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Management of hilum infiltrating tumors of the liver: The impact of experience and standardization on outcome

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ABSTRACT

Background: The primary endpoint of this study was to evaluate the outcome of surgery for perihilar cholangiocarcinoma in a high-volume tertiary referral center.
Methods: The study population consisted of 196 consecutive patients with histologically confirmed perihilar cholangiocarcinoma-PHC-who were candidates to surgical treatment. Factors affecting postoperative morbidity were evaluated in the whole series (primary endpoint) and after stratification of patients according to the following criteria: (a) perioperative management protocol implementation; (b) monocentric management (secondary endpoint).
Results: The postoperative morbidity rate was 51.5% and mortality 4.1%. The most frequent cause of death was postoperative liver failure. At multivariate analysis, factors affecting the risk of morbidity were: side of hepatectomy, liver volume, intraoperative blood loss, preoperative optimization and single-center management. Patients treated according to preoperative optimization protocol, as well as patients with monocentric management experienced a significant reduction of postoperative morbidity. Preoperative optimization and single-center management significantly affected even long term outcome of patients.
Conclusion: Despite continuous improvement in the surgical field, hilum-infiltrating tumors still remain associated with therapeutic and management challenges: a correct preoperative management in a tertiary referral center provides a benefit in terms of morbidity and mortality, thus improving long term results.

1. Introduction

Up to two-thirds of patients with perihilar cholangiocarcinoma (PHC) present with clinical and radiological signs of infiltration of the hepatic hilar structures at diagnosis. Jaundice and lobar atrophy are important manifestations of the involvement of the biliary duct and vascular structures by the disease that lead to challenges in the clinical and surgical management [1–4]. This leads to a progressive deterioration of the patient's performance status and results in a decrease in the patient's capability to tolerate surgical stress. [1–4]. In such complex setting, surgical resection with negative margins represents the only potentially curative treatment option and remains the only significant survival prognostic factor that can be affected by pre- and intra-operative management. The multidisciplinary management should therefore focus on this main endpoint as a flagship issue. Major hepatectomy associated with biliary confluence resection and locoregional lymphadenectomy is indeed recommended for PHC in order to reduce the risk of recurrence within the liver and along the bile ducts [5–7]. However, it should be taken into account that the extensive parenchymal demolition, together with the high preoperative incidence of cholestasis-related complications, are responsible for a significantly higher risk of postoperative morbidity (29–75%) and mortality (0–17%), when compared to conventional hepatic surgery [8].

To minimize the rate and the severity of postoperative complications, thorough preoperative optimization is fundamental and should be performed in a multidisciplinary setting [9,10], based on an established specific expertise. The application of optimization protocols as well as experienced surgical planning and complication management are indeed essential for a favorable outcome. Hence, the primary endpoint of this study was to evaluate the perioperative and long-term outcome of surgery for PHC in a high-volume tertiary referral center. The secondary endpoint was to assess the impact of center experience in terms of perioperative

