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LIVER TRANSPLANTATION OUTCOMES AFTER TRANSARTERIAL CHEMOTHERAPY FOR HEPATOCELLULAR CARCINOMA

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ABSTRACT

Background: The use of transarterial chemoembolisation (TACE) in hepatocellular carcinoma (HCC) patients awaiting liver transplantation is widespread, despite a lack of evidence that it improves oncological outcomes, and amid concerns that it may increase the risk of post-transplant complications. In this study, the impact of TACE on post-transplant outcomes in the UK were evaluated between 2006 and 2016.

Methods: HCC recipients of a liver transplant were identified and stratified according to whether they had received TACE. Cox regression methods were used to estimate hazard ratios (HR) for post-transplant mortality and graft failure adjusted for donor and recipient characteristics.

Results: 968 patients were included with 385 (39.8%) having received TACE. 5-year post-transplant patient survival was 75.2% (95%CI: 68.8% to 80.5%) with TACE and 75.0% (70.5% to 78.8%) without TACE. With adjustment for donor and recipient characteristics, no statistically significant differences in mortality (HR: 0.96, 0.67 to 1.38; p=0.82) or graft failure (HR: 1.01, 0.73 to 1.40; p=0.96) were identified. The impact of TACE did not differ according to the number of TACE treatments (≥2 TACE treatments HR: 0.97, 0.61 to 1.55; p=0.90) or the time-period after transplantation (patient mortality before and after 90 days; p=0.29). The incidence of hepatic artery thrombosis was low both in those who had and had not received TACE (1.3% and 2.5%, respectively; p=0.23).

Conclusion*:* The use of TACE in about 40% of HCC patients before they received a liver transplant in England did not significantly affect the risk of post-transplant complications, patient mortality or graft failure.

INTRODUCTION

In many countries, the number of patients with hepatocellular carcinoma (HCC) who are candidates for a liver transplant has significantly increased.[1] This has put pressure on liver transplant waiting lists with many listed patients in danger of having to wait longer to receive a transplant, especially in countries where there is a chronic shortage of donor livers.[1-2] In response, more HCC patients on the liver transplant waiting list are now receiving transarterial chemoembolisation (TACE) to minimise the growth of their tumour and prevent their disease progressing beyond transplantable criteria.[1]

TACE, a form of locoregional therapy (LRT), is an angiographic procedure that involves the local administration of chemotherapeutic agents into the hepatic artery followed by the embolisation and subsequent blockade of the arterial branch(s) that are supplying the targeted HCC nodules.[3] The procedure can induce decompensation of the cirrhotic liver and can also cause damage to the inner lining or the intima of the hepatic artery, potentially increasing the risk of hepatic artery thrombosis (HAT).[3-5] A recent systematic review representing 1 122 patients from 14 retrospective studies, found that TACE increased the overall risk of hepatic artery complications after liver transplantation.[(5)]

So far, there is no evidence that the use of TACE in HCC patients on the waiting list for transplantation has an impact on post-transplant survival. Analyses of the US Multicenter HCC Transplant Consortium (UMHTC) database, including 3601 transplantations carried out between 2002 and 2013, and the European Liver Transplant Registry (ELTR), including 4978 transplantations between 1990 to 2016 found no statistically significant effect of TACE.[6-7] However, both the US and European studies represent a selected group of patients with the UMHTC database containing only 20 out of the 144 registered liver transplant centres in the US and the ELTR containing information on LRT for only one fifth of all HCC recipients in Europe.[6-7] Also, the use of TACE was relatively high with 79% of the US patients and 72% of the European patients receiving TACE before transplantation.

Since 2017, formal allocation policies in the UK recommend the use of TACE and other LRTs in all HCC patients who are predicted to wait 6 months or more to receive a liver transplant.[1,8] The impact of TACE on post-transplant survival is likely to depend on the specific patient selection and organ allocation policies that are being followed in a particular country.[1] Until 2018, the selection of HCC patients for transplantation in the UK mainly followed the Milan criteria defining the maximum number and size of the tumours in the liver and donor organs were being allocated to patients on the waiting list according to a modified Model for End-stage liver disease (MELD) score.[9] In 2018, a national selection and allocation policy was introduced in the UK that also takes account of the primary liver disease and AFP levels and number and size of tumours in HCC patients. [10]

