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Original Article

Transarterial chemoembolization of hepatocellular carcinoma before liver transplantation and risk of post-transplant vascular complications: a multicentre observational cohort and propensity score-matched analysis

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Abstract

Background: Transarterial chemoembolization (TACE) in patients with hepatocellular cancer (HCC) on the waiting list for liver transplantation may be associated with an increased risk for hepatic artery complications. The present study aims to assess the risk for, primarily, intraoperative technical hepatic artery problems and, secondarily, postoperative hepatic artery complications encountered in patients who received TACE before liver transplantation.

Methods: Available data from HCC liver transplantation recipients across six European centres from January 2007 to December 2018 were analysed in a 1 : 1 propensity score-matched cohort (TACE *versus* no TACE). Incidences of intraoperative hepatic artery interventions and postoperative hepatic artery complications were compared.

Results: Data on postoperative hepatic artery complications were available in all 876 patients (425 patients with TACE and 451 patients without TACE). Fifty-eight (6.6 per cent) patients experienced postoperative hepatic artery complications. In total 253 patients who had undergone TACE could be matched to controls. In the matched cohort TACE was not associated with a composite of hepatic artery complications (OR 1.73, 95 per cent c.i. 0.82 to 3.63, $P = 0.149$). Data on intraoperative hepatic artery interventions were available in 825 patients (422 patients with TACE and 403 without TACE). Intraoperative hepatic artery interventions were necessary in 69 (8.4 per cent) patients. In the matched cohort TACE was not associated with an increased incidence of intraoperative hepatic artery interventions (OR 0.94, 95 per cent c.i. 0.49 to 1.83, $P = 0.870$)

Conclusion: In otherwise matched patients with HCC intended for liver transplantation, TACE treatment before transplantation was not associated with higher risk of technical vascular issues or hepatic artery complications.

Introduction

Arterial revascularization is a critical step during liver transplantation. Postoperative hepatic artery complications, such as thrombosis, stenosis or (pseudo)aneurysm formation, often result in loss of the allograft. Hepatic artery thrombosis may result in graft loss in up to 80 per cent of events and is associated with a mortality rate between 10 and 50 per cent[1–6]. Technical difficulties encountered during implantation may result in prolonged arterial ischaemia, eventually resulting in ischaemic biliary tract damage[7].

Transarterial chemoembolization (TACE) is the most frequently used pretransplant locoregional therapy for bridging or downstaging of hepatocellular carcinoma (HCC) in candidates for liver transplantation[8,9]. Recent studies showed that preoperative TACE significantly improves post-transplant disease-free survival, when a complete pathological response is obtained[10,11].

While TACE is a commonly known concept, considerable procedure variation exists between centres in relation to both timing and frequency of neoadjuvant TACE[9,12,13]. TACE consists of

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Lay summary

Patients with liver cancer may be treated with transarterial chemoembolization (TACE) during the period on the transplant waiting list. With TACE, chemotherapeutic coils are injected directly into the small arteries supplying the tumour, after which these vessels are closed. The aim of this therapy is to decrease the tumour size and slow down tumour growth. However, concerns are raised that manipulation of the main hepatic artery by TACE may cause damage to the artery itself. If this would result in problems during or after liver transplantation when the artery is connected to the artery supplying the donor liver, this may endanger the donor liver graft survival. The present study shows no increased risk in problems to connect the artery during liver transplantation after TACE treatment. Also, arterial complications after liver transplantation did not occur more frequently if patients had received TACE treatment. The authors therefore conclude that TACE treatment before liver transplantation could be considered a safe approach.

selective administration of chemotherapeutic drugs into the alimentary arteries supplying the tumour(s), followed by infusion of an embolic agent. Alternatively, drug-eluting beads may be used[14].

Several complications, such as postembolization syndrome, abscess formation, access site injury, pulmonary embolism and even hepatic failure, have been reported after TACE[14–16]. Additionally, intra-arterial manipulation and infusion of chemotherapeutic drugs and embolic agents may damage the arterial wall and lead to arterial dissection, occlusion and extensive periarterial inflammation[17–19]. It is unclear if such vascular damage compromises the allograft implantation technique.

A previous meta-analysis suggested that pretransplant TACE increases the risk for hepatic artery complications and a recent case-control study reported an increased risk for hepatic artery thrombosis[20,21]. However, the included reports only provided uncorrected univariable analysis or studied a small sample of patients. Moreover, data on intraoperative handling of the hepatic artery anastomosis was lacking in most included studies. Therefore, the present multicentre study investigated whether pretransplant TACE was associated with vascular alterations leading to a more complex arterial reconstruction. The occurrence of postoperative hepatic artery complications and arterialization times were studied secondarily.

