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THE ROLE OF RADIAL MARGIN STATUS IN PERIHILAR CHOLANGIOCARCINOMA

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THE ROLE OF RADIAL MARGIN STATUS IN PERIHILAR CHOLANGIOCARCINOMA

Perihilar cholangiocarcinoma (PHCC) is the most frequent type of biliary cancer representing approximately 60% of all cholangiocarcinoma. It is an aggressive tumor of the extrahepatic bile ducts placed at the biliary confluence proximal to the origin of the cystic duct. It was first described by Altemeier in 1957 and then well defined by Klatskin in 1965. Prognosis of peri-hilar cholangiocarcinoma is poor because of the frequent delay of both symptoms and diagnosis. About 30% of patients are deemed unresectable at diagnosis and died within 1 year usually for liver failure or cholangitis. The management of patients with PHCC is complex and curative-intent resection is the most effective treatment associated with long-term survival. The goal of surgery is to obtain negative margins while preserving sufficient volume and function of remnant liver with adequate portal venous and hepatic arterial blood supply. Surgery of PHCC is technically demanding since it involves a major hepatectomy with en-bloc resection of caudate lobe and extrahepatic bile duct. Furthermore, to achieve negative margins, it may be necessary to perform concomitant vascular resection or pancreatoduodenectomy. Despite this aggressive approach, recurrence is often observed considering 5-year RFS below 15%, and 5-year OS that barely exceeds 40%.

The literature reports that survival rates are better in patients with negative margins and surprisingly R0 resections range between 19% and 95%. This variability is probably due to different surgical strategies and the pathologist's expertise with specimens.

The evaluation of surgical margins in resected PHCC remains a challenging issue. Both ductal (DM) and radial margin (RM) should be considered to define true radical resections (R0). Although DM status is routinely described in pathological report, RM status is often overlooked. Currently, detailed pathological reports are lacking and there is a likelihood of misinterpreting residual disease status due to the missing of RM description and the utilization of various definitions for surgical margins. Therefore, the frequency of true R0 and its impact on survival might be biased.

The objective of the present PhD research project was to improve the evaluation of RM status, assess its impact on survival, and investigate the ensuing implications for surgical planning.

The results of this work have been published in two papers listed below:

1) The Prognostic Role of True Radical Resection in Perihilar Cholangiocarcinoma after Improved Evaluation of Radial Margin Status. Cancers (Basel). 2022.
2) The relevance of radial margin status in perihilar cholangiocarcinoma: a state-of-the-art narrative review. Digestive Surgery. 2023

The prognostic role of true radical resection in perihilar cholangiocarcinoma after improved evaluation of radial margin status

ABSTRACT

Background. The evaluation of surgical margins in resected perihilar cholangiocarcinoma (PHCC) remains a challenging issue. Both ductal (DM) and radial margin (RM) should be considered to define true radical resections (R0). Although DM status is routinely described in pathological report, RM status is often overlooked. Therefore, the frequency of true R0 and its impact on survival might be biased.

Objective. To improve the evaluation of RM status and investigate the impact of true R0 on survival.

Methods. From 2014 to 2020, 90 patients underwent curative surgery for PHCC at Verona University Hospital, Verona, Italy. Both DM (proximal and distal biliary margin) and RM (hepatic, periductal, and vascular margin) status were evaluated by expert hepatobiliary pathologists. Patients with lymph-node metastases, or positive surgical margins (R1) were candidate to adjuvant treatment. Clinicopathological and survival data were retrieved from an Institutional database.

Results. True R0 were 46% (41) and overall R1 were 54% (49). RM positivity resulted higher than DM positivity (48% versus 27%). Overall survival was better in patients with true R0 than in patients with R1 (median survival time: 53 vs 28 months; P=0.016). Likewise, the best recurrence-free survival was observed in R0 compared with R1 (median survival time: 32 vs 15 months; P=0.006). Multivariable analysis identified residual disease status as independent prognostic factor of both OS (P=0.009, HR=2.68, 95% CI=1.27–5.63) and RFS (P=0.009, HR=2.14, 95% CI=1.20–3.83).

Conclusion. Excellent survivals are observed in true R0 patients. The improved evaluation of RM status is mandatory to properly stratified prognosis and select patients for adjuvant treatment.

BACKGROUND

Perihilar cholangiocarcinoma (PHCC) is the most common type of biliary tract cancer and has a dismal prognosis with 5-year survival rates of 35-44% in high-volume centers.[1,2,3] Surgery is the only treatment that can provide the chance for a cure. Surgical resection requires a major hepatectomy with en bloc resection of the caudate lobe and the extrahepatic bile duct, in addition to locoregional lymphadenectomy. Also, concomitant vascular resections or pancreatoduodenectomy are performed to aim for a radical resection (R0). R0 is defined as the histological evidence of tumor-free margins and is a strong positive prognostic factor since ensures long recurrence-free (RFS) and overall survival (OS).[4] The correct evaluation of residual disease in resected PHCC must consider both the ductal (DM) and radial margin (RM) status.[5] DM status is determined by the proximal and distal biliary margins whereas RM status by the transection margin of the hepatic parenchyma along with the dissection margin of the hepatoduodenal ligament and the vascular margin. Unfortunately, recent studies[6,7] showed that pathological reports of resected PHCC offer a poor assessment of surgical margins, especially in Western Centers where completeness of pathology reports ranges from 10% to 45%. RM status is frequently overlooked even though a positive RM is observed more often than a positive DM. Furthermore, the criteria for the definition of R0 are not univocal and the differences concern the length of tumor clearance.[8] For the above reason, the reported rates of R0 in published literature are very variable ranging between 19% to 95%[9,10,11,12,13] and it is not always clear which surgical margins were evaluated and how their status was defined. Incomplete assessment of surgical margins status may overestimate R0 resections and thus prevent proper staging and comparison of survival studies. Our pathology service has gained extensive experience in the systematic evaluation of DM and RM status of resected PHCC by applying a standardized protocol for grossing and reporting. The aim of this study is to review our tertiary center experience in surgical treatment of PHCC after improved evaluation of RM status and consequently investigate the impact of true R0 on survival.

PATIENTS AND METHODS

Study population

Consecutive patients who underwent curative intent resection for PHCC from 2014 through 2020 at the Division of General and Hepatobiliary Surgery, Verona University Hospital, Italy were identified from an institutional database. All surgical specimens were submitted to an improved pathological examination in order to properly identify and describe RM status. PHCC was defined as a biliary tumor involving the hepatic duct confluence according to the definition of the Japanese Society of Biliary Surgery (JSBS).[14] Exclusion criteria were resection with macroscopic residual disease (R2), evidence of metastases including lymph-node metastases beyond the hepatoduodenal ligament, and excision of only the extrahepatic bile duct. Written informed consent was obtained in all patients before surgical procedure. Data collection and analysis were performed according to the institutional guidelines conforming to the ethical standards of the Helsinki Declaration and the study was approved by local ethics committee.

Preoperative management

The type of surgery was planned according to the hepatic location of the tumor, the presence of vascular invasion, the liver function, and the future remnant liver volume. Patients with tumor involvement of the portal vein and hepatic artery on the side of the future remnant liver without the possibility of a vascular reconstruction, extensive bilateral proximal infiltration beyond secondary biliary radicles and/or massive extension into the liver parenchyma were deemed unresectable. Jaundice patients underwent either endoscopic or transhepatic biliary drainage and surgery was performed after serum total bilirubin levels dropped to less than 3 mg/dL. Liver function was assessed by indocyanine green retention rate test at 15 min and levels less than 14 %/min were considered appropriate for major hepatectomy. When the future liver remnant volume was less than 35% of the total, portal vein embolization (PVE) was performed. MRI and CT scan with contrast enhancement were routinely performed for tumor staging and selected patients also underwent PET scan to evaluate presence of extrahepatic disease. The extent of ductal infiltration was assessed by cholangiography or cholangioscopy with mapping biopsy and classified according to the Bismuth-Corlette classification. Preoperative chemotherapy and/or radiotherapy was not routinely administrated.

Surgery

Resectability was assessed by abdominal exploration and intraoperative ultrasound. The parenchymal transection was performed using the ultrasonic surgical aspirator system with intermittent Pringle's maneuver. Resection of liver segment I was always performed whereas resection of the portal vein and/or hepatic artery was performed only when macroscopic vascular invasion was suspected. Combined pancreatoduodenectomy was performed in cases of tumor spreading towards the common bile duct or bulky node metastases around the pancreatoduodenal region. In order to easily evaluate the RM status and increase the chance of R0, we isolate the common bile duct towards the upper border of the pancreas and the hepatic artery as far as possible from the tumor, then we proceed towards the hilum peeling the portal vein up to its confluence with complete en bloc excision of the bile duct and the fatty tissue of the hepatoduodenal ligament. Dissection of vessels was limited to the future remnant liver avoiding unnecessary dissection and detachment of vessels from the peritumoral tissue if technically possible. Frozen sections of proximal and distal bile duct margins were routinely performed. If positive DM, additional bile duct resection was performed as far as technically feasible to obtain R0. Lymphadenectomy was classified according to the classification of the JSBS.[14] Lymph nodes of the hepatoduodenal ligament (station 12), the proper hepatic artery (station 8) and the posterior surface of the head of the pancreas (station 13) were routinely retrieved. Interaortocaval lymph nodes (station 16) were retrieved only when macroscopically abnormal.