A cohort based study of the impact of TACE on post-transplant outcomes of HCC recipients was carried out using complete national data from the Standard National Liver Transplant Registry, including all patients who had a liver transplantation in England in the period from 2006 to 2016, linked at patient level with administrative data of all hospital admissions in the English National Health Services (NHS). This fully representative cohort with

highly complete follow-up was used to compare post-transplant complications (HAT, biliary tract leak and biliary tract stricture), mortality and graft failure between HCC patients who received TACE before liver transplant and those who did not. This included a comparison of causes of death between the two groups, including death from recurrence of malignant disease. In a further step, the extent to which the impact of TACE on patient mortality and graft failure differed according to time after transplantation (before and after 90 days) was also explored in order to examine the effect of TACE on surgical complications and cancer recurrence separately.

PATIENTS AND METHODS

Standard National Liver Transplant Registry

The Standard National Liver Transplant Registry contains information about all liver transplants carried out in all six liver transplant centers in England. It is managed by National Health Service Blood and Transplant.[11] This registry was used to identify HCC recipients of a liver transplant and to capture information on donor and recipient characteristics, including tumour characteristics at the time of registration on the waiting list, post-transplantation outcomes (HAT, biliary tract leak and biliary tract stricture) within 3 months following transplantation, and date and cause of death.[11]

Hospital Episodes Statistics (HES) database

The HES database is an administrative dataset capturing records of all admissions to English NHS hospitals.[8] Each HES record can contain up to 20 diagnoses using codes based on the 10th revision of the International Classification of Disease (ICD-10) and up to 24 operations and procedures using codes from the Office of Population, Census and Surveys Classification of Surgical Operations and Procedures (OPCS-4).[12] The linked HES records provided information on patients who have received TACE (OPCS-4 codes J101, J103, J108 and J109) and on the patients' socioeconomic status based on the area-based Index of Multiple Deprivation (IMD), grouped according to national quintiles.

Linkage of the national datasets

HES records were linked to patient records from the Standard National Liver Transplant Registry at patient level using the following identifiers: NHS number (the unique patient identifier used in the NHS), gender, date of birth, and postcode. The data linkage was performed by NHS Digital who used a hierarchical deterministic linkage approach following a stepwise approach with increasingly less strict matching criteria.[12,13] A previous validation study of records from the Standard Liver Transplant Registry linked to HES following this approach has shown that 99.3% of linked HES records have at least one diagnosis code relevant to an indication for liver transplantation.[13]

Study population

All patients (aged 16 years or older) who had received a liver transplant for HCC between 1st January 2006 and 31st December 2016 were eligible for inclusion. The diagnosis of HCC for each patient was identified from the three diagnostic fields available in the Standard National Liver Transplant Registry. To limit heterogeneity of the study cohort, patients who underwent transplantation for types of liver cancer other than HCC and those who underwent multi-visceral, super-urgent, domino or living-related liver transplantations were excluded, as well as those who received a liver transplant for other disease indications including those with acute liver failure. Patients whose survival data was missing were also excluded (Figure S1) as were listed patients who had received LRTs other than TACE and those who had received TACE in addition to other LRTs.

Recipients' lifestyle activity was assessed using a 5-point scale ranging from 'able to carry out normal

activity without restriction' to 'completely reliant on nursing/medical care').[14] The United Kingdom Model for End-Stage Liver Disease (UKELD) was used to score the severity of the liver disease.[15] Waiting list time was calculated from the point of registration on the waiting list to the point of transplantation. Values for ethnicity were grouped into white and non-white groups. Complications following transplantation were recorded at 3 months and included HAT, biliary tract leak and biliary tract stricture. The TACE treatments that were administered were done so according to previously described protocols.[16] HCC patients selected to receive TACE as a bridging therapy were done so based on the decisions of centre-specific multi-disciplinary team meetings. There was no information in the Standard National Liver Transplant Registry on explant pathology.

A total 1 204 HCC recipients of a liver transplant were identified of which 1 122 (93.2%) were found to have at least one matched patient record in HES. Each linked HES record was explored to identify patients on the transplant waiting list who had received a TACE treatment prior to their liver transplant. Listed patients who had received LRTs other than TACE were excluded as were those who had received TACE in addition to other LRTs (Figure S1).