Methods

This study was conducted according to the RECORD (REporting of studies Conducted using Observational Routinely-collected health Data) recommendations for observational studies, an extension of the STROBE guidelines[22,23].

Survey

Patients from six European centres (Queen Elizabeth Hospital Birmingham, Katholieke Universiteit Leuven Hospital, Cliniques Universitaires Saint-Luc Brussels, Erasmus University Medical Centre Rotterdam, Policlinico Tor Vergata Rome, Sapienza University Hospital Rome) were screened retrospectively for inclusion in the study.

To assess intercentre comparability, a survey on centre-specific approaches was first conducted. In this survey differences in approach concerning locoregional therapies and arterialization in potential HCC liver transplant recipients were assessed (*Table S1*).

Study design

All adult (older than 18 years) patients with HCC transplanted during the period January 2007 until December 2018 were eligible for inclusion. Patients presenting with incidental HCC on pathological examination of the hepatectomy specimen, patients receiving living donor liver transplantation or retransplantation were excluded.

Patients who had received TACE before liver transplantation were compared with patients who did not receive TACE (control group). The control group also included patients who received locoregional therapy in form of radiofrequency treatment. The primary outcome of the study was the occurrence of intraoperative hepatic artery problems requiring technical adaptations or interventions related to the hepatic artery anastomosis. These were defined as the necessity for an alternative arterial reconstruction (no end-to-end anastomosis of the donor artery to the left or right, proper or common hepatic artery (including gastroduodenal patch) of the recipient); vascular interposition graft to the abdominal aorta (arterial conduit); redo hepatic artery anastomosis; arterial thrombectomy; or other non-predefined interventions. An alternative reconstruction necessary due to donor or recipient anatomical arterial variations only was not considered an alternative reconstruction. Secondary outcomes included postoperative hepatic artery complications, such as thrombosis, stenosis and (pseudo)aneurysm formation. Both intraoperative hepatic artery interventions and postoperative hepatic artery complications were primarily studied as composite outcomes, including all aforementioned events. Additionally, arterial revascularization time, defined as time between unclamping of the portal vein and unclamping the hepatic artery, was recorded. Arterial complications were diagnosed using Doppler ultrasonography, CT or MR angiography and/or regular angiography. The radiological follow-up protocols concerning hepatic artery patency, as well as postoperative anticoagulation protocols for each centre are specified in *Table S1*. Graft-survival rates in TACE *versus* no TACE patients, and for patients with and without intraoperative hepatic artery interventions were compared.

Data collection

Data were extracted from each centre-specific prospective database using a standardized form and definitions, as provided by the study protocol. Additional retrospective data, donor and recipient characteristics and intraoperative details were added to these databases. Donor characteristics included: age, sex, BMI, donation after cardiac (DCD) or brain death, donor risk index, split liver graft, hepatic artery anatomical variation, arterial back-table reconstruction of donor hepatic artery, cold and warm (during implantation) ischaemia time[24]. Recipient characteristics included: age, sex, BMI, laboratory Model for End-stage Liver

Disease (MELD) score at transplantation, number of TACE sessions, delay between TACE and transplantation, radiofrequency treatment, previous liver resection, insulin-dependent diabetes, antihypertensive treatment, hepatic artery anatomical variation, alpha-fetoprotein level at transplantation, number of tumours and cumulative tumour size (as reported on imaging reports before locoregional therapy). Outcome data comprised incidence of intraoperative hepatic artery interventions and postoperative arterial complications. Initial treatment of hepatic artery complications was recorded, as well as time span between transplantation and diagnosis of complications. Graft survival times were recorded.

Statistical analysis

Statistical analysis was performed with R-studio (Rversion 4.0.3, RStudio®, Boston, USA). BA power calculation was performed in advance of the study (see supplementary material online). Categorical variables were presented as absolute numbers with percentages. Continuous variables were presented as mean(s.d.) or median (i.q.r.). Categorical variables were statistically compared with the χ^2 test and continuous variables were compared either with the Student *t* test or Mann–Whitney U test as appropriate. In the matched sample, categorical variables were compared with the McNemar test or McNemar–Bowker test, continuous variables were assessed with the Wilcoxon signed rank test.

