Retrospective Cohort Study

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Defining and predicting textbook outcomes for perihilar cholangiocarcinoma: analysis of factors improving achievement of desired postoperative outcomes

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Background: Definition of textbook outcome (TO), defined as a single indicator combining the most advantageous short-term outcomes, is still lacking for perihilar cholangiocarcinoma (PHC). The primary endpoint of the present study is to analyze the rate of achievement of a disease-specific TO for PHC within a high volume tertiary referral centre. Secondary endpoints are to identify predictive factors of TO-achievement and to analyze the impact of achieving TO on long-term results.

Methods: Between 2010 and 2022, a total of 237 patients undergoing combined liver and biliary resection for PHC at tertiary referral centre were included. Disease-specific TO were defined as: no 90-day mortality, no postoperative complications, no readmission, no intraoperative transfusions and resection margins. A logistic regression model was developed to identify predictors associated with TO-achievement. Kaplan–Meier curves were designed to determine TO's impact on survival.

Results: TO was achieved in 60 (25.3%) patients. At multivariate logistic regression, preoperative biliary drainage [odds ratio (OR) 2.90 (1.13–3.40), $P=0.026$], high prognostic nutritional index [OR 7.11 (6.71–9.43), $P=0.007$[and minimally invasive approach [OR 3.57 (2.31–3.62), $P=0.013$] were identified as independent predictors of TO. High ASA score [OR 0.38 (0.17–0.82), $P=0.013$] decreased the odds of TO. A significant improvement in both overall survival and disease-free survival was associated to TO fulfilment.

Conclusion: Since the achievement of TO correlates with better disease-free and overall survival, every effort should be made to ameliorate modifiable aspects prior to surery: management within referral centres with dedicated experience in biliary tract cancer and preoperative optimization protocol may positively contribute to improve postoperative outcomes, increasing the chance to obtain TO. Moreover, the implementation of advanced minimally invasive programs plays as well.

Keywords: Liver surgery, minimally invasive surgery, morbidity, nutrition, PeriHilar cholangiocarcinoma, textbook outcomes

Introduction

Perihilar cholangiocarcinoma (PHC) is a malignant tumour arising in the biliary tree between the insertion of the cystic duct into the common bile duct and the second-order bile ducts, and accounts for ~60–70% of all cholangiocarcinoma[1,2]. It is characterized by a dismal prognosis, with a median survival of 6–12 months in most untreated patients[3]. The only potentially curative treatment for PHC patients is surgical resection with negative margins (R0), resulting in a median survival time of 27–58 months[4]. Nowadays, major hepatectomy plus caudate lobectomy associated with biliary confluence resection and lymphadenectomy is the gold standard in resectable PHC, resulting in a decrease risk of loco-regional recurrence[5]. However, this type of surgical procedure is associated with the highest postoperative morbidity and mortality rates within hepato-bilio-pancreatic surgery[6].

Postoperative morbidity and mortality are important parameters of healthcare quality, and these individual measures,

HIGHLIGHTS

- Textbook outcome (TO) in patients who underwent curative-intent resection for perihilar cholangiocarcinoma was reached in 25.3%.
- Preoperative biliary drainage, high prognostic nutritional index, and minimally invasive approach were identified as independent predictors of TO.
- High American Society of Anesthesiologists score is an independent risk factor for non -achievement of TO.
- The fulfilment of TO is correlated with better disease-free and overall survival.

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together with the length of hospital stay and readmission rates, have been widely used to assess surgical performance and define the level of risk. Information on single individual outcomes, however, does not provide a multidimensional view of the overall surgical process because hospital performance can differ among these parameters[7]. Recently, composite measures have been suggested to be superior to individual outcome measures in assessing the overall quality of surgical care and the probability to achieve optimal outcomes[8]. The textbook outcome (TO) is the most commonly used composite measure. It is an "all-or-none" combined outcome tool that is achieved only if the most desirable postoperative outcomes are reached simultaneously, representing the ideal ("textbook") hospitalization[9]. Thanks to these features, TO is a more patient-centred benchmark and can be easily used to assess the quality of surgical care and determine the ideal hospitalization from the patient perspective[10].

Several studies have investigated TOs in liver surgery[11–14]. However, surgical treatment of PHC is more challenging than liver resection for others malignancies both because of baseline characteristics of patients and challenges of required surgical procedures. As reported in the literature, there are some risk factors for postoperative morbidity and mortality after surgery for PHC, including American Society of Anesthesiologists (ASA) score greater than or equal to III, right-sided hepatectomy, advanced age and preoperative cholangitis[15]. However, a proper definition of TO in PHC surgery is still lacking, hence defining an unmet clinical need, to be addressed in the setting of tertiary referral centres: indeed patients undergoing complex surgical procedure show better outcomes when treated at dedicated-cancer centres—thus increasing the odds of TO achievement—that constitute the setting where adequately study this topic to overcome possible bias due to heterogeneities among hospitals[16].

The primary endpoint of the present study is to analyze the rate of achievement of a disease-specific TO for PHC, provided its importance as a tool for hepato-biliary surgeons for better understanding the impact of the single individual outcome measure in determining the ideal postoperative course after curative-intent resection of PHC. The primary endpoint lays the groundwork to identify predictive factors of TO-achievement and to analyze the impact of achieving TOs on long-term results (secondary endpoints).

Materials and methods

Patients and study design

Data from all 237 patients who underwent curative-intent surgical resection for suspected PHC—defined as a biliary stricture or mass arising in the biliary tree proximal to the insertion of the cystic duct into the common bile duct—between January 2010 and July 2022, at a tertiary referral centre were retrieved from the prospectively collected institutional database: this population constituted the study cohort. Only patient with a at least six months of follow-up were included in the study.