Statistical analysis

Donor and recipient characteristics, post-operative complications and cause of death and graft failure were compared between HCC recipients who had received TACE and those who had not. Chi-squared tests were used for categorical variables and t-tests for continuous variables. Tumour characteristics at the time of registration on the waiting list were also compared between TACE and non-TACE cohorts, according to factors that are predictive of post-transplant survival including size of largest nodule, total number of tumours, total tumour diameter, radiological evidence of vascular invasion and maximum alpha fetoprotein level prior to transplantation.[16] Published service evaluations by NHS Blood and Transplant (NHSBT) indicate only a maximum of 8 patients were transplanted following downstaging of their tumour(s) and none before 2015.[17]

The Kaplan-Meier method was used to compare post-transplant patient and graft survival, and Z-tests for a difference in proportions were used to compare post-transplant complications, in liver transplant recipients who did or did not receive TACE. Follow-up data – including data on mortality, graft failure and post-operative complications - was available until 14th April 2017. Patients with a functioning graft or alive at their last follow-up visit were considered to be censored observations. Graft loss was defined as either re-transplantation or patient death. Differences in patient and graft survival were assessed with the log-rank test.

Multivariable Cox regression was used to examine the prognostic impact of TACE on patient and graft survival in the first five years after transplantation. Hazard ratios (HRs) comparing post-transplant outcomes in liver transplant recipients who did or did not receive TACE were estimated with and without adjustment for

donor and recipient characteristics.

Interaction terms in the Cox regression model were included to assess whether the prognostic impact of TACE varied according to time after transplantation (before and after 90 days) or according to donor type (DCD vs DBD). A period of 90 days after transplantation was chosen as mortality in this period is likely to reflect the occurrence of surgical complication whereas mortality between 90 days and 5 years is more likely to reflect tumour recurrence, which is an indicator of the 'curative success' of cancer treatment.[18] The significance of the interaction terms was tested using the Wald test.

All recipient and donor factors included in the regression models were chosen because they were thought to be clinically plausible risk factors of post-transplant outcomes.[19] Missing patient and donor characteristics were imputed using chained equations creating ten complete datasets.[20] The Cox regression results for each of these datasets were pooled using Rubin's rules.[20]

Stata V15 (StataCorp, College Station, Texas, USA) was used for all statistical analyses. A p-value < 0.05 was considered significant for each statistical analysis.

RESULTS

A total of 968 HCC recipients between 2006 and 2016 were included in the study, of which 385 patients (39.8%) received TACE before transplant and 583 (60.2%) did not. 166 HCC patients (17.2%) had more than one treatment of TACE. The use of TACE as a bridging therapy increased from 29.8% (139/467) between 2006 and 2010 to 49.1% (246/501) between 2011 and 2016. At the time of registration on the waiting list, patients who did receive TACE were more likely to have tumour characteristics predictive of poorer outcomes but these differences were not statistically significant (Table 1). Patients receiving TACE were also more physically active, had better liver function, and were less likely to show signs of end-stage liver disease. In addition, patients who received TACE were on average 156 days on the waiting list for liver transplantation whereas the corresponding figure was 100 days in patients who did not receive TACE. The median time from TACE to transplantation was 154 days (IQR 72 – 278 days) and 62.3% (240/385) of these patients had TACE prior to being registered on the waiting list. There were only small differences in the characteristics of HCC recipients whose transplant records could and those whose records could not be linked to records from HES (Table S1).

There were no statistically significant differences between TACE and non-TACE recipients in the occurrence of HAT at 3 months (1.3% (5/385) and 2.4% (14/583), respectively, p=0.23, Table 3), biliary tract stricture (4.7% (18/385) and 3.6% (21/583), p=0.41) or biliary tract leak (5.7% (22/385) and 4.3% (25/583), p=0.31).

No statistically significant differences in the 5-year patient survival of patients who received TACE (75.2%, 95%CI: 68.8% to 80.5%) compared to those who did not were found (75.0%, 95%CI: 70.5% to 78.8%; HR: 0.93, 95%CI: 0.69 to 1.27; p=0.66; Figure 1 and Table 2). Neither were there statistically significant differences in 5-year graft survival (71.3%, 95%CI 64·9% to 76·8% and 71·1%, 95%CI 66·6% to 75·1%, respectively; HR: 0.95, 95%CI: 0.72-1.25; p=0·60; Figure 1 and Table 2). Adjustment for both patient and recipient characteristics had little impact on these comparisons. The impact of TACE on patient mortality and did not increase with the number of received treatments (≥2 TACE treatments HR: 0.97, 0.61 to 1.55; p=0.90) and neither was there an impact on graft failure **(HR: 1.02, 0.66 to 1.56; p=0.67, Table S2)**.

