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Original Article

Role of neoadjuvant chemoradiotherapy in liver transplantation for unresectable perihilar cholangiocarcinoma: multicentre, retrospective cohort study

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Abstract

Background: The Mayo protocol for liver transplantation in patients with unresectable perihilar cholangiocarcinoma is based on strict selection and neoadjuvant chemoradiotherapy. The role of neoadjuvant chemoradiotherapy in this scenario remains unclear. The aim of this study was to compare outcomes after transplantation for perihilar cholangiocarcinoma using strict selection criteria, either with or without neoadjuvant chemoradiotherapy.

Methods: This was an international, multicentre, retrospective cohort study of patients who underwent transplantation between 2011 and 2020 for unresectable perihilar cholangiocarcinoma using the Mayo selection criteria and receiving neoadjuvant chemoradiotherapy or not receiving neoadjuvant chemoradiotherapy. Endpoints were post-transplant survival, post-transplant morbidity rate, and time to recurrence.

Results: Of 49 patients who underwent liver transplantation for perihilar cholangiocarcinoma, 27 received neoadjuvant chemoradiotherapy and 22 did not. Overall 1-, 3-, and 5-year post-transplantation survival rates were 65 per cent, 51 per cent and 41 per cent respectively in the group receiving neoadjuvant chemoradiotherapy and 91 per cent, 68 per cent and 53 per cent respectively in the group not receiving neoadjuvant chemoradiotherapy (1-year hazards ratio (HR) 4.55 (95 per cent c.i. 0.98 to 21.13), $P = 0.053$; 3-year HR 2.07 (95 per cent c.i. 0.78 to 5.54), $P = 0.146$; 5-year HR 1.71 (95 per cent c.i. 0.71 to 4.09), $P = 0.229$). Hepatic vascular complications were more frequent in the group receiving neoadjuvant chemoradiotherapy compared with the group not receiving neoadjuvant chemoradiotherapy (nine of 27 *versus* two of 22, $P = 0.045$). In multivariable analysis, tumour recurrence occurred less frequently in the group receiving neoadjuvant chemoradiotherapy (HR 0.30 (95 per cent c.i. 0.09 to 0.97), $P = 0.044$).

Conclusion: In selected patients undergoing liver transplantation for perihilar cholangiocarcinoma, neoadjuvant chemoradiotherapy resulted in a lower risk of tumour recurrence, but was associated with a higher rate of early hepatic vascular complications. Adjustments in neoadjuvant chemoradiotherapy reducing the risk of hepatic vascular complications, such as omitting radiotherapy, may further improve the outcome in patients undergoing liver transplantation for perihilar cholangiocarcinoma.

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Introduction

Cholangiocarcinoma (CCA) is a heterogeneous malignancy that can arise anywhere in the biliary tree. On the basis of the anatomical site of origin, CCA can be divided into intrahepatic CCA, perihilar CCA (pCCA), or distal CCA. pCCA is the most common type, accounting for 50–67 per cent of all CCAs[1,2], and is localized between the second-order bile ducts and the insertion of the cystic duct into the common bile duct[3,4]. Of all patients diagnosed with pCCA, less than 35 per cent are candidates for curative resection at the time of diagnosis[5]. Overall 5-year survival rates of 35–53 per cent have been reported in patients after curative resection, limited mainly due to locoregional recurrence and distant metastasis[5–9].

Since the late 1990s, liver transplantation (LT) has been explored as a treatment strategy for pCCA, with the aim of achieving negative resection margins. Although the initial results in unselected patients were poor[10], pioneering work at the University of Nebraska and the Mayo Clinic led to substantial improvement in outcomes. The 'Mayo protocol' is based on a strict patient selection procedure (based on patient history and tumour characteristics), followed by a neoadjuvant therapy (NAT) regimen consisting of external beam radiation therapy with concomitant 5-fluorouracil followed by bile duct brachytherapy and subsequent capecitabine maintenance treatment until the time of LT. Data from 12 large-volume centres in the USA have shown promising results with this protocol, resulting in 5-year intention-to-treat survival of up to 68 per cent and a 5-year recurrence-free survival rate of 65 per cent, which increases to 72 per cent if criteria are strictly followed[11,12]. However, it remains unclear whether these favourable results are attributable to the very strict patient selection or NAT, as similar survival outcomes have been observed among centres using different NAT protocols[11]. NAT is supposed to increase R0 margin rates and recurrence-free survival by reducing tumour volume and potential micrometastatic disease after surgery[13–15]. However, NAT has also been associated with a high rate of vascular complications after LT[11,16]. Moreover, in a retrospective, multicentre study, favourable survival outcomes were reported in transplanted patients who met the strict selection criteria, but who did not undergo NAT[17].

