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Impact of neoadjuvant transarterial chemoembolization on tumor recurrence and patient survival after liver transplantation for hepatocellular carcinoma: a retrospective analysis

Seehofer D, Nebrig M, Denecke T, Kroencke T, Weichert W, Stockmann M, Somasundaram R, Schott E, Puhl G and Neuhaus P. Impact of neoadjuvant transarterial chemoembolization on tumor recurrence and patient survival after liver transplantation for hepatocellular carcinoma: a retrospective analysis.

Abstract: Transarterial chemoembolization (TACE) has gained wide acceptance as a bridge to liver transplantation (LT) in patients with hepatocellular carcinoma (HCC). Aim of this analysis was to compare long-term results with and without neoadjuvant TACE and to identify subgroups, which particularly benefit from TACE.
Patients with HCC transplanted at our center were retrospectively analyzed. The following were excluded to increase consistency: incidental-HCC, Child-C, living-related-LT, other HCC-specific-treatment. Of 336 patients, 177 were subject of this analysis, 71 received TACE and 106 no HCC therapy.
Patients with and without TACE showed similar five-yr survival (73/67%) and recurrence rates (23/29%). Progression on the waiting list was associated with a higher recurrence rate in the TACE (50 vs.12%) and the non-TACE group (40 vs. 22%). HCC recurrence was reduced in patients inside Milan (0.053) and UCSF (0.037) criteria by neoadjuvant TACE but not outside UCSF (0.99). Also a trend towards an improved survival was seen within these criteria.
Our large single center experience suggests that TACE lowers the HCC recurrence rate in patients inside the Milan and UCSF criteria. Moreover, the response to TACE is a good indicator of low recurrence rates. The effect of TACE might be more pronounced in patients with longer waiting time than in this cohort (mean, 4.6 months).

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Key words: bridging – hepatocellular carcinoma – liver transplantation – long-term survival – transarterial chemoembolization

Abbreviations: CR, complete response; CT, computed tomography; HCC, hepatocellular carcinoma; LT, liver transplantation; n.s., not significant; PD, progressive disease; PR, partial response; SD, stable disease; TACE, transarterial chemoembolization

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Liver transplantation (LT) represents an established curative treatment for early-stage hepatocellular carcinoma (HCC) in patients with cirrhosis of the liver. After liver resection for HCC in cirrhosis five-yr recurrence rates, up to 80% are reported even in early stage tumors (1, 2) and a 10-yr disease-free survival between 10% and 20% (1, 3, 4). LT is the only treatment that removes both the tumor and the liver cirrhosis with multifocal HCC potential. Patients within the Milan criteria reveal

five-yr tumor recurrence rates below 20% and five-yr survival rates above 70% after LT (5–7).

It is generally accepted that patients outside the Milan criteria have a substantially higher recurrence risk (5, 6, 8). However, certain subgroups of patients outside the MiIan criteria are supposed to have a more favorable prognosis. Recently, a DNA index below 1.5 has been reported to predict a low risk of HCC recurrence independently of the Milan criteria (6). Tumor gene expression profiles have also been shown to predict the risk of tumor recurrence after liver resection (9). As further "tumor-biological" selection criterion, the response to neoadjuvant transarterial chemoembolization (TACE) has been postulated (10). This and several other studies have addressed the value of neoadjuvant TACE before LT (11–17). In these studies, the objective of TACE as neoadjuvant procedure before liver transplantation is manifold:

1. Improvement of tumor staging and closer surveillance on the waiting list.
2. Control of tumor growth and vascular invasion and thereby avoidance of dropout during waiting time (10).
3. Induction of tumor necrosis to reduce tumor dissemination during transplantation (12).
4. Downstaging of patients outside defined criteria to make patients eligible for LT and reduce the risk of tumor recurrence (10, 14).
5. Overall improvement of the post-transplant outcome by reducing the recurrence risk (11, 15, 16).

Not all of these benefits are finally verified, because results are conflicting and randomized controlled trials in LT patients are lacking. Only few reports have addressed the question whether preoperative TACE is capable of influencing overall recurrence rates, which is still under debate. Nevertheless, TACE has gained wide acceptance as bridging to LT, although this is supported only by a low level of evidence, especially in patients with an expected short waiting time. As TACE is widely used before LT in most transplant centers nowadays (18), the implementation of a large randomized trial is unlikely. Even large retrospective analyses are rare, but important to better understand the value of TACE before LT.

Patients and methods

This retrospective analysis included patients transplanted between January 1989 and December 2008 for HCC at our center. Diagnosis was confirmed upon evaluation for LT by multiphasic contrast enhanced computed tomography (CT) and at least one additional imaging method (US or MRI) or biopsy with the largest nodule measuring at least 15 mm on CT. Only patients without vascular invasion and without extrahepatic disease based on CT scans of the chest and abdomen were placed and maintained on the waiting list. Patients with regional lymph node involvement, detected by preoperative imaging and biopsy or intraoperative frozen section, did not undergo LT. Until the year 2000, patient selection followed the Milan criteria; thereafter, the UCSF criteria were used for listing to LT. Patients who were listed for transplantation were maintained on the waiting list, unless they developed the following contraindications: detectable macrovascular invasion, multifocal disease (>5 nodules), or extrahepatic tumor manifestation. Date of last follow-up was December 2009.