The impact of TACE on post-transplant mortality was also found not to differ before (HR: 0.69, 95%CI: 0.34-1.41) or after 90 days (HR: 1.04, 95%CI: 0.71-1.54; p=0.29; Table S3) nor did it differ for graft survival before 90 days (HR: 0.92, 95%CI: 0.55-1.55) and after (HR: 1.05, 95%CI: 0.75-1.52, p =0.67). There was also no evidence suggest that the impact of TACE on post-transplant outcomes was affected by whether DBD or DBD livers were used (Table S4).

The biggest difference in the causes of death between TACE and non-TACE patients was the recurrence of malignant disease in patients who died between 90 days and 5 years after transplantation (Table 4). Of the 52 patients who had TACE and who died in that period, 16 patients (30.8%) had recurrence of malignant disease as their cause of death compared to 15 of the 90 patients (16.7%) who did not have TACE and who

died in the same period TACE (p=0.05). In those who lost their graft due to occlusive events (including vascular occlusion, acute vascular occlusion and non-thrombotic infarction, **Table 5**), the proportions of patients who did and did not receive TACE were similar (8.0% (11/137) and 6.7% (5/75), respectively, p=0.74).

DISCUSSION

Summary of results

About forty percent of HCC patients who received a liver transplant between 2006 to 2016 in England had received at least one treatment of TACE. Recipients who were treated with TACE were more likely to have tumour characteristics that are predictive of poorer post-transplantation outcomes but less likely to have signs of end-stage liver disease. TACE recipients were also more likely to have waited longer for their liver transplant. There was no evidence that TACE increases the risk of surgical complications including HAT. Treatment with TACE before transplantation did not affect the risk of post-transplant mortality or graft failure and these results did not depend on the number of TACE treatments each patient received or on the type of donor organ (DCD or DBD).

Methodological limitations

A key limitation is that information on tumour characteristics at the time of transplantation were not available. Therefore, the extent to which the tumour characteristics responded to the TACE treatment acts as prognostic marker for survival following transplantation could not be assessed. Another limitation is that we only included in our analysis patients who went on to receive a liver transplant. The included cohort may therefore represent a selective sample of HCC patients who had more favourable tumour biology than those who died before transplantation and those who were removed from the waiting list due to their tumour progressing beyond transplantable criteria.

The frequency of HAT and biliary complications following transplantation that we observed in our study may represent an underestimation of their true frequency.[4] These post-transplantation complications, although known to be rare, can be quiescent in their clinical presentation, especially HAT where the rapid development of collateral circulation can quickly compensate for occlusion of the hepatic artery.[21] Therefore, the small number of these complications that were identified in the Standard National Liver Transplant Registry may have precluded us from being able to detect significant differences between those receiving TACE and those who did not. However, we must also state that the frequency of complications that we found is consistent with other studies.[4,5]

A final limitation is that we could include only 385 patients who received TACE and it could be argued that our study was underpowered. However, the 5-year post-transplant survival of patients with and without TACE was very similar and the results for the different outcomes, including patient mortality, graft failure and post-transplant complications, were very consistent, which provides further strength to our interpretation that TACE does not affect post-transplant outcomes.

Comparison with other studies

The results of our national cohort study of HCC patients receiving a liver transplant in England are in line with those of the two recent multi-centre studies carried out in the US and Europe (albeit we cannot identify from the European study if any UK liver transplant centres contributed their data for their analysis).[6,7] An important

difference to note is that with about 40% of HCC recipients having received TACE before transplantation the use of TACE in England was considerably lower than in the US (79%) and in the European studies (72%) **which is likely to be explained by patients having relatively short waiting list times for liver transplantation in England.**[6-7] On the other hand, there was no evidence in our study of an increase in the occurrence of HAT, biliary tract strictures or leaks which is in contrast to the recent meta-analysis of the impact of TACE on post-transplant complication that found evidence of an 1.6-fold increase in the frequency of hepatic artery complications.[5]