Therefore, the aim of the current study was to examine the role of NAT in patients undergoing LT for unresectable pCCA. To the best of the authors' knowledge, this is the first international outcome comparison in strictly selected patients undergoing LT for unresectable pCCA, either with or without NAT. In the Netherlands, a national protocol for LT in patients with unresectable pCCA was implemented in 2011. According to this protocol, patients are selected based on the strict Mayo Clinic criteria, but do not undergo NAT[18]. At the same time, in France, a similar protocol is used, which does include NAT before LT. Comparison of outcomes in the two cohorts allowed the assessment of the role of NAT in selected patients undergoing LT for unresectable pCCA.

Methods

Study design

This international, multicentre, retrospective cohort study included patients with unresectable pCCA who underwent LT under a centre-approved implemented clinical management protocol. A Dutch cohort of all consecutive patients who underwent LT for unresectable pCCA between April 2011 and July 2020 and who were selected based on the strict Mayo Clinic selection criteria, but did not receive NAT (No-NAT group), was retrospectively compared with a French cohort of consecutive patients who underwent transplantation for unresectable pCCA according to the Mayo Clinic selection criteria during the same time interval and received NAT (NAT group)[19].

In the Netherlands, LTs are performed in Rotterdam, Leiden, and Groningen. The Dutch cohort consists of all patients who underwent transplantation for unresectable pCCA from these centres. For the French cohort, tertiary high-volume (greater than 70 LTs/year) centres were invited to participate, of which five had patient data available and agreed to participate: Toulouse, Lyon, Bordeaux, Lille, and Rennes. The study adhered to the Declaration of Helsinki and is in concordance with the principles of the Declaration of Istanbul on Organ Trafficking and Transplant Tourism. The study was approved by and performed under the auspices of the Dutch national platform Liver Transplantation, part of the Dutch Transplant Society. Dutch data were extracted from the national registry of the protocol LT for pCCA and the French data were extracted from the ABM (Agence de la biomédicine) database. According to the Central Committee on Research Involving Human Subjects, this type of study using anonymized data does not require approval from an ethics committee. This study adhered to STROBE guidelines[20].

Selection criteria

Unresectability was defined as the impossibility of performing extrahepatic bile duct resection in combination with a partial hepatectomy, due to the poor quality of the remaining liver secondary to the presence of underlying chronic liver diseases, such as primary sclerosing cholangitis (PSC), insufficient future liver remnant volume, vascular involvement, and/or extended biliary involvement. The (presumed) diagnosis of pCCA was based on histological proof (cytology or endoscopic biopsy positive for, or suspicious of, malignancy) and on imaging (the presence of a suspicious mass lesion or stricture)[11,18].

In the No-NAT group, if all selection criteria, including a negative staging laparotomy, were met (*Table S1*), patients were placed on the Dutch transplant waiting list for LT with a non-standard exception (NSE) status equivalent to a model for end-stage liver disease (MELD) score of 38 points. In the NAT group, patients followed the usual 'Mayo protocol', including strict selection (*Table S1*), combined with NAT associating external radiotherapy and systemic chemotherapy (*Table S2*), and were placed on the French transplant waiting list with 800 points (equivalent to a MELD score of 38).

Endpoints and definitions

The main endpoint of this study was overall post-transplant survival (defined as the time between the date of LT and the date of death or last follow-up, with death as event). The secondary endpoints were the post-transplant morbidity rate, including vascular complications, and time to recurrence (defined as the time between the date of LT and the date of recurrence, death (without recurrence and due to complications), or last follow-up, with recurrence as event). As no dropout data for the NAT group were available, an additional survival analysis from the time of referral to death or last follow-up was performed.

