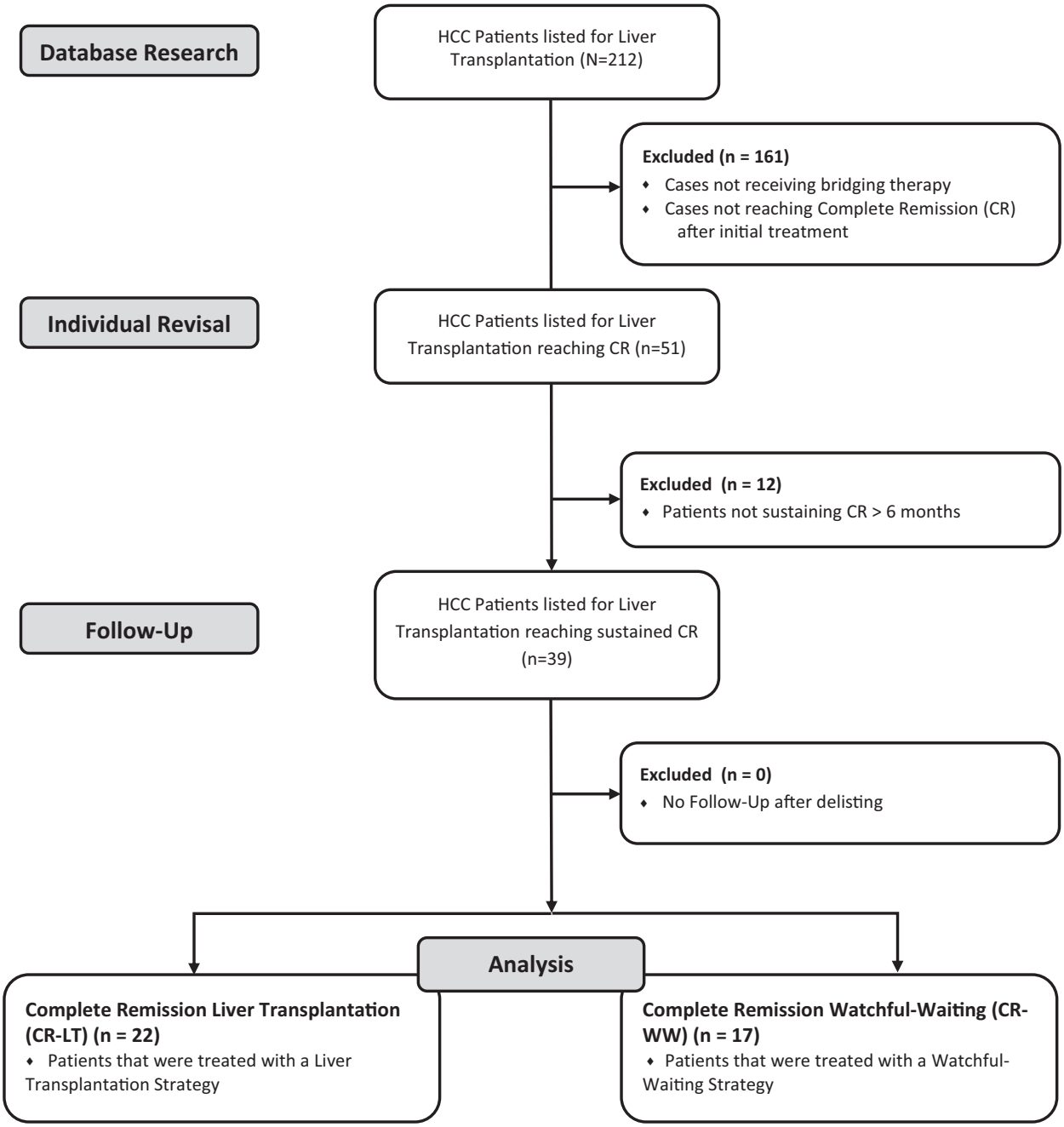

Figure 1 Patient cohort analysis with exclusion criteria. CR, complete remission; CR-LT, complete response liver transplantation strategy; CR-WW, complete response watchful waiting strategy.

Overall survival in CR-LT patients was 90.9% [68.3%; 97.6%] after 1 year, 83.9% [56.8%; 94.7%] after 3 years, and 83.9% [56.8%; 94.7%] after 5 years of follow-up. The 1-, 3-, and 5-year survival for CR-WW was 100%, 86.2% [55.0%; 96.4%], and 75.4% [39.8%; 91.7%], respectively (Fig. 3). There was no statistically significant difference regarding OS ($P = 0.96$; Fig. 3).