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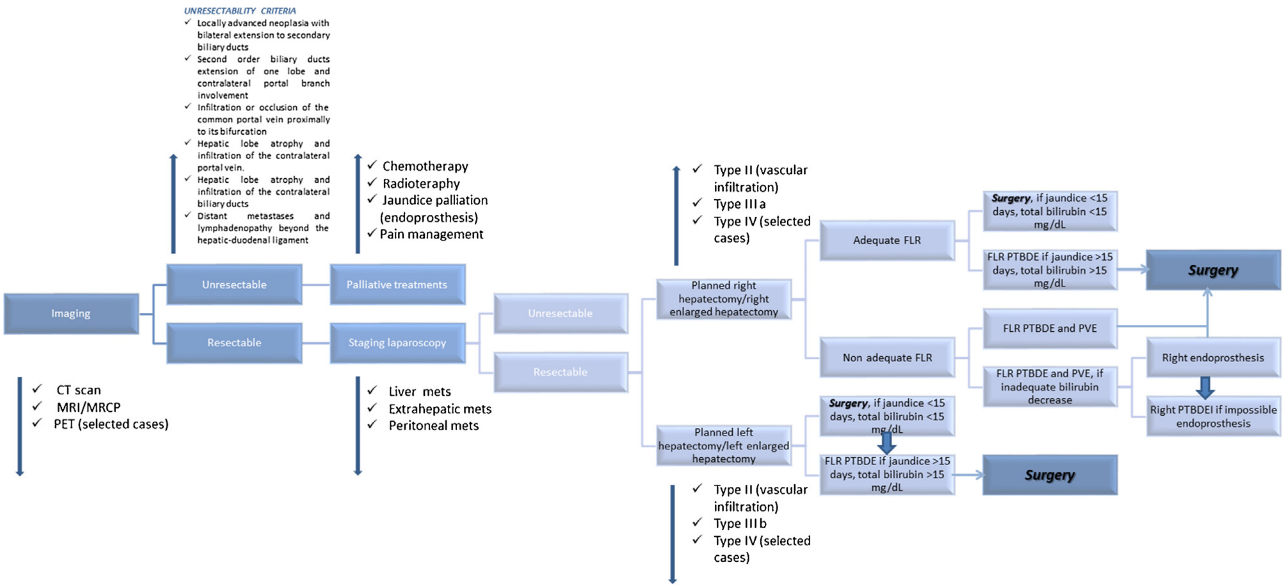

Fig. 1. Protocol of preoperative optimization for patients with PHC.

management protocol implementation and monocentric management.

2. Materials and methods

2.1. Patients

Between January 2004 and December 2017, 196 patients with PHC were candidates for surgery with curative intent at the Hepatobiliary Surgery Division of San Raffaele Hospital in Milan, Italy. Data from these patients were collected in a prospective database and were retrospectively reviewed for this study. The study population was defined after excluding procedures with any of the following characteristics: intrahepatic cholangiocarcinoma with no evidence of disease infiltration of the hepatic hilum (diagnosed both preoperatively or during surgery); gallbladder cancer; evidence of extrahepatic metastases or locally advanced unresectable disease during imaging staging; isolated biliary confluence resection with no associated hepatectomy; unconfirmed diagnosis of PHC at final histopathological examination; fewer than six months of follow-up. The study group finally consisted of 196 consecutive patients. In order to evaluate the secondary endpoints, the following criteria were used to classify the series into groups: (a) standard protocol implementation, where the introduction of the "preoperative optimization protocol" (see later) into the clinical practice was used as a time-landmark to divide the (i) Before Preoperative Optimization Protocol Group (BPOP-Group) from the (ii) After Preoperative Optimization Protocol Group (APOP-Group); and (b) monocentric/multicentric management, where patients with single center management (SCM Group) were divided from patients who were referred after other interventional procedures such as biliary drainage, endoscopic endoprostesis, and PVE were performed (MCM Group, Multi Centric Management Group). Approval to perform this retrospective study was obtained from the IRB and patient consent was waived.

2.2. Preoperative workup

Preoperative workup has been described elsewhere [10]. Standard thoracoabdominal imaging (computed tomography and magnetic resonance cholangiopancreatography) was routinely performed in all candidates prior to surgery. PET scan was considered in selected cases to rule out the presence of extrahepatic metastases. Both disease infiltration along the bile ducts and infiltration and/or encasement of the portal/arterial vessels were considered before planning the side and extent of resection.

2.3. Tumor classification and histopathological examination

Histological staging was determined according to the TNM classification following the criteria of the American Joint Committee on Cancer (AJCC 8th edition). Frozen sections of both proximal and distal margins were intraoperatively examined to rule out residual disease along the bile ducts.

2.4. Resectability criteria

The Memorial Sloan Kettering Cancer Center (MSKCC) staging system was used to assess PHC resectability [2]. Briefly, the following criteria were considered contraindications to surgery: involvement of secondary order branches of the biliary tree, involvement of secondary order branches of the biliary tree of a lobe and involvement of contralateral portal branch, infiltration or occlusion of the common trunk of the portal vein proximal to the bifurcation; lobar atrophy and contralateral infiltration of the portal branch; lobar atrophy and contralateral infiltration of the biliary tree. Nodal involvement was not considered an absolute contraindication to surgery unless metastases beyond the hepatoduodenal ligament were detected [2].