Transarterial chemoembolization

Before 1997, TACE was not performed as bridging procedure. Between 1997 and 2002, patients with HCC measuring at least 15 mm listed for LT were considered for TACE at the time of LT evaluation. However, in this period, TACE was applied only sporadically without any special selection of tumor number or diameter. After 2003, all suitable patients with an HCC underwent TACE at the time of listing for LT. Patients required being free of significant ascites, to have a prothrombin time <1.5 times control, a creatinine level <2 mg/dL, and a total bilirubin value <3 mg/dL. If indicated, TACE was repeated every six to eight wk based on the results of repeated contrast enhanced multiphasic CT examinations.

Patients received supraselective TACE by use of microcatheters after initial angiographic visualization of the abdominal vessels. Depending on the tumor location and arterial supply, the tip of the catheter was placed in a second- or third-order branch of the right or left hepatic artery in close proximity to the tumor for selective embolization. All relevant visible lesions within a lobe were addressed in a single session, provided that functional liver reserve was considered sufficient. A mixture of doxorubicin, cisplatin, and iodized oil (2.5 mg doxorubicin, 2.5 mg cisplatin, and 0.5 mL lipiodol within 1 mL suspension) was used as chemoembolization agent. The maximum applied dose was 50 mg/m^2 doxorubicin, 50 mg/m^2 cisplatin, and 10 mL lipiodol. In case of persistent arterial inflow within the selected arteries after application of the maximum dose, additional embolic agent (polyvinylalcohol particles) was

applied until stasis. After embolization, devascularization was confirmed by angiography. After embolization, retention of iodized oil in the tumor was documented by unenhanced CT.

Evaluation of tumor response

For assessment of treatment response, all patients were categorized according to the RECIST criteria by comparing the histopathological findings (number of lesions and size of lesions) to the CT findings at the time of evaluation for LT (19). Thereby complete response (CR) was defined as disappearance of all target lesions, partial response (PR) as least 30% decrease in the sum of the longest diameter of target lesions, progressive disease as at least 20% increase, and stable disease (SD) as neither sufficient shrinkage to qualify for partial response nor sufficient increase to qualify for progressive disease. In the group without TACE, overall radiological staging concerning the Milan criteria compared with the final pathological investigation was adequate in the majority of patients. Correlation between staging and histology in the non-TACE group revealed that 22% of patients were understaged and 11% overstaged. These rates did not change over the years and are well within the range reported from most centers (20, 21). Therefore, an analysis based on the radiogical staging at the time of listing, that is, prior to TACE in the interventional group, is not expected to have a relevant systematical error in one over the other group and the only reasonable parameter for comparison of both groups.

Immunosuppression

Cyclosporine and tacrolimus were used as primary immunosuppressive agents. Tacrolimus in combination with low dose steroids was used as standard primary immunosuppressive regimen since 1992. In the early phase, an induction therapy with either ATG or IL2 receptor antibodies was performed. Immunosuppression was completed by azathioprine or mycophenolate moffetil, if required. Steroids were tapered and discontinued within six months. Since 2006, adequate HCC patients were enrolled in a prospective randomized multicenter trial with the use of sirolimus, otherwise no special immunosuppressive protocols were performed in the subgroup of patients with HCC, and especially no differences in those with or without TACE were found. However, reduction in immunosuppression as far as possible was ensured in all patients with HCC independently of the used agents.

Study population

The following patients were excluded from the analysis (n = 159 patients, some of them had more than one exclusion criterion) to increase the comparability of the groups with and without TACE: patients with an HCC found incidentally in the explanted liver (n = 50), patients with Child C cirrhosis (as in more than 90% of Child-C patients of the present series, TACE was contraindicated based on the given parameter and no Child C patient in the present series underwent preoperative TACE, n = 50), patients who underwent living-related LT who were not considered for bridging therapy because of the short waiting time (n = 24), and patients who underwent any other HCC-specific treatment before LT (n = 61, e.g., liver resection, radiofrequency ablation [RFA], percutaneous ethanol injection [PEI]), even if they received TACE before or after the respective procedure. During the study period, in total 336 patients with HCC were transplanted. By application of these aforementioned criteria, 177 patients were subject of this analysis. Of these, 71 had at least one TACE (Group A) and 106 had no HCC therapy before LT (Group B). The in-hospital mortality as possible confounder during the relatively long study period did not significantly change over time. All patients were followed at our outpatient department regularly. Follow-up investigations including X-ray of the chest, abdominal ultrasound, AFP levels, and CT scans if indicated were performed initially every six months and thereafter at least yearly.