Pathological evaluation

The specimens were fixed in 4% buffered formalin for approximately 24-48 hours. Then, all surgical margins were stained according to a color code for easy recognition under the microscope. Briefly, the resection margin of the distal bile duct, proximal bile duct(s), hepatic artery, and portal vein were sampled. After, the specimens were sliced in 3- to 5-mm-thick slices following an axial plane perpendicular to the extrahepatic bile duct axis up to the biliary confluence in order to left intact the periductal tissue surrounding the tumor that is the dissection margin of the hepatoduodenal ligament (retroperitoneal surface). Crossed the biliary confluence, the slicing carried on in a coronal plane to better appreciate the tumor growth along the intrahepatic bile ducts and identify suspected infiltration of the hepatic parenchymal transection margin. The samples were embedded in paraffin and prepared for microscopic examination using hematoxylin and eosin staining. Pathological reports were drafting according to the International Collaboration on Cancer Reporting[15] and the TNM Classification of Malignant Tumors by the International Union Against Cancer (8^{th} edition, 2016). DM was classified as positive when invasive carcinoma was identified at the proximal or distal bile duct margin, literally at the edge of surgical cut. DM with different grade of dysplasia up to carcinoma in situ was considered as negative.[16] RM was classified as positive when tumor cells were identified less than 1 mm from the transection plane of the hepatic parenchyma, the dissection plane of the hepatoduodenal ligament, or the vascular stumps. The involvement of the peritoneal surface of the hepatoduodenal ligament by the tumor was not considered as a margin since the surgeon does not cut or dissect any tissue.[15] Finally, surgery was defined as (true) R0 if both DM and RM status was negative or as R1 if either DM or RM was positive.

Follow-up

The decision to administer adjuvant therapy was made by a multidisciplinary team. In principle, patients with lymph node metastases or R1 resection are candidates for chemotherapy and/or radiotherapy. All patients underwent surveillance for recurrence with CT scan or MRI usually every 4-6 months. In cases of questionable radiological diagnosis, PET scan was performed. Pathologic confirmation was not routinely carried out. When feasible, recurrence was treated with either surgery, or chemotherapy, or radiotherapy.

Statistical analysis

Statistical analysis was performed with SPSS (version 20.0, SPSS Inc.). Categorical variables were expressed in numbers and percentages and were compared among groups using Fisher’s exact test or the Pearson’s chi-square test, as appropriate. Continuous variables were expressed as median values with the interquartile range (IQR) and were compared using Mann-Whitney U test. RFS and OS curves were constructed using the Kaplan-Meier method from the time of surgery to the time of recurrence, death or last follow up. Differences between survival probabilities were compared using the log-rank test excluding from the analysis postoperative deaths, defined as any deaths occurring within 90 days of surgery or during the same hospital stay, whenever it occurred. A multivariate analysis was performed using the Cox proportional hazards model to identify prognostic factors by backward elimination. $P \leq 0.05$ was considered to indicate statistical significance.

RESULTS

Baseline characteristics of our cohort

A total of 90 patients were included in this study. Median age was 70 (IQR, 62-76) year and 60 (67%) patients were male. Median CEA and CA19-9 were 2 (IQR, 2-2.8) ng/mL and 222.8 (IQR, 47.5-918.8) U/mL, respectively. Seventy-seven (86%) patients underwent preoperative biliary drainage. Radiologic imaging showed biliary strictures as Bismuth type IV in 32 (36%) patients. Thirteen (14%) patients received portal vein embolization. Forty-nine (54%) patients underwent left hepatectomy, 28 (31%) right hepatectomy, 6 (7%) left trisectionectomy, 4 (4%) mesohepatectomy, 2 (2%) right trisectionectomy, 1 (1%) hepatopancreatoduodenectomy. Vascular resection was performed in 15 (17%) patients, namely 14 (16%) portal vein resection and 1 (1%) hepatic artery resection.

Histopathological findings

The most common tumor growth pattern was the periductal infiltrating type which was observed in 72 (80%) patients whereas satellitosis was observed in 9 (10%) patients. Median tumor diameter was 2.5 (IQR, 1.7-3.5) cm and 46 (51%) patients had pT3/4 tumor. Poorly differentiated or undifferentiated adenocarcinoma was noticed in 25 (28%) patients. Fifty-one (57%) patients had positive lymph nodes and median number of lymph node harvested was 9 (IQR, 6-13). Two (2%) patients had PHCC stage 1, 21 (23%) stage II, 11 (12%) stage IIIA, 5 (6%) stage IIIB, 41 (46%) stage IIIC, 10 (11%) stage IVA. Demographic, clinicopathological, and operative features were summarized in table 1.

Table 1. Demographic, clinicopathological, and operative features of 90 perihilar cholangiocarcinoma patients compared according to residual disease and radial margin status

Variables	R0 (n=41)	R1 (n=49)	P value	RM- (n=47)	RM+ (n=43)	P value
Age, years	69 (58-77)	70 (65-76)	0.279	70 (62-76)	70 (63-76)	0.475
Gender, male	22 (54)	38 (78)	**0.017**	27 (51)	33 (77)	0.052
CEA ng/mL	2 (2-2.7)	2 (1.6-3.4)	0.967	2 (2-2.7)	2 (1.7-4)	0.481
CA19-9 U/mL	81 (26-538)	429 (93-1194)	**0.012**	75 (27-587)	439 (156-1151)	**0.014**
Bismuth classification			0.069			0.093
Type II	4 (10)	0 (0)		4 (9)	0 (0)	
Type IIIa	6 (15)	13 (27)		9 (19)	10 (23)	
Type IIIb	18 (44)	17 (35)		21 (45)	14 (33)	
Type IV	13 (32)	19 (39)		13 (28)	19 (44)	
PVE	5 (12)	8 (16)		7 (15)	6 (14)	
Type of resection			0.285			0.349
Left-sides hepatectomy	29 (68)	27 (55)		32 (68)	24 (56)	
Right-sides hepatectomy	11 (29)	19 (39)		14 (30)	16 (37)	
Mesohepatectomy	1 (2)	3 (6)		1 (2)	3 (7)	
Vascular resection	4 (10)	11 (22)	0.108	5 (11)	10 (23)	0.109
Histopathological tumor grade			**0.047**			0.153
Well/moderately	33 (80)	30 (61)		36 (77)	27 (63)	
Poorly/undifferentiated	8 (20)	19 (39)		11 (23)	16 (37)	
Satellitosis	1 (2)	8 (16)	**0.029**	1 (2)	8 (19)	**0.009**
Tumor diameter, cm	2 (1.5-3)	3 (2-4)	**0.025**	2 (1.5-3.5)	3 (2-4)	**0.044**
AJCC pT classification			0.094			0.202
T1/T2	24 (59)	20 (41)		26 (55)	18 (42)	
T3/T4	17 (41)	29 (59)		21 (45)	25 (58)	
Perineural invasion	39 (95)	45 (92)	0.534	43 (91)	41 (95)	0.463
Ductal margin positivity	0 (0)	24 (49)	**<0.0001**	6 (13)	18 (42)	**0.002**
Lymph node metastasis	21 (51)	30 (61)	0.340	25 (53)	26 (60)	0.487
Lymph node harvasted	8 (6-13)	10 (7-16)	0.074	8 (5-13)	10 (7-16)	0.082
Severe complication (Dindo ≥ 3)	9 (22)	20 (41)	0.129	11 (23)	18 (42)	0.128
90-day/in-hospital Mortality	1 (2)	4 (8)	0.238	1 (2)	4 (9)	0.138
Adjuvant chemo/radiotherapy	23 (56)	32 (65)	0.372	29 (62)	26 (60)	0.904

Categorical variables are expressed in numbers and percentages. Continuous data are expressed as median values and interquartile range.

Abbreviations: BMI, Body Mass Index; ASA, American Society of Anesthesiologists; CEA, Carcino-Embryonic Antigen; CA19-9, Carbohydrate Antigen 19-9; PVE, Portal Vein Embolization; PI, periductal Infiltration; IG, Intraductal growth, MF, Mass Forming; AJCC, American Joint Committee on Cancer staging system 8th edition.

Surgical margins

A total of 41 (46%) patients underwent R0 whereas the remaining 49 (54%) patients had R1. In particular, DM positivity was observed in 24 (27%) and RM positivity in 43 (48%) patients. The site of positive DM was proximal bile duct in 24 (27%) patients and distal bile duct in 5 (6%) patients. The site of positive RM was the periductal tissue in 39 (43%) patients, the liver parenchyma in 11 (12%) patients, and the vascular stumps in 4 (4%) patients (figure1). Six (7%) patients had positive DM alone, 18 (20%) had both positive DM and positive RM, and 25 (28%) had positive RM alone.

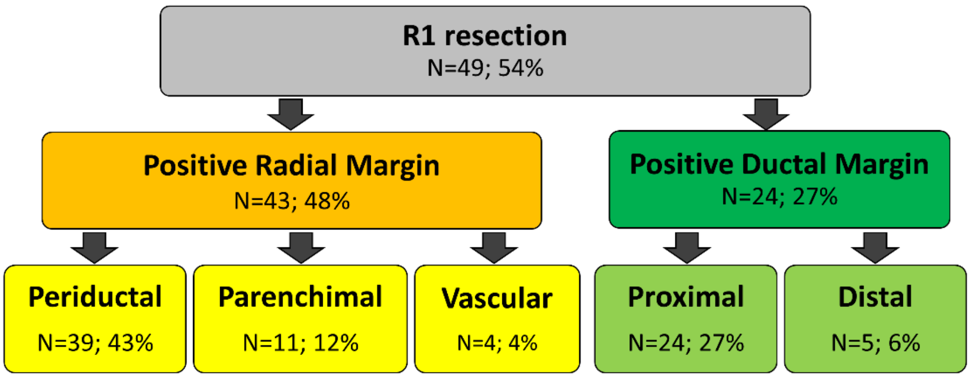

Figure 1. Comprehensive analysis of surgical margins positivity in R1 resection.