2.5. Preoperative optimization

Standard preoperative management has been described elsewhere [10]. Briefly, placement of percutaneous transhepatic biliary drainage (PTBD) in the future liver remnant (FLR) was indicated in jaundiced patients who were candidates for portal vein embolization (PVE) because of inadequate FLR volume (<40%) at CT scan [11,12]. In patients with adequate FLR, the need for PTBD of the FLR was indicated according to the severity (total bilirubin >15 mg/dL) and duration (>15 days) of jaundice. The preoperative optimization protocol is represented in Fig. 1.

Table 1a
Patients characteristics.

	PHC (n = 196) n (%)
Age, median (range)	62 (41–82)
Gender (M), n (%)	81 (41.3)
BMI, median (range)	24.6 (19.5–28.7)
ASA score, n (%)	
1	4 (2.0)
2	93 (47.4)
3	90 (45.9)
4	9 (4.6)
Diabetes, n (%)	29 (14.8)
Previous abdominal surgery, n (%)	31 (15.8)
Previous ChemoTherapy, n (%)	17 (8.7)
Number of cycles, median (range)	2 (1–4)
Preoperative jaundice, n (%)	182 (92.9)
Total bilirubin at diagnosis in mg/dL, mean ± SD	15.2 ± 7.3
Bili >15 mg/dL, n (%)	143 (73)
Jaundice >15 days, n (%)	151 (77)

Abbreviations: PHC, perihilar cholangiocarcinoma; BMI, body mass index; ASA, American Society Anaesthesiology; SD, standard deviation.

2.6. Surgery

Lymphadenectomy and segment 1 resection were routinely performed. Tumor infiltration at intraoperative frozen section examination constituted an indication to widen the resection margins as much as technically feasible along with multiple segmental biliary enteric anastomosis.

2.7. Outcome evaluation

Preoperative patient and disease characteristics as well as requirement for biliary drainage and PVE were recorded. Postoperative complications occurring 90 days following liver resection were reviewed and graded retrospectively according to the Dindo–Clavien classification of surgical complications [13]. Postoperative mortality was defined as any death during hospitalization or within 90 days after resection. Postoperative liver failure was defined according to the ISGLS definition [14]. Patient survival was determined from surgery until the time of death or most recent follow-up. Three- and five-year overall and disease-free survival were evaluated using the Kaplan–Meier method.

2.8. Statistical analysis

Comparisons were performed using the χ^2 test or Fisher's exact test for categorical data and the Mann–Whitney U test for ordinal data. Cox regression was used to determine independent predictors of severe (Dindo–Clavien ≥3) complications, using survival as the dependent variable and the factors found to be significant ($p < 0.05$) in univariate analysis as covariates. Nonparametric data analysis was performed using the χ^2 or Fisher's exact test as appropriate. All data are expressed as mean plus standard deviation or as median and range when appropriate. Significance was defined as $p < 0.05$. All analyses were performed using the statistical package SPSS 18.0 (SPSS, Chicago, IL, USA).

3. Results

3.1. Preoperative characteristics

The preoperative characteristics of the 196 patients treated with curative intent surgery are summarized in Tables 1a. Eighty-one males (41.3%) and 115 females (58.7%) with a median age of 62 years (range: 41–82 years) were included in the study. The incidence of jaundice was 92.9% (182 patients), but the number of patients with total bilirubin >15 mg/dL was lower (73%, 143 patients).

Table 1b
Surgical details.