Statistical analysis

Data are given as mean and standard error of mean (SEM). Patient survival and tumor recurrence rates were calculated using the Kaplan–Meier method. For tumor recurrence rate, recurrence was counted as an event, whereas death from other reasons (without tumor recurrence) was censored. Differences were examined using the log-rank test. Variables with a significant prognostic impact on univariate analysis ($p < 0.1$) were included in a multivariate analysis applying the Cox multiple stepwise regression model. Comparisons of categorical and continuous variables were performed using the chi-square test and the Mann–Whitney *U*-test, respectively. Differences were considered statistically significant if the p value was <0.05. All statistical analyses were performed using PASW Statistics 18.0 (SPSS Inc., Chicago, IL, USA).

Results

Study groups

Patient characteristics in both groups were comparable, but tumor characteristics showed more advanced tumors in the TACE group. Thus, the percentage of patients outside the Milan criteria – for the reason of comparability between the groups based on imaging studies at the time of listing for LT – was significantly higher in group A (Table 1). The mean time on the waiting list for the whole study population was 139 ± 14 d. As a result of a generally increasing waiting time during the last decade, the mean waiting time in Group A (TACE group, 187 ± 28 d) was longer than in Group B (111 ± 14 d); however, the difference was not statistically significant (p = 0.067). In the TACE group, a mean number of 2.1 ± 0.2 (range, 1–7) TACE applications was performed per patient during the waiting time. Detailed patient and tumor characteristics at the time of listing for liver transplantation (i.e., before application of TACE in Group A) are shown in Table 1.

Table 1. Comparison of patient characteristics in both study groups at listing for liver transplantation (LT), that is, before transarterial chemoembolization (TACE) in group A

	Group A (n = 71) TACE prior LT (%)	Group B (n = 106) no HCC treatment prior LT (%)	p[a]
Male	63 (89)	88 (83)	0.293
Underlying liver disease			
Alcohol	25 (35)	24 (23)	0.503
HCV	23 (32)	40 (38)	
HBV	10 (14)	15 (14)	
Cryptogenic	8 (11)	13 (12)	
Others	5 (7)	14 (13)	
Milan criteria fulfilled			
CT[b]	38 (54)	79 (75)	0.003
Pathological report	39 (55)	62 (59)	0.639
Maximum diameter of largest tumor on (CT/MRI, mm)	42 ± 3	33 ± 3	0.002
Recipient blood group			
0	14 (23)	27 (26)	0.963
A	35 (57)	57 (55)	
AFP-category			
<20	30 (42)	51 (48)	0.246
21–100	15 (21)	19 (18)	
101–1000	19 (27)	20 (19)	
>1000	6 (9)	7 (7)	
Not determined	1 (1)	9 (9)	
Child-Pugh stadium A	35 (49)	44 (42)	0.108
Mean waiting time	187 ± 28	111 ± 14	0.067
Waiting time			
<90 d	33 (46)	61 (58)	0.010
91–180 d	10 (14)	26 (25)	
180–365 d	18 (25)	16 (15)	
>365 d	10 (14)	3 (3)	
Follow up after LT (yr)	6.5 ± 0.5	9.6 ± 0.5	<0.001

HCC, hepatocellular carcinoma.
[a]By chi-square test.
[b]In group A before first TACE application in group B at listing for LT.

Response to TACE

In the TACE group, 53/71 patients (75%) did not show tumor progression during the waiting time. This number was slightly but not significantly higher than in the group without TACE, where 68/106 patients (64%) revealed no tumor progression during the waiting period (p = 0.23). The mean diameter of the largest nodule remained stable during the waiting period in the TACE group (42 ± 3 mm before TACE compared with 42 ± 4 mm in the pathological examination), whereas a mean increase of 5 mm was seen in Group B without neoadjuvant HCC treatment (33 ± 3 mm at listing for LT compared with 38 ± 3 mm in the pathological examination). The relative number of patients outside the Milan criteria was higher in the TACE group before TACE, but the histological findings revealed a comparable percentage of patients outside the Milan criteria in both groups (Tables 1 and 2), indicating some effect of TACE in terms of down-sizing.

The histological tumor response, determined by the extent of tumor necrosis, showed a complete or near total necrosis in about one-third of patients in all tumor diameter categories (Table 3). However, total tumor necrosis with no remaining viable tumor cells was detected predominantly in lesions smaller than 30 mm (Table 3). In contrast, the interval between the last application of TACE and transplantation did not significantly correlate with the degree of histological tumor necrosis (p = 0.589), and also the number of TACE applications showed no correlation with the histological response (p = 0.930).