Short- and long-term outcomes

Morbidity was 71% (64) and severe complications (Dindo grade ≥ 3) were observed in 32% (29) of cases. The main complications were biliary fistula and post-hepatectomy liver failure which occurred in 22 (24%) and 22 (24%) patients, respectively. 90-day mortality was 6% (5). Fifty-five (61%) patients underwent adjuvant therapy. Different regimens were used for chemotherapy and median number of treatment cycles was 6 (IQR, 2-8). Regarding radiotherapy, the radiation dose of 45Gy was administered in 25 fractions. In our cohort, the rate of OS at 1-, 3-, and 5-year was 88%, 60%, and 36%, respectively; the rate of RFS at 1-, 3-, and 5-year was 64%, 28, and 13%, respectively. The median follow-up time was 41 months.

Overall survival was better in patients with R0 than in patients with R1 (median survival time (MST) 53 vs 28 months; P = 0.016; hazard ratio (HR) 2.42, 95% confidence interval (CI) 1.18–4.95). Likewise, the best RFS was observed in R0 compared with R1 (MST 32 vs 15 months; P = 0.006; HR 2.23, 95% CI 1.26–3.94). OS and RFS curves are showed in figure 2.

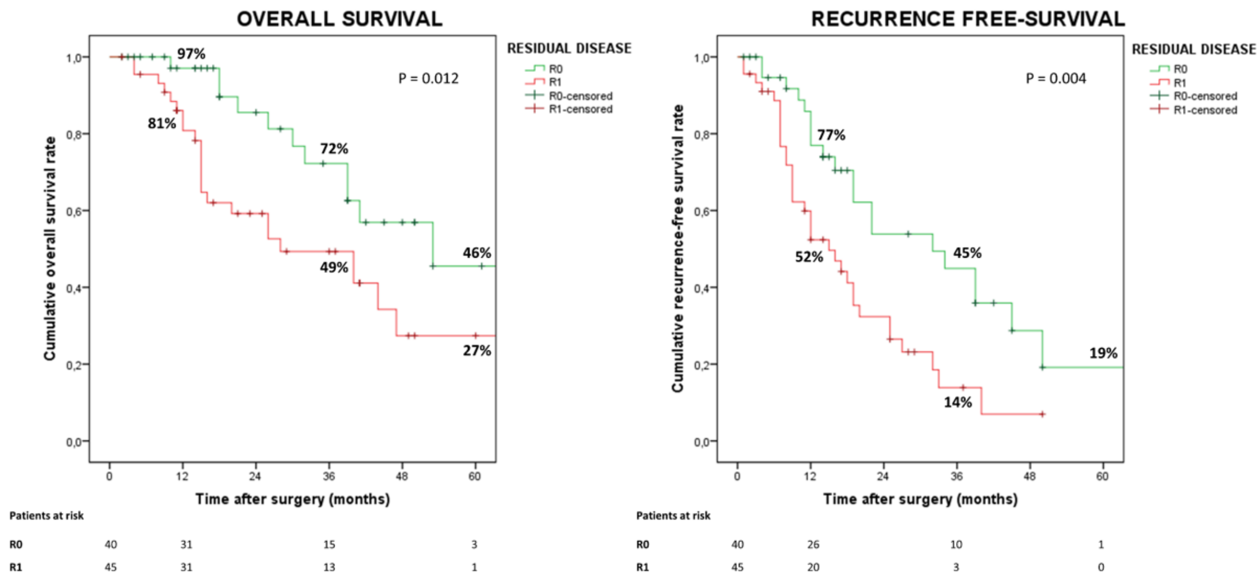

Figure 2. Overall and recurrence-free survival according to residual disease status.

RM status, rather than DM status, was associated with OS (P = 0.013) and RFS (P = 0.031). Patients with negative RM compared to those with positive RM showed both prolonged OS (MST 53 vs 28 months; P < 0.017; HR 2.35, 95% CI 1.17–4.75) and RFS (MST 32 vs 15 months; P < 0.037; HR 1.80, 95% CI 1.04–3.12) (figure 3).

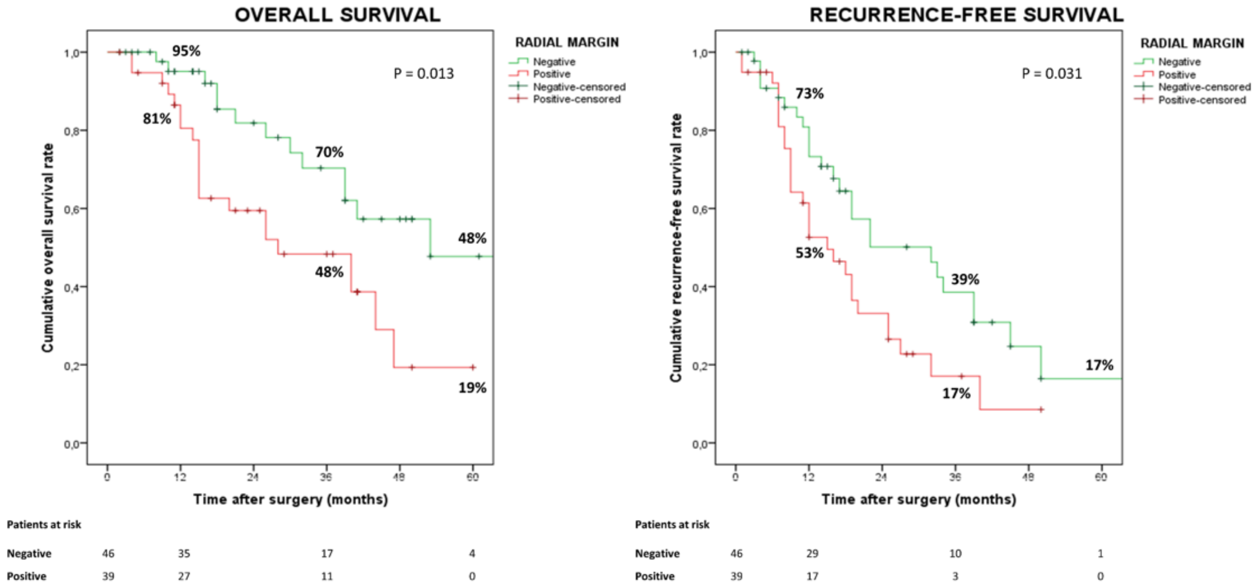

Figure 3. Overall and recurrence-free survival according to residual disease status.

Survival probabilities were also analyzed according to the operative procedures performed (extended versus non-extended hepatectomies, left-sided versus right-sided hepatectomies), but no significant differences were observed. Conversely excellent survivals were observed in patients with both negative lymph-nodes and surgical margins (figure 4).

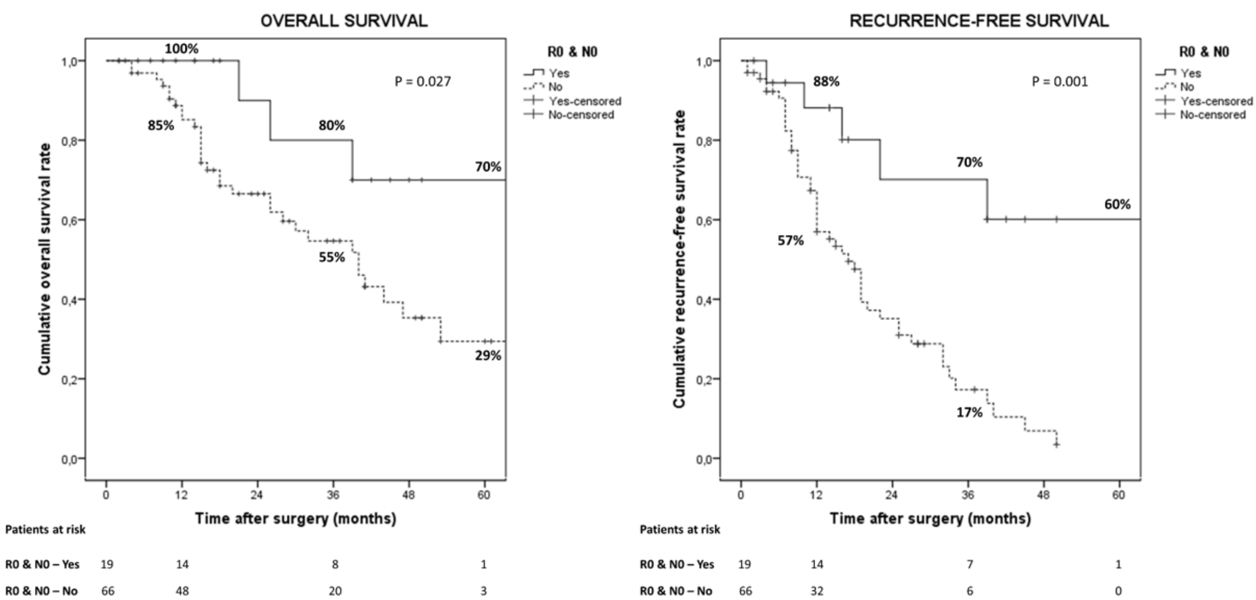

Figure 4. Overall and recurrence-free survival according to residual disease and lymph-nodes status.

Residual disease status was an independent prognostic factors for both OS (P = 0.009, HR = 2.68, 95% CI = 1.27–5.63) and RFS (P = 0.009, HR = 2.14, 95% CI = 1.20–3.83). Multivariable analyses are reported in table 2 and 3.