	PHC (n = 196) n (%)
Staging LPS	159 (81.1)
Preoperative biliary drainage, n (%)	153 (78.1)
Unilateral	105 (53.6)
Bilateral	48 (24.5)
Type of biliary drainage, n (%)	
Percutaneous	94 (48)
Endoscopic	28 (14.3)
Percutaneous + endoscopic	31 (15.8)
Portal vein embolization/ligation, n (%)	66 (33.7)
Number of resected segments, median (range)	4 (4–6)
Extent of hepatectomy, n (%)	
Major	136 (69.4)
Extended	60 (30.6)
Lymphadenectomy (yes/no), n (%)	192 (98.0)
Pringle maneuver, n (%)	191 (97.4)
Intraoperative blood loss, mean ± SD	350 ± 350
Intraoperative blood transfusions, n (%)	48 (24.5)
Intraoperative plasma transfusions, n (%)	19 (9.7)
Lenght of surgery in min, mean ± SD	310 ± 210

Abbreviations: LPS, laparoscopy; SD, standard deviation.

Table 1c
Hystopathological data in patients with perihilar cholangiocarcinoma.

Staging	PHC (n = 196) n (%)
T, n (%)	
1	20 (10.2)
2	119 (60.7)
3	57 (29.1)
G, n (%)	
1	31 (15.8)
2	141 (71.9)
3	24 (12.2)
N, n (%)	
0	78 (39.8)
1	94 (48)
2	24 (12.2)
R, n (%)	
0	129 (65.8)
1	61 (31.1)
2	6 (3.1)
Perineural invasion, n (%)	101 (51.5)
Lymphatic invasion, n (%)	107 (54.6)
Microvascular invasion, n (%)	121 (61.7)
Macrovascular invasion, n (%)	99 (50.5)
Portal vein	75 (38.3)
Hepatic artery	64 (32.7)

Abbreviations: T, tumor; G, grading; N, nodal status; R, resection margin.

3.2. Preoperative management and surgical details

Among jaundiced patients, 78.1% underwent preoperative biliary drainage; with 24.5% requiring bilateral drainage. Drainage characteristics are detailed in Table 1b. Sixty-six patients (33.7% of the whole series) underwent PVE for inadequate FLR, with a mean volume increase of 52.6% ± 31.5%. Sixty extended resections (left or right trisectionectomy) and 136 major resections (left or right hepatectomy) were performed.

Histopathological data are summarized in Table 1c.

Table 2
Postoperative morbidity.

	PHC (n = 196) n (%)
Morbidity, n (%)	101 (51.5)
Urinary tract infection	13 (6.6)
Haemorrage	8 (4.1)
Biliary fistula	38 (19.4)
Wound infection	30 (15.3)
Pleural effusion	51 (26.0)
Fever/sepsis	57 (29.1)
Pneumonia	8 (4.1)
Atrial fibrillation	17 (8.7)
DVT/PE	2 (1.0)
Liver failure	22 (11.2)
Hepatic abscess	9 (4.6)
Morbidity according to severity, n (%)	
Minor	66 (33.7)
Dindo I	22 (11.2)
Dindo II	44 (22.4)
Major	35 (17.9)
Dindo IIIa	10 (5.1)
Dindo IIIB	12 (6.1)
Dindo IV	5 (2.6)
Dindo V	8 (4.1)
Mortality, n (%)	8 (4.1)
Postoperative transfusions, n (%)	60 (30.6)
Total transfusions, n (%)	67 (34.2)
Re-laparotomy, n (%)	4 (2.0)
Lenght of postoperative stay, median (range) days	13 (6–79)
Need for ICU, n (%)	7 (3.6)
Lenght of ICU stay, median (range) days	2 (1–12)

Abbreviations: DVT, deep vein thrombosis; PE, pulmonary embolism; ICU, intensive care unit.

3.3. Postoperative outcome

Whole series morbidity was 51.5% with 4.1% mortality. Postoperative complications are detailed in Table 2. The most frequent complications were infectious (wound infection occurred in 15.3% of patients and fever in 29.1%), biliary (biliary fistula occurred in 19.4% of patients), and related to liver function (22 patients showed signs of postoperative liver failure including ascites, hyperbilirubinemia, and coagulation disorders). Eight patients died in the postoperative period. Irreversible and progressive signs of liver failure occurred in five patients, two of which showed severe isolated hyperbilirubinemia without evidence of biliary obstruction and with clinical evidence of encephalopathy and hepatic coma, one developed refractory ascites and pleural effusion complicated by pneumonia and subsequent respiratory failure, and one showed hyperbilirubinemia together with portal hypertension leading to gastric bleeding refractory to endoscopic treatment. Two patients developed septic shock from cholangitis. One patient from the left group had a severe bilateral pulmonary embolism leading to respiratory failure and then cardiac arrest. The median length of stay was 13 days.