Long-term outcome

Both groups showed similar overall survival and recurrence rates (Fig. 1). A separate analysis of patients within the Milan criteria revealed a strong tendency towards an improved survival in the TACE group (Fig. 2). The five-yr survival rate in Milan patients was 87% in Group A and 69% in Group B; however, the difference was not statistically significant. In parallel, the five-yr HCC recurrence rate was reduced in the TACE group in patients fulfilling the Milan criteria (8.4%) compared with patients without TACE fulfilling the Milan criteria (23.5%), although

Table 2. Comparison of pathological findings in the explanted liver

	Group A (n = 71) TACE prior LT (%)	Group B (n = 106) no HCC treatment prior LT (%)	p[a]
Number of nodules			
1 nodule	41 (58)	53 (50)	0.378
2 or 3 nodules	19 (27)	39 (37)	
4 or 5 nodules	4 (6)	6 (6)	
>5 nodules	7 (10)	8 (8)	
Maximum tumor diameter (CT)			
<30mm	30 (42)	64 (60)	0.332
31–50mm	23 (32)	31 (29)	
>50mm	18 (25)	11 (10)	
Pathological maximum diameter of largest nodule (mm)	42 ± 4	38 ± 3	0.651
Vascular invasion			
Microvascular	16 (23)	31 (29)	0.400
Macrovascular	6 (9)	8 (8)	0.827
Tumor grading			
G1	7 (10)	21 (20)	<0.001
G2	38 (54)	61 (58)	
G3	13 (18)	24 (23)	
Gx[b]	13 (18)	0	
Extent of tumor necrosis			
Complete, no viable tumor	13 (18)	0	<0.001
Subtotal necrosis	9 (13)	1 (1)	
Partial necrosis	30 (42)	14 (13)	
Minimal or no necrosis	19 (27)	91 (86)	

HCC, hepatocellular carcinoma; LT, liver transplantation; TACE, transarterial chemoembolization.
[a]By chi-square test.
[b]Histopathological grading could not be determined because of complete necrosis of the tumor.

Table 3. Treatment response in the transarterial chemoembolization (TACE) group in relation to the size of the largest tumor nodule

	≤ 30 mm (n = 30) (%)	31–50 mm (n = 23) (%)	>50 mm (n = 18) (%)	p[a]
RECIST category				
CR/PR	10 (33)	6 (26)	2 (11)	0.207
SD	16 (53)	9 (39)	10 (56)	
PD	4 (13)	8 (35)	6 (33)	
Histological necrosis				
Total (no viable tumor)	8 (27)	3 (13)	2 (11)	0.464
Near total (>90%)	1 (3)	4 (17)	4 (22)	
Partial	12 (40)	10 (44)	8 (44)	
Minimal/none (<10%)	9 (30)	6 (26)	4 (22)	

[a]By chi-square test.

statistical significance was not completely reached (p = 0.053, Fig. 3). In contrast, patients with and without neoadjuvant TACE outside the Milan criteria showed no differences in survival (Fig. 2) and recurrence rates (Fig. 3). An additional analysis using the UCSF criteria was added. In patients within the UCSF criteria, neoadjuvant TACE significantly decreased the HCC recurrence rate (p = 0.037, Fig. 4A). This suggests that the difference was most pronounced in the patient group exceeding the Milan criteria but inside the UCSF criteria. However, owing to small numbers, this subgroup *per se* showed only a trend towards a lower recurrence rate after preoperative TACE (p = 0.27, Fig. 4B). In patients outside the UCSF criteria, the recurrence rate with and without TACE was nearly identical (p = 0.99, five-yr recurrence rate >50%, data not shown).

In patients outside the Milan criteria, tumor progression on the waiting list was significantly associated with an increased risk of recurrence in the TACE group as well as in the group without bridging therapy (Fig. 5). This difference was less pronounced in patients inside the Milan criteria (Fig. 4). The relative proportion of patients inside Milan with tumor progression was significantly lower in the TACE group (13%) than in the group without any bridging therapy (38%; p = 0.006, Fig. 5). In patients outside the Milan criteria undergoing TACE as neoadjuvant therapy, tumor recurrence was low in case of down-sizing to the Milan criteria (Fig. 6); however, this was achieved in five of 33 (15%) patients only.

No significant correlation between the histological tumor viability and the risk of tumor recurrence was found, neither in all patients after TACE (data not shown) nor in patients outside the Milan criteria who had undergone TACE (Fig. 6). The rate of complete tumor necrosis was low in larger tumors (Table 3).

Other known risk factors for HCC recurrence were also associated with an increased risk of HCC recurrence in the present series. Thus, patients not fulfilling the Milan criteria (p < 0.01), patients with a larger maximum tumor diameter (p < 0.01), vascular invasion (p < 0.01), or a DNA index above 1.5 (p < 0.01) had a significantly increased recurrence rate in both groups. Only the histological tumor grading was inconclusive in terms that G3 tumors had a significantly increased risk of tumor recurrence (p < 0.01) in group B, but not in the TACE group (p = 0.497). Overall analysis revealed in both groups no significant difference in tumor recurrence between patients who spent less than the median waiting time on the waiting list and those who waited longer than the median time (p = 0.158). The underlying liver disease (alcohol vs. viral hepatitis vs. other etiologies) showed no differences in tumor recurrence rates in both