The following data were prospectively collected in institutional databases: recipient characteristics (age, sex, BMI, and underlying liver disease), tumour characteristics (classification according to Bismuth–Corlette[21], cancer antigen (CA) 19–9 levels, imaging data,

and final pathological examination of the resected liver), donor characteristics (age, sex, BMI, type of donor, and cold ischaemia time), post-transplant complications occurring within 3 months graded according to the Clavien–Dindo grade[22], hospital length of stay, last follow-up date, and status at last follow-up (death, recurrence, or alive without recurrence).

Transplantation procedure and perioperative management

All LTs were performed using a deceased donor liver graft, either from a donation after circulatory death (DCD) or donation after brain death (DBD) donor. The procedure started with an explorative laparotomy with re-inspection of the abdominal cavity. Suspect nodes were biopsied and sent for frozen-section analysis. If frozen-section analysis identified metastatic tumour cells, the procedure was aborted. The distal bile duct was cut at the level of the pancreatic head and the resection margin was sent for frozen-section analysis. If positive, pancreaticoduodenectomy was additionally performed. After transection of the distal bile duct, the liver was resected *en bloc* with regional hilar lymph nodes, the extrahepatic bile duct, the portal vein, and the proper hepatic artery.

After hepatectomy, graft implantation started with the caval anastomosis using a piggyback implantation technique. The graft was then vascularized via reconstruction of the portal vein prior to the arterial anastomosis and the subsequent biliary anastomosis (hepaticojejunostomy).

After the procedure, patients were transferred to the intensive care unit (ICU) until graft function was satisfactory and the recipient stable. Immunosuppressive therapy was similar in all centres and based on initial calcineurin inhibitor (usually tacrolimus) therapy, combined with mycophenolate mofetil and a rapid taper of corticosteroids. Mechanistic target of rapamycin (mTOR) inhibitors were introduced in most patients not earlier than 3 months after LT. Hepatic Doppler-ultrasonography was performed routinely on postoperative days 1 and 7, with contrast-enhanced CT performed upon clinical necessity.

After discharge, patients were followed according to centre policy. Systematic cross-sectional imaging was performed at least every 6 months during the first year, and yearly thereafter. No adjuvant treatment was administered.

Statistical analysis

Continuous variables are presented as median and interquartile range (i.q.r.) and groups were compared using the Mann–Whitney *U* test. Categorical data are presented as numbers and compared using the chi-squared test or Fisher's exact test. Logistic regression served to test the association of variables with binary outcomes. Survival plots are presented using Kaplan–Meier methods and differences in survival between both groups were analysed using Cox regression analysis with hazards ratios (HRs) and 95 per cent c.i. A multivariable Cox regression analysis with backward elimination was performed to determine prognostic factors of recurrence and calculate the adjusted HR. Patients with no malignancy in the resected liver and no malignancy in pre-transplant histological exams were excluded from recurrence analyses. Included variables were cohort type (NAT or No-NAT), those with *P* values <0.20 in univariable analysis, and those identified as significant baseline differences between both groups to correct for these differences. For all analysis, two-sided *P* values <0.05 were considered statistically significant. All analyses were performed with the use of SPSS software, version 23.0 (IBM, Armonk, NY, USA).

Results

Patient, donor, and pathological characteristics

Out of 30 patients in the No-NAT group who fulfilled the Mayo selection criteria, eight patients did dropout prior to LT due to positive staging during laparotomy or laparoscopy (four patients) or due to clinical deterioration (four patients). In total, 22 patients underwent LT for unresectable pCCA without NAT and 27 patients underwent LT after NAT. None of the patients had positive frozen-section analysis for metastasis during LT. NAT consisted of external beam radiation therapy (range 45–55 Gy) and systemic chemotherapy (details provided in *Table S2*). In total, there were 34 men and 15 women with a median age of 54 (i.q.r. 46–61) years. Indication for LT was based on unresectability due to vascular involvement (21 patients), underlying liver disease (19 patients), extended biliary involvement (five patients), or insufficient future liver remnant volume (four patients).

Baseline recipient and donor characteristics for the two groups are presented in *Table 1*. There were no major baseline differences, except for a lower percentage of patients with underlying PSC in the NAT group compared with the No-NAT group (three of 27 *versus* 11 of 22, $P < 0.01$) and no DCD donors in the NAT group (zero of 27 *versus* nine of 22, $P < 0.01$). The median time between the date of referral to a tertiary centre and the date of LT was 8.3 months for the NAT group *versus* 3.4 months for the No-NAT group ($P < 0.01$).