3.4. Prognostic factors

Prognostic factors for 90-day morbidity after resection were evaluated in the entire series (196 patients). Nine out of 12 clinical and management factors were found to significantly affect prognosis at univariate analysis (see Table 3 for details). Multivariate analysis revealed monocentric management, use of preoperative optimization protocols, side of hepatectomy, volume of remnant liver, and blood loss to be independent prognostic factors for postoperative complications.

In particular, when BPOP (n = 38) and APOP (n = 158) Groups were compared, patients treated according to the preoperative optimization protocol experienced a lower incidence of postoperative complications, including both minor (respectively 57.9% and 27.8%, $p = 0.012$) and major (respectively 26.3% and 15.8%, $p = 0.031$) complications, and a lower mortality rate, as reported in Table 4a.

The same findings were confirmed comparing groups according to monocentric/multicentric preoperative management. Patients in the SCM group (n = 99) had a lower postoperative morbidity and mortality (Table 4b).

3.5. Long-term survival

The median follow-up was 34 months. The 3- and 5-year survival rates were 49.5% and 36.7%. Disease-free survival was 36.2% at 3 years and 17.9% at 5 years. (overall and disease-free survival curves are shown in Fig. 2). Fifteen factors potentially affecting long term survival (age, sex, extent of hepatectomy, side of hepatectomy, combined vascular resection, Bismuth type, grade of differentiation, N status, perineural invasion, microvascular invasion, lymphatic invasion, margins, adoption of preoperative optimization, complications and monocentric management) were analyzed. A multivariate analysis of factors resulting significant at univariate analysis was then performed: side of hepatectomy, Bismuth type, grade of differentiation, nodal status and resection margins confirmed their association with long term survival; furthermore, use of preoperative optimization (RR 1.65; CI 1.41–2.01) and monocentric management (1.98; CI 1.45–2.131) conferred a significant survival benefit.

4. Discussion

Recent advances in surgical and anesthesiological management of patients requiring huge liver parenchymal demolitions associated with complex biliary resections have improved perioperative outcomes [9,10]. Today, morbidity and mortality reported in the literature are acceptable, despite still being higher [8,15] than in conventional hepatic surgery. The present study focuses on the importance of the monocentric management of patients with PHC because expertise and implementation of specific management protocols allows for an amelioration of short term outcomes and for an increase in disease-free and overall survival. In fact, uni- and multivariate analyses showed that both the absence of monocentric management (RR 1.44, $p = 0.041$) and the absence of a preoperative optimization protocol (RR 1.66, $p = 0.041$) are associated with a significantly increased risk of postoperative complications. The same finding was confirmed when the analysis was applied to long-term outcomes.

Bile duct resection combined with major hepatectomy represents the standard treatment for PHC over more conservative strategies such as bile duct resection alone or associated with resection of Sg4b-5 [1–3,5,6]. Nevertheless, complex biliary and hepatic resections performed to achieve a radical surgery are associated with a significantly higher risk of morbidity and mortality. Most series in literature report a morbidity between 14% and 76% and a mortality between 0% and 19%, which are explained by the high incidence of life threatening complications. Postoperative liver failure-because of the extensive liver resection and the underlying liver functional impairment due to steatosis or cholestasis- and septic complications-including cholangitis, liver and intra-abdominal abscesses, and wound infections-account for 50%–80% of all complications [8,14]. Since infections in patients with a baseline functional impairment dramatically worsen the liver functional reserve, they should be aggressively prevented and treated [16].

In a previous study, we concluded that adequate preoperative management of patients with PHC that are surgical candidates should be the main target of the multidisciplinary

Table 3
Uni- and multivariate analysis for factors affecting the risk of postoperative morbidity.