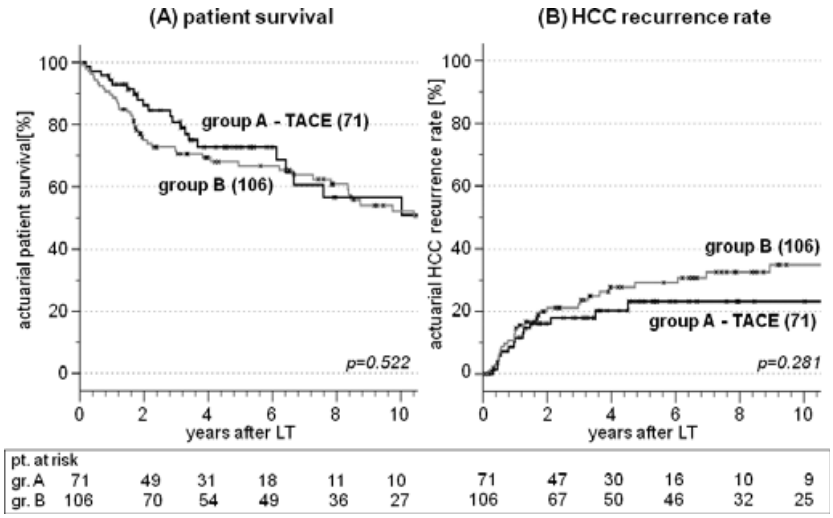

Fig. 1. Overall actuarial survival (A) and hepatocellular carcinoma (HCC) recurrence rate (B) in both study groups.

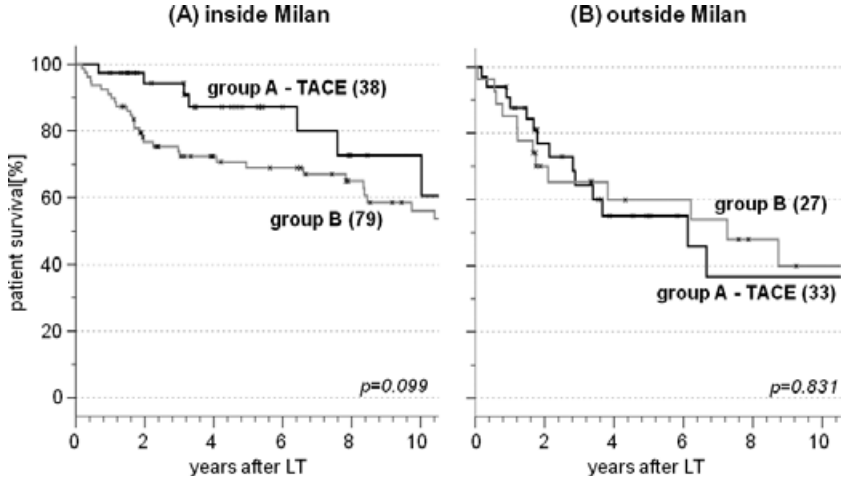

Fig. 2. Patient survival in patients inside (A) and outside (B) the Milan criteria in correlation with application of preoperative transarterial chemoembolization (TACE).

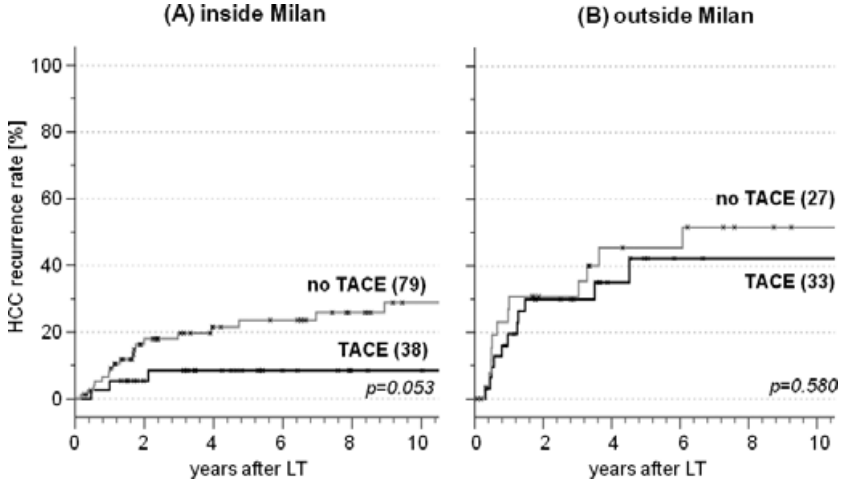

Fig. 3. Hepatocellular carcinoma (HCC) recurrence rates in patients inside (A) and outside (B) the Milan criteria (based on radiological staging at the time of listing for liver transplantation, LT) with and without neoadjuvant TACE.