Approval to perform the study was obtained from the institutional review board and the need for consent was waived. The study has been reported in line with the STROCSS criteria[17].

Institutional criteria to define irresectable disease at presentation for PHC are described elsewhere. Patients with any of the following characteristics were excluded from the analysis: evidence of extrahepatic and/or locally advanced disease during staging laparoscopy constituting a criteria of drop-out from surgical program; alternative diagnoses from PHC at the histopathological examination of the specimen, such as benign stenosis of the biliary tree, intrahepatic cholangiocarcinoma with involvement of the hepatic hilum, gallbladder cancer with involvement of the hepatic hilum, and biliary tree thrombosis due to metastases from colonic neoplasms; less than 6 months of follow-up.

Data collection and definitions

For each patient, data regarding demographic characteristics and comorbidities, perioperative variables and histopathological characteristics were collected. Postoperative morbidity, length of hospital stay, 90-day mortality and TNM stage (according to the AJCC 8th edition[18]) were also recorded.

Pre-existing liver disease was defined as a known diagnosis of liver cirrhosis, primary sclerosing cholangitis, or a serological diagnosis of hepatitis B/C.

Preoperative liver atrophy was defined as future liver remnant less than 30%, which is a major risk factor for postoperative liver failure[19].

The preoperative prognostic nutritional index (PNI) was calculated using the following formula: $[(10 \times \text{serum albumin (g/dl)}] + [0.005 \times \text{total lymphocyte count}]$[20]. The population was divided into three groups according to the results (<40, 40–45, >45). Tumour-free R0 margin was defined as no evidence of microscopic disease in the margins. Postoperative mortality was defined as death during postoperative hospitalization or within 90 days of the surgical procedure. Readmission was defined as hospital access for surgical complications within 90 days of resection. Postoperative complications were classified according to the Clavien–Dindo classification[21]. Post-hepatectomy liver failure and postoperative bile leakage were defined and classified according to the ISGLS definition[22,23].

TO was defined as follows: absence of postoperative complications, no postoperative 90-day mortality, absence of intraoperative transfusion, no readmission within 90 days and presence of R0 resection margins. The TO was achieved when all individual parameters were observed in one patient.

Preoperative evaluation and optimization

Before resection, all patients underwent thoracoabdominal computed tomography and MRI with Magnetic resonance Cholangio Pancreatography. The Bismuth–Corlette classification was used to assess tumour extension along the bile duct, based on preoperative imaging, and to evaluate the side of hepatectomy[24].

The multidisciplinary preoperative optimization protocol has been described elsewhere[25,26]. Briefly, the protocol consists of percutaneous transhepatic biliary drainage (PTBD) and preoperative hypertrophy-inducing techniques (portal vein embolization, Portal Vein Embolization, or hepatic vein deprivation in patients with an inadequate future liver remnant. Prior to PTBD and Portal Vein Embolization or hepatic vein deprivation staging laparoscopy was performed to rule out distant intra-abdominal metastases. In patients with adequate future liver remnant, biliary decompression was performed according to the severity and duration of the cholestasis. External PTBD was preferred over external–internal drainage. PTBD was placed in the future liver remnant, reserving drainage of the affected hemiliver in patients with persistent hyperbilirubinaemia.

Surgery

Both open and minimally invasive techniques were used and details of surgical technique are described elsewhere[27]. As dictated by principles of oncologic surgery of PHC, formal lymphadenectomy and caudate lobectomy were standardly. Frozen sections of the distal and proximal bile duct margins were subjected to histopathological examination. Additional resections of the bile stumps were performed in cases of intraoperative R1 resections.

Statistical analysis

Statistical analyses were performed using SPSS 28.0 (SPSS). Statistical significance was set at P less than 0.05 for all analyses. Non-normally distributed continuous variables are expressed as median and interquartile range and were compared using the Mann–Whitney U test for non-normally distributed data. Categorical variables are represented as numbers and percentages, and differences between them were tested using the $\chi 2$ test with Yates correction or Fisher exact test when appropriate. To identify predictive factors associated with achieving TO, univariate and multivariate analyses were performed. Variables with a significance level of P less than 0.100 in the univariate analysis, were included in the multivariate analysis. To reduce potential bias owing to the large number of variables considered, a backward stepwise regression model was used for multivariate analyses. Results were reported as odd ratio (OR) and 95% CI. Overall and disease-free survival (DFS) curves were generated using the Kaplan–Meier method and compared using the log-rank test.

Results

Among 237 patients included in the study, TO was achieved in 60 (25.3%) patients. Regarding each specific item included in the TO definition: intraoperative transfusions were performed in 66 (27.8%) patients; tumour-free resection margins were reached in 141 patients (59.5%), and 56.5% ($n=134$) had postoperative complications of any grade. Fifteen (6.3%) patients died within 90 days of surgery, and 8% ($n=19$) required hospital readmission due to surgical complications. Figure 1 summarizes the TO evaluation.