Table 2. Univariable and multivariable analysis of overall survival

		OS (%)			Univariable	Multivariable	
Variables	**N**	**1-yr**	**3-ys**	**5-yr**	**P value**	**HR (95% CI)**	**P value**
Gender					**0.049**		
Female	29	96	74	54			
Male	56	89	53	28			
Bismuth type IV					0.875		
No	53	94	60	40			
Yes	32	79	58	21			
Side of hepatectomy*					0.489		
Left	54	90	61	37			
Right	28	87	54	22			
Combined vascular resection					0.211		
No	73	89	63	38			
Yes	12	80	41	21			
Tumor diameter, cm					0.213		
<3	45	90	65	39			
≥3	40	86	54	33			
Histopathological tumor grade					**0.042**		**0.045**
Well/moderately	60	95	68	35		1	
Poorly/undifferentiated	25	72	37	37		2.07 (1.02-4.21)	
Perineural invasion					0.405		
No	6	63	31	/			
Yes	79	90	60	37			
AJCC pT classification					0.086		
T1/T2	42	92	71	59			
T3/T4	43	84	50	22			

Residual disease status					**0.012**		**0.009**
R0	40	97	72	46		1	
R1	45	81	49	27		2.68 (1.27-5.63)	
Lymph node					**0.015**		**0.008**
N0	36	93	73	63		1	
N+	49	84	49	20		2.73 (1.29-5.75)	
Dindo classification ≥ 3					0.960		
No	56	91	61	33			
Yes	29	82	55	/			
Adjuvant therapy					0.823		
No	30	85	63	38			
Yes	55	90	58	35			

Five postoperative deaths, defined as any deaths occurring within 90 days of surgery or during the same hospital stay, whenever it occurred, were excluded from the analysis.

*Three mesohepatectomy were excluded.

Abbreviations: AJCC, American Joint Committee on Cancer staging system 8th edition.

Table 3. Univariable and multivariable analysis of recurrence-free survival

		RFS (%)			Univariable	Multivariable	
Variables	**N**	**1-yr**	**3-ys**	**5-yr**	**P value**	**HR (95% CI)**	**P value**
Gender					0.976		
Female	29	62	30	/			
Male	56	64	27	9			
Bismuth type IV					0.583		
No	53	62	23	/			
Yes	32	66	35	14			
Side of hepatectomy*					0.548		
Left	54	60	29	/			
Right	28	75	20	/			
Combined vascular resection					0.122		
No	73	64	33	15			
Yes	12	62	/	/			

Tumor diameter, cm					0.064		
<3	45	70	38	14			
≥3	40	56	19	/			
Histopathological tumor grade					0.227		
Well/moderately	60	69	26	12			
Poorly/undifferentiated	25	51	33	/			
Perineural invasion					0.932		
No	6	50	25	/			
Yes	79	65	29	12			
AJCC pT classification					**0.014**		**0.030**
T1/T2	42	67	48	/		1	
T3/T4	43	61	11	4		1.85 (1.05-3.24)	
Residual disease status					**0.004**		**0.009**
R0	40	77	45	19		1	
R1	45	52	14	/		2.14 (1.20-3.83)	
Lymph node					0.069		
N0	36	67	38	33			
N+	49	61	20	/			
Dindo classification ≥ 3					0.884		
No	56	66	27	13			
Yes	29	59	38	/			
Adjuvant therapy					0.076		
No	30	63	38	31			
Yes	55	64	22	/			

Five postoperative deaths, defined as any deaths occurring within 90 days of surgery or during the same hospital stay, whenever it occurred, were excluded from the analysis.

*Three mesohepatectomy were excluded.

Abbreviations: AJCC, American Joint Committee on Cancer staging system 8th edition.

DISCUSSION

The improved evaluation of RM status in resected PHCC allows to detect true RO. The present study shows that RM positivity is the most frequent cause of R1, and multivariable analysis identifies residual disease status as the main independent factor affecting both RFS and OS.

Unfortunately, pathological reports of several Western Centers do not provide a thorough assessment of all surgical margins in resected PHCC. A French multi-institutional survey[6] found that RM status was frequently overlooked, indeed periductal soft tissue circumferential margin, vascular margin, and liver margin were assessed in only 10%, 13%, and 20% of cases, respectively. Likewise, a Dutch audit[7] demonstrated that residual disease status was unclear in 29% of cases and could be re-classified from R0 to R1 in 15%.

Our hepatobiliary pathologists have gained more than 10 year of experience with the systematic evaluation of both DM and RM status developing a standardize protocol for grossing and reporting according to the ICCR guidelines.[15] We believe that the correct evaluation of RM status is hindered by the complexity of PHCC specimen and above all by the lack of familiarity with the identification of the periductal circumferential margin in the soft tissue of the hepatoduodenal ligament. In fact, the periductal margin is a dissection plane unlike ductal, hepatic and vascular margin that are resection margins.

Stremitzer et al.[17] sought to investigate the prognostic role of the isolated positive periductal dissection margin by retrospectively review data of 83 patients from two European Centers over a period of 10 year (2006-2016). The authors considered DM and hepatic transection margin as "surgical margin" and the interface of the extrahepatic bile duct with the surrounding lymphatic/fatty tissue as "circumferential margin". The median OS in patient with R0, isolated positive circumferential margin, and positive surgical margins was 45.6, 32.7 and 14.5 months, respectively ($P = 0.011$) whereas the median RFS showed no statistically significant differences. Both positive isolated circumferential and positive surgical margins were predictors of poor OS at multivariable Cox regression analysis.

Mueller et al. identify R0 $\geq$ 56.7% and R1 $\leq$ 43% as benchmark cut-offs for PHCC surgery, however, it is not clear whether RM status was assessed in all the high-volume Centers that participated in the study. In our cohort, if the assessment of surgical margins was incomplete, in other words by neglecting the condition of RM status, the rough R0 survival curve became steeper than the true R0 (median survival time 40 vs 53 months). Therefore, 25 (28%) cases could be misclassified as R0 (figure 5).

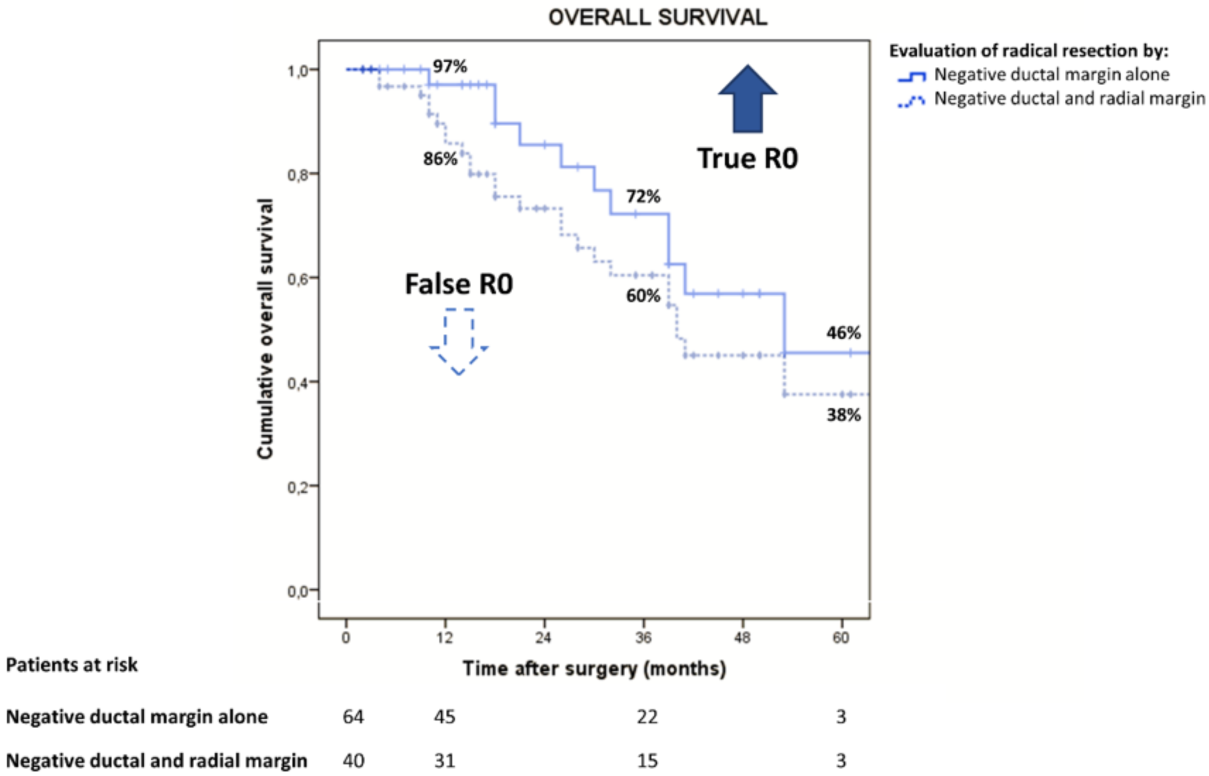

Figure 5. Overall survival in perihilar cholangiocarcinoma by different evaluation of radical re-section.

Very few studies have specifically addressed the issue of RM status in resected PHCC[8,18,19] and the group of Nagoya University, Japan, published the largest series so far.[20] This tertiary level Eastern Center retrospectively analyzed 478 consecutive cases over a period of 5 years (2001-2006) and reported 18% (85) of R1. RM positivity was 11% (52) and resulted the most common cause of residual disease. In particular, periductal margin positivity was 4% (20), hepatic margin 4% (20), and vascular 3% (12). The reason for this surprisingly low percentages could be explained by a different surgical strategy or patient selection. Shinohara et al.[20] found that survival time of patient with positive RM was significantly shorter compared to that of R0 resection (median survival time 2.1 vs 4.9 years; $P < 0.001$; HR = 2.06, 95% CI = 1.49–2.84). Instead, no survival difference was noted between RM and DM positivity. Both RM (HR = 1.48; 95% CI = 1.05 - 2.08; P = 0.023) and DM positivity were independent prognostic factors of poor OS.

D'Amico et al.[21] retrospectively analyzed 75 patients over a period of 12 years (2005-2017) and reported 45% (34) of R1. The authors confirmed higher rate of RM positivity (35%, N=26) compared to DM positivity (23%, N=17) and observed, instead, that patients with isolated positive RM (23%, N=17) had statistically similar OS and RFS to patients with R0 (55%, N=41). The latter study, though, had a smaller sample, only 9% (7) of pT3/4 tumors and included 6 PHCC Bismuth type I who did not undergo hepatic resection.

