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CLINICAL INVESTIGATION

Preoperative Chemoembolization in Patients with Hepatocellular Carcinoma Undergoing Liver Transplantation: Influence of Emergent Versus Elective Procedures on Patient Survival and Tumor Recurrence Rate

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Abstract Our purpose was to compare the recurrence rate and survival in patients with hepatocellular carcinoma (HCC) who had elective transarterial chemoembolization (TACE), immediate preoperative TACE, or no treatment prior to orthotopic liver transplantation (OLT). A total of 132 patients with HCC had TACE prior to OLT. Eighteen patients had no TACE before OLT and functioned as a control group. The urgent group included 35 patients embolized less than 24 h before OLT and the elective group included 97 patients embolized greater than 1 day before transplantation. These groups were compared with regard to tumor staging, hepatic synthetic function, and post-TACE tumor necrosis and survival and recurrence rates.

Patients were followed for a mean of 780 days post OLT (1–2912 days). The tumor staging was similar between groups but the Childs-Pugh score in the urgent and untreated group was significantly higher than that of the other groups. The degree of necrosis at explant was also significantly different between the two treated groups, with an average 35% necrosis in the patients embolized less than 24 h before OLT vs 77% in the elective group ($p < 0.002$). Recurrence rate in the urgent group was 8 of 35 (23%) in a median of 580 days, 20 of 97 (21%) in a median of 539 days in the elective group, and 2 of 18 (11%) in a median of 331 days in the no-TACE group. Survival at 1, 3, and 5 years was 91%, 80%, and 72% in the elective group, 79%, 58%, and 39% in the urgent group, and 69%, 61%, and 41% in the no-TACE group, respectively. The urgent and no-TACE groups had significantly worse survival compared with the other groups; however, the tumor recurrence rates were statistically the same among all three groups. TACE within 24 h of OLT causes an average of 35% necrosis and elective TACE increases necrosis further to 77%. Despite this difference, the tumor recurrence rate in the three groups is equivalent and no different from that in the group that received no treatment before OLT. The decreased survival in the immediate and no-TACE groups was due to non-cancer-related deaths.

Keywords Transarterial chemoembolization · Hepatocelllular carcinoma · Orthotopic liver transplantation

Cirrhotic patients develop complicating hepatocellular carcinoma (HCC) at a rate of 3% to 4% per year [1, 2]. Due to the frequent advanced stage of disease at presentation and the tenuous hepatic synthetic reserve in most of these patients, curative hepatic resection is considered in only 20% of patients. Early results of orthotopic liver transplantation (OLT) for HCC were disappointing but have improved considerably with more stringent patient selection criteria. HCC was the indication for OLT in about 3% of transplant surgeries according to a UNOS report in 2003 and is becoming a more frequent indication as liver transplant centers multiply and selection criteria produce improved clinical outcomes [3]. Currently, liver transplantation leads to a reasonable 70% 5-year survival rate and 15% recurrence rate in patients satisfying the Milan criteria (one lesion<5 cm or up to three lesions, none >3 cm, and no regional or distant metastases or vascular

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invasion) [4–6]. While waiting for a suitable organ, transplant physicians will frequently refer patients for transarterial chemoembolization (TACE) with the intent of confining tumor to the liver, shrinking tumors and thwarting progression to vascular invasion, or reducing the chances of viable tumor embolizing systemically during hepatic manipulation at transplant hepatectomy [7–9]. However, the validity of the above assumptions remains questionable. While some reports indicate a reduction of tumor recurrence rates after transplantation in patients treated with TACE preoperatively, other studies, notably two large studies from European investigators, refute this claim and assert that preoperative TACE has no bearing on survival or recurrence rates after OLT for liver cancer. [10, 11]. In fact, a recent report involving a small series of transplant patients suggests that TACE and the resulting partial necrosis of liver tumors actually predisposes patients to higher recurrence rates after transplantation, presumably due to induced ischemic changes reducing the adhesion between tumor cells and allowing easier systemic spread during surgery [12]. This situation was also described by Adachi et al., who claimed that TACE-induced complete necrosis led to improved survival post-OLT, while patients with only partial necrosis suffered an increased recurrence rate [13]. Since our transplant service frequently requests TACE prior to OLT in virtually all patients with HCC, even as early as several hours prior to surgery, this study concerned us. To evaluate the long-term clinical impact of pretransplantation TACE in light of the above reports, we reviewed the survival and recurrence rates among patients who had TACE urgently (≤24 h prior to OLT) versus patients who received more elective TACE (>1day prior to OLT). We felt that it was important to determine whether urgent TACE facilitates early recurrence or lower survival rates due to incomplete tumor necrosis or acute ischemic changes. Urgent TACE was performed in patients who had marginal liver reserve or significant comorbidities and were deemed high risk for complications after chemoembolization. TACE was not done in the other group of patients for the same reason, although their overall health status was even more critically reduced. Therefore, the urgent and no TACE groups of patients in this study had worse hepatic dysfunction and more overall debilitation than those in the elective group, who generally had TACE shortly after the initial diagnosis of HCC.