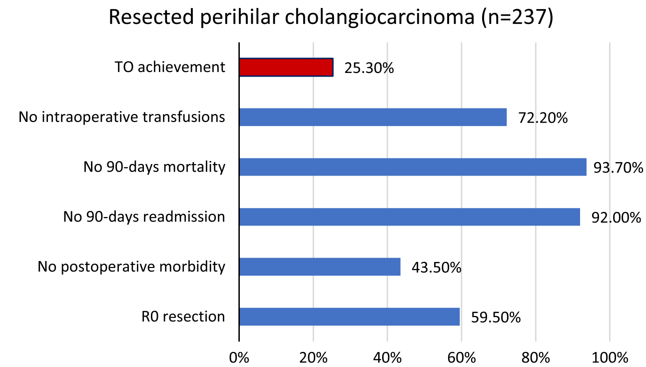

Figure 1. Textbook outcome evaluations. R0 resection, negative resection margins; TO, textbook outcome.

Comparison between TO-achievement and no TO-achievement

Patient characteristics stratified according to achievement of TO are summarized in Table 1.

Patients who achieved TO had lower ASA scores (I–II 73.3% vs. 53.1%, III–IV 26.7% vs. 46.9%, $P=0.006$) and a higher PNI (>45 61.7% vs. 23.2%, 40–45 31.7% vs. 40.7%, <40 6.7% vs. 36.2%, $P=0.001$). Pre-existing liver disease and preoperative liver atrophy were more frequent in the group that did not reach the TO (11.3% vs. 1.7%, $P=0.032$ and 24.9% vs. 11.7%, $P=0.04$, respectively). While an higher proportion of patients achieving TO underwent preoperative biliary drainage (80% vs. 61.6%, $P=0.011$), post-procedural complications were more frequent in patients who did not achieve TO (29.4% vs. 13.3%, $P=0.016$): within this latter group, a second biliary procedure was more frequently required compared to TO group due to failure of the first biliary drainage (11.3% vs. 1.7%). No differences were observed between the two groups in terms of biliary drainage type and need for hypertrophy techniques prior to surgery. Within TO group, the proportion of patients operated by minimally invasive approach was higher compared with non-TO group (35% vs. 7.9%, $P<0.001$). Vascular resection was needed more frequently in the non-TO group (39% vs. 23.3%, $P=0.041$). Regarding tumour characteristics, Bismuth-type III–IV and higher histopathological grade were more frequent in the groups that did not achieve TOs (Bismuth–Corlette ≥ III:67.2% vs. 55%, $P=0.088$; histopathological grade $P=0.006$). The length of hospital stay was significantly longer in the no-TO group (20 vs. 12 days, $P<0.001$).

Evaluation of independent risk factors for achieving TOs

To assess independent risk factors for not achieving TO, logistic regression analysis was performed, as reported in Table 2.

In the univariate analysis, factors associated with the achievement of TO were: ASA score greater than or equal to III (OR 0.41, 95% CI, 0.22–0.78; $P=0.007$), PNI greater than or equal to 40 (PNI 40–45: OR 3.42, 95% CI, 1.75–3.70; $P<0.001$; PNI >45: OR 7.80, 95% CI, 6.69–9.64; $P<0.001$), preoperative biliary drainage (OR 3.12, 95% CI, 1.49–3.56; $P=0.003$), complications of preoperative biliary drainage placement (OR 0.37, 95% CI 0.16–0.83; $P=0.016$), preoperative serum bilirubin level greater than or equal to 2 mg/dl (OR 0.30, 95% CI, 0.15–0.60; $P<0.001$), and minimally invasive approach (OR 3.16, 95% CI, 2.07–3.34; $P<0.001$). Logistic regression analyses showed that ASA score greater than or equal to 3 was associated with lower odds of achievement (OR 0.38, 95% CI 0.17–0.82; $P=0.013$), while preoperative biliary drainage (OR 2.90, 95% CI, 1.13–3.40; $P=0.026$), PNI greater than 40 (40v45: OR 3.89, 95% CI, 2.59–4.05; $P=0.003$; >45: OR 7.11, 95% CI, 6.71–9.43; $P=0.007$), and minimally invasive approaches (OR 3.57, 95% CI, 2.31–3.62; $P=0.013$) were associated with higher odds of achieving TO. Although tumour characteristics, such as grade greater than 2 and lymph-node status, were associated with non-achievement of the TO in univariate analyses, they were not independent risk factors of non-TO (grading >G2: OR 0.77, 95% CI 0.30–1.95, $P=0.579$, lymph-node status N1–2: OR 0.87, 95% CI 0.32–1.39, $P=0.790$). The same can be said for morbidity after decompression of the biliary tree (OR 0.56, 95% CI 0.22–1.44, $P=0.231$) and preoperative serum bilirubin greater than or equal to 2 mg/dl (OR 0.53, 95% CI, 0.23–1.22; $P=0.136$).

Table 1

Characteristics of patients achieving textbook outcomes (TO).