Recent systematic reviews and meta-analyses of resected PHCC reported that positive surgical margins are prognostic factors of poor survival,[4,22] however even among resected patients with declared negative surgical margins, short RFS and OS are frequently observed.[9,23] We speculate that this finding may be due to the lack of a comprehensive evaluation of RM status. We also hypothesized that short RM tumor clearance might be related to high rate of local recurrence and short survivals. If we select a cut-off of 0 mm tumor clearance to define RM positivity, we still observe significantly different survivals curves by RM and residual disease status. Instead, selecting a cut-off of less than 2 mm, we observe no survival differences. Therefore, although the cut-off of 1 mm tumor clearance arbitrarily used to define RM positivity seems to be appropriate, the authors are aware that no definitive conclusion can be drawn by these findings since the sub-cohorts with different RM tumor clearance are small (table 4).

Table 4. Definition of positive radial margin according to different tumor clearances and reclassification of residual disease status with the corresponding 5-year survivals rates

RM clearance	RM-	RM+	5-y OS RM-/RM+	P value	5-y RFS RM-/RM+	P value	R0	R1	5-y OS R0/R1	P value	5-y RFS R0/R1	P value
0 mm	68 (76%)	22 (24%)	39/26%	**0.012**	14/0%	0.053	50 (56%)	40 (44%)	25/42%	**0.015**	20/0%	**0.003**
<1 mm	47 (52%)	43 (48%)	48/19%	**0.013**	17/0%	**0.031**	40 (44%)	50 (56%)	28/46%	**0.014**	19/0%	**0.006**
<2 mm	8 (9%)	82 (91%)	50/32%	0.279	17/0%	0.393	8 (9%)	82 (91%)	32/50%	0.279	17/0%	0.393

Recently, D'Souza et al.[24] pointed out that there is no universal agreement on the definition of what constitutes R0 and how wide the tumor-free margin should be, but failed to prove a significant impact of the chosen definition of R0 (>0 mm or >1 mm to cancer-involved resection margin or dissection plane) on OS or RFS. Seyama et al.[25] in a series of 58 consecutive major hepatectomies found that a surgical margin over 5 mm provided a significantly better survival. On the other hand, the survival after R0 with narrow margin (< 5 mm) was nearly the same as after R1.

The main limitations of the present study are the small sample, the analysis of data from a single Center, and the use of different regimens of chemotherapy. Nevertheless, our findings are of great value since the evaluation of RM status was assessed prospectively and the tumor distance from surgical margin was precisely classified. Thus, the risk of underestimating RM positivity is low and the frequency of reported true R0 is reliable. Lastly, the present study reported the largest Western data so far and first demonstrate RM positivity as prognostic factor of both poor OS and RFS. The improved evaluation of RM status could lead to a more accurate selection of patients for adjuvant therapy. In fact, little evidence exists about survival benefit of chemo/radiotherapy in patients underwent PHCC resection with R1[26,27,] and the lack of information about RM status jeopardizes the credibility of survival studies.

CONCLUSION

Evidence of negative surgical margins is a strong predictor of good survivals hence both the RM and DM status need to be analyzed in PHCC specimens. Only by properly distinguishing patients between true R0 and R1, the prognosis can be adequately stratified. Furthermore, since residual disease status is one of the main criteria for the administration of adjuvant treatments, the improved evaluation of RM status is mandatory to compare survival studies.

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The Relevance of Radial Margin Status in Peri-hilar Cholangiocarcinoma: a State-of-the-art Narrative Review

ABSTRACT

Background. Prognosis of peri-hilar cholangiocarcinoma (PHCC) is poor and curative-intent resection is the most effective treatment associated with long-term survival. Surgery is technically demanding since it involves a major hepatectomy with en-bloc resection of caudate lobe and extrahepatic bile duct. Furthermore, to achieve negative margins, it may be necessary to perform concomitant vascular resection or pancreatoduodenectomy. Despite this aggressive approach, recurrence is often observed considering 5-year RFS below 15%, and 5-year OS that barely exceeds 40%.

Summary. The literature reports that survival rates are better in patients with negative margins and surprisingly R0 resections range between 19% and 95%. This variability is probably due to different surgical strategies and the pathologist's expertise with specimens. In fact, a proper pathological examination of residual disease should take into consideration both the ductal and the radial margin (RM) status. Currently, detailed pathological reports are lacking and there is a likelihood of misinterpreting residual disease status due to the missing of RM description and the utilization of various definitions for surgical margins.

Key Messages. The aim of PHCC surgery is to achieve negative margins including RM. More clarity in reporting on RM is needed to define true radical resection and consistent design of oncological studies for adjuvant treatments.

INTRODUCTION

Perihilar cholangiocarcinoma (PHCC) is the most common biliary tract cancer, accounting for about 60% of all cholangiocarcinomas [1]. Curative-intent resection is the only treatment offering patients the chance for a cure [2]. The resectability of PHCC depends on various factors such as tumor location, extension along biliary ducts, radial growth, relationship with hilar vessels, the estimation of adequate future remnant liver volume, and the absence of metastatic disease. Unfortunately, the prognosis is greatly influenced by the prevalence of advanced stages of the disease upon initial diagnosis or surgical examination [3]. Additionally, surgery is technically demanding since requires a major hepatectomy with en-bloc resection of the caudate lobe and extrahepatic bile duct and regional lymphadenectomy. In case of advanced local disease, concomitant vascular resections or pancreatoduodenectomy are performed if histologically negative resection margins can be reached [4]. Although this aggressive surgical approach resulted in improved long-term survival, the prognosis remains still dismal. The 3- and 5-year overall survival (OS) rate ranges from 27% to 56% and from 13% to 42%, respectively [5]. These results reflect the high risk of recurrence considering 3- and 5-year recurrence-free survival (RFS) rates as low as 35% and 15%, respectively [6]. A recent meta-analysis showed that survival rates are better in patients with a well-differentiated tumor, with no lymph node metastasis, and with negative surgical margin [5]. Of these prognostic factors affecting long-term survivals, resection margin is the only one that can be affected by the surgeon. In fact, tumor-related factors as lymph nodes status and differentiation grade are determined at presentation and cannot be modified, whereas surgeon's skill and expertise can increase the chances of obtaining R0 resection. The reported rates of R0 resection in the literature are very variable, ranging from 19% to 95% [7]. Several factors likely contribute to the differences observed between studies, not only the variation in patient selection criteria and surgical strategies, but also the complexity of surgical specimen and the lack of a systematic evaluation of the radial margin (RM) status. Obtaining clear resection margins has always been the core issue of surgery, therefore a proper pathological examination of residual disease should take into consideration both ductal margin (DM) and RM status.

The evaluation of RM status and the ensuing implications for surgical planning are reviewed and discussed in relation to survival outcomes.

MAIN TEXT

Definition of surgical margins in perihilar cholangiocarcinoma

PHCC has the characteristic of growing along the bile ducts and laterally spreading towards the common bile duct and the intrahepatic bile ducts, but it can also infiltrate the liver parenchyma and the periductal soft tissue of the hepatoduodenal ligament via a submucosa route. Hence, the length of longitudinal tumor spread may involve the cut edge on proximal and/or distal bile duct (i.e., DM), while the circumferential tumor growth may involve the dissection plane at the hepatic hilum including portal vein (PV) and hepatic artery (HA), and/or the transection of liver parenchyma (i.e., RM).

There are no universal criteria for defining R1 resections and the differences concern the distance of the tumor from the resection margin [8,9]. For example, in Japan a distance of 5 mm has been proposed to define R0 resections [2,10,11]. In Western countries, instead, no recommendations were provided, so that only the presence of cancer cells literally at the edge of surgical cut (margin clearance of 0 mm) was considered to define R1 resection [12,13]. Notably, pancreatic duct adenocarcinoma (PDAC) and PHCC share several biological, pathological, and prognostic features [13]. Therefore, given the absence of evidence-based recommendations about the length of margin clearance in resected PHCC, the International Collaboration on Cancer Reporting and the Royal College of Pathologists recommend using the same definition of R1 resection for both PDAC and PHCC. Therefore, detection of cancer cells less than 1 mm from the transection or dissection margin is considered as microscopically residual disease [14,15]. Studies with higher levels of evidence would be desirable to revise this arbitrary distance.

Since the review of the literature reveals a different nomenclature and indication of surgical margins, we would like to clarify that RM in resected specimen of PHCC consists not only with the periductal dissection plane in the hepatoduodenal ligament (and possibly the vascular stumps), but also with the liver transection plane. In fact, tumor radial growth coming from the biliary confluence or the intrahepatic right and/or left bile duct infiltrates liver parenchyma and accordingly could also involve the liver transection plane. The surgical margins of resected perihilar cholangiocarcinoma are specified in figure 1.

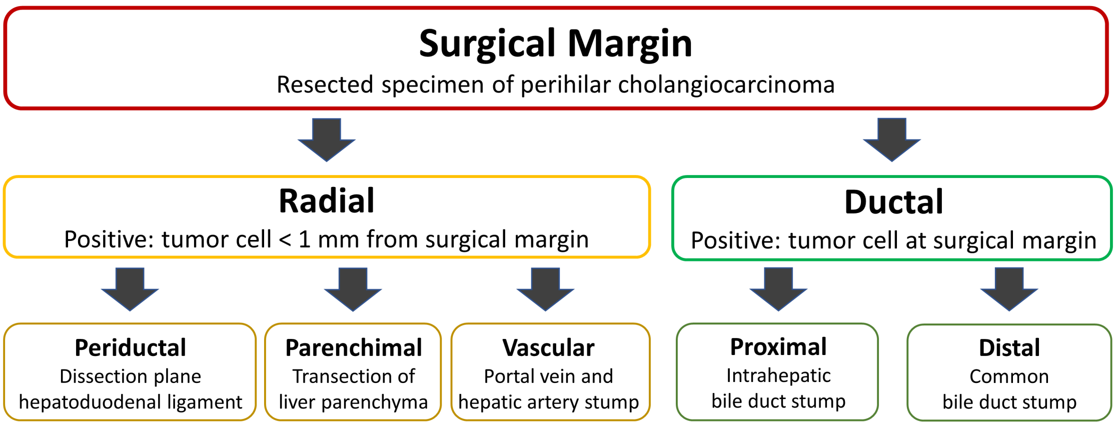

Figure 1. Surgical margins in perihilar cholangiocarcinoma
The proper assessment of residual disease in resected perihilar cholangiocarcinoma considers both the radial and the ductal margin status. A positive radial margin is defined as the presence of cancer cell less than 1 mm from the dissection plane of the periductal soft tissue in the hepatoduodenal ligament, from the portal vein or hepatic artery stumps, or from the transection plane of liver parenchyma. Whereas a positive ductal margin is defined as the presence of cancer cell at the cut edge of the proximal or distal bile ducts stumps.