Two groups of recipients were defined: the TACE group and control (no TACE) group. The proportion of missing data was low and is presented for each variable in both groups in *Table S2*. Since missing data were probably caused by missing entries in prospective databases or omissions in the patient records, and not related to study outcomes nor groups, missing data were assumed to be missing at random. To compensate for missing data from explanatory variables, multiple imputations were performed. Missing data from outcome variables were excluded from analysis, without imputation. Outcome variables were, however, used as predictors in the imputation model. The following variables were included in the imputation model: centre of listing, recipient variables (sex, age, BMI, MELD score, insulin-dependent diabetes, antihypertensive drug use, presence of anatomical hepatic artery variation, number of HCC nodules and cumulative tumour size, radiofrequency treatment, previous liver resection), donor variables (age, sex, BMI, DCD graft, split graft, back-table reconstruction, presence of anatomical hepatic artery variations, warm and cold ischaemia time), and outcome variables (postoperative hepatic artery complications and intraoperative technical hepatic artery problems). Continuous variables were imputed according to the predictive mean matching method, categorical variables with use of logistic regression. A total of 10 imputations for each missing value were performed. Subsequently logistic regression was used to calculate propensity scores for TACE and control patients in all imputed datasets.

Among variables included in the propensity score model it was decided not to match tumour characteristics, as by definition patients treated with TACE will usually present with more and larger tumours compared with the control patients. The mean propensity score for each patient in the imputed datasets was pooled and added to the original dataset. TACE patients were matched to control patients 1:1 based on the obtained propensity scores according to the nearest neighbour method, matching in random order, with a calliper of 0.1. TACE and control patients with propensity scores outside the region of common support were discarded. For all variables included in the propensity model, the balance of the matching model was assessed with use of standardized mean differences (<0.1), quantile–quantile, and empirical distribution function (ECDF) plots. Additionally, baseline variables in the matched sample were compared between the two groups.

The incidence of hepatic artery complications and intraoperative technical hepatic artery problems in TACE and control patients was compared in the unmatched and matched samples, with use of (conditional) logistic regression with strata for matched pairs. Combined neoadjuvant TACE and radiofrequency treatment, time intervals between TACE and transplantation, and TACE technique were studied in additional univariable stratified analysis (unmatched data).

Time-to-event data were studied graphically in Kaplan–Meier graphs. Graft survival after occurrence of intraoperative hepatic artery interventions was compared with that for patients who had not had intraoperative interventions with the Gehan Breslow Wilcoxon test (assigning more weight to early events). Graft survival in the TACE and no TACE groups was compared with the log rank test. $P < 0.050$ was considered statistically significant.

Results

Results of the survey on centre-specific approaches concerning the hepatic artery anastomosis and locoregional therapy are presented in *Table S1*. Donor and recipient characteristics of the unmatched and propensity score-matched sample are depicted in *Table 1*. Median follow-up was 48.1 (i.q.r. 22.3–70.8) months. In total, 253 TACE patients were matched to 253 control patients with similar propensity scores. One control patient and 19 TACE patients were discarded since the propensity scores were outside the region of common support. Another 153 TACE patients could not be matched. After propensity score matching the groups only differed significantly on tumour characteristics which were not included in the matching model. To assess the balance of the propensity score-matched sample, standardized mean differences are reported in *Fig. S1*. Additional quantile–quantile, ECDF plots and box plots for continuous variables are provided in *Figs S2 and S3*.

Intraoperative hepatic artery modifications and technical adaptations

Data on intraoperative technical hepatic artery problems were not available in 51 (5.8 per cent) patients. Intraoperative hepatic artery interventions were necessary in 69 of 825 (8.4 per cent) recipients. Frequencies of different interventions are summarized in *Table 2*, results of logistic regression are summarized in *Table 3*. In the propensity score-matched sample, TACE was not significantly associated with increased incidence of intraoperative hepatic artery interventions (OR 0.94, 95 per cent c.i. 0.49 to 1.83, $P = 0.870$, TACE: 252 patients, no TACE: 235 patients). This effect remained similar for patients who underwent two or more TACE treatments (OR 1.14, 95 per cent c.i. 0.41 to 3.15, $P = 0.796$, ≧ 2 TACE tratments: 107 patients, no TACE: 235). Overall, median arterialization time was similar in TACE and no TACE patients (TACE: 31 (i.q.r. 20–44) minutes *versus* no TACE: 30 (i.q.r. 22–41) minutes, $P = 0.498$).