Resected perihilar cholangiocarcinoma ($n=237$)	Textbook outcomes (yes) $n=60$ (25.3)	Textbook outcomes (no) $n=177$ (74.7)	*P*
Age	70 (59–76)	69 (64–76)	0.367
Sex, *n* (%)			0.760
Male	38 (63.3)	106 (59.9)	
ASA score, *n* (%)			
1–2	44 (73.3)	94 (53.1)	0.006
3–4	16 (26.7)	83 (46.9)	
Pre-existing liver disease, *n* (%)			
Yes	1 (1.7)	20 (11.3)	0.032
Previous biliary tract surgery, *n* (%)			0.767
Yes	3 (5.0)	13 (7.3)	
Preoperative liver atrophy, *n* (%)			0.044
Yes	7 (11.7)	44 (24.9)	
Peak serum bilirubin			0.210
(≥10 mg/dl)	17 (28.3)	68 (38.4)	
Preoperative biliary drainage			0.011
Yes	48 (80.0)	109 (61.6)	
Biliary drainage type, *n* (%)			0.431
EBD	18 (37.5)	46 (42.2)	
PTBD	26 (54.2)	57 (52.3)	
PTBD + EBD	4 (8.3)	6 (5.5)	
Type of PTBD chosen, *n* (%)			
EIBD	15 (57.7)	31 (54.4)	
ExBD	8 (30.8)	21 (36.8)	
EIBD + ExBD	3 (11.5)	5 (8.8)	0.829
Drainage side			
Ipsilateral to tumour	1 (2.1)	9 (8.2)	
Future liver remnant	24 (50.0)	56 (51.4)	
Bilateral	5 (10.4)	8 (7.4)	
Other	18 (37.5)	36 (33.0)	0.473
Time from preoperative biliary drainage to resection (day)	24 (18–40)	27 (16–40)	0.260
No. preoperative biliary procedures, *n* (%)			
> 1	1 (1.7)	20 (11.3)	0.044
Morbidity after biliary drainage, *n* (%)			0.016
Yes	8 (13.3)	52 (29.4)	
Portal vein embolization, *n* (%)			
Yes	16 (26.7)	60 (33.9)	0.339
Preoperative serum bilirubin (≥2 mg/dl), *n* (%)	12 (20.0)	81 (45.7)	< 0.001
Preoperative Carcinoembryonic antigen (ng/ml)	3.7 (2.3–5.2)	3.5 (2.2–6.0)	0.754
Preoperative Carbohydrate antigen 19-9 (U/ml)	84 (35–834)	202 (66–397)	0.168
Preoperative nutritional index (PNI), *n* (%)			< 0.001
> *45*	37 (61.7)	41 (23.2)	
40–45	19 (31.7)	72 (40.7)	
< 40	4 (6.7)	64 (36.2)	
Approach, *n* (%)			< 0.001
Minimally invasive	21 (35)	14 (7.9)	
Type of resection, *n* (%)			0.019
Right hepatectomy	11 (18.3)	55 (31.1)	
Right trisectionectomy	7 (11.7)	29 (16.4)	
Left hepatectomy	32 (53.3)	50 (28.2)	
Left trisectionectomy	2 (3.3)	5 (2.8)	
Central hepatectomy	0 (0.0)	5 (2.8)	
Resection of Sg 4b + extrahepatic bile duct + biliary confluence	8 (13.3)	33 (18.6)	
Caudate lobe resection, *n* (%)			0.203
Yes	51 (85.0)	135 (76.3)	
Biductal hepatico-jejunostomy, *n* (%)			0.438
Yes	19 (31.6)	45 (25.4)	
Pringle Maneuvre, *n* (%)			0.224
Yes	41 (68.3)	105 (59.3)	
Pringle Maneuvre time (min)	30 (20–40)	30 (20–40)	0.763
Vascular resection, *n* (%)			0.041
Yes	14 (23.3)	69 (39.0)	
Bismuth–Corlette, *n* (%)	27 (45)		0.088
1–2	33 (55)	58 (32.8)	
3–4		119 (67.2)	
T stage, *n* (%)			
Tis	6 (10)	6 (3.3)	0.212
T1	2 (3.3)	2 (1.1)	
T2a	14 (23.3)	33 (18.6)	
T2b	14 (23.3)	42 (23.7)	
T3	21 (35.0)	72 (40.7)	
T4	3 (5.0)	22 (12.4)	
Histopathological grading, *n* (%)			
G1	7 (12.7)	5 (2.9)	0.006
G2	32 (58.2)	92 (52.9)	
G3	16 (29.1)	77 (44.3)	
Lymph-node status, *n* (%)			
N0	40 (66.7)	76 (42.9)	0.004
N1	18 (30.0)	80 (45.2)	
N2	2 (3.3)	21 (11.9)	
No. metastatic lymph nodes	0 (0 – 1)	1 (0 – 2)	0.003
No. examined lymph nodes	6 (3 – 8)	7 (4 – 11)	0.275
Length of hospital stay (day)	12 (8 – 12)	20 (12 – 31)	< 0.001

ASA, American Society of Anesthesiologists; EBD, endoscopic biliary drainage; EIBD, external–internal biliary drainage; ExBD, external biliary drainage; PTBD, percutaneous transhepatic biliary drainage.

Power analysis

At multivariate regression analysis, ASA score greater than or equal to III, preoperative biliary drainage, morbidity after biliary drainage, preoperative serum bilirubin greater than or equal to 2 mg/dl, high PNI, minimally invasive approach, high grading and positive lymph-node status were used to predict TO's achievement.

Table 3 shows the regression's model summary:

G*Power was used to estimate the sample size needed to test the regression model at a desired level of power. The inputs used were:

(1) Alpha level (customarily 0.05).
(2) Number of predictors used in the regression model (8).
(3) Desired power (tested for both 0.80, conventional and 0.90).
(4) Effect size: Given the conditional probability $p_1 = p(Y = 1 | X = 1)$ under H0, we may define the effect size either by specifying $p_2 = (Y = 1 | X = 1)$ under H1 or by specifying the odds ratio $OR = [p_2/(1 - p_2)]/[p_1(1 - p_1)$.

An "a priori" logistic regression power analysis was performed: (Figs. 2 and 3).

To ensure an adequate sample size for the regression analysis, a 'a priori' logistic regression power analysis was performed using G*Power software. The inputs used for the power analysis were an alpha level of 0.05, 8 predictors in the regression model, and the effect size represented by the odds ratio.