Pathological examination confirmed the presence of pCCA in 46 out of 49 patients. The tumour characteristics of these patients are summarized in *Table 2*. In three patients (all in the No-NAT group) no malignancy was found in the resected liver or in pre-transplant histological exams. These patients underwent transplantation based on highly suspicious imaging findings, combined with brush cytology showing severe atypical cells, suspicious of malignancy. Complete tumoral necrosis was found in two patients in the NAT group, both of which had pre-transplant evidence of malignancy based on cytology and/or histology.

Postoperative course

The post-transplant outcome data within 3 months after LT are presented in *Table 3*. There were no significant differences in hospital length of stay (a median of 15 (i.q.r. 10–22) days for the NAT group *versus* a median of 13 (i.q.r. 10–16) days for the No-NAT group, $P = 0.600$) or the overall rate of major complications (Clavien–Dindo grade greater than or equal to IIIA).

Overall hepatic vascular complications were significantly more frequent in patients who received NAT compared with those who did not receive NAT (nine of 27 *versus* two of 22, $P = 0.045$). This difference was largely explained by the higher rate of hepatic artery complications in the NAT group (*Table 3*). Re-transplantation was required in two patients in the NAT group *versus* one in the No-NAT group. The indications for re-transplantation were a portal vein thrombosis with liver failure, arterial thrombosis and portal vein stenosis with sepsis resulting in liver necrosis, and severe sepsis due to biliary complications.

Tumour recurrence

During follow-up, recurrences were found in eight of 27 patients in the NAT group and in 10 of 19 patients in the No-NAT group ($P = 0.116$). Recurrence occurred locally (around the liver hilum or in the liver parenchyma) in seven patients in the NAT group and in six patients in the No-NAT group ($P = 0.746$). Distant recurrence (peritoneal, bone, or pulmonary) was observed in one patient in

Table 1 Recipient and donor characteristics of transplanted patients with unresectable perihilar cholangiocarcinoma

	Total ($n = 49$)	NAT group ($n = 27$)	No-NAT group ($n = 22$)	P
Recipient age (years), median (i.q.r.)	54 (46–61)	53 (48–60)	56 (39–62)	0.896
Recipient sex ratio (M : F)	34 (69) : 15 (31)	20 (74) : 7 (26)	14 (64) : 8 (36)	0.538
Recipient BMI (kg/m^2), median (i.q.r.)	24 (21–25)	23 (20–26)	24 (20–25)	0.546
Underlying PSC				0.004
No	35 (71)	24 (89)	11 (50)	
Yes	14 (29)	3 (11)	11 (50)	
CA 19–9 level (kU/L), median (i.q.r.)	143 (12–890)	159 (44–1821)	94 (8–775)	0.372
Bismuth–Corlette classification				0.548
3A	7 (14)	4 (15)	3 (14)	
3B	8 (16)	3 (11)	5 (23)	
4	34 (69)	20 (74)	14 (64)	
Donor age (years), median (i.q.r.)	54 (48–67)	54 (45–72)	55 (48–62)	0.960
Donor sex ratio (M : F)	23 (47) : 26 (53)	13 (48) : 14 (52)	10 (46) : 12 (55)	0.851
Donor BMI (kg/m^2), median (i.q.r.)	25 (21–27)	25 (21–27)	24 (22–26)	0.658
Donor type				<0.001
DBD	34 (69)	27 (100)	13 (59)	
DCD	15 (31)	0 (0)	9 (41)	
Cold ischaemia time (min), median (i.q.r.)	394 (272–480)	423 (364–538)	359 (318–441)	0.052
Pancreaticoduodenectomy	4 (8)	1 (4)	3 (14)	0.314

Values are *n* (%) unless otherwise indicated. NAT, neoadjuvant therapy; i.q.r., interquartile range; PSC, primary sclerosing cholangitis; CA, cancer antigen; DBD, donation after brain death; DCD, donation after circulatory death.