Postoperative hepatic artery complications

Fifty-eight (6.6 per cent) of 876 patients experienced postoperative hepatic artery complications. Frequencies of different types

Table 1 Patient and donor characteristics

	Unmatched sample			Propensity score-matched sample		
	No TACE ($n = 451$)	TACE ($n = 425$)	P	No TACE ($n = 253$)	TACE ($n = 253$)	P
Matched variables						
Recipient						
Centre			<0.001			0.464
QEH Birmingham	181 (40.1)	73 (17.2)		78 (30.8)	70 (27.7)	
UCL Brussels	26 (5.8)	131 (30.8)		26 (10.3)	28 (11.1)	
KU Leuven	102 (22.6)	68 (16)		57 (22.5)	61 (24.1)	
SU Rome	43 (9.5)	44 (10.4)		33 (13)	35 (13.8)	
PTV Rome	22 (4.9)	65 (15.3)		22 (8.7)	25 (9.9)	
EMC Rotterdam	77 (17.1)	44 (10.4)		37 (14.6)	34 (13.4)	
Sex (female)	89 (19.7)	72 (16.9)	0.286	47 (18.6)	51 (20.2)	0.720
Age (years)*	59.13(8.35)	60.16(7.28)	0.152	60.06(8.13)	59.57(7.56)	0.278
BMI (kg/m^2)*	27.84(4.61)	27.34(4.65)	0.117	27.56(4.44)	27.33(4.7)	0.560
MELD at liver transplantation*	12.82(5.5)	11.29(4.68)	<0.001	11.86(4.98)	12.07(5.16)	0.715
Insulin-dependent diabetes	89 (19.8)	91 (21.7)	0.491	50 (19.9)	56 (22.5)	0.428
Antihypertensive treatment	153 (34.1)	166 (39.7)	0.085	88 (35.1)	90 (36.3)	0.784
Anatomical hepatic artery variation	61 (13.6)	52 (12.6)	0.637	35 (14)	34 (13.9)	0.999
Radiofrequency ablation	178 (39.5)	91 (21.4)	<0.001	74 (29.2)	79 (31.2)	0.688
Liver resection	31 (6.9)	38 (9.0)	0.252	21 (8.3)	18 (7.1)	0.742
Donor						
Age (years)*	52.04(16.89)	53.49(16.37)	0.202	53.36(16.74)	52.57(16.52)	0.815
Sex (female)	176 (39.1)	189 (44.7)	0.095	107 (42.5)	109 (43.3)	0.999
BMI (kg/m^2)*	25.67(4.12)	25.87(4.18)	0.385	25.58(4.13)	25.77(4.17)	0.506
DCD	122 (27.1)	67 (15.8)	<0.001	53 (20.9)	52 (20.6)	0.999
Split graft	12 (2.7)	5 (1.2)	0.111	5 (2)	5 (2)	0.999
Back-table hepatic artery reconstruction	78 (17.8)	70 (17.5)	0.907	42 (17.4)	46 (18.8)	0.999
Anatomical hepatic artery variation	105 (23.8)	91 (21.8)	0.489	55 (22.4)	54 (21.9)	0.999
Warm ischaemia time (min)*	41.42(12.74)	43.67(13.3)	0.006	43.08(13.29)	42.99(12.29)	0.979
Cold ischaemia time (min)*	434.18(146.17)	461.49(153.5)	0.025	447.17(153.04)	434.64(145.34)	0.162
Donor risk index*	2.11(0.58)	2.12(0.56)	0.443	2.09(0.53)	2.08(0.57)	0.794
Unmatched variables						
AFP (μg/l)*†	130.14(829.04)	170.02(1110.24)	0.756	129.57(944.69)	238.27(1418.07)	0.090
Number of tumours*†	1.5(0.84)	1.77(1.28)	0.005	1.54(0.92)	1.85(1.36)	0.272
Cumulative tumour size (cm)*†	3.27(2.58)	4.01(2.47)	<0.001	3.2 (1.73)	4.34(2.59)	0.489
≥2 TACE	–	215 (50.5)	–	–	107 (42)	–
≥3 TACE	–	91 (21.4)	–	–	38 (15)	–
Drug-eluting bead TACE	–	234 (55.1)	–	–	135 (53.4)	–
Time between TACE and liver transplantation (months)*	–	6.71(10.09)	–	–	7.28(9.41)	–