Variable	n	Morbidity	Univariate, p	Risk ratio (95% confidence interval)	Multivariate, p
Age			NS		
<70	138	66 (47.8)			
>70	62	32 (51.6)			
Sex			NS		
Male	82	40 (48.8)			
Female	118	58 (49.2)			
Diagnosis			NS		
Perihilar cholangiocarcinoma	136	65 (47.8)			
Gallbladder cancer	64	33 (51.6)			
Monocentric management			0.032		0.041
Yes	101	30 (29.7)		1	
No	99	68 (68.7)		1.44 (1.06–2.01)	
Preoperative optimization protocol			0.031		0.041
Yes	152	58 (38.1)		1	
No	48	40 (83.3)		1.66 (1.11–2.21)	
Preoperative biliary drainage			NS		
Yes	149	69 (46.3)			
No	51	28 (54.9)			
Portal vein embolizatiom			0.048		
Yes	64	24 (37.5)			
No	136	74 (54.4)			
Extent of hepatectomy			NS		
Major	138	65 (47.1)			
Extended	62	34 (54.8)			
Side of hepatectomy			0.029		0.039
Left	87	31 (35.6)		1	
Right	113	67 (59.3)		1.95 (1.33–2.27)	
Preoperative cholangitis			0.049		
Yes	69	27 (39.1)			
No	131	61 (46.6)			
Chronic liver disease			0.05		
Yes	24	14 (58.3)			
No	176	84 (47.7)			
Liver volume			0.042		0.05
>40%	134	57 (42.5)		1	
<40%	66	41 (62.1)		1.19 (1.01–1.62)	
Preoperative albumin			NS		
>30 g/L	96	48 (50)			
≤30 g/L	104	50 (48.1)			
Blood loss			0.039		
>1000 mL	67	44 (65.7)			
≤1000 mL	133	54 (40.6)			

Table 4a
Characteristics and outcome of patients stratified according to preoperative optimization protocol introduction.

	BPOP-group n = 48	APOP-group n = 152	p
Preoperative jaundice, n (%)	39 (81.3)	137 (90.1)	NS
Total bilirubin at diagnosis in mg/dL, mean ± SD	15.2 ± 5.4	14.9 ± 7.0	NS
Bili >15 mg/dL, n (%)	26 (54.2)	86 (56.6)	NS
Jaundice >15 days, n (%)	27 (56.3)	94 (61.8)	NS
Tumor type, n (%)			NS
Perihilar cholangiocarcinoma	35 (72.9)	101 (66.4)	
Gallbladder cancer	13 (27.1)	51 (33.6)	
Morbidity according to severity, n (%)			
Minor	29 (60.4)	35 (23)	0.012
Dindo I	10 (20.8)	11 (7.2)	
Dindo II	19 (39.6)	24 (15.8)	
Major	11 (22.9)	23 (15.1)	0.031
Dindo IIIa	3 (6.3)	7 (4.6)	
Dindo IIIb	4 (8.3)	8 (5.3)	
Dindo IV	1 (2.1)	5 (3.3)	
Dindo V	3 (6.3)	3 (2.0)	
Mortality, n (%)	3 (6.3)	3 (2.0)	0.042
Postoperative transfusions, n (%)	14 (29.2)	45 (29.6)	NS
Total transfusions, n (%)	17 (35.4)	49 (32.2)	NS
Lenght of postoperative stay, median (range) days	17 (10–69)	12 (8–55)	NS

Abbreviations: BPOP, before preoperative optimization; APOP, after preoperative optimization.

Table 4b
Characteristics and outcome of patients stratified according to monocentric/multicentric management.