Table 2 Post-transplant pathology characteristics of transplanted patients with proven perihilar cholangiocarcinoma

	Total ($n = 46$)	NAT group ($n = 27$)	No-NAT group ($n = 19$)	P
Tumour diameter (mm), median (i.q.r.)	25.0 (15.0–40.0)	24.5 (15.6–48.8)	25.0 (14.0–34.0)	0.586
R1 resection margin*	3 (7)	1 (4)	2 (11)	0.561
Positive lymph nodes	12 (26)	5 (19)	7 (37)	0.190
Vascular invasion	14 (30)	6 (22)	8 (42)	0.149
Perineural invasion	33 (72)	22 (82)	11 (58)	0.080

Values are *n* (%) unless otherwise indicated. *Wall of the portal vein (1 patient), wall of the bile duct (1 patient), and surrounding soft tissue (1 patient). NAT, neoadjuvant therapy.

Table 3 Major post-transplant complications within 3 months of transplanted patients with unresectable perihilar cholangiocarcinoma

	Total ($n = 49$)	NAT group ($n = 27$)	No-NAT group ($n = 22$)	OR	95% c.i.	P
Overall major complications	20 (41)	11 (41)	9 (41)	0.99	0.32,3.12	0.990
Vascular complications	14 (29)	11 (41)	3 (14)	4.35	1.03,18.37	0.045
Hepatic artery complications	11 (22)	9 (33)	2 (9)	5.00	0.95,26.28	0.057
Aneurysm	3 (6)	3 (11)	0 (0)			
Bleeding	4 (8)	2 (7)	2 (9)			
Stenosis	1 (2)	1 (4)	0 (0)			
Bleeding and stenosis	2 (4)	2 (7)	0 (0)			
Thrombosis	1 (2)	1 (4)	0 (0)			
Portal vein complications	7 (14)	5 (19)	2 (9)	2.27	0.40,13.05	0.357
Thrombosis	4 (8)	2 (7)	2 (9)			
Stenosis	3 (6)	3 (11)	0 (0)			
Biliary complications	15 (31)	6 (22)	8 (41)	0.50	0.14,1.76	0.279
Stenosis	4 (8)	0 (0)	4 (18)			
Leakage	6 (12)	4 (15)	2 (9)			
Leakage and stenosis	2 (4)	1 (4)	1 (5)			
Necrosis and stenosis	1 (2)	1 (4)	0 (0)			
Cholangitis	1 (2)	0 (0)	1 (5)			
Re-transplantation	3 (6)	2 (7)	1 (5)	1.68	0.14,19.85	0.681
Death within 1 year due to vascular complications*	6 (12)	5 (19)	1 (5)	4.77	0.51,44.33	0.169

Values are *n* (%). Only major (Clavien–Dindo grade greater than or equal to IIIA) post-transplant complications are shown. *Cause of death: NAT group: hepatic artery hemorrhage (2 patients), hepatic artery aneurysm (2 patients), and hepatic artery stenosis (1 patient); No-NAT group: portal vein thrombosis (1 patient). NAT, neoadjuvant therapy; OR, odds ratio.

the NAT group and in three patients in the No-NAT group ($P = 0.292$).

Next, the role of NAT in tumour recurrence was investigated. The unadjusted risk of recurrence at 5 years post-transplant was not different between the two groups (HR 0.69 (95 per cent c.i. 0.27 to 1.76), $P = 0.435$) (*Fig. 1*). However, as there were significant baseline differences between the two groups in the percentage of patients with PSC as underlying disease and the use of DCD liver grafts, these variables were included in a multivariable Cox regression analysis. In addition, recipient and