Frequency of RM margin involvement

Very few studies have specifically evaluated the radial margin status in PHCC. The first pioneering data date back to the 90s and are difficult to interpret and compare due to the important limitations that arise from unspecified surgical strategy, simultaneous analysis of mixed extrahepatic biliary tract cancer, and different definition of RM. Whereas, the majority of recent studies reported only the percentage of R1 resections without specifying RM status, much less which margins were evaluated. Bosma [16] reported 85% of dissection margin positivity in patients underwent surgery for Klatskin tumors and affirmed that dissection (cleavage) planes should be fully taken into consideration to evaluate the complete surgical extirpation of the tumor. Liver resection plane resulted positive in 82% of patients (9 out of 11) treated with bile duct resection combined with major hepatectomy. Yamaguchi et al. [17] showed that 54% of patients with upper bile duct carcinoma had microscopic residual disease in the "posterior excised aspect" of the resected margin, namely the portion of the extrahepatic biliary tract not covered by the peritoneum. However, no data on the hepatic parenchymal margin was available. Likewise, Kayahara et al. [18] found that positive periductal, proximal, and distal margin in middle bile duct carcinomas were 50%, 29%, and 14%, respectively. Of note, the main site of surgical margin involvement was the dissected periductal soft tissue adjacent to the PV, instead of the ductal margins. Sakamoto et al. [19,20] identified RM as surgical margin other than the ductal margins of the resected specimens of middle and distal cholangiocarcinoma (i.e., pancreatoduodenectomy and middle bile duct segmental resection), therefore they referred exclusively to the periductal dissection margin whose positivity ranged between 14 and 22%. Stremitzer et al. [21], instead, reported 30% of isolated periductal margin positivity in resected PHCC. The authors defined the transection sites (proximal and distal) of the bile duct and the liver parenchyma as surgical margins and the interface of the extrahepatic bile duct with the surrounding lymphatic/fatty tissue as circumferential margin.

As regard the assessment of RM in resected PHCC, few small series were published by Western Centers. Castellano-Megias et al. [9] and D'Amico et al. [22] reported 38% and 35% of RM positivity, respectively, though the rate of positive periductal, vascular, and hepatic margins was missing. To our knowledge, the largest Western series published to date is from the University of Verona, Italy. De Bellis et al. [23] analyzed 90 consecutive cases and reported that RM positivity was more frequent than DM positivity (48% vs. 27%). Specifically, the overall rate of positive RM was 48%, with 43% positive periductal margin, 11% positive liver parenchyma margin, and 4% positive vascular margin. The first large and comprehensive study focusing on RM status in resected PHCC was published by Nagoya University, Japan. Shinoara et al. [24] analyzed 478 consecutive cases and reported only 18% of R1 resection. RM positivity was 11% and resulted the most common cause of residual disease. In particular, periductal margin positivity was 7% (positive stumps of vascular resections included) and hepatic margin positivity was 4%. Similarly, Noji et al.[25] analyzed an Eastern cohort of 210 patients and found that R1 resection was 8% and RM positivity was 5%. The percentages of RM positivity are summarized in table 1.

Table 1. Review of the literature on radial margin status in resected biliary tract cancer.

Reference (Author, year)	Patients	Biliary tract cancer	Type of surgery	R1	Radial margin positivity			5-year OS rate		
					Overall	Periductal	liver	RM+	RM-	R0
De Bellis 2022 [23]	90	Perihilar	HEP, HPD	49 (54)	43 (48)	39 (43) *	11 (12)	19	48	46
D'Amico 2022 [22]	75	Perihilar	HEP, BD	34 (45)	26 (35)	NA	NA	24	NA	41
Stremitzer 2021 [21]	83	Perihilar	HEP	43 (52)	NA	25 (30)	NA	33°	NA	47
Noji 2021 [25]	210	Perihilar	HEP	16 (8)	10 (5)	NA	NA	22	NA	50
Shinohara 2021 [24]	478	Perihilar	HEP, HPD	85 (18)	52 (11)	32 (7) *	20 (4)	21	NA	49
Castellano 2013 [9]	29	Perihilar	HEP	17 (59)	11 (38)	NA	NA	NA	NA	NA
Sakamoto 2010 [20]	77	Middle	HEP, BD, HPD, PD	43 (56)	NA	17 (22)	NA	10	38	35
Sakamoto 2005 [19]	55	Middle, Distal	HEP, BD, HPD, PD	13 (24)	NA	7 (13)	NA	0	34	NA
Gerhards 1999 [31]	63	Perihilar	HEP, BD	59 (94)	NA	55 (87)	20 (65)"	15	NA	NA
Kayahara 1999 [18]	50	Middle, Distal	HEP, BD, PD	14 (28)	NA	11 (22)	NA	0	NA	48
Yamaguchi 1997 [17]	46	Perihilar, Middle, Distal	HEP, BD, PD	22 (48)	NA	17 (37)	NA	NA	NA	NA
Bosma 1990 [16]	26	Perihilar	HEP, BD	24 (92)	NA	22 (85)	9 (82)"	NA	NA	NA

Data are reported as number and percentage, N (%).
* Including vascular margin positivity.
° Patients with isolated positive periductal margin.
"Percentages are calculated based on the total number of hepatectomies performed.
Abbreviations: HEP, hepatectomy with bile duct resection; BD, bile duct resection; HPD, hepatopancreatoduodenectomy; PD, pancreatoduodenectomy; NA, not available.

Survival outcomes according to radial margin status

Among patients who underwent surgery for middle and distal cholangiocarcinomas, Sakamoto et al.[19,20] demonstrated that a positive RM was a stronger predictor of survival compared with positive DM with 0-10% and 25-35% 5-year OS, respectively. Stremitzer et al. [21] investigated the effect of a positive periductal margin on survival in patients who underwent surgery for PHCC. The authors defined the bile duct transection sites (i.e., proximal and distal) and the liver parenchyma as surgical margins. In contrast, the area surrounding the extrahepatic bile duct and containing lymphatic/fatty tissue was defined as a circumferential margin. Notably, patients with positive surgical margins had the lowest rates of 1-, 3- and 5-year OS (65%, 19%, and 0%, respectively) compared with patients with positive circumferential margins (72%, 46%, and 33%, respectively) and patients with negative resection margins (89%, 56%, and 47%, respectively). Accordingly, patients with positive surgical margins had the lowest median OS compared with patients with positive circumferential and negative margins (14.5 vs 32.7 vs. 45.6 months, respectively; P = 0.011), whereas the median RFS showed no statistically significant differences. Additionally, positive circumferential or surgical margins were both independent predictors of poor OS.

Conversely, D'Amico et al. [22] aimed to investigate the effect of RM status on the survival of patients who underwent resection for PHCC. Their findings showed no significant differences in OS (median survival time [MST] 43.9 vs. 39.5 months; P = 0.361) and RFS (MST 30.0 vs. 20.0 months; P = 0.390) between the R0 group and the group with isolated positive RM. On multivariate analyses, DM positivity was an independent negative prognostic factor for both OS and RFS.

All the studies mentioned above had certain limitations due to their retrospective design, small sample size, length of the study period, and failure to report or distinguish the various surgical planes included in the definition of RM. Conversely, Shinohara et al. [24] analyzed the survival outcomes in an Eastern cohort who underwent curative-intent resection for PHCC over 5 years. The authors reported shorter survival time among patients with positive RM compared with R0 resection (MST 2.1 vs 4.9 years; P < 0.001; hazard ratio [HR] 2.06, 95% confidence interval [CI] 1.49–2.84), while no survival difference was noted between positive RM and DM. Notably, positive RM (HR 1.48; 95% CI 1.05-

2.08; P = 0.023) and DM (HR 1.83; 95% CI 1.22–2.74; P = 0.004) were independent prognostic factors for poor OS.

Recently, De Bellis et al. [23] prospectively analyzed RM status in a Western cohort who underwent curative-intent resection for PHCC over 7 years. Although the assessment of RM improved over time, the authors found that patients with negative RM had prolonged OS (MST 53.0 vs. 28.0 months; P < 0.017; HR 2.35, 95% CI 1.17–4.75) and RFS (MST 32.0 vs. 15.0 months; P < 0.037; HR 1.80, 95% CI 1.04–3.12) compared with patients with positive RM. Additionally, R1 status was an independent prognostic factor for both OS (HR 2.68, 95% CI 1.27–5.63; P = 0.009) and RFS (HR 2.14, 95% CI 1.20–3.83; P = 0.009). The rates of 5-year OS reported in the literature are summarized in table 1.