The power analysis results are as follows: with a desired power level of 0.80, the predicted sample size needed was $n = 162$, and with a desired power level of 0.90, the predicted sample size needed was $n = 216$.

It is worth noting that the overall patient size in this study was 237. Therefore, the sample size of 216 achieved for the higher desired power level (0.90) is in line with the power analysis and meets the statistical requirements for conducting the multivariate logistic regression analysis.

Table 4: estimated probabilities of achieving TO for different combinations of independent predictors in a multivariate logistic regression model. The independent predictors include ASA Score (I–II), preoperative biliary drainage, minimally invasive approach, and PNI >45. Each row in the table represents a unique combination of these predictors, and the corresponding estimated probability of achieving TO is reported in the last column. The independent predictors take binary values (0 or 1), which results in $2^4 = 16$ different combinations in total.

Green: positive outcomes. For example ASA I/II; presence of preoperative biliary drainage; application of a minimally invasive approach and PNI greater than 45.

Red: negative outcomes: ASA III/IV; absence of preoperative biliary drainage; open approach and PNI less than 45.

In this analysis, we used a multivariate logistic regression model to estimate the probabilities of an event based on multiple independent predictors. The logistic regression formula is given by:

$$\ln\left(\frac{p}{1-p}\right) = \beta_0 + \beta_1 x_1 + \beta_2 x_2 + \beta_3 x_3 + \beta_4 x_4$$

p represents the probability of the event occurring, β_0 is the intercept term, and β_1 to β_4 are the coefficients associated with each predictor variable. To calculate the estimated probabilities, we first obtained the linear predictor (LP) by summing the product of each predictor's coefficient and its corresponding value. Next, we converted the linear predictor to the probability (p) using the logistic function, which is $p = \frac{\exp(\beta_0 + \beta_1 X_1 + \beta_2 X_2 + \beta_3 X_3 + \beta_4 X_4)}{\exp(\beta_0 + \beta_1 X_1 + \beta_2 X_2 + \beta_3 X_3 + \beta_4 X_4) + 1}$

The equation was applied to various scenarios, varying the values of the predictors (ASA, preoperative biliary drainage, minimally invasive approach, and PNI), to estimate the probability of the event being predicted by the model. The estimated probabilities represent the likelihood of the event occurrence in each specific scenario.

Table 5 reports the intercept and the beta values (coefficients) for the multivariate logistic regression model:

The intercept represents the constant term in the logistic regression equation, and the β values (coefficients) for each predictor indicate the strength and direction of the relationship between the respective predictor and the predicted probability of the event occurrence. By plugging in the values of these coefficients along with the corresponding predictor values into the logistic regression formula, we can estimate the probabilities for different scenarios and gain insights into the factors influencing the outcome.

A practical example of Scenario 1:

ASA Score I/II = 0
Preoperative biliary drainage (Yes) = 1
Minimally invasive approach (Yes) = 1
PNI (> 45) = 1

To Calculate the linear predictor (LP):

$$\text{LP} = \beta_0 + \beta_1 x_1 + \beta_2 x_2 + \beta_3 x_3 + \beta_4 x_4 = -0.101 + (-0.907*0) + (0.715*1) + (1.682*1) + (1.2*1)$$

$$\text{LP} \quad -0.101 + 0 + 0.715 + 1.682 + 1.2$$

$$\text{LP} = 3.496$$

The linear predictor is converted into the probability (p) using the logistic function:

$$p = \frac{e^{lp}}{1 + e^{lp}}$$

$$p = \frac{e^{3.496}}{1 + e^{3.496}}$$

$$p = \frac{32.98}{1 + 32.98}$$

$p \approx 0.970$

Survival analyses

The median overall survival (OS) in the whole study cohort was 23 months (range, 13–38 months). The median OS in the TO group was 17 months (range, 9 – 25 mo). The median OS in the group that did not achieve the TO was 13 months (range, 7 – 20 mo), significantly shorter compared with the TO group ($P < 0.001$; Fig. 4).

The median DFS of all patients was 20 months (range, 16–27 months). The median DFS in the group that achieved TO was 15 months (range: 10–21 months). The median DFS in patients who did not achieve the TO was 12 months (range: 9–19 months), significantly shorter compared with the TO group ($P = 0.003$, Fig. 5).

Discussion

In the present series, TO—as per definition designed specifically in the setting of PHC—was achieved in 25.3% of patients. This study highlights high PNI, preoperative biliary drainage, and minimally invasive approach as independent predictors of TO achievement. High ASA score—on the other hand—decreased the odd of TO-achievement. The results of the study are in line with what can be read in literature as regards the ASA score; however, they differ in relation to the resection side and preoperative biliary drainage[15,28].

Even if the need to use a different definition of TO for PHC patients hinders a comparison with already existing reports regarding TO in the setting of conventional liver surgery (TO-achievement rates are between 48 and 80.5%)[14,29–31], it seems that the possibility to achieve TO in PHC is generally reduced, as suggested even in other reports focusing on biliary tract cancer[12,28,32]. This emphasizes the greater complexity of surgical procedures for biliary tract cancer, especially in cases of PHC,

Table 2

Univariate and multivariate logistic regression analyses for predictors of TO-achievement.