Explanation of results

The characteristics of the HCC recipients who received TACE reflect the current aims of this therapy. TACE was given to those who had more severe tumour biology, those who were considered at least risk of hepatic and renal decompensation and to those who had to wait longer to receive a transplant.[1] It must therefore be acknowledged that patients selected to receive TACE prior to transplantation are different from those who are not. Possible residual confounding may explain why a post-transplant survival advantage linked to TACE was not observed, even with adjustment for recipient and donor characteristics.[1] Similarly, differences in tumour characteristics may also explain why in our analysis patients who received TACE more often died from tumour recurrence. **Lastly, TACE itself might also have caused an increase in circulating tumour cells, but it is unlikely that this has contributed to a higher mortality due to HCC.[22]**

No differences in the incidence of HAT and other potentially TACE-related complications such as biliary strictures and leaks were identified.[21,23] Therefore, TACE either does not confer an increased risk of the early post-transplantation complications which that are sometimes attributed to surgical technical failure [24] or improvements in administration of TACE and in surgical technique mean that TACE related intimal injuries, including odema, aneurysm, fibrosis and thrombosis do not translate into increases in post-operative complications or early graft failure.[23] In this context, it is also important to note that a difference in impact of TACE on post-transplant outcomes according to whether DBD or DCD had been used was not observed.[25]

Implications

Our observations in a complete national cohort of HCC patients in England found that from the time of transplantation, TACE is neither a risk factor for early complications nor a protective factor for longer-term patient outcomes. These are important findings as it is unlikely that in the future the use of TACE before transplantation will decline in the UK. It has been shown that under the new national recipient selection and organ allocation scheme introduced in 2018 patients with HCC who have preserved liver function may have to wait significantly longer before they receive a liver transplant.[26] Furthermore, our study provides evidence that the use of TACE in patients on the waiting list for transplantation should not be considered as a contra-indication for the use of DCD livers.

Between 2006 and 2016, almost 40% of HCC patients who underwent a liver transplantation in England received at least one treatment of TACE. From the time of transplantation, TACE did not increase the risk of

HAT and early biliary complications, nor did it affect patient mortality or graft failure. The potential benefit of the use of TACE is restricted to its impact on tumour growth and prevention of their disease progressing beyond transplantable criteria in HCC patients while waiting for a liver transplant.

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NIHR Statement

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Data Statement

The Standard National Liver Transplant Registry is available on request from National Health Service Blood and Transplant.

Declaration of interests

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FIGURE LEGENDS

Figure 1: Five-year patient and graft survival stratified by TACE status 2006-2016 (n=968).

TABLES

Table 1: Donor and recipient characteristics in patients undergoing liver transplantation for HCC stratified by pre-transplantation use of TACE (n=968).