Values in parentheses are percentages unless indicated otherwise, categorical variables were statistically compared with the $\chi 2$ test and continuous variables were compared either with the Student t test or Mann–Whitney U test as appropriate. In the matched sample, categorical variables were compared with the McNemar test or McNemar–Bowker test, continuous variables were assessed with the Wilcoxon signed rank test; *values are mean(s.d.). †locoregional therapy. QEH, Queen Elizabeth Hospital Birmingham; KU, Katholieke Universiteit Leuven; UCL, Cliniques Universitaires Saint-Luc Brussels; EMC, Erasmus University Medical Centre Rotterdam; PTV, Policlinico Tor Vergata Rome; SU, Sapienza University Rome; TACE, transarterial chemoembolization; MELD, model for end-stage liver disease; AFP, alpha-fetoprotein; DCD, donation after cardiac death.

Table 2 Frequency of intraoperative arterial interventions and postoperative complications

	Unmatched sample		Propensity score-matched sample	
	TACE	No TACE	TACE	No TACE
Intraoperative hepatic artery intervention	$n = 422$	$n = 403$	$n = 252$	$n = 235$
	35 (8.3)	34 (8.4)	19 (7.5)	18 (7.7)
Redo arterial anastomosis	15 (3.6)	16 (4.0)	8 (3.2)	7 (3.0)
Alternative arterial reconstruction	13 (3.1)	10 (2.5)	6 (2.4)	7 (3.0)
Arterial conduit to aorta	10 (2.4)	10 (2.5)	6 (2.4)	5 (2.1)
Arterial thrombectomy	4 (0.9)	5 (1.2)	3 (1.2)	2 (0.9)
Other	1 (0.2)	0	0	0
Hepatic artery complication after liver transplantation	$n = 425$	$n = 451$	$n = 253$	$n = 253$
	27 (6.4)	31 (6.9)	19 (7.5)	11 (4.3)
Thrombosis	15 (3.5)	14 (3.1)	11 (4.3)	3 (1.2)
Stenosis	8 (1.9)	12 (2.7)	5 (2.0)	5 (2)
(Pseudo-)aneurysm	3 (0.7)	2 (0.4)	2 (0.8)	1 (0.4)
Other*	1 (0.2)	3 (0.7)	1 (0.4)	2 (0.8)

Values in parentheses are percentages. *Includes hepatic artery dissection ($n = 1$), splenic steel syndrome ($n = 2$), and stenosis of the left hepatic artery only ($n = 1$). Data on intraoperative technical hepatic artery problems were not available in 51 (5.8%) patients. TACE, transarterial chemoembolization.

Table 3 Effect of TACE on occurrence of intraoperative hepatic artery modifications and technical adaptations

	Odds ratio (95% c.i.)	*P*	*n*	*n* (per cent) with event
Unmatched sample				
TACE *versus* no TACE				
No TACE	(reference)	–	403	34 (8.4)
TACE	0.98 (0.60, 1.61)	0.941	422	35 (8.3)
Effect of multiple TACE treatments				
No TACE	(reference)	–	403	34 (8.4)
Single TACE	1.03 (0.57, 1.87)	0.927	208	18 (8.7)
≥2 TACE	0.94 (0.51, 1.72)	0.832	214	17 (7.9)
Propensity score-matched sample				
TACE *versus* no TACE				
No TACE	(reference)	–	235	18 (7.7)
TACE	0.94 (0.49, 1.83)	0.870	252	19 (7.5)
Effect of multiple TACE treatments				
No TACE	(reference)	–	235	18 (7.7)
Single TACE	0.81 (0.34, 1.97)	0.655	145	11 (7.6)
≥ 2 TACE	1.14 (0.41, 3.15)	0.796	107	8 (7.5)

Results of (conditional) logistic regression with stratification for matched pairs. Data on intraoperative technical hepatic artery problems were not available in 51 (5.8%) patients. *P* for Wald statistic in logistic regression models. TACE, transarterial chemoembolization.