Discussion

Liver transplantation is the optimal treatment for HCC in cirrhosis [5]. As a result of the lack of donor organs, not all patients can be transplanted. Extended-criteria donor organs are utilized to bridge the gap. This use of higher risk donor organs increases the risk of perioperative morbimortality [18]. In these patients, the increased

Table 1. Definition of the mRECIST for HCC classification system according to Lencioni *et al*. [9].

Assessment of target lesion response: mRECIST for HCC	
CR	Disappearance of any intratumoral arterial enhancement in all target lesions
PR	At least a 30% decrease in the sum of diameters of viable (enhancement in the arterial phase) target lesions, taking as reference the baseline sum of the diameters of target lesions
SD	Any cases that do not qualify for either partial response or progressive disease
PD	An increase of at least 20% in the sum of the diameters of viable (enhancing) target lesions, taking as reference the smallest sum of the diameters of viable (enhancing) target lesions recorded since treatment started

risks of transplantation must be balanced against the risk of tumor progression. In this context, many studies have investigated patients outside the overly strict MILAN criteria (MC) for added net benefit through transplantation. In general, these patients benefit from transplantation (even from extended-criteria donors) compared with LRT or systemic therapy [19,20]. Up to now, however, no publication has investigated whether there are patients who can be taken off the waiting list when excellent response to bridging therapy is observed. In this study, we compared two treatment strategies [transplantation (CR-LT) versus watchful waiting (CR-WW)] that were followed by the attending physicians in two German transplantation centers. Bridging therapy was performed according to the recommendations of the interdisciplinary tumor and joint liver transplantation board, which include various LRTs for patients not eligible for resection. With this strategy, we achieved 18.4% sCR in transplant candidates. Compared with the literature, this percentage of CR patients is lower. Some authors report CR in up to 60% to over 90%. However, these results were either achieved in very early HCC or with a very short follow-up [1,2]. This is also underlined by the fact that despite complete response, some patients in these reports had to be treated again because of recurrence. Also, these patients reportedly showed a high proportion of patients with vital tumor cells (>70%) in explantation pathology [2,21]. It was repeatedly reported that sustained tumor control is a hallmark of good tumor biology. Consequently, as mentioned above, we defined sCR after initial treatment without recurrence for 6 months. The reevaluation within a time frame of 6 months is supported by the new OPTN/UNOS guideline and published data [22]. If the tumor is recurrent within this short time frame, this reflects poor tumor biology. Moreover, definition of sCR after resection was equally strict. Resection patients were only rated as having a sCR if the pathology report rated resection margins as R0 and no recurrence occurred within 6 months. As a result of these strict standards and the time frame for defining sCR, explantation pathology in our cohort showed a very low percentage of vital tumor cells (34.6%).

Overall 5-year patient survival of the CR-WW group [75.4% (39.8%; 91.7%)] was comparable to the CR-LT group [83.9% (56.8%; 94.7%)] ($P = 0.97$). However, judging by the large confidence interval data was not able to estimate this rate sufficiently. The predictive value of tumor response to treatment has been investigated in several studies. The principal idea that tumor response could predict survival after LT was introduced by Otto et al. 2006 and was confirmed by other studies [23,24]. The degree of response correlates well with the tumor recurrence after LT [4,15,21,25]. However, whether CR indicates complete elimination of tumor cells [complete pathological response (cPR)], the reduction of the tumor load, or whether it is indicative for a slowly growing tumor is still controversial [4,15,24,26]. Because of this uncertainty, it is not yet clear whether these patients still need transplantation. As expected, we observed that 8 (52.9%) CR-WW and 2 (9.1%) CR-LT patients experienced recurrences during the follow-up period. In the CR-WW group, 4 (23.53%) patients received a rescue liver transplantation because of recurrence and 3 (17.65%) CR-WW patients with a late recurrence received LRT. Although 8 (52.9%) of CR-WW patients experienced recurrence, only 2 (13.3%) patients developed extrahepatic metastases (1 after salvage transplantation) and had to be treated palliatively with good survival. This shows that even after recurrence, most HCCs could be controlled with aggressive treatment for a follow-up of at least 5 years. Because of the small sample size, analysis of a 10-year follow-up was not possible. Our observation suggests that the long-term survival of HCC transplantation patients is largely determined by other factors, such as perioperative complications rather than tumor recurrence. Therefore, watchful waiting would eliminate this risk and

Table 2. Demographic data of the study cohort.