Surgical technique

Surgical strategy plays a fundamental role in achieving disease-free margins. A meticulous preoperative assessment of tumor extent is mandatory to plan patient-tailored surgical strategy which allows to obtain negative margins and reduce the risk of serious postoperative complications. The side of major hepatectomy for PHCC is determined according to the spreading of the tumor along the bile ducts and toward the hepatic vessels and liver parenchyma. Several authors [26,27] recommend performing right hepatectomy with caudate lobectomy for patients with Bismuth type I, II, IIIa, and IV tumors. For patients with Bismuth type IIIb, a left hepatectomy with caudate lobectomy is preferred. Theoretically, right hepatectomy may offer the best chance of cure for several anatomical and surgical reasons. By removing the inferior part of segment IV, a right hepatectomy enables a transection plane that can be created away from the hepatic hilum. This is because the left hepatic duct has a longer length and more distant segmental branching than the right hepatic duct. Accordingly, performing the bilio-enteric anastomosis at a more proximal location can prevent tumor exposure. Whereas in left hepatectomy the right anterior Glissonean pedicle must be preserved, so the transection plane is likely to come near the hepatic hilum where the tumor expands. This narrow transection plane may lead to higher RM (parenchyma) positivity. Planning an extended hepatectomy as the right or left trisectionectomy allows the surgeon to move the hepatic transection plane much further away from the biliary confluence reducing the risk of a positive hepatic margin. Another crucial factor that significantly impacts RM status is the dissection of the hepatoduodenal ligament. Anatomically, the right HA runs behind the common hepatic duct close to the biliary confluence and is therefore susceptible to PHCC invasion. The left HA, instead, runs along the left part of the hepatoduodenal ligament, away from the common bile duct. Consequently, right hepatectomy with en-bloc resection of right HA and biliary confluence favors wide clearance of periductal tissue up to the PV wall and ensure a more radical resection of the hepatic parenchyma by resecting the base of segment IV which rests on the biliary confluence.

Shinohara et al.[24] investigated the association between operative procedure and RM status and found the incidence of residual disease was higher in left hepatectomy than in other major resections as left trisectionectomy, right hepatectomy and right trisectionectomy (17.7% vs 7.6%, P = 0.001). Similarly, Ratti et al. [27] analyzed short- and long-term outcomes of patients underwent surgery for PHCC depending on the side of hepatectomy. The authors reported higher rates of R1 resection and local recurrence following left hepatectomy compared with right hepatectomy (R1: 36.4% vs. 23.0%; local recurrence: 87.0% vs 69.0%), whereas postoperative liver failure was more frequent in right-sided hepatectomies (4.5% vs. 11.5%) (all $p<0.05$). Although right hepatectomy has shown promising oncological outcomes, left hepatectomy has been increasingly performed due to the larger volume of the remaining liver spared and hence the lower risk of post-hepatectomy liver failure. However, during a left-sided hepatectomy, surgeons should be cautious when dissecting the right HA from the bile duct where the tradeoff should be considered between the risks associated with vascular reconstruction and the consequences of a positive RM.

Regardless of the side of the hepatectomy, we believe that the cause of frequent local recurrence is the presence of cancer cells on the PV wall and/or around the preserved HA. Therefore, to ensure a tumor-free RM (periductal), creating the widest possible dissection plane in the hepatoduodenal ligament may be beneficial. In our surgical practice we avoid skeletonizing the biliary tract by isolating the common bile duct towards the upper border of the pancreas, isolate the HA as far as possible from the tumor, and peel the PV up to its confluence leaving the periductal tissue intact (shown in Fig. 2). In this way we can easily evaluate RM status and increase the chances that this is negative. For the above reasons, planning extended hepatectomy, creating a deeper dissection plane around the hepatic hilum, and considering vascular resection are crucial to achieve negative surgical margins in locally advanced PHCC. Neuhaus et al. [28] proposed right trisectionectomy with routine PV resection for PHCC as a so-called "no-touch technique". This extended resection is thought to avoid positive RM in the periductal tissue and microscopic dissemination of tumor cells during skeletonization of the hepatoduodenal ligament looking for right HA and PV bifurcation. However, this procedure is associated with high mortality (17%) and his principle can be hardly applied in left-sided hepatectomy since right HA runs between tumor (biliary confluence) and PV. Therefore, we do not recommend this approach in all cases.

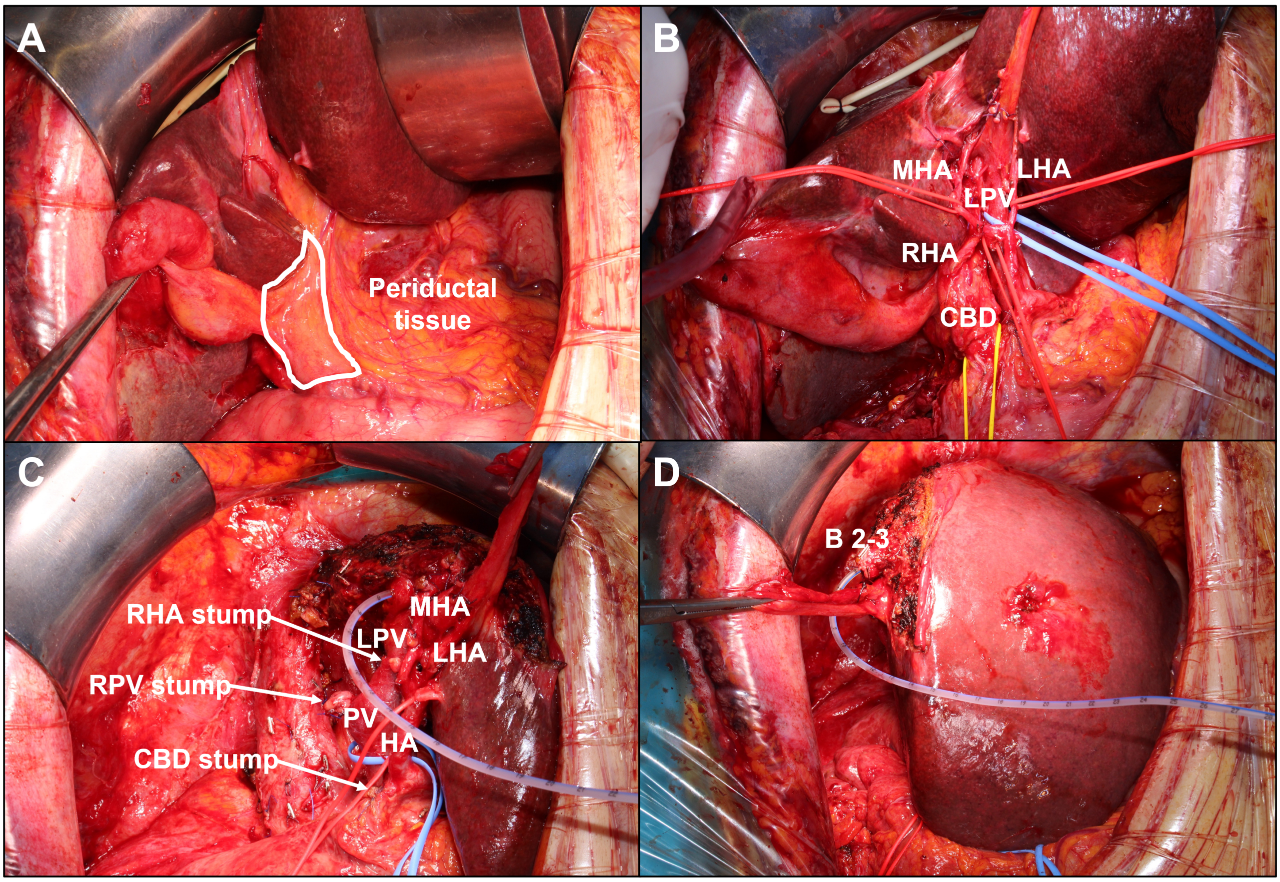

Figure 2. Surgical technique of en bloc hepatic pedicle dissection for anatomic right trisezionectomy. Patient with perihilar cholangiocarcinoma Bismuth type IIIa undergoing percutaneous biliary drainage of the left lobe and right portal vein embolization for planned right trisectionectomy. **(A)** Surgical field showing the periductal tissue of the hepatoduodenal ligament. **(B)** Management of hepatic pedicle without the skeletonization of the common bile duct to avoid tumor exposure along the periductal soft tissue. **(C)** Stump

of the common bile duct sutured on the upper edge of the pancreas to promote a tumor-free distal ductal margin. **(D)** Future remnant liver and proximal ductal margin highlighted by the insertion of the catheter.

Pathological examination

A Dutch audit [29] showed that pathology reports of resected PHCC offer a poor evaluation of surgical margins. Periductal dissection plane was missing in 35% of reports and residual disease could be re-classified from R0 to R1 in 15% of patients. Furthermore, a French multi-institutional survey demonstrated that only 10% of pathology reports described RM status even though a positive RM is observed more often than a positive DM [30].

These shortcomings may be justified in some cases by the lack of information on the type of surgical resection, by the non-highlighting of anatomical landmarks, and by the fragmentary nature of some specimens. In fact, surgical specimens should consist of en-bloc hepatectomy, caudate lobectomy and common bile duct resection with the whole periductal tissue of the hepatoduodenal ligament. Moreover, crucial anatomical structures and relevant resection planes should be marked for proper recognition and evaluation. Nevertheless, pathologists need to be aware that in a PHCC resection specimen may be up to five surgical margins to be reported namely the proximal, distal, periductal, hepatic, and vascular margins. The most overlook margin is the periductal plane maybe because it is a dissection plane rather than a resection plane (shown in Fig. 3).