Materials and Methods

We reviewed the surgical and radiology databases from 1998 to 2006 to find patients who had OLT and HCC. We excluded those patients with incidental tumors found only at surgery. All patients in this study had a vascular lesion in the liver treated by TACE prior to OLT. No other ablative therapies were employed (i.e., radiofrequency ablation, cryoablation). There were 1409 liver transplant surgeries and 159 patient with HCC (11%) who had TACE prior to OLT, 11 patients were excluded because of benign histology in the resected native liver. Sixteen additional patients were excluded due to macrovascular invasion. The final group was 132 patients with HCC, pathologically documented, with no vascular invasion, and all imaged and treated by TACE prior to transplant. There were a total of 35 patients embolized ≤24 h before OLT (urgent group), while 97 patients were embolized >24 h prior to surgery (elective group). During our mining of the various databases, we found a small third group of patients (18 subjects) who had a preoperative diagnosis of HCC but, due to severely impaired hepatic function or significant comorbidities, did not have TACE prior to OLT. We used this third group (no TACE group) as a control group to compare with the urgent and elective TACE groups, although its statistical value was limited due to the small number of patients within it. To ascertain the similarity among the three groups, we compared the Cancer of the Liver Italian Program staging (CLIP), Childs-Pugh class, Model of End Stage Liver Disease (MELD) scores, α-fetoprotein (AFP) levels, and size and number of liver tumors. The differences among the thee groups regarding these parametric variables were calculated using standard t tests. Using Kaplan-Maier analysis, we compared the survival rates, recurrence rates, and disease-free survival rates of the three groups and these curves were compared with the use of a log-rank test for significance. All 132 patients and associated variables were then studied with the Cox proportional hazards method to ascertain factors that had significant correlations with survival and tumor recurrence. p values <0.05 indicated significant differences between groups.

Results

Both groups of patients were followed for 1–2912 days post-OLT. No patients were taken off of the waiting list. The average follow-up for the elective group was 846 days (SD = 694 days), while the average follow-up for the urgent group was 618 days (SD = 518 days) and the average follow-up for the no-TACE group was 574 days (SD = 525 days). The mean age of both groups was 59 years and the sex distribution was similar, with 25% females in the elective group versus 23% females in the urgent group and 28% females in the no-TACE group. Patients in both groups had from one to three TACE procedures before OLT. The average number of procedures was the same for the two treated groups, however, with 1.2 TACE

procedures per patient on average ($p = 0.8$). As a reflection of more advanced cirrhosis in the urgent group, the CLIP scores and Childs-Pugh scores were significantly higher compared to those of the elective group (Table 1). The average AFP level was higher in the urgent group, at 491, versus 152 in the elective group, however, this difference did not reach statistical significance ($p = 0.07$). As noted in Table 1, the number of patients exceeding Milan criteria was similar in the three groups, ranging from 20% to 25%. Imaging was used to determine the Milan status of our patients. The TNM staging of HCC in the three groups was similar, as neither vascular invasion nor metastases were present in any study patient, and as shown in Table 1, the average tumor diameter and number of tumors were statistically the same for both groups. Histopathology results from the resected liver specimen showed no difference in the degree of dysplasia among the three groups, with an Edmondson tumor score of 1.9 for the urgent group versus 1.8 for the elective and no-TACE groups. However, the mean degree of necrosis was significantly different between the two groups, with just 35% necrosis in the urgent group versus 77% in the elective group ($p < 0.002$). Necrosis was often estimated by the pathologist and we assigned 90% necrosis to those patients with ''complete necrosis'' and 10% necrosis to those patients with ''completely viable'' tumors post-TACE. Therefore, the quantification of necrosis in our patients is an approximation. Kaplan-Meier curves were constructed for overall survival (Fig. 1), recurrence of HCC (Fig. 2), and disease-free survival (Fig. 3) among the three groups. Log-rank testing of the above curves showed a significantly reduced survival in the no-TACE and urgent groups compared to