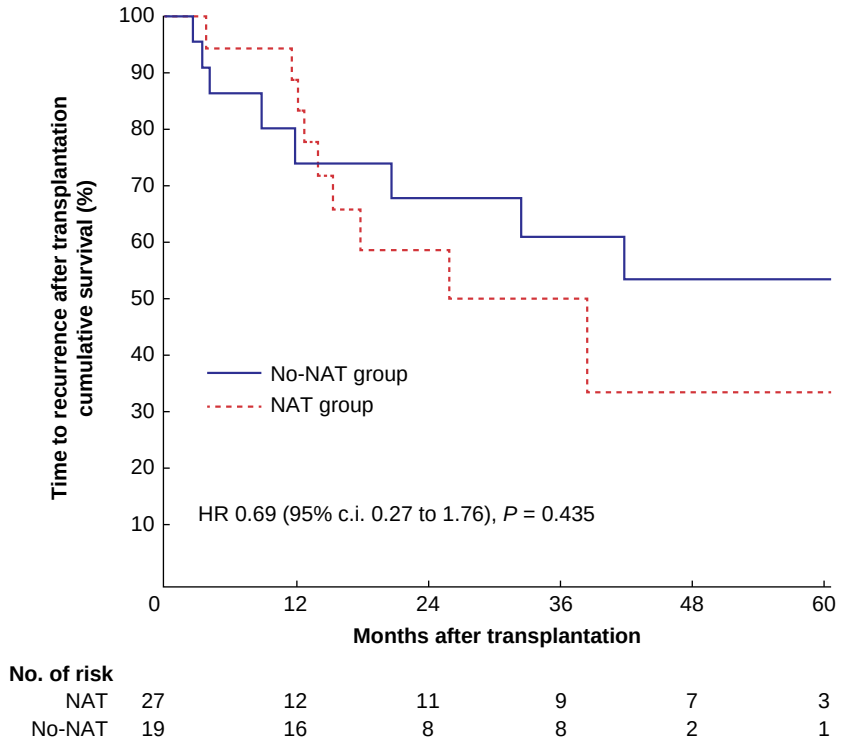

Fig. 1 Kaplan–Meier curves of time to recurrence after liver transplantation for unresectable perihilar cholangiocarcinoma

The No-NAT group included only patients who did not receive neoadjuvant chemoradiation therapy with confirmed malignancy. The NAT group included patients who did receive neoadjuvant chemoradiation therapy. HR, hazards ratio; c.i., confidence interval; NAT, neoadjuvant therapy.

Table 4 Results of univariable and multivariable Cox regression analyses of risk factors of recurrence

Characteristics	Univariable			Multivariable		
	HR	95% c.i.	P	HR	95% c.i.	P
NAT	0.67	0.27,1.76	0.435	0.30	0.09,0.97	0.044
Recipient male sex	0.99	0.35,2.77	0.979			
Recipient age in years	0.97	0.93,1.02	0.230			
Recipient BMI >30 kg/m^2	8.97	1.79,44.84	0.008	40.36	4.69,347.33	<0.001
Underlying PSC	1.01	0.36,2.84	0.983	0.31	0.06,1.57	0.158
CA 19–9 level	1.00	1.00,1.00	0.555			
Tumour size in final pathology	1.31	1.01,1.69	0.044	1.23	0.90,1.66	0.190
Vascular invasion	6.14	2.08,18.16	0.001	1.49	0.27,8.21	0.648
Perineural invasion	3.08	0.89,10.68	0.076	14.68	2.07,104.37	0.007
Lymph node invasion	1.83	0.71,4.73	0.212			
Donor male sex	1.46	0.58,3.71	0.423			
Donor age in years	1.02	0.99,1.05	0.191	1.02	0.99,1.06	0.213
DCD donor	1.82	0.65,5.15	0.258	2.57	0.49,13.55	0.265
R1 resection margin	1.40	0.18,10.89	0.745			

Only patients with a malignancy in the resected liver or in the pre-transplant histological exams were included in the recurrence analyses (46 patients). Recurrence occurred in 18 of 46 patients. HR, hazards ratio; NAT, neoadjuvant therapy; PSC, primary sclerosing cholangitis; CA, cancer antigen; DCD, donation after circulatory death.

tumour characteristics with a *P* value <0.20 in univariable analysis (recipient BMI greater than 30 kg/m^2, tumour size in final pathology, vascular invasion, perineural invasion, and donor age in years) were included as covariates. After multivariable Cox regression analysis, the adjusted risk of recurrence at 5 years post-transplant was significantly lower for the NAT group compared with the No-NAT group (HR 0.30 (95 per cent c.i. 0.09 to 0.97), *P* = 0.044) (*Table 4*).

Patient survival

After a median follow-up of 25 (i.q.r. 6–49 in the NAT group and 16–45 in the No-NAT group) months, the uncorrected 1-, 3-, and 5-year post-transplant survival was 65 per cent, 52 per cent, and 41 per cent respectively in the NAT group and 91 per cent, 68 per cent, and 53 per cent respectively in the No-NAT group. Post-transplant survival at 1 year (*P* = 0.053), 3 years (HR 2.07 (95 per cent c.i. 0.78 to 5.54), *P* = 0.146), and 5 years (*P* = 0.229) was equal in the two groups (*Fig. 2*). Causes of death within 1 year due to post-transplant vascular complications are presented in *Table 3*, showing that all deceased patients in the NAT group died due to the consequences of hepatic artery complications. Additional survival analysis from the date of referral to the last follow-up showed no significant survival difference (*P* = 0.445; *Fig. S1*). As three patients were not proven to