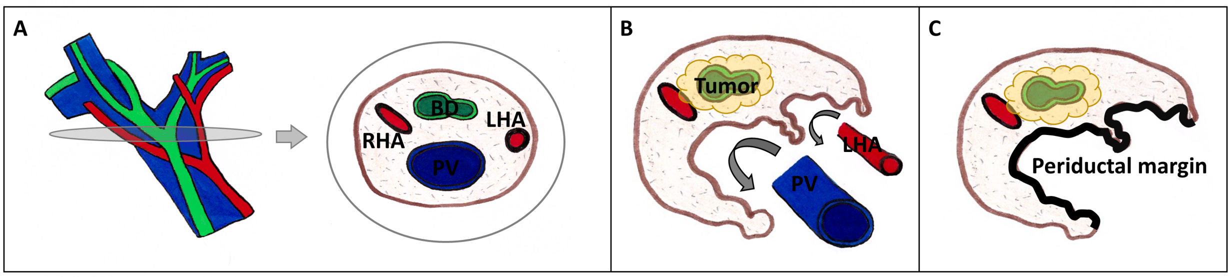

Figure 3. Schematic representation of enbloc hepatic hilum dissection for perihilar cholangiocarcinoma requiring right hepatectomy.
(A) Anatomical structures of the hepatic hilum and their relationship in the axial plane passing through the biliary confluence. **(B)** Tumor involving the biliary confluence has a close relation with right hepatic artery and may extend towards surgical cleavage plane. Therefore, left hepatic artery and portal vein should be peeled leaving as much as periductal tissue as possible. **(C)** Periductal dissection margin at hepatoduodenal ligament of a right hepatectomy.

We would like to stress that the peritoneal surface involvement was not considered as R1 resection since the surgeon does not transect or dissect any tissue, but invasion of this surface may be associated with worse prognosis. Gerhards et al. [31] made a clear distinction between the resection margins that were defined as the surgical resection planes of distal and proximal bile ducts or the liver, and the dissection margins that constitute the surgical cleavage planes with adjacent hilar structures, such as the PV. The authors noted that if the liver and ductal resection margins status were evaluated alone, the defined R0 resection rate was 25%. Instead, considering all the resection and dissection margins, overall R0 resection was achieved only in 6% of patients. Therefore, the assessment of the comprehensive RM status is essential not to underestimate residual disease.

The completeness of PHCC pathology reports varies in literature ranging 10% to 45% of specimens, [29,30] though distance from tumor to margin in millimeters is very often missing. This means that the margin is uncertain since even if reported as negative, the distance of the tumor from the resection can still be less than 1 millimeter and therefore the resection could be classified as R1.

The lack of consensus regarding the definition of microscopic margin involvement, the use of confusing nomenclature for surgical margins and the absence of a standardized protocol for the pathological dissection of the specimen, might lead to a misinterpretation of residual disease status. The ambiguity in reporting on surgical margins impedes correct staging and the consistent design of future studies, hence jeopardize our understanding of the natural history of PHCC.

The quality of reports increases when surgical margins are evaluated by dedicated gastro-intestinal pathologists. Experienced and meticulous histopathological examination is essential to routinely determine RM status and accordingly the true residual disease. An example of grossing technique in PHCC is illustrated in figure 4.

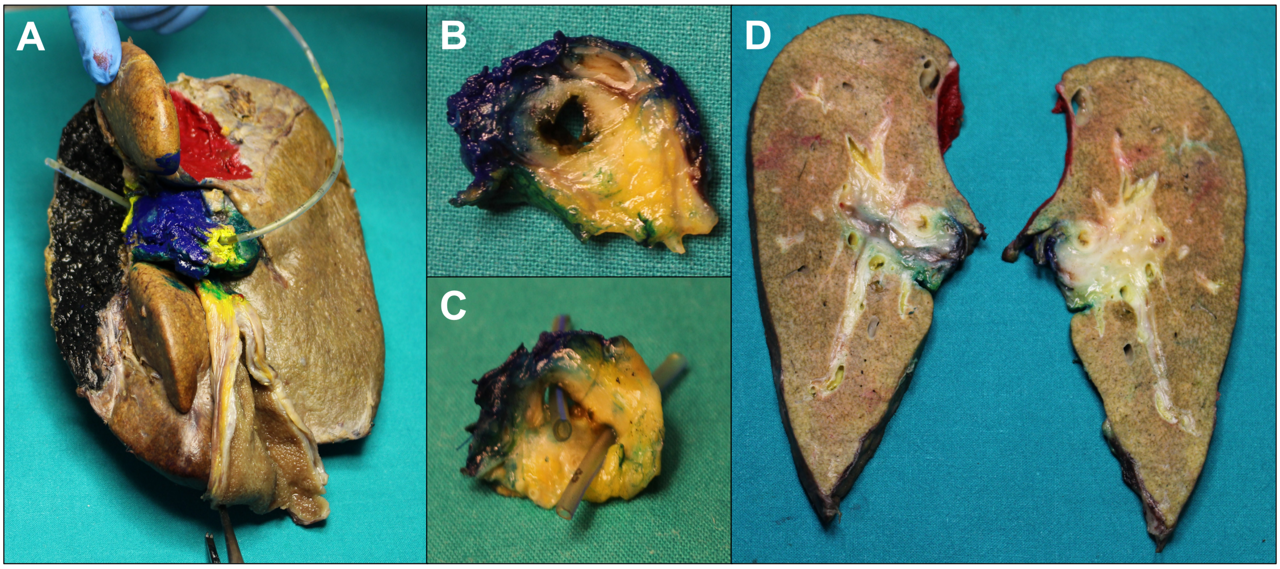

Figure 4. Grossing of perihilar cholangiocarcinoma specimen (right trisectionectomy with en bloc resection of caudate lobe, bile duct and gallbladder).
To optimize the assessment of radial margin status, specimen needs to be fixed in 4% buffered formalin for approximately 24-48 hours. **(A)** The circumferential dissection margin (blue), the proximal and distal bile duct margins (yellow), the liver transection plane (black), the peritoneal surface of the extrahepatic bile duct (green) and the sulcus for inferior vena cava (red) are stained according to a color code. The annular margins of PV and hepatic artery were previously excised and taken into consideration for the assessment of the R status. **(B-C)** The specimen is then sliced in 3- to 5-mm-thick slices following an axial plane perpendicular to the extrahepatic bile duct axis up to the biliary confluence. Thus, the periductal tissue surrounding the tumor is left intact and the extent of the tumor toward the dissection plane can be easily assess. If vascular resection is performed also vascular invasion can be examined. **(D)** Crossed the biliary confluence, the slicing carries on in a perpendicular fashion to the hepatic parenchymal transection plane. In this way, the relationship between tumor growth and intrahepatic bile ducts can be better appreciated as well as the suspected infiltration of the liver resection margin.

True R1 resection as a criterion for adjuvant therapy

Even among resected patients with declared negative surgical margins, short disease-free and overall survivals are frequently observed [7,32]. The high rates of locoregional recurrence offer a rationale for the administration of adjuvant therapy. Yet, little evidence exists regarding the benefit of adjuvant treatment and there are not established strategies for the use of chemo- and/or radio-therapy regimens [33–35]. The few randomized clinical trials group all biliary tract malignancies together without taking into account the different tumor biology [36–38] . Conversely, a propensity matched study by Nassour et al. [39] specifically focused on PHCC and demonstrated that the group of patients underwent adjuvant therapy had improved overall survival compared to the observation group. On subgroup analysis adjuvant therapy showed the best benefit in patient with positive resection margins.

In addition, the authors also found the combination of adjuvant chemo-radiotherapy was associated with longer survival times when compared to chemotherapy alone. Im et al. [40], as well, observed that adjuvant chemotherapy and chemo-radiotherapy improved OS especially in R1 resection patients.

Despite no definitive conclusions can be drawn from these studies, the American Society of Clinical Oncology (ASCO) Clinical Practice Guidelines [41] suggests adjuvant chemotherapy for all patients underwent PHCC resection (including patients with negative resection margin) and chemo-radiotherapy for patient with positive resection margin. Whereas, both the National Comprehensive Cancer Network (NCCN) guidelines and an expert consensus meeting of the American Hepato-Pancreato-Biliary Association (AHPBA) [42] advocate the administration of adjuvant therapy only in patients with high-risk pathology as presence of lymph node metastasis or positive surgical margin. In our clinical practice, the multidisciplinary team makes the decision to recommend an adjuvant treatment taking into account the risk factors for recurrence such as lymph node metastases, positive surgical margins, vascular invasion, satellitosis, and poor tumor differentiation grade. In principle, we propose chemotherapy if lymph node metastases are reported and chemo-radiotherapy if positive margins are observed. Hence, our oncologists administer oral capecitabine (1250 mg/m2 twice daily on days 1–14 of a 21-day cycle, for eight cycles) according to the findings of the BILCAP trial [37]. Instead, our radiotherapists give a dose of 50.4 greys divided in 28 fractions with concurrent radiosensitizing oral capecitabine (800-900 mg/m2 twice daily), despite the data supporting the benefits of adjuvant radiotherapy are very scarce nowadays. In patients with presence of both lymph node metastases and positive margins, the above adjuvant treatments can be given in sequence, approximately two weeks apart.

We emphasize that without the assessment of RM status, several patients could be misclassified as R0, while they did have a R1 owing to a RM positivity. Hence, we speculate that proper assessment of residual disease could lead to a more accurate selection of patients for adjuvant therapy. On the other hand, the lack of information about RM status in pathological report may jeopardize the credibility of survival studies in patients underwent resection for PHCC. The more accurate and complete the pathological reports are, the easier it will be to correlate positivity (or distance) of RM with local recurrence and survival. Of note, it has already been shown that RM status has a prognostic significance in other gastrointestinal tumors such as pancreatic, esophageal, and colorectal carcinoma [43–45].

CONCLUSION

Resection margins and above all RM status are prognostic factors of survival in patients underwent surgery for PHCC. Nevertheless, RM is often overlooked probably due to complexity and rarity of the specimens. The correct evaluation of all resection and dissection margins is a matter of both surgical technique and pathological examination. In fact, while it is true that the evidence of positive margin depends on the accuracy of the pathological examination, also no amount of clever microscopy can redeem a poorly dissected specimen. Knowing the RM status allows physicians to precisely define the presence or absence of residual disease and consequently refine the criteria for adjuvant chemo- and/or radio-therapy and the consistency of survival studies.

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