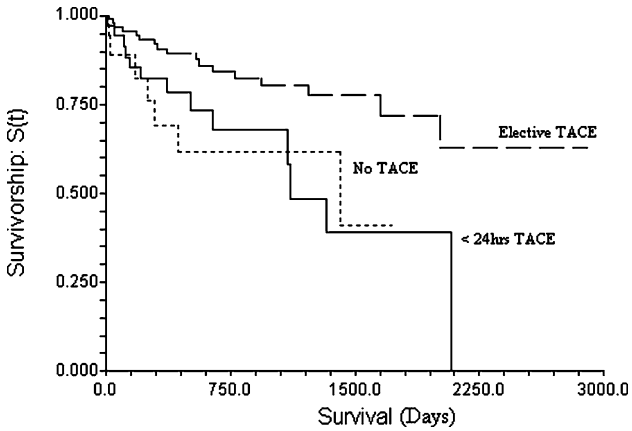

Fig. 1 Kaplan-Meier survival curve of patients treated by elective TACE more than 1 day before OLT (elective group), patients treated with TACE <24 h before OLT (urgent group), and patients who had no embolization prior to OLT (no-TACE group). There is a significant survival disadvantage for the urgent and no-TACE groups (log-rank p value = 0.01)

Table 1 Characteristics of urgent and elective TACE groups

	Urgent TACE ($n = 35$)	Elective TACE ($n = 97$)	No TACE ($n = 18$)	p value
Patient characteristics				
Mean age (yr)	59	59	59	NS
No. of females	8 (23%)	24 (25%)	5 (28%)	NS
Childs-Pugh	7.9	7.1	9.6	0.04
MELD score	13.1	10.2	19	0.02
CLIP score	1.71	1.28	2.2	0.05
Serum bilirubin	4.4	2.4	5.6	0.04
Serum AFP	491	152	81	0.07
Tumor characteristics				
Edmonson tumor grade	1.9	1.8	1.8	0.7
Average diameter of largest tumor	3.7	3.6	3.0	0.24
Average number of tumors	3	2.1	3.2	0.13
No. of patients exceeding Milan criteria	7/35 (20%)	24/97 (25%)	4/18 (22%)	NS
Treatment characteristics				
Average % necrotic tumor post-TACE	77	34.6	N/A	<0.002
Average no. of TACE procedures	1.2	1.2	0	0.8
Follow-up characteristics				
Average follow-up duration (days)	618	846	574	
Recurrences	8/35 (23%)	20/97 (21%)	2/18 (11%)	
Average time to recurrence (days)	580	539	331	
30-day mortality	1	1	2	

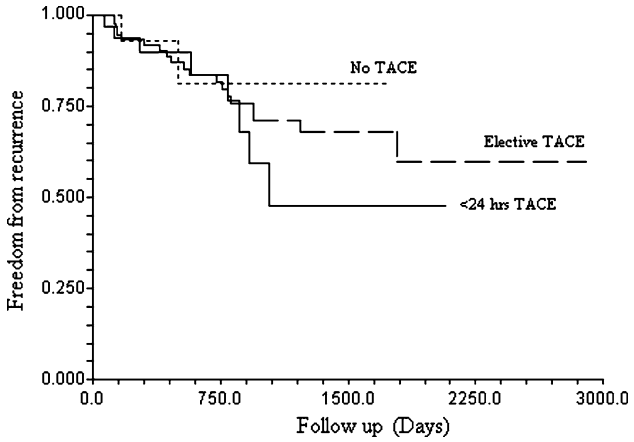

Fig. 2 Tumor recurrence curves for the three groups of patients. There is no significant difference among the three groups' recurrence rates (log-rank p value = 0.7)