Characteristic	CR-WW *n* = 17	CR-LT *n* = 22	*P*-value
Age at listing in years, median (Quartile)	64 (57.2, 67.2)	57.50 (55,64)	0.022
α-Fetoprotein at listing, median (Quartile)	11 (4.75, 16.35)	11 (4.75, 25.25)	0.734
α-Fetoprotein prior LT in ng/ml, median (Quartile)		8.4 (4.5, 14.95)	
Sex, *n* (%)			
Male	15 (88.2%)	15 (68.2%)	0.251
Female	2 (11.8%)	7 (31.8%)	
Cirrhosis, *n* (%)			
Child-Turcotte-Pugh A	16 (94.1%)	18 (81.8%)	0.782
Child-Turcotte-Pugh B	1 (5.9%)	3 (13.6%)	
Child-Turcotte-Pugh C	0 (0%)	1 (4.6%)	
Cause of cirrhosis, *n* (%)			
Hepatitis C	6 (35.3%)	8 (36.4%)	0.753
Hepatitis B	7 (41.2%)	5 (22.7%)	0.299
Alcohol	4 (23.5%)	9 (40.9%)	0.318
Other	2 (11.8%)	3 (13.6%)	
No. of tumors at baseline, *n* (%)			
1	12 (70.6%)	15 (68.2%)	0.986
2	2 (11.8%)	5 (22.7%)	
3	3 (17.7%)	2 (9.1%)	
>3			
Initial largest tumor diameter in mm, median (IQR)	28 (12)	25 (6.5)	0.461
BCLC stage			
0	2 (11.76%)	0 (0%)	0.427
A	14 (82.4%)	21 (95.5%)	
B	1 (5.9%)	1 (4.6%)	
Bridging therapy, *n* (%)			
Resection only	8 (47.1%)	4 (18.2%)	0.152
Thermoablation only	2 (11.8%)	6 (27.3%)	
Combination therapy	7 (41.2%)	12 (54.6%)	
TACE with thermoablation	5 (29.4%)	10 (45.5%)	
TACE with resection	1 (5.9%)	1 (4.5%)	
TACE with SBRT	0 (0%)	1 (4.5%)	
Resection with thermoablation	1 (5.9%)	0 (0%)	
Delisted patients, *n* (%)	8 (47.1%)	(0) 0%	
Pathology			
Residual vital tumor cells	2 (40%)	7 (31.8%)	0.726
Salvage transplantation	5 (29.4%)	0 (0%)	

CR, complete remission; CR-LT, complete remission liver transplantation strategy; CR-WW, complete remission watchful waiting strategy; SBRT, selective body radiation therapy.

may be a reasonable tool to reduce the pressure on the donor pool. As exemplified by our data, subjecting about 20% of the patients (CR) to watchful waiting could lead to about 10–15% less HCC patients on the waiting list. This is especially relevant in light of the scarcity of donor organs for other indications for liver transplantation. Also, immune treatment by checkpoint inhibitors has substantially modified the treatment of HCC with 10% of patients exhibiting a complete response and altogether one third of these patients experiencing a durable response. The use of these agents in regimens of combined local treatment and systemic treatment or in the adjuvant setting may further improve the recurrence rate in the CR-WW patients [27].

The limitations of the study include the clinical and not randomized allocation to the respective therapy strategies, which may have led to a selection bias. As a result of the small sample size, no adjustment for this could be performed. Therefore, the patients in both treatment groups are not completely comparable. We observed that older patients in particular have decided