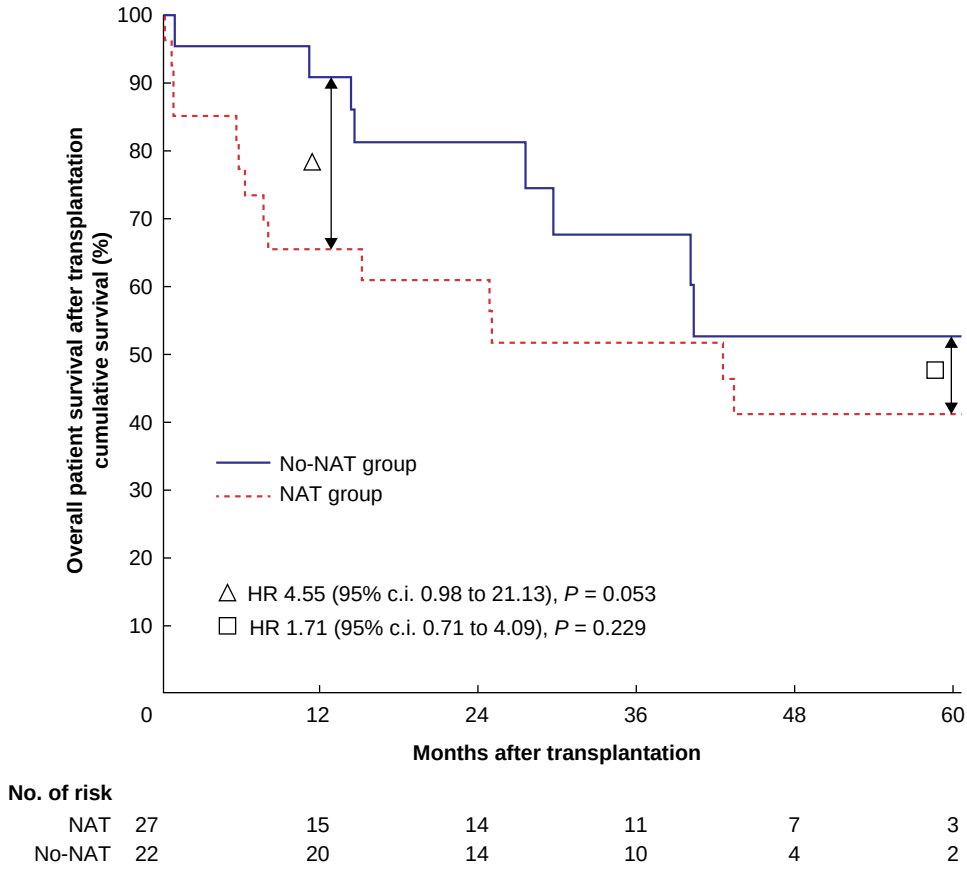

Fig. 2 Kaplan–Meier curves of overall patient survival after liver transplantation for unresectable perihilar cholangiocarcinoma

The No-NAT group included patients who did not receive neoadjuvant chemoradiation therapy. The NAT group included patients who did receive neoadjuvant chemoradiation therapy. HR, hazards ratio; NAT, neoadjuvant therapy.

have a malignancy, additional overall post-transplant survival analysis excluding these patients was performed and also did not show a relevant survival difference between the two groups (*Fig. S2*).

Discussion

This retrospective cohort study evaluated outcomes after LT in patients with unresectable pCCA receiving NAT according to the Mayo regimen or directly undergoing LT. No difference in overall 5-year post-transplant survival or oncological survival from time of referral was found in patients who received pre-transplant NAT compared with a contemporary cohort of patients selected according to the Mayo clinic protocol, but not receiving pre-transplant NAT. In fact, short-term post-transplant survival (1 year) tended to be lower in patients after NAT, which could be explained by a higher rate of hepatic vascular complications (nine of 27 *versus* two of 22), especially arterial complications, compared with patients without NAT. This difference, however, disappeared in subsequent years when patients after NAT had a lower rate of tumour recurrence. These findings indicate that the overall benefit of NAT in strictly selected patients undergoing LT for unresectable pCCA is limited. If, however, morbidity due to hepatic vascular complications can be reduced, the favourable effect of NAT on tumour recurrence might result in improved survival.