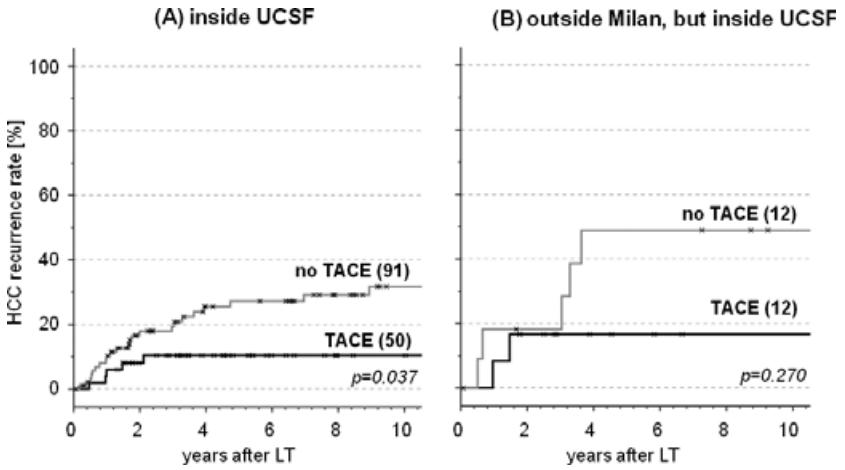

Fig. 4. Hepatocellular carcinoma (HCC) recurrence rates in patients inside the UCSF criteria (A) and in the subgroup of patients outside the Milan criteria but fulfilling the UCSF criteria (B) (based on radiological staging at the time of listing for liver transplantation, LT) with and without neoadjuvant transarterial chemoembolization (TACE).

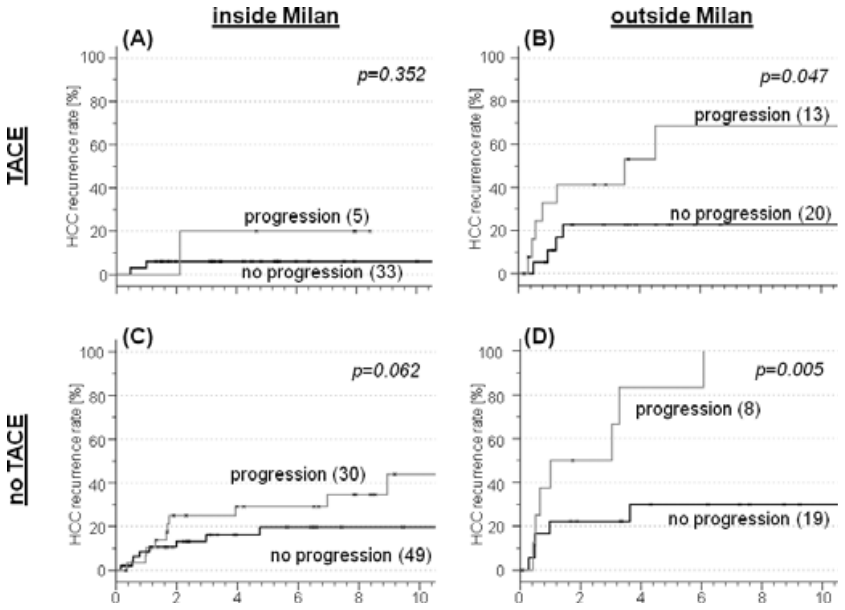

Fig. 5. Impact of tumor progression on the risk of hepatocellular carcinoma (HCC) recurrence after liver transplantation in patients inside (A, C) and outside (B, D) the Milan criteria (radiological staging at the time of listing for liver transplantation, LT). Results of the transarterial chemoembolization (TACE) and no TACE group are given separately.

groups. Also, AFP levels >300 were not significantly associated with tumor recurrence, neither in the TACE group ($p = 0.763$) nor in the group without TACE ($p = 0.122$). Very high AFP levels (>1000) were associated with an increased recurrence rate in the non-TACE group only ($p = 0.017$).

There was no significant difference in the pattern of tumor recurrence between group A and B. Primary manifestation of recurrence was intrahepatic only in 4.2% and 5.7% of patients in group A and B, respectively. Slightly more patients with pulmonary metastases as initial manifestation of recurrence were seen in group B (7.5%) than in group A (2.8%, n.s.). In the remaining patients, tumor recurrence occurred either as bone, peritoneal, or lymph node metastases or recurrent tumor was detected at multiple locations simultaneously; again, there was no difference between group A and B.

Multivariate analysis of factors with a significant influence on recurrence rate in the univariate analysis (Milan criteria, vascular invasion, RECIST category, TACE before LT) revealed vascular invasion and the Milan criteria as the most important risk factor for tumor recurrence (Table 4). However, in the group outside the Milan criteria, the tumor course on the waiting list according to