Indication group		**TACE N=385**	**No TACE N=583**		
DONOR		**% / N**	**% / N**	**Missing values**	**p-value**
Sex	Female	41.3% (159)	41.0% (239)	0	0.93
Cause of death	Trauma	9.9% (38)	10.5% (61)	0	0.96
Donor Type	DCD	28.6% (110)	31.9% (186)	0	0.27
ABO Match	Identical	98.2% (378)	98.5% (574)	0	0.47
Graft Type	Segmental	6.2% (24)	5.8% (34)	0	0.80
Organ appearance	Abnormal	28.0% (85)	35.0% (171)	176	0.04
Steatosis	Presence	47.9% (182)	46.0% (265)	12	0.57
Capsular damage	Presence	15.3% (58)	15.1% (87)	13	0.93
Age (years)	Mean (SD)	49.2 (16.3)	48.2 (15.7)	0	0.32
Donor BMI, kg/m²	Mean (SD)	26.4 (4.6)	26.6 (5.2)	3	0.67
Cold Ischaemic Time (mins)	Mean (SD)	504.3 (164.7)	503.3 (162.9)	80	0.93
RECPIENT					
Sex	Female	16.6% (64)	19.9% (116)	0	0.20
Age (years)	Mean (SD)	58.1 (7.3)	56.8 (8.5)	0	0.01
Ethnicity	Non-White	20.3% (78)	16.1% (94)	0	0.10
IMD quintiles	Most deprived	12.0% (45)	19.7% (102)	81	0.003
Tumor Characteristics	Max tumour >3cm	11.1% (37)	9.5% (39)	227	0.47
	Total tumour diameter >5cm	2.7% (9)	1.7% (7)	227	0.35
	>1 nodule	33.4% (115)	31.7% (131)	211	0.62
	Radiological evidence of vascular invasion	3.0% (10)	2.8% (11)	232	0.9
	AFP level (ng/mL)	85.9 (295)	88.1 (337.5)	279	0.93
Blood group	A	40.3% (155)	47.7% (278)	0	0.15
	AB	5.2% (20)	4.8% (28)		
	B	11.4% (44)	10.6% (62)		
	0	43.1% (166)	36.9% (215)		
Era of Transplantation	2006-2010 2011-2016	36.1% (139) 63.9% (246)	56.3% (328) 43.7% (255)	0	<0.001
HCV status	Positive	49.6% (180)	37.3% (201)	66	<0.001
Diabetes	Positive	31.84 (111)	31.1% (156)	112	0.93
Cirrhosis	Positive	94.0% (362)	91.4% (533)	0	0.13
Pre-transplant in patient status	Inpatient	2.6% (10)	7.2% (42)	0	0.002
Pre-transplant renal support	Presence	2.6% (10)	4.7% (27)	3	0.11
Previous abdominal surgery	Presence	4.9% (19)	6.5% (38)	2	0.30
Ascites	Presence	18.4% (71)	41.0% (238)	2	<0.001
Encephalopathy	Presence	7.9% (30)	20.6% (120)	4	<0.001
Varices	Presence	11.7% (45)	23.7% (138)	9	<0.001
Functional status	Restricted	47.2% (179)	39.5% (227)	14	<0.001
BMI, Kg/m2	Mean (SD)	28.2 (4.6)	27.9 (4.9)	3	0.46
Creatinine	Mean (SD)	80.9 (28.5)	86.5 (29.9)	0	0.46
UKELD	Mean (SD)	49.7 (4.0)	52.4 (5.4)	13	<0.001
Days on waiting list	Mean (SD)	156.6 (155)	100.0 (117)	0	<0.001

Table 2: Impact of TACE on 5-year patient and graft survival (n=968).

	TACE compared to no TACE Hazard ratio (95% CI)	
Post-transplant survival	**Patient Survival**	**Graft Survival**
Unadjusted analysis	0·93 (0·69-1·27)	0·95 (0·72-1·25)
Adjusted for recipient characteristics only*[1]	0·93 (0·66-1·31)	0·96 (0·70-1·48)
Adjusted recipient and donor characteristics*[1]	0.96 (0.67-1.38)	1.01 (0.73-1.40)

**[1]Adjusted for a) Recipient characteristics; sex, age, ethnicity, socioeconomic status, size of maximum tumour, total tumour diameter, number of tumours, AFP level, vascular invasion, diabetes, HCV status, pre-transplant inpatient status, presence of cirrhosis, ascites, encephalopathy, pre-transplant renal support, previous abdominal surgery, presence of varices, functional status, bmi, UKELD, waiting list time and era of transplantation.*

Table 3: Post-operative complications recorded at 3-months (n=968).

Complication	TACE vs No TACE (n=968)			Number of treatments of TACE (n=385)			Time from TACE to Transplantation (n=385)		
	TACE	No TACE	P-value	1 treatment	≥2 treatments	P-value	≤ 3 months	> 3 months	P-value
Hepatic artery thrombosis	1.3% (5)	2.4% (14)	0.23	1.8% (4)	0.6% (1)	0.30	1.6% (2)	1.2% (3)	0.69
Biliary tract stricture	4.7% (18)	3.6% (21)	0.41	4.6% (10)	4.8% (8)	0.91	4.9% (6)	4.6% (12)	0.88
Biliary tract leak	5.7% (22)	4.3% (25)	0.31	5.9% (13)	5.4% (9)	0.83	6.6% (8)	5.3% (14)	0.63

Table 4: Cause of death following liver transplantation for HCC patients in two separate epochs of follow-up time and stratified by pre-transplantation use of TACE (n=180).