In a previous study including 68 patients who underwent LT for pCCA after NAT, high rates of arterial and portal vein complications (21 and 22 per cent respectively) were found[23]. The high rate of hepatic vascular complications has been explained by the neoadjuvant radiation therapy[23,24], which raises questions about the role of radiation therapy and whether NAT should be based on chemotherapy alone. Indeed, in patients with intrahepatic CCA undergoing LT, NAT consisting of systemic chemotherapy without radiation has not been associated with such a high rate of vascular morbidity[25]. Interestingly, from the data presented here, it seems that NAT does not decrease the risk of local recurrence. Gemcitabine and cisplatin (GEMCIS) is currently considered as the most widely accepted systemic treatment in (advanced) biliary tract cancer[26]. Recently the efficacy and safety of the combination fluorouracil, leucovorin, irinotecan plus oxaliplatin (FOLFIRINOX) has been described in patients with advanced biliary tract cancer following the encouraging results of this regimen in advanced pancreatic cancer[27]. Therefore, based on the findings, one might consider an adjusted NAT regimen based on chemotherapy alone, such as FOLFIRINOX or GEMCIS, without radiation therapy, in order to reduce the risk of vascular complications, while having the benefit of reducing the risk of recurrence.

LT is recognized as an effective therapeutic option for unresectable pCCA in selected patients[11]. A recent large meta-analysis including 20 studies comprising 428 patients with unresectable pCCA, who underwent LT, reported 1-, 3-, and 5-year pooled survival of 77 per cent, 55 per cent, and 45 per cent respectively, which is comparable to the overall survival rates of the present study[28]. In the meta-analysis, the data showed a survival benefit for patients who received NAT: 1-, 3-,

and 5-year survival rates of 83, 66 and 65 per cent respectively for patients who received NAT *versus* 71, 48, and 32 per cent respectively for patients who did not receive NAT. The current study shows that when controlling for baseline differences and tumour characteristics, patients who underwent NAT had a lower risk of recurrence, which might explain the better long-term survival observed in the meta-analysis.

Currently, there is accumulating evidence that shows favourable results after LT for oncological indications[29]. In 2018, Ethun *et al.*[30] presented in a multicentre study their results on the influence of type of surgery (transplantation *versus* resection) on overall survival in patients with pCCA. Transplantation was associated with improved survival over resection, although justifiable comments on this study were that the described overall survival for resection was lower than commonly reported in the literature[31]. To answer the question of whether patients with resectable disease are better treated with LT *versus* resection, the results from the TRANSPHIL study are eagerly awaited. Already initiated in 2012, this prospective, randomized, multicentre study for pCCA aims to compare NAT followed by LT with conventional partial liver and bile duct resection (clinicaltrials.gov; NCT02232932).

The current study has several limitations and the results should therefore be interpreted with caution. First, while the data comprise national experiences over a time course of 10 years, the study population remains small, resulting in a limited power and potential overfitting of the multivariable analysis. Second, there were some baseline variations between the two groups, especially regarding the presence of underlying PSC and the use of DCD liver grafts, which may be responsible for bias[12]. Third, due to a longer pre-transplant interval inherent to NAT, there could be a selection bias in favour of NAT patients, as these patients have a longer observational interval. NAT patients also have longer overall oncological survival given the extended pre-transplantation time, which should be kept in mind when discussing post-transplant survival. Unfortunately, due to the retrospective nature of the study, dropout rates could not be retrieved and no 'intention-to-treat' analysis could be performed. Finally, the median follow-up time is only 25 months and long-term survival should be further assessed. Future studies will provide more insights regarding long-term outcomes.

This multicentre comparison showed that strict selection alone can provide similar overall survival for patients with unresectable pCCA undergoing LT without NAT compared with patients who did receive NAT. Although NAT was associated with less post-transplant tumour recurrence, it was also associated with a higher rate of hepatic vascular complications. These findings suggest that future studies should focus on alternative NAT regimens, possibly without radiation therapy, that may further improve the outcome after LT as treatment for patients with pCCA.

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Disclosure

The authors declare no conflict of interest.

Supplementary material

Supplementary material is available at *BJS Open* online.

Data availability

The study permissions do not allow individual patient data sharing.

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