Table 4 Effect of TACE on postoperative arterial complications

	Odds ratio (95% c.i.)	*P*	*n*	*n* (per cent) with event
Unmatched sample				
TACE *versus* no TACE				
No TACE	(reference)	–	451	31 (6.9)
TACE	0.92 (0.54–1.57)	0.760	425	27 (6.4)
Effect of multiple TACE treatments				
No TACE	(reference)	–	451	31 (6.9)
Single TACE	0.68 (0.33–1.41)	0.297	210	10 (4.8)
v≥2 TACE	1.16 (0.63–2.15)	0.630	215	17 (7.9)
Hepatic artery thrombosis				
TACE *versus* no TACE				
No TACE	(reference)	–	451	14 (3.1)
TACE	1.14 (0.54–2.40)	0.725	425	15 (3.5)
Propensity score-matched sample				
TACE *versus* no TACE				
No TACE	(reference)	–	253	11 (4.3)
TACE	1.73 (0.82–3.63)	0.149	253	19 (7.5)
Effect of multiple TACE treatments				
No TACE	(reference)	–	253	11 (4.3)
Single TACE	1.50 (0.53–4.21)	0.442	146	9 (6.2)
≥2 TACE	2.0 (0.68–5.85)	0.206	107	10 (9.3)
Hepatic artery thrombosis				
TACE *versus* no TACE				
No TACE	(reference)	–	253	3 (1.2)
TACE	3.67 (1.02–13.14)	0.046	253	11 (4.3)

Results of (conditional) logistic regression with stratification for matched pairs. *P* for Wald statistic in logistic regression models. TACE, transarterial chemoembolization.

of hepatic artery complications are summarized in *Table 2*, results of logistic regression are summarized in *Table 4*. In the propensity score-matched samples, TACE was not associated with increased incidence of hepatic artery complications (OR 1.73, 95 per cent c.i. 0.82 to 3.63, $P = 0.149$, TACE: 253 patients, no TACE: 253 patients). Increasing number of TACE treatments did show a potential dose effect in the propensity score-matched sample, with increasing incidence rates of hepatic artery complications, however without reaching significance (2 or more TACE, OR 2.0, 95 per cent c.i. 0.68 to 5.85, $P = 0.206$, ≧ 2 TACE tratments: 107 patients, no TACE: 253). Although TACE was not associated with an increased incidence of hepatic artery thrombosis in the unmatched sample, hepatic artery thrombosis occurred in 1.2 per cent of no TACE controls *versus* 4.3 per cent in TACE patients within the propensity score-matched sample, and this difference was statistically significant (OR 3.67, 95 per cent c.i. 1.02 to 13.14, $P = 0.046$, TACE: 253 patients, no TACE: 253 patients).

Results of univariable stratified analysis

Detailed results of univariable stratified analysis on unmatched data are presented in *Tables S3 and S4*. In summary, repeated TACE treatments, drug-eluting bead TACE and TACE combined with radiofrequency treatment showed no significant association with either intraoperative hepatic artery interventions nor with postoperative hepatic artery complications.

Timing of hepatic artery complications

Timing of hepatic artery complications are summarized in *Fig. 1*. Median time between transplantation and hepatic artery complications was not significantly different between TACE and no TACE patients (TACE: 15 (i.q.r. 1–75) days *versus* no TACE: 50 (i.q.r. 3.5–148) days, $P = 0.231$). Most patients (72 per cent, 54 patients) that developed complications did so within the first 3 months after transplantation.

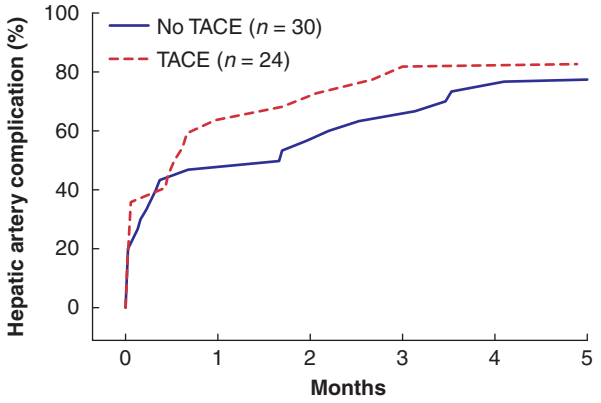

Fig. 1 Incidence of hepatic artery complications through time

Includes only patients with hepatic artery complications. Time-to-event data were missing in four patients. TACE, transarterial chemoembolization.

Outcome for patients with intraoperative arterial interventions and postoperative arterial complications

The incidence of hepatic artery complications was significantly increased after prior intraoperative hepatic artery interventions (12 of 69 patients (17.4 per cent) *versus* 43 of 756 patients (5.7 per cent), $P = 0.001$) (*Table* S5). Data on management of hepatic artery complications were available in 49 patients: 13 (27 per cent) were relisted, 12 (25 per cent) needed a relaparotomy, 11 (23 per cent) had interventional radiology, eight (17 per cent) were treated conservatively (for example, anticoagulation or fibrinolysis) and four patients (8 per cent) received palliative supportive care. Graft survival in TACE and no TACE patients and after intraoperative hepatic artery complications is depicted in *Fig.* 2.