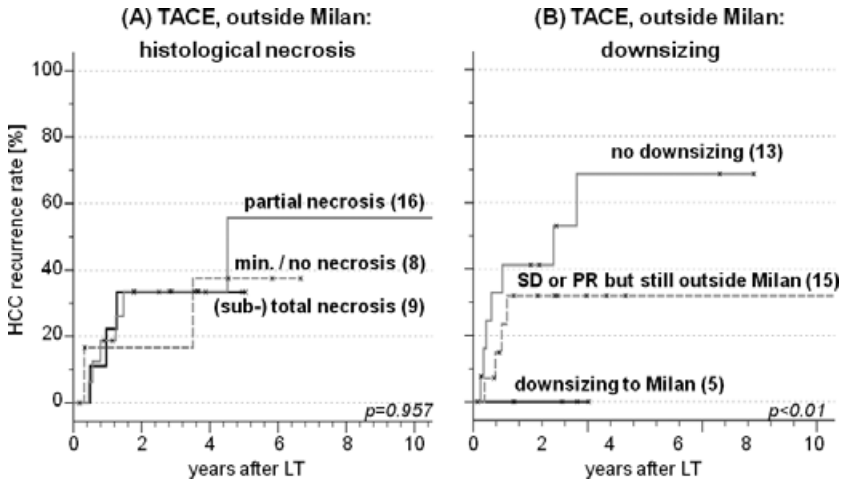

Fig. 6. Recurrence rate in patients outside the Milan criteria (at the time of listing) did not correlate with the histological tumor response (A) but showed a correlation with tumor downsizing to within the Milan criteria (B).

Table 4. Multivariate analysis of factors influencing tumor recurrence after liver transplantation (LT; HR and p values obtained by Cox regression are given)

	HR (95% CI)	Univariate	Multivariate
Inside Milan			
Vascular invasion	2.67 (1.08–6.62)	0.003	0.034
RECIST category	1.34 (0.54–3.35)	0.037	0.526
TACE before LT	2.63 (0.76–9.06)	0.053	0.126
Outside Milan			
Vascular invasion	4.27 (1.56–11.6)	< 0.001	0.005
RECIST category	3.20 (1.32–7.77)	0.001	0.010
TACE before LT	1.60 (0.69–3.75)	0.580	0.275
All patients			
Milan criteria	2.78 (1.49–5.21)	0.001	0.001
Vascular invasion	3.11 (1.62–5.95	< 0.001	0.001
RECIST category	2.12 (1.14–3.96)	< 0.001	0.018
TACE before LT	1.68 (0.87–3.25)	0.281	0.125

TACE, transarterial chemoembolization.

Table 5. Corresponding multivariate analysis of the same factors concerning patient survival (HR and p values obtained by Cox regression are given)

	HR (95% CI)	Univariate	Multivariate
Inside Milan			
Vascular invasion	1.29 (0.64 ± 2.62)	0.325	0.477
RECIST category	1.01 (0.50 ± 2.07)	0.505	0.974
TACE before LT	1.90 (0.82 ± 4.41)	0.099	0.135
Outside Milan			
Vascular invasion	2.75 (1.23 ± 6.17)	0.008	0.014
RECIST category	1.13 (0.50 ± 2.55)	0.472	0.769
TACE before LT	0.99 (0.46 ± 2.20)	0.831	0.999
All patients			
Milan criteria	1.76 (1.06–2.92)	0.018	0.030
Vascular invasion	1.87 (1.13–3.10)	0.003	0.015
RECIST category	1.04 (0.62–1.75)	0.335	0.882
TACE before LT	1.30 (0.77–2.21)	0.522	0.125

LT, liver transplantation; TACE, transarterial chemoembolization.

the RECIST definition had also a significant impact on tumor recurrence. In patients inside the Milan criteria, this factor was not statistically significant in the multivariate analysis. Neither was TACE a significant factor in the multivariate analysis. Similar results were obtained in the multivariate analysis of patients within the UCSF criteria (data not shown).

Discussion

TACE before liver LT has gained wide acceptance in many transplant centers. However, the evidence for the efficacy of this treatment is still limited, because no randomized trials are available and even large retrospective analyses are rare (11, 15, 22, 23). Major drawback of many of these retrospective analyses – including the present – is the historic nature of the control group. As perioperative management, allocation policy, and listing criteria have changed over the years, other confounding factors cannot be ruled out completely. To minimize these confounding parameters and to avoid a selection bias in the TACE group, emphasis of this analysis was to achieve a maximum consistency of the control and the interventional group. Thus, patients with incidental HCC were excluded, as these tumors are usually small and bridging therapy is not feasible. Patients with Child C cirrhosis were excluded, because TACE is contraindicated in most of these patients and patients with a very high MELD score are known to have an increased perioperative mortality (24, 25), which would negatively bias patient survival in the non-TACE group. To adjust different populations in the groups with and without TACE, a

subgroup analysis of patients inside and outside the Milan criteria was performed. Histopathological vascular invasion as the strongest predictive factor of (26) could not be used in the present setting, because a grouping variable before intervention was imperative. Moreover, neoadjuvant TACE might influence the emergence of vascular invasion.