Cause of Death	Overall			0-90 days			90 days – 60 months		
	TACE (n=65)	**No TACE (n=115)**	**p-value**	**TACE (n=13)**	**No TACE (n=25)**	**p-value**	**TACE (n=52)**	**No TACE (n=90)**	**p-value**
Recurrence of disease – malignant	24.7% (16)	13.0% (15)	**0.10**	0.0% (0)	0.0% (0)	**N/A**	30.8% (16)	16.7% (15)	**0.12**
Malignancy – other*[1]	13.9% (9)	20.0% (23)	**0.38**	0.0% (0)	4.0% (1)	**0.47**	17.3% (9)	24.4% (22)	**0.42**
Graft failure	1.5% (1)	1.7% (2)	**0.92**	0.0% (0)	4.0% (1)	**0.47**	1.9% (1)	1.1% (1)	**0.70**
Sepsis	27.7% (18)	29.5% (34)	**0.84**	61.5% (8)	52.0% (13)	**0.77**	19.2% (10)	23.4% (21)	**0.65**
Single organ failure*[2]	9.2% (6)	13.9% (16)	**0.41**	7.7% (1)	12.0% (3)	**0.71**	9.6% (5)	14.4% (13)	**0.46**
Haemorrhage	0.0% (0)	4.4% (5)	**0.10**	0.0% (0)	16.0% (4)	**0.16**	0.0% (0)	1.1% (1)	**0.45**
CVA	1.5% (1)	0.9% (1)	**0.68**	0.0% (0)	4.0% (1)	**0.47**	1.9% (1)	0.0% (0)	**0.19**
Other*[3]	16.9% (11)	9.6% (11)	**0.20**	30.8% (4)	8.0% (2)	**0.13**	13.5% (7)	10.0% (9)	**<0.001**
Unknown	4.6% (3)	7.0% (8)	**0.55**	0.0% (0)	0.0% (0)	**N/A**	5.8% (3)	8.9% (8)	**0.53**

**[1] Includes both lymphoid and non-lymphoid malignant disease*

**[2] 'Single organ failure 'includes death from pulmonary, renal, cardiac, hepatic and gastrointestinal failure.*

**[3] Other includes causes of death from hemorrhage, cerebrovascular accident and benign recurrence of disease.*

Table 5: Cause of graft failure following liver transplantation for HCC patients in two separate epochs of follow-up time and stratified by pre-transplantation use of TACE (n=212).

Cause of Graft Failure	Overall			0-90 days			90 days – 60 months		
	TACE (n=75)	No TACE (n=137)	p-value	TACE (n=24)	No TACE (n=43)	p-value	TACE (n=51)	No TACE (n=94)	p-value
Acute rejection	1.3% (1)	0.0% (0)	**0.18**	4.2% (1)	0.0% (0)	**0.19**	0.0% (0)	0.0% (0)	**N/A**
Chronic rejection	2.7% (2)	4.4% (6)	**0.55**	0.0% (0)	2.3% (1)	**0.46**	3.9% (2)	5.3% (5)	**0.72**
PNF	12.0% (9)	8.8% (12)	**0.50**	37.5% (9)	27.9% (12)	**0.56**	0.0% (0)	0.0% (0)	**N/A**
Acute vascular Occlusion	5.3% (4)	4.3% (6)	**0.77**	8.3% (2)	14.0% (6)	**0.54**	3.9% (2)	0.0% (0)	**0.06**
Vascular Occlusion	0.0% (0)	1.5% (2)	**0.30**	0.0% (0)	0.0% (0)	**N/A**	0.0% (0)	2.1% (2)	**0.30**
Non-thrombotic infarction	1.3% (1)	2.2% (3)	**0.67**	4.2% (1)	4.7% (2)	**0.93**	0.0% (0)	1.1% (1)	**0.46**
Recurrent disease*[1]	20.0% (15)	18.3% (25)	**0.80**	4.2% (1)	0.0% (0)	**0.19**	27.5% (14)	26.6% (25)	**0.93**
Biliary Complications	5.3% (4)	3.7% (5)	**0.58**	0.0% (0)	0.0% (0)	**N/A**	7.8% (4)	5.3% (5)	**0.57**
Graft still functioning at death	34.7% (26)	24.0% (33)	**0.22**	29.1% (7)	23.2% (10)	**0.68**	37.3% (19)	24.5% (23)	**0.24**
Other	10.7% (8)	24.8% (34)	**0.04**	12.5% (3)	23.2% (10)	**0.37**	9.8% (5)	25.5% (24)	**0.06**
Unknown	6.7% (5)	8.0% (11)	**0.74**	0.0% (0)	4.7% (2)	**0.29**	9.8% (5)	9.6% (9)	**0.97**

*[1] *Includes the recurrence of HCV and the cholestatic liver diseases (PSC & PBC).*