Discussion

In the present study, TACE treatment of HCC before liver transplantation was not associated with an increased incidence of intraoperative technical hepatic artery problems or a prolonged arterialization time. The present study did not find a substantial increase in the incidence of overall hepatic artery complications after pretransplant TACE. Pretransplant TACE may be associated with hepatic artery thrombosis when compared with patients with a similar risk profile.

Incidences of technical hepatic artery problems and postoperative complications were in line with previous literature. The incidence of hepatic artery complications after adult liver transplantation ranges between 5 and 10 per cent; the incidence of hepatic artery thrombosis has been estimated to be 2.9 per cent[1,21,25]. The incidence of intraoperative hepatic artery interventions and technical adaptations is infrequently reported, and ranges between 5 and 15 per cent[18,26,27].

Few studies have explored the relationship between pretransplant TACE and hepatic artery complications[17–19,26–35]. A recent meta-analysis reported an association between TACE before liver transplantation and an overall increased risk for hepatic artery complications (OR 1.57, 95 per cent c.i. 1.09 to 2.26; $P = 0.02$)[21]. These results were not reproducible based on current data. These differences may be explained by multiple reasons. The meta-analysis included studies covering, in part, an earlier time period (publication years: 1997–2015). Increased experience in interventional radiology and the increased use of (super)selective and drug-eluting bead TACE during the past decade may explain a reduced incidence of hepatic artery complications related to TACE. Previous studies often included non-HCC patients in the reference group; these patients are derived from a different 'source population' and may have a different risk profile. Additionally, previous single-centre cohort studies or case-control studies rarely controlled for confounding factors. However, the present analysis was not powered to study postoperative hepatic artery