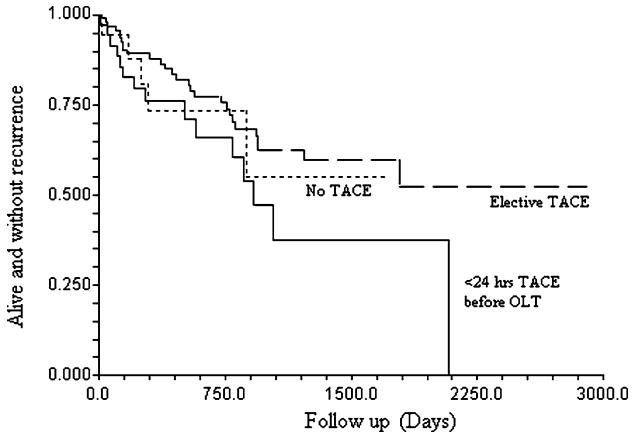

Fig. 3 Disease-free survival curves for the three groups of patients. There is no statistically significant difference in the three curves (log-rank p value = 0.07 in the urgent versus elective groups)

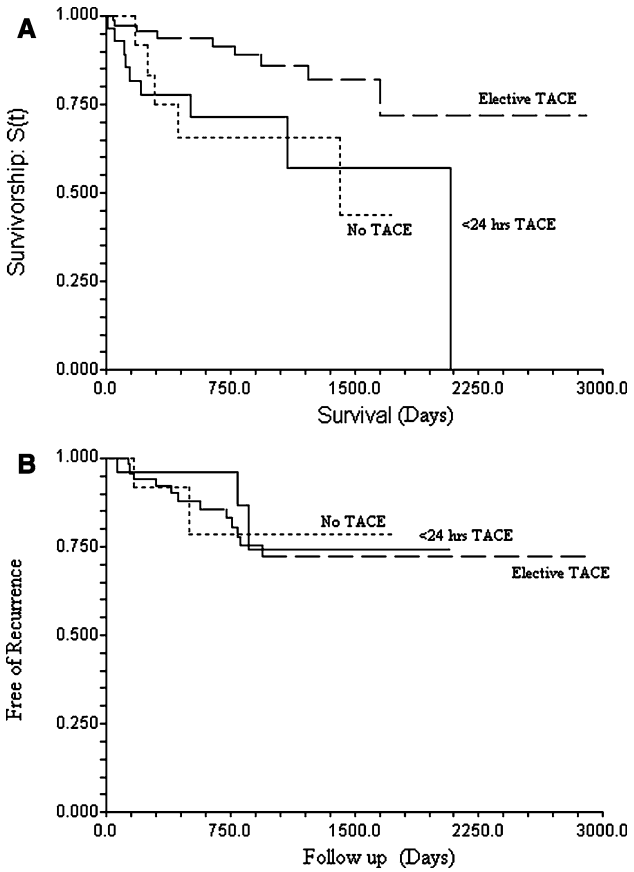

Fig. 4 (**A**) Survival curves for the three groups after exclusion of patients who did not satisfy Milan criteria. As in Fig. 1, the survival is significantly worse in the urgent and no-TACE groups (log-rank p value = 0.01). (**B**)Tumor recurrence rates in the three groups showed no significant difference even when patients outside of the Milan criteria are excluded (log-rank p value = 0.9)

the elective group (p = 0.03 to 0.06). The disease-free survival was diminished in the no-TACE and urgent groups compared to the elective group, although the difference was not significant (p = 0.07). However, the recurrence rates were not significantly different among the three groups (p = 0.66). Univariate regression analysis of the percentage tumor necrosis at explant histology with survival showed no correlation either (p = 0.6). Since the <24-h-preoperative TACE and no-TACE groups had the poorest overall health, a survival disadvantage was expected. When we excluded patients who exceeded the Milan criteria for liver transplantation the survival curves again showed significantly improved survival in the elective group, but the tumor recurrence curves again showed no significant difference among the three groups (Fig. 4). The specific recurrence rate in the urgent group was 8 of 35 (23%), versus 20 of 97 (21%) for the elective group and 2 of 18 (11%) for the no-TACE group. The median time of recurrence was <2 years in the urgent and elective groups (580 versus 539 days, respectively). One, three-, and five-year survival rates were 79%, 58%, and 39% in the urgent group, versus 91%, 80%, and 72% in the elective group and 69%, 61%, and 41% in the no-TACE group, respectively. Since the tumor recurrence was equal among the three groups, the decreased survival in the immediate and no TACE groups suggests non-cancer-related deaths.

