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ORIGINAL ARTICLE

Resectional surgery in gallbladder cancer with jaundice—how to improve the outcome?

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Abstract

Purpose To evaluate the surgical outcomes of patients with gallbladder cancer (GBC) with jaundice due to as-yet unelucidated prognostic factors.

Methods A total of 348 GBC patients underwent resection at our institute between 1985 and 2016. Of these, 67 had jaundice (serum total bilirubin ≥ 2 mg/dL). Preoperative biliary drainage was performed, with portal vein embolization as required. All patients underwent radical surgery. We retrospectively evaluated the outcomes, performed multivariate analysis for overall survival, and compared our findings to those reported in the literature.

Results The 5-year survival rate of M0 (no distant metastasis) GBC patients with jaundice, who underwent resectional surgery, was 21.9%, versus 68.3% in those without jaundice ($p < 0.05$). Since 2000, surgical mortality in GBC patients with jaundice has decreased from 12 to 6.8%. Patients with jaundice had more advanced disease and underwent major hepatectomies and vascular resections; however, preoperative jaundice alone was not a prognostic factor. Multivariate analysis of jaundiced patients revealed that percutaneous biliary drainage (PTBD) (vis-à-vis endoscopic drainage [EBD], hazard ratio [HR] 2.82), postoperative morbidity (Clavien–Dindo classification ≥ 3, HR 2.31), and distant metastasis (HR 1.85) were predictors of poor long-term survival. The 5-year survival and peritoneal recurrence rates in M0 patients with jaundice were 16% and 44%, respectively, for patients with PTBD and 39% ($p < 0.05$) and 13% ($p = 0.07$) for those with EBD.

Summary In this study, we present our experience of over 40 years in managing patients with gallbladder cancer with jaundice who underwent resectional surgery. The importance of this article is that it focusses on identifying patients and practices that may result in long-term survival in these patients.

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Conclusion M0 GBC patients with jaundice should undergo surgery if R0 resection is possible. Preoperative EBD may be superior to PTBD in M0 GBC patients with jaundice, although further studies are needed.

Keywords Gallbladder cancer · Surgery in gallbladder cancer with jaundice · Surgery · Outcome of surgery in gallbladder cancer with jaundice

Introduction

Jaundice in patients with gallbladder cancer (GBC) is an ominous sign [1]. Moreover, data showing the benefit of resectional surgery in these patients are limited [2, 3]. With meticulous evaluation and protocol-based approaches, some form of treatment can be offered to most patients. This paper discusses our experiences in managing patients with GBC with jaundice who underwent resectional surgery. These patients may, at times, be confused with patients of hilar cholangiocarcinoma because of the similarities in presentation and management. However, they are a different class of patients.

The cause of jaundice in GBC may be the early invasion of the common bile duct (CBD) by a mass in the neck of the gall bladder, or direct invasion of the hilum by an expanding or infiltrating mass. Jaundice may also result from lymph node compression/infiltration at the porta or infiltration of the lymphatic channels [4]. However, intraluminal tumor extension and incidental stones in the CBD are uncommon causes [5, 6].

Thus, this is a heterogeneous group of patients with differing prognoses, and more than one cause may be at play. While early involvement of the CBD by a tumor at the neck of the CBD and stone in the CBD offers an opportunity for early identification and surgery, the management of GBC patients with jaundice with direct infiltration of the hilum is technically challenging. Surgery involves resection of the tumor with negative margins and periportal lymph nodes with CBD resection. The extent of liver resection depends upon the extent of liver infiltration by the tumor or involvement of the right portal pedicle, which is managed by extended right hepatectomy. However, some institutes consider patients with severe bile duct infiltration, in whom resection may be possible by hepatopancreatoduodenectomy, to be inoperable because of the poor outcome; hence, a consensus has not yet been reached [7–11].

Furthermore, there are no clear-cut guidelines regarding the management of these patients, with the expertise limited to few high-volume centers.

Methods

This retrospective study analyzed data from a prospectively maintained database of patients with GBC who underwent resectional surgery at our institute between 1985 and 2016. Of 348 cases of GBC who underwent resectional surgery, 67 patients had preoperative jaundice (total bilirubin ≥ 2 mg/dL). Patients with incidental GBC and palliative resections were excluded.