Variable	OR (95% CI)	Univariate analysis (*P*)	OR (95% CI)	Multivariate analysis (*P*)
ASA, (III/IV vs. I/II)	0.41 (0.22–0.78)	0.007	0.38 (0.17–0.82)	0.013
Pre-existing liver disease	0.13 (0.017–1.01)	0.052		
Preoperative Liver atrophy	0.40 (0.17–0.94)	0.136		
Preoperative Biliary Drainage	3.12 (1.49–3.56)	0.003	2.90 (1.13–3.40)	0.026
No. preoperative biliary procedures, (> 1 vs. <1)	0.72 (0.23–2.24)	0.569		
Morbidity after biliary drainage	0.37 (0.16–0.83)	0.016	0.56 (0.22–1.44)	0.231
Preoperative serum bilirubin (≥2 mg/dl vs. <2 mg/dl)	0.30 (0.15–0.60)	< 0.001	0.53 (0.23–1.22)	0.136
PNI				
< 40	Reference	< 0.001	Reference	0.003
40–45	3.42 (1.75–3.70)	< 0.001	3.89 (2.59–4.05)	0.007
> 45	7.80 (6.69–9.64)		7.11 (6.71–9.43)	
Approach, (MIS vs. open)	3.16 (2.07–3.34)	< 0.001	3.57 (2.31–3.62)	0.013
Resection side, (left vs. right)	1.05 (0.945–1.16)	0.382		
Vascular resection	0.551 (0.28–1.08)	0.082		
Bismuth–Corlette, (3–4 vs. 1–2)	0.57 (0.29–1.13)	0.105		
Grading, (> G2)	0.50 (0.26–0.94)	0.032	0.77 (0.30–1.95)	0.579
Lymph-node status, (N1–2 vs. N0)	0.43 (0.23 – 0.81)	0.009	0.87 (0.32–1.39)	0.790
No. metastatic lymph nodes, continuous	1.07 (0.92–1.25)	0.352		

ASA, American Society of Anesthesiologists; MIS, Minimally Invasive Surgery; OR, odds ratio; PNI, prognostic nutritional index; TO, textbook outcome.

where the association between major or extended liver surgery with biliary reconstruction creates a dangerous synergy between parenchymal demolition and risk of septic complications.

Most frequent reasons for the allocation of patients within non-TO group were postoperative morbidity and R1 resection. The close proximity of the biliary confluence to the liver parenchyma and vascular structures, which are frequently involved in the tumour, explains the high risk of non-radical resection (R1). This result is in line with the current literature, as Gorgec *et al.*[29] and Tsilimigras *et al.*[9] reported that R1 resection is the most limiting factor in TO achievement in their experience.

In our series, the postoperative morbidity rate is 56.5% which is lower than previously reported in other Western series[6,28]. It is likely that implementation and strict adhesion to the multidisciplinary preoperative optimization protocol for PHC allows to significantly reduce the risk of perioperative events thanks to a general improvement of patient's general condition and tolerance to surgical stress. The aforementioned protocol was adopted into clinical practice in 2010 which was indeed chosen as the starting date for recruitment of patients in the present series in order to obtain a homogeneous population.

Within the protocol, multidisciplinary assessment of the patient's general condition aims to correctly evaluate patient fitness and carefully choose the best surgical approach. The appraisal of patient's performance status using the ASA score is critical, considering that an ASA score greater than or equal to 3 is correlated with a higher risk of postoperative complications and is an independent risk factor for 90-day mortality after liver surgery[33,34]. This is confirmed by the present report, since an ASA score greater than or equal to 3 reduces the likelihood of TO-achievement at multivariate logistic regression.

Table 3

Regression model summary.

Model	Standard error	B	Exp (B)	Significance
1	0.154	0.989	2.69	< 0.001

Exp, experiment.

Furthermore, evaluation of the nutritional status is a key point in the preoperative assessment to control subsequent surgical risk. Malnutrition is frequently observed among patients scheduled for liver resection, and several studies have identified poor nutritional status as an independent risk factor for postoperative morbidity and mortality because it might affect postoperative metabolism, liver function and regenerative capacity, and inflammation[35,36]. In recent years, the PNI has been widely used as a prognostic factor for surgery. The PNI is an inflammation-based marker that is simply calculated using serum albumin concentration—which is associated with a patient's nutritional status—and total lymphocyte count,—which reflects the patient's immunological status. A low PNI is associated with a greater risk of postoperative complications in gastrointestinal surgery and has recently been reported as a negative prognostic factor for various malignancies, including hepatocellular carcinoma[37]. Two studies have analyzed the role of PNI in short-term and long-term outcomes after curative-intent resection for cholangiocarcinoma, demonstrating how a PNI less than 40 is an independent risk factor for severe complication and is correlated to a worse overall survival[38,39]. Moreover, a recent study has demonstrated that a PNI less than 40 is a risk factor for failure to rescue in PHC surgery[40]. These findings are in line with present results, reporting high PNI as an independent predictor of TO-achievement. Therefore, evaluation of nutritional status is essential since perioperative nutritional supplementation may decrease the risk of postoperative complications, improve liver regeneration capacity and function, and ameliorate long-term survival. Enteral nutrition via naso-jejunal tube is the best modality for this purpose, since it prevents gastrointestinal mucosa atrophy and it maintains the normal growth of gut microbiota, thus improving the intestinal mucosa barrier function which translates in reducing bacterial translocation responsible for postoperative infectious complications[41].