Cox proportional hazards analysis indicated that tumors beyond Milan criteria and minimal post-TACE tumor necrosis were significantly associated with increased tumor recurrence (p = 0.03 and 0.04, respectively). Survival and disease-free survival, however, correlated only when patients exceeded Milan criteria (p = 0.05). Factors lacking significant correlation with survival/recurrence include microvascular invasion, Childs-Pugh or MELD score, and tumor grade. These results seem to validate the utility of

the Milan criteria for liver transplantation. Additionally, other recent investigations support the idea that HCC with a good response to TACE (i.e., extensive TACE-induced necrosis) portends low recurrence rates posttransplant [14].

Discussion

The findings of messenger RNA AFP(mRNA-AFP) fragments in the peripheral blood of patients after liver transplant surgery or hepatic resection confers decreased survival and increased tumor recurrence rates [15, 16]. This leads some to reason that preoperative TACE may limit the shedding of these isolated tumor cells during surgical manipulation and thus impede the process of distant metastasis. Several shortcomings affect this premise, however. First, positivity for mRNA-AFP in untreated HCC patients did not correlate with disease-free survival in one study [17]. Second, it has never been firmly established whether TACE diminishes tumor dispersion by manipulated tumor. In fact, TACE has been shown to actually convert some HCC patients to mRNA-AFP positivity [17]. Finally, it is well established that TACE rarely induces 100% tumor death and it remains a noncurative adjunct or therapy. Will surgical manipulation of a liver with a near–100%-viable, 3-cm HCC be more likely to systemically embolize tumor cells during surgery than that of a liver with a 3-cm tumor with 70% necrosis? Although we found a significant difference in the degree of tumor necrosis between the urgent and the elective groups, this did not translate into a significant difference in recurrence rates. We were unable to confirm the findings of Ravaioli that the degree of necrosis facilitated recurrence in OLT patients after preoperative TACE. Our studies differ, however, in that Ravaioli's group contained a large number of patients with vascular tumor invasion—a subset of patients that were excluded in our cohort. It is possible that partial necrosis in HCC with existing vascular invasion carries a higher risk of recurrence. Although our results show that urgent TACE does not seem to carry an increased risk of tumor embolization and earlier recurrence compared to elective TACE, the advantages of urgent TACE are lacking as well. Any benefits of TACE in down-staging tumors and perhaps even delaying vascular invasion would not be applicable to such therapy provided within a mere 24 h. Given that two recent studies found no benefit of TACE prior to transplantation in recurrence or survival rates, it is likely that elective as opposed to urgent TACE similarly has no significant impact on the posttransplant risk of tumor recurrence in these patients [10, 11]. The survival analysis of our limited data set of patients with no treatment prior to OLT adds some support to this hypothesis. Given our data and those of other investigators, the select use of TACE prior to OLT seems prudent, with the primary focus aimed at down-staging patients exceeding Milan (or other) criteria. In fact, recent reports show the utility of locoregional therapy to drive HCC into Milan compliance, finding that these patients then enjoy the survival and recurrence rates of those patients meeting the criteria from the beginning [19, 20]. We were unable to confirm these findings, as post-TACE and pretransplant imaging in our patient cohorts was rarely performed and the waiting time for organs was short, averaging only 43 days in the elective group. The survival of the elective group was better than that of the urgent and no-TACE groups, and this finding is certainly due to the more severe comorbidities in the urgently and not-embolized group. The significantly increased CPS and MELD scores in these higher-risk groups clearly illustrate their poorer hepatic function and overall health and explain their worse survival post-OLT. Although the degree of cirrhosis differed between the two groups, the tumor stage was comparable, with a similar size and number of hepatic lesions and no macrovascular tumor invasion by imaging or histologic analysis. In addition, the tumor dysplasia score did not differ among the three groups. Therefore, the equivalence of recurrence rates among these groups is the most significant result of this study.

Conclusion

TACE performed urgently (within 24 h of OLT) induces significantly less tumor necrosis than does earlier, elective TACE (35% vs 77%). Due to patient selection issues, sicker and more cirrhotic patients had no TACE or urgent TACE prior to OLT and suffered significantly reduced survival postoperatively. However, all three groups (no TACE, urgent TACE, and elective TACE) experienced the same recurrence rate over a mean follow-up period of about 2 years. Urgent TACE will not significantly change preoperative tumor staging. It follows that TACE is best suited as elective therapy in select patients awaiting OLT for the purpose of down-staging or limiting tumor progression. Among all patients with HCC, higher degrees of necrosis post-TACE, seen at histopathology of the liver explant, predict lower tumor recurrence rates.

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