	SCM-group n = 101	MCM-group n = 99	p
Preoperative jaundice, n (%)	91 (90.1)	85 (85.9)	NS
Total bilirubin at diagnosis in mg/dL, mean ± SD	16.2 ± 5.5	14.6 ± 5.5	NS
Bili >15 mg/dL, n (%)	54 (53.5)	58 (58.6)	NS
Jaundice >15 days, n (%)	64 (63.4)	57 (57.6)	NS
Tumor type, n (%)			NS
Perihilar cholangiocarcinoma	68 (67.3)	68 (68.7)	
Gallbladder cancer	39 (38.6)	25 (25.3)	
Morbidity according to severity, n (%)			
Minor	22 (21.8)	42 (42.4)	0.039
Dindo I	9 (8.9)	13 (13.1)	
Dindo II	13 (12.9)	30 (30.3)	
Major	8 (7.9)	26 (26.3)	0.027
Dindo IIIa	3 (3.0)	7 (7.1)	
Dindo IIIb	3 (3.0)	9 (9.1)	
Dindo IV	1 (1.0)	5 (5.1)	
Dindo V	1 (1.0)	5 (5.1)	
Mortality, n (%)	1 (1.0)	5 (5.1)	0.045
Postoperative transfusions, n (%)	24 (23.8)	35 (35.4)	0.049
Total transfusions, n (%)	29 (28.7)	37 (37.4)	0.005
Lenght of postoperative stay, median (range) days	11 (8–52)	13 (8–69)	NS

Abbreviations: SCM, single center management; MCM, multi center management.

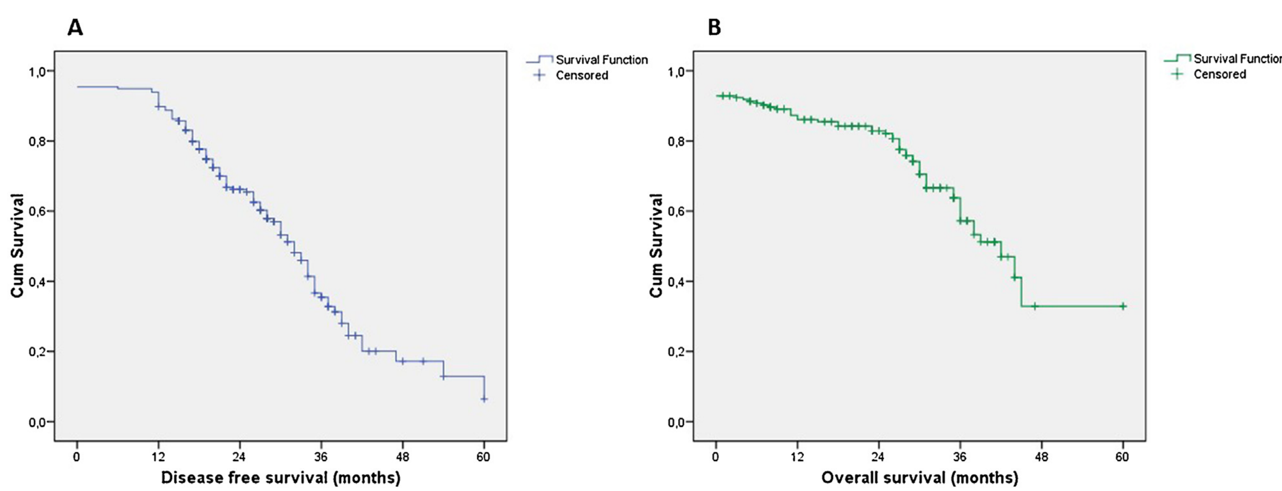

Fig. 2. a. Disease free survival. b. Overall survival.

team involving surgeons, interventional radiologists, medical oncologists and endoscopists [10]. To this end, we proposed a preoperative optimization program based on three flagship steps: staging laparoscopy, biliary drainage, and eventual PVE. As it has been demonstrated that the establishment and adoption of evidence-based guidelines improves surgical outcomes [17], we implemented the preoperative optimization protocol into the daily clinical practice. Because of encouranging results it was also implemented to encompass patients with hilum infiltrating gallbladder cancer. A series by Grandadam et al. [18] highlighted the reduction in intra-abdominal septic complications following a step-by-step preoperative optimization, but did not focus on an impact on long term survival, which we demonstrate in the present study.