Benzing *et al.*[28] ruled out preoperative biliary drainage as an independent risk factor for non-achievement of TO. Contrary to

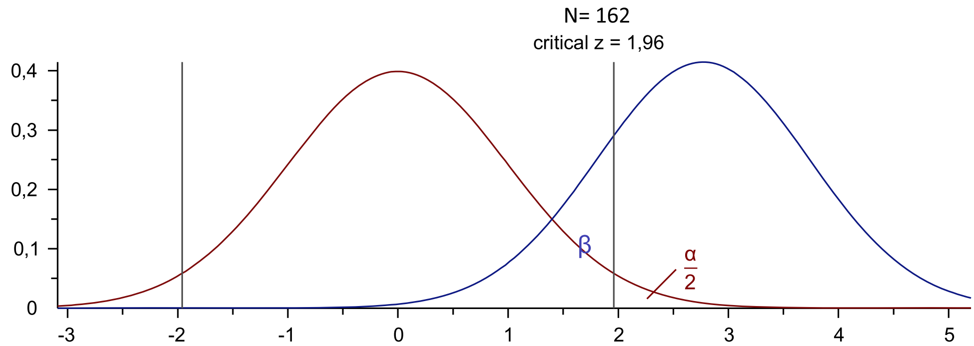

Figure 2. Shows the predicted sample size needed to the desired amount of power (set at 0.80) for the multivariate logistic regression assessed ($n = 162$).

this result, this study highlights preoperative biliary drainage as independent predictor of TO-achievement. Biliary tree decompression of the future liver remnant is strongly encouraged in surgical candidates: almost all patients with PHC present with obstructive jaundice at the time of diagnosis. Biliary obstruction is an important risk factor for postoperative morbidity and mortality, since hyperbilirubinemia causes cholestasis and coagulopathy, increases the risk of biliary infection, reduce the liver regeneration capacity, and is associated with a pro-inflammatory state[42–44]. In this series, patients who underwent preoperative biliary drainage had smaller liver remnants, cholangitis, higher bilirubin levels at diagnosis, or prolonged cholestasis. Therefore, the possible negative effect of post-procedural morbidity seen in univariate analyses may be due to underlying patient characteristics rather than the PBD itself and is counterbalanced by the improvement in cholestasis-associated liver dysfunction and by the improvement in liver regeneration capacity, thereby reducing the risk of postoperative liver failure.

The benefit of the preoperative optimization protocol can also be inferred from the lack of correlation between resection side and TO-achievement. Traditionally, right-sided hepatectomy for PHC was associated with significantly higher postoperative morbidity and mortality rates than left-sided ones; however, long-term survival was poorer in left-sided hepatectomy, probably because of a lower rate of R0 resection[45]. The implementation of the preoperative optimization protocol results in a reduction in postoperative morbidity and mortality after right-sided resection, given above all by a reduction in post-hepatectomy liver failure rate[25,26]. Major risk factors for post-hepatectomy liver failure are serum bilirubin level greater than 3 mg/dl, preoperative cholangitis, and future liver remnant volume less than 30%[46]. It is therefore understood how preoperative biliary drainage and hypertrophy-inducing techniques, which are flagship of the preoperative optimization protocol, play a key role in improving postoperative outcomes, making right-sided resection feasible and safe as left-sided resection with the advantage of long-term outcomes.

A real benefit of a minimally invasive approach on short-term postoperative outcomes in PHC is strongly documented by present results. While minimally invasive liver resection is routinely performed in almost all centres with a liver resection activity because of its documented benefits over the open counterpart, while preserving oncological adequacy[47], challenges associated with PHC (lymphadenectomy, segment 1 resection, major or extended liver surgery and need for biliary resection and reconstruction) have limited its adoption in the setting of PHC. It is likely that the wide scale diffusion of the robotic platform may change this scenario, especially if strongly supported by data documenting a significant perioperative and oncological advantage provided by this approach in PHC. The robotic approach seems to help in lymphadenectomy for biliary tract cancers, reducing the operation time with comparable oncological radicality compared to the laparoscopic approach[48]. Moreover, the three-dimensional view of the surgical field, together with instruments with a higher degree of freedom compared to laparoscopic ones, makes the robotic approach ideal for the most complex hepatectomy, thus increasing the feasibility rate of resection[49].

The lack of correlation between achievement of TO, T stage and Bismuth-type seems to disprove the hypothesis that patients with

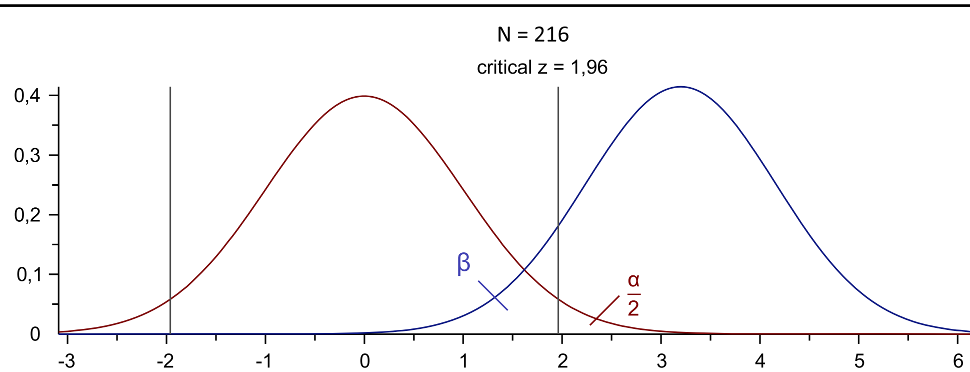

Figure 3. Shows the predicted sample size needed to the desired amount of power (set at 0.90) for the multivariate logistic regression assessed ($n = 216$).

Table 4

Estimated probabilities of achieving TO for different combinations of independent predictors in a multivariate logistic regression model.