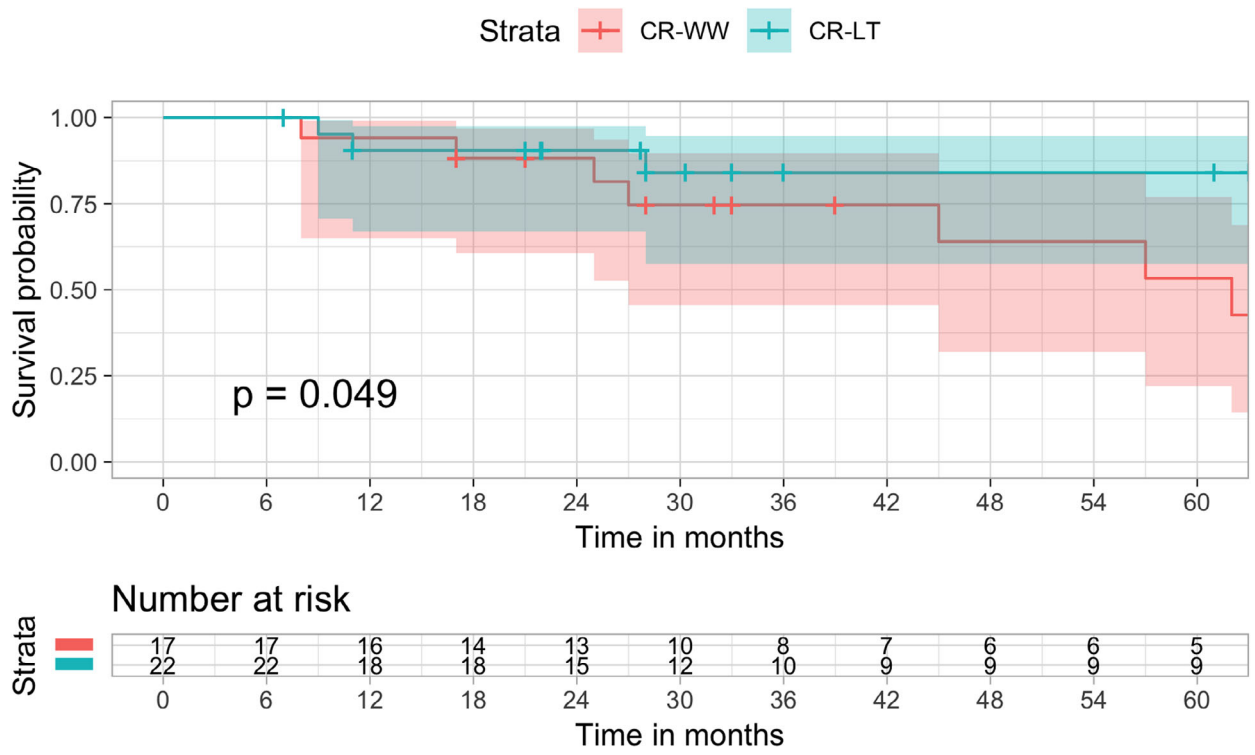

Figure 2 Recurrence-free survival in HCC patients after complete remission (liver transplantation vs. watchful waiting strategy) (P = 0.049). CR-LT, complete remission liver transplantation strategy; CR-WW, complete remission watchful waiting strategy.