As in several other studies (see below), no significant overall reduction in tumor recurrence could be detected in the present series. However, in most other studies, the patient cohorts with and without TACE are not completely comparable for several reasons. For example, a retrospective study published by Yao et al. (15) included different locoregional therapies (TACE, RFA, PEI), many incidental tumors, and a high number of Child C patients. Accordingly, Majno et al. (27) have not seen a general benefit from preoperative TACE application, but again, almost 50% Child C patients were included in the control group and the mean tumor size was markedly smaller, because the control group contained 20% incidental tumors. The results of the largest published series so far – a French multicenter analysis of 14 transplant centers using a matched pair design with 100 patients per group (11) – found also no differences in patient survival. However, the TACE group within the Milan criteria revealed an approximately 15% lower three-month survival. Despite this increased perioperative mortality, the five-yr survival was almost identical in both Milan groups (TACE vs. no-TACE). The authors excluded the perioperative deaths from the final calculation of disease-free survival, which leads to an imbalance towards patients outside the Milan criteria in the TACE group. Nevertheless, the five-yr disease-free survival was higher in the TACE group (69%) than in the non-TACE group (64%). Moreover, the five-yr HCC recurrence rate of all patients was 13% in the TACE and 23% in the non-TACE group, although this failed to reach statistical significance. In contrast to our analysis, the recurrence rate for patients within and outside the Milan criteria was not indicated separately. Therefore, if considered in detail, these results are not contradictory to the present data. After exclusion of the most obvious confounding variables, in the present series, a clear trend towards a reduced recurrence rate was seen in the TACE group, in patients fulfilling the Milan criteria.

In this analysis, neoadjuvant TACE resulted in a marked reduction in tumor recurrence in patients outside the Milan criteria ($p = 0.053$), but this difference became significant if all patients within the UCSF criteria were analyzed ($p = 0.037$). This suggests that especially those patients outside the Milan but inside the UCSF criteria did benefit from TACE application. However, owing to the small number of patients in this subgroup (24), no statistical difference was reached, although the five-yr recurrence rate with TACE was 18% compared with 50% without TACE.

Patients inside the Milan criteria have a known low recurrence rate. However, the recurrence rate in Fig. 3A in the non-TACE group appears relatively high (*c*. 20% at five yr). This is because of the fact that the Milan criteria in the present series are based on imaging studies at the time of listing for LT. If recurrence is calculated using histological data, one-, three-, and five-yr recurrence rates in all patients within the Milan criteria during the study period were 4.5%, 8.5% and 11.6% without any neoadjuvant therapy.

Major goal of neoadjuvant TACE is avoidance of tumor progression during the waiting time (28). In the present cohort, the number of patients fulfilling the Milan criteria by means of cross-sectional imaging (CT) upon listing remained the same as compared to the histopathological assessment in the TACE group, while the number of intra-Milan patients in the non-TACE group decreased from listing to LT (75% vs. 59%). This can be interpreted as a progression retarding effect of TACE or – given the known inaccuracy of CT with a tendency to underestimate the hepatic tumor load (29) – even as an indicator for successful downstaging by TACE.

It has been shown that a good response to TACE is associated with a low recurrence rate (10) and might serve as selection parameter for LT. The use of TACE as "tumorbiological selection parameter" was delineated first in a series of Otto et al. (10). One-third of patients were delisted because of tumor progression, and those who were finally transplanted without progression had an excellent outcome, even if they did not fulfill the Milan criteria before TACE. These data have been confirmed in other studies (30, 31). Majno et al. (27) also found an improved five-yr recurrence-free survival in patients transplanted for an HCC larger than 3 cm in whom down-staging was achieved by TACE. Accordingly, Concejero et al. (32) have shown very low recurrence rates in patients, who were down-staged to the Milan criteria by various interventions. This is also in accordance with the present data. In our analysis, the histological necrosis rate did not correlate with tumor recurrence, as suggested in other series (33).This lack of correlation might be based on varying time intervals between the last TACE and LT, which might influence the necrosis rate at least in patients with non-complete necrosis.

Owing to its retrospective nature, this analysis has some limitations that need to be minded:

1. A selection bias might be present, because in the second period, only a part of patients underwent TACE. However, for compensation of a possible unequal distribution, a subgroup analysis for patients inside and outside the Milan criteria was performed.
2. No intention-to-treat analysis can be performed because of incomplete data of the early period. However, within the later years of the analysis, the tumor-related drop-out rate was low and did not change markedly over the years. In addition, drop out rate is difficult to interpret between the both groups, because drop-out is also a function of time and the waiting time was longer in the TACE group.
3. Although this represents a large single center analysis, the overall sample size is relatively small, especially for a multivariate analysis. On the other hand, in larger multicentric, e.g., registry data, many of the detailed informations provided in this study are not available and the general management might differ between centers.

In conclusion, this analysis is to our knowledge the largest single-center report on neoadjuvant TACE before LT. A recent review of the literature revealed in accordance with our data a reduced recurrence rate after pretransplant bridging therapy (23). In our series, a markedly reduced HCC recurrence rate was observed in the TACE group in patients within the Milan criteria and this difference was even significant in patients within the UCSF criteria. Interestingly, this improvement occurred despite a relatively short mean waiting time (below six months in 60% of TACE patients). It might be speculatet that the difference becomes even more significant in case of a longer waiting time. Additionally, the treatment response to TACE but not the histological necrosis rate was confirmed as prognostic parameter. Only in patients inside the Milan criteria, a trend towards improved survival was seen in the TACE group, which confirms the efficacy of the modern preoperative management in LT for HCC. However, other contributing factors cannot be completely excluded by this analysis because of its limitations discussed earlier.

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