The concept of preoperative optimization includes the definition of a standard management protocol with specific indications for biliary drainage and PVE. Our protocol for preoperative optimization includes biliary drainage of the remnant liver in patients with an inadequate FLR requiring PVE and biliary drainage in patients with an adequate FLR if a severe or prolonged cholestasis is recorded. It is documented in the medical literature that adopting protocols positively affects the outcome of patients, reducing the risk of clinical errors, diverging behaviors inside a team, and consequently improving the quality of the medical service. In patients treated before the protocol implementation, the decision to drain was done on a case by case basis, the indication for drainage in patients requiring PVE was not homogeneous, and staging laparoscopy was not performed on a standard basis. The strict adherence to a clinical protocol allows standardization of treatment, reducing the risk of unpredictable and unexpected events, without being in contrast with the concept of a patient-tailored strategy. In fact, after staging laparoscopy, patient management diverges depending on the planned strategy, being defined according to the the predominant side of the tumor and therefore the hepatectomy side [15].

When a right resection is required, if the FLR is inadequate in terms of volume, then an external PTBD is positioned followed by PVE to induce liver hypertrophy. Instead, if the FLR is adequate, then the timing of surgery depends on the severity of jaundice. Upfront surgery is indicated in patients with a recent onset of jaundice, lasting fewer than 15 days, and a bilirubin level lower than 15 mg/dL. While in patients with prolonged jaundice, lasting more than 15 days, and/or a bilirubin level greater than 15 mg/dL, then the placement of external PTBD in the FLR (left liver) is indicated and surgery is delayed until bilirubin is effectively reduced. In contrast, left hepatectomy or left trisectionectomy is on principle associated with an adequate FLR, so the timing of surgery should be based only on the need for jaundice resolution. This approach is in accordance with two recent reviews [19,20] that concluded that FLR drainage is strongly recommended in the following situations: planned PVE because of an inadequate FLR; borderline FLR, even in the absence of planned PVE; and when cholestasis-related complications occur.

Furthermore, many studies demonstrated that outcomes of complex surgical procedures (e.g. esophagectomies, pancreatectomies, concomitant colorectal and hepatic resections) strictly correlate with hospital volume and therefore with surgical and clinical expertise [21,22]. Nagino et al. [6] reported how the steady evolution in the management of PHC and the acquisition of specific expertise have resulted in progressively improving results; however, in this study we also focus on the outcome of monocentric versus multicentric managed patients.

The extensive debate on of hilum infiltrating tumors and the discrepancies in the policies adopted by different centers have resulted in discordant management strategies and complex centralization. Firstly, the curative role of surgery for patients with PHC and locally advanced gallbladder cancer has long been underestimated. Some patients, even today, are upfront candidates to palliative oncological treatments or, worse, to best supportive care without even undergoing a surgical evaluation. Secondly, the number of patients considered unresectable might be overestimated in centers without specific expertise in the field of hilum infiltrating lesions, as a consequence of lack of both radiological and surgical commitment.

Despite patient referral to high volume centers, the incorrect decision on the necessity and/or the type of biliary drainage leads to treatment delays and possibly severe consequences on prognosis. The delay that results from infectious complications following drainage or from the attempt to restore an adequate performance status might be a the basis for the dismal prognosis of lately referred patients. Indeed, inadequate management correlates with a suboptimal disease control and consequently with the treatment of a more advanced disease.

The benefits of a monocentric management can be summarized as follows: more accurate definition of resectability, reduced number of unnecessary procedures (surgical and radiological), lower morbidity and adverse events (both preoperatively and postoperatively), and longer survival (possibly due to a shorter length of stay and earlier functional recovery of patients that are therefore fit for adjuvant therapies).

The future perspective for hilum infiltrating tumors will be the standardization toward optimization of neoadjuvant and adjuvant therapies, whose role are still controversial and debated in the literature.

Our results allow us to conclude that preoperative optimization is fundamental to reduce the postoperative complication rate in patients with PHC. In addition, patients should be managed in a multidisciplinary setting [8,9], based on an established specific expertise. Indeed, the implementation of optimization protocols as well as experience in both surgical planning and complication management are essential for a favorable short and long term outcome. Strategy planning in a tertiary referral center should therefore be strongly encouraged at diagnosis.

Conflict of interest

None declared.

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