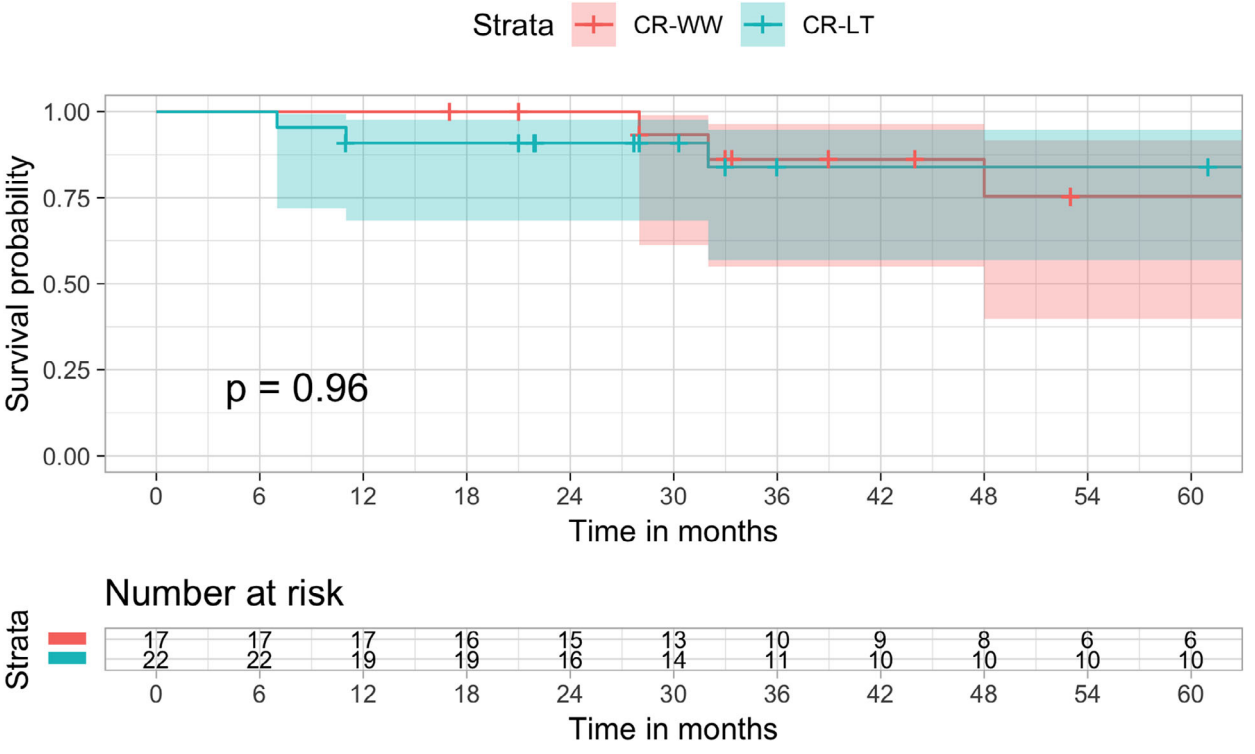

Figure 3 Overall survival in HCC patients after complete remission (transplantation vs. watchful waiting strategy) (P = 0.96). CR-LT, complete remission liver transplantation strategy; CR-WW, complete remission watchful waiting strategy.

to choose a CR-WW strategy. Since transplantation is physically demanding and older patients have a shorter life expectancy, watchful waiting could be an acceptable strategy despite the observed higher recurrence rate. Even though the number of patients in our study was small and follow-up is limited to 5 years, our first results warrant a more in-depth analysis of a larger multicenter collective, ideally in a randomized clinical trial. However, out of ethical reasons a randomized clinical trial might not be possible.

In conclusion, our analysis shows that the intuitive decision made by our patients in agreement with their treating physicians for a watchful waiting strategy in sCR can be justified. In particular, elderly, comorbid patients or patients that are likely to be matched with a marginal donor organ may benefit the most from CR-WW. Applied on a larger scale, this strategy could help to reduce the pressure on the donor pool.

Authorship

MBS: contributed substantially to the conception and design of the study, and acquisition, analysis and interpretation of the data; drafted the manuscript; and provided final approval of the version to be published. UE: contributed substantially to the acquisition of the data and interpretation of the data; provided critical revision of the manuscript; and provided final approval of the version to be published. AU: contributed substantially to the acquisition of the data and interpretation of the data; provided critical revision of the manuscript; and provided final approval of the version to be published. JNB: contributed substantially to the acquisition of the data and interpretation of the data; provided critical revision of the manuscript; and provided final approval of the version to be published. DTK: contributed substantially to the acquisition of the data; provided critical revision of the manuscript; and provided final approval of the version to be published. NB: contributed substantially to the acquisition of the data; provided critical revision of the manuscript; and provided final approval of the version to be published. HN: contributed substantially to the acquisition of the data; provided critical revision of the manuscript; and provided final approval of the version to be published. GD: contributed substantially to the acquisition of the data and interpretation of the data; provided critical revision of the manuscript; and provided final approval of the version to be published. EDT: contributed substantially to the acquisition of the data and interpretation of the data; provided critical revision of the manuscript; and provided final approval of the version to be published. MS: contributed substantially to the acquisition of the data and interpretation of the data; provided critical revision of the manuscript; and provided final approval of the version to be published. JA: contributed substantially to the acquisition of the data and interpretation of the data; provided critical revision of the manuscript; and provided final approval of the version to be published. MKA: contributed substantially to the acquisition of the data and interpretation of the data; provided critical revision of the manuscript; and provided final approval of the version to be published. Jens Werner: contributed substantially to the conception and design of the study, acquisition, analysis and interpretation of the data, and drafting and revision of the manuscript; and provided final approval of the version to be published. MOG: contributed substantially to the conception and design of the study, acquisition, analysis and interpretation of the data, and drafting and revision of the manuscript; and provided final approval of the version to be published.

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Conflicts of interest

The authors have no conflicts of interest to declare.

Ethical approval

The research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Detailed patient level data for patients treated with the liver transplantation strategy (CR-LT). TACE (transarterial chemoembolisation).

Table S2. Detailed patient level data for patients treated with the watch and wait strategy (CR-WW). TACE (transarterial chemoembolisation).

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