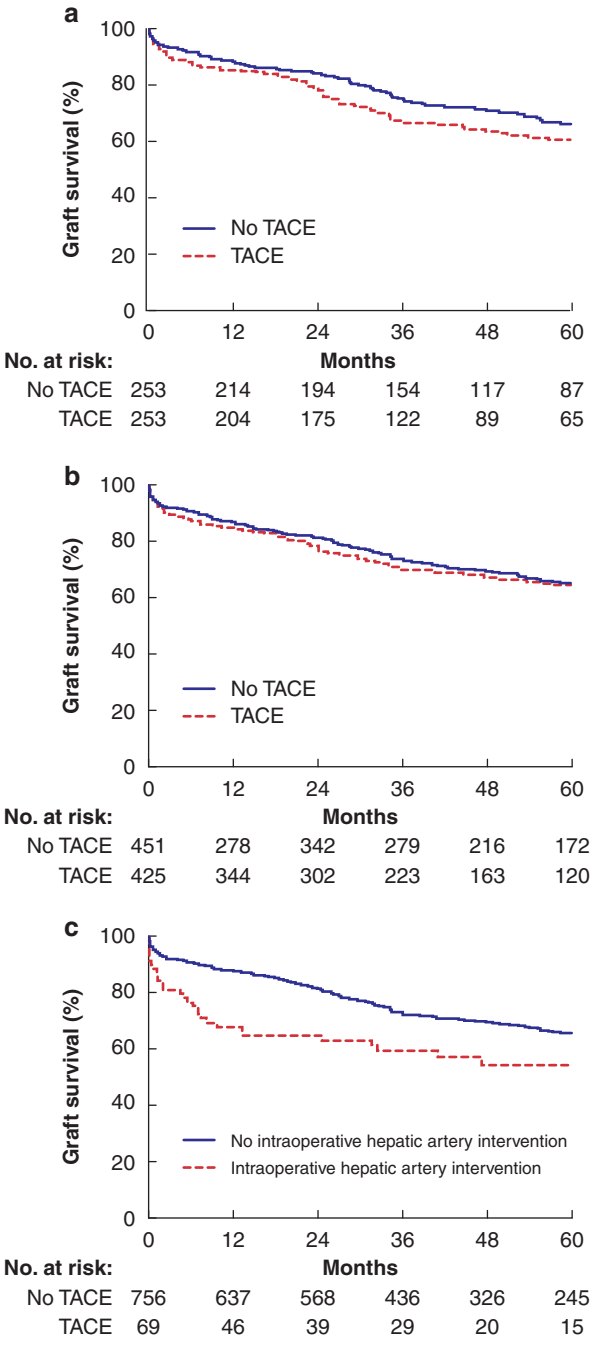

Fig. 2 Kaplan–Meier curves of 5-year graft survival

a Graft survival in TACE *versus* no TACE patients in the propensity score-matched sample. $P = 0.212$ (log rank test). **b** Graft survival in TACE *versus* no TACE patients in the unmatched sample. $P = 0.720$ (log rank test). **c** Graft survival in patients with intraoperative hepatic artery interventions *versus* patients with no intraoperative hepatic artery interventions. $P < 0.001$ (Gehan Breslow Wilcoxon test). TACE, transarterial chemoembolization.

complications. When assessing this outcome in a larger sample, significant small differences could potentially become apparent.

A recent study (not included in the meta-analysis) using UK registry data did not find an increased incidence of hepatic artery thrombosis after liver transplantation in patients pretreated with TACE[36]. However, this comparison was not adjusted for confounders. The current study suggests TACE may be associated with hepatic artery thrombosis when compared with patients with a similar risk profile (propensity score-matched analysis). However, this was not a predefined outcome of the study and clinical relevance of the finding is uncertain due to below-average incidence of hepatic artery thrombosis in the control group rather than a marked increased incidence in patients receiving TACE. The authors therefore reviewed this finding with caution, as the overall incidence of hepatic artery thrombosis in TACE patients remained low (3.5 per cent).

In the overall population, the incidence of hepatic artery complications after TACE appears comparable to that in patients who did not undergo TACE. The presumed aetiology of TACE-induced hepatic artery complications is that intra-arterial catheterization and infusion of toxic drugs as well as embolic agents of different types will undoubtedly lead to endothelial damage and (peri-) arterial inflammation explaining the thrombogenicity of this radiological intervention[17–19]. These modifications to the arterial wall could theoretically result in procedural problems as well as in post-transplant arterial complications and thrombosis. When technical difficulties are encountered, these may be resolved by increasing surgical experience leading to safe alternatives or to salvage procedures such as thrombectomy or redo anastomosis based on intraoperative flow measurements. Extensive freeing of the artery from the frequently present periarterial fibrosis or changing the anastomotic site towards the coeliac trunk or splenic artery are examples of such flexibility. One could expect a delay in allograft arterialization as well as more anastomotic problems in TACE patients. However, no evidence of the latter was found in the present study. Therefore, the hypothetical 'technical risk' of the TACE procedure would probably be very small and not outweigh the drop-out risk on the waiting list due to tumour progression[37–40].

It has been postulated that the arterial endothelium may remain thrombogenic up to 3 months after TACE, so one could argue to postpone liver transplantation for at least 3 months after the last TACE procedure[41,42]. However, the data presented here did not show that patients transplanted within this time frame had an increased risk of intraoperative technical hepatic artery problems or hepatic artery complications.

Graft survival after hepatic artery complications is significantly reduced[1,25]. Based on current data, patients in whom intraoperative hepatic artery interventions were necessary had significantly impaired graft survival. Patients with intraoperative hepatic artery interventions had a 3.7-fold increased risk for hepatic artery complications and thrombosis. In such patients systematic and repeated doppler ultrasonography to assess arterial patency is warranted and anticoagulation prophylaxis should be considered.

This study has several limitations: the retrospective study design limits the potential to assess causality. Due to the relatively low incidence of studied endpoints, composite endpoints were used. However, not all events included in these composite endpoints may have a similar pathogenesis, therefore risks associated with a specific type of event could have been underestimated. The multicentric design of the study probably caused bias related to centre-specific approaches and a different case mix. However, the propensity score-matched analysis resulted in a sufficient balance of the TACE and no TACE patients across the different centres, accounting in part for unknown centre-specific factors. Missing data were most likely to be unrelated to the studied endpoints or interventions. Therefore, missing observations were considered missing at random and multiple imputations allowed for inclusion of all patients, including those with incidental missing data. The present study was not powered to study postoperative hepatic artery complications, so these results should be interpreted with caution. However, due to the low incidence of hepatic artery complications, a small increased risk associated with TACE, if present, would not be of major clinical concern in absolute numbers. Finally, the incidence of biliary tract complications was not considered in this study, as previous studies did not report a significant association between pretransplant TACE and postoperative biliary tract complications[21].

Disclosure. The authors declare no conflict of interest related to the submitted work.

Supplementary material

Supplementary material is available at *BJS* online.

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