	ASA Score (I-II)	Preoperative biliary drainage	Minimally-Invasive approach	PNI > 45	Estimated Probability of TO's achievement
1					0.970
2					0.908
3					0.860
4					0.649
5					0.941
6					0.829
7					0.750
8					0.475
9					0.930
10					0.800
11					0.732
12					0.428
13					0.867
14					0.663
15					0.548
16					0.266

The independent predictors include ASA Score (I–II), preoperative biliary drainage, minimally invasive approach, and prognostic nutritional index (PNI > 45). Each row in the table represents a unique combination of these predictors, and the corresponding estimated probability of achieving TO is reported in the last column. The independent predictors take binary values (0 or 1), which results in 24 = 16 different combinations in total.

ASA, American Society of Anesthesiologists; PNI, prognostic nutritional index; TO, textbook outcome.

early stage disease more easily reach TO, and that this patients are the same ones that are scheduled for minimally invasive approach.

Patients who achieve TO are more likely to promptly initiate adjuvant therapy, with oral capecitabine being the most commonly used regimen: this partially explains the survival benefit of the patient group that reached TO, together with improved

Table 5

Intercept and coefficients for multivariate logistic regression model.

Predictor	Coefficient (β)
Intercept (β_0)	– 0.101
ASA (I/II vs. III/IV)	– 0.907
Preoperative biliary drainage (yes)	0.715
Minimally invasive approach (yes)	1.682
Prognostic nutritional index (> 45)	1.2

ASA, American Society of Anesthesiologists.

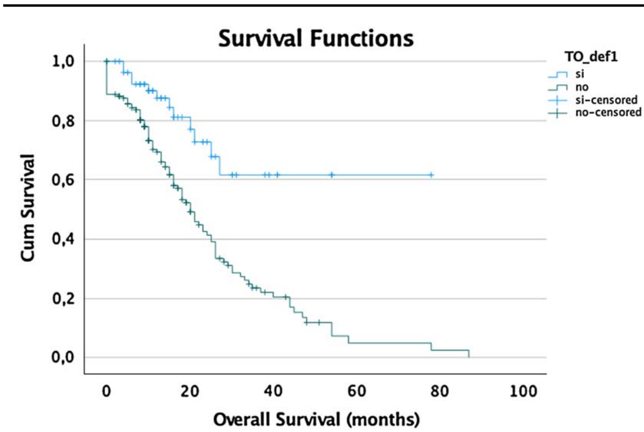

Figure 4. Kaplan–Meier curves showing overall survival (OS) according to the outcome group. TO, textbook outcome.

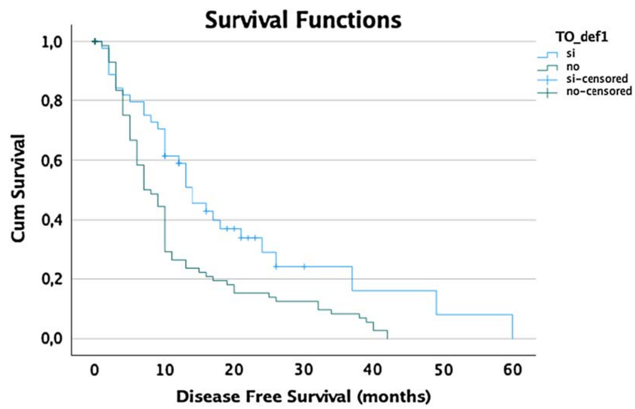

Figure 5. Kaplan–Meier curves showing disease-free survival (DFS) according to the outcome group. TO, textbook outcome.

immunological patency allowing a more effective control of disease spread. Another explanation of the positive effect of achieving TO on long-term outcomes is inherent in the proposed definition of TO: one of the fundamental parameters is the radical resection (R0), which is the only modifiable prognostic factor for both disease-free and overall survival[50]. Moreover, in the proposed TO definition we included the absence of intraoperative transfusion and complications: the impact of these factors on long-term outcomes in malignancies is well known, as they correlate with a higher risk of tumour recurrence due to increased immunosuppression[51].

Limitations

This study has several limitations. First, its retrospective nature required an a posteriori allocation to TO or non-TO groups possibly leading to analytic biases. Moreover, while the importance to develop and test the definition of TO in PHC in a tertiary referral centre is crucial, further future evaluations should focus on the superiority of the proposed TO definition over the conventional TO definition in the setting of liver surgert. Furthermore, a multicenter evaluation of TO in PHC will be advisable in order to detect inter-hospital differences and describe benchmark values, allowing to improve the assessment of surgical care quality.

Conclusion

The TO is a useful patient-centred tool for evaluating the quality of surgical care. The present study demonstrated that achievement of TO in candidates for surgery for PHC in a tertiary referral centre was possible in only one-quarter of patients, mirroring the complexity of the disease and surgery. Since the achievement of TO correlates with better disease-free and overall survival, every effort should be made to ameliorate modifiable aspects prior to surgery. Preoperative nutritional supplementation must be considered in malnourished patients, and preoperative biliary drainage must be placed in selected patients based on future liver remnant and severity and duration of jaundice. Moreover, the implementation of advanced minimally invasive programs plays a kay role in improvement postoperative outcomes, increasing the chance to obtain TO.

Ethical approval

Liver registry San Raffaele, Comitato Etico OSR, STS-CE 057/4, 14/07/2021.

Consent

Informed consent was not required for this Cohort Study.

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Author contribution

L.C.: writing the paper. R.M.: data collection and analysis. R.F.: study concept and design. F.P.: data interpretation. A.C.G.: data interpretation. D.L.: review of the paper. L.A.: supervisor.

Conflicts of interest disclosure

None.

Research registration unique identifying number (UIN)

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Guarantor

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Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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