Preoperative management

Almost all patients underwent computed tomography (CT, after 1986) scan or multi-detector row CT (after 2005). Some patients underwent positron emission tomography (PET)-CT (after 2005) when metastasis was suspected, depending upon their availability at our institute. Patients with cholestasis underwent preoperative biliary drainage, bile cytology analysis, and biopsy of the stenotic portions for proof of cancer. We usually performed percutaneous transhepatic biliary drainage (PTBD) until 2002. Subsequently, the use of endoscopic nasal biliary drainage (ENBD) has increased, and it has gradually become the method of choice at our center [12].

Surgery was usually performed when the total bilirubin level fell below 2 mg/dL when major hepatectomy was planned (median 1.8 [range 0.4–8.1] mg/dL). For patients in whom the bilirubin level did not fall below 2 mg/dL despite trying to control cholangitis and even after waiting for several weeks, surgery was performed after obtaining a high-risk consent.

The function of the expected remnant of the liver was assessed using the indocyanine green (ICG) clearance test from 1984 (only when the total bilirubin was 2 mg/dL or less as ICG antagonizes bilirubin [13]) and CT volumetry from 1986 (three-dimensional [3D] volumetry using a high-speed 3D image analysis system [SYNAPSE VINCENT, Tokyo, Japan] from 2011) [12].

Portal vein embolization (PVE) was indicated when the volume of the future remnant liver (FRL) was < 30%. In

high-risk patients requiring complicated surgeries such as combined pancreatoduodenectomy or hepatic artery resection, or who were elderly and/or had multiple comorbidities, PVE was indicated if the volume of FRL was less than 35% [14]. The future remnant liver volume divided by total liver volume was used as the future remnant liver rate [12]. PVE was performed when the total serum bilirubin level decreased below 10 mg/dL. If PVE did not result in significant hypertrophy of the future remnant liver, re-PVE was considered upon recanalization of the embolized portal vein, and a change in surgical procedure was considered otherwise. Patients underwent surgery 3 weeks or more after PVE (n = 18).

Surgical procedure

Patients underwent surgery in the form of radical cholecystectomy with resection of the gallbladder with liver bed and regional lymph node dissection. When required, major hepatectomy (resection of three or more segments) or PD was performed to achieve negative margins. Bile duct resection (BDR) was performed in all jaundiced patients. Portal vein resection with reconstruction and arterial resection was performed if they were intraoperatively involved with the disease.

Major hepatectomy (resection of three or more segments) was planned in cases with deep liver infiltration or infiltration of the hilum or right portal pedicle. During surgery, if peritoneal dissemination or obvious liver or para-aortic lymph node metastasis was detected, resectional surgery was not performed.

Pathological examination

Formalin-fixed, paraffin-embedded tissue sections were examined histologically according to the General Rules for Surgical and Pathological Studies on Cancer of the Biliary Tract of the Japanese Society of Biliary Surgery and TNM classification system [15, 16].

Definitions

Postoperative mortality was defined as that occurring within the hospital after surgery. Postoperative morbidity was assessed using the Clavien–Dindo classification [17].

Adjuvant therapy

Adjuvant therapy was administered according to the clinician's discretion and was based on the nodal status, margins, and performance status of the patient. The patients were followed up every 3 months or earlier during the first 3 years. Recurrence was detected using ultrasound or CT and tumor markers.

Statistics

The statistical analyses were performed in the R environment (R version 3.4.0; The R Foundation for Statistical Computing, Vienna, Austria). Univariate and multivariate analyses were performed using Cox proportionate hazards to identify the factors affecting prognosis in all resected patients and jaundiced patients separately. Only factors that were significant in univariate analysis were included in the multivariate analysis. The time factor was re-included in multivariate analysis to address the impact of time in a robust statistical manner because surgical techniques and perioperative care have significantly changed from those in the 1980s and the 1990s. Survival analysis was performed using Kaplan–Meier plots. p values < 0.05 were considered significant. A thorough search of Medline indexed journals was performed for similar studies by using the search terms "Surgery in gallbladder cancer with jaundice" or "Resection" or "Management of gallbladder cancer with jaundice." The search identified very few studies addressing these patients specifically. We present the findings of our series below and compare them to those reported in the literature.

Results

Among the 67 patients with jaundice, 24 were men and 43 were women. The mean age of the jaundiced patients was 66 years (Table 1). More patients with jaundice presented with advanced disease, and underwent more major hepatectomies, vascular resections, and bile duct resections. The surgeries were longer with more blood loss and higher chances of postoperative morbidity and R1 resections. Twenty-five percent of patients with jaundice received postoperative adjuvant chemotherapy (Table 1). The incidence of preoperative cholangitis in patients with drainage for jaundice was approximately 8% (5/66), with no difference between the EBD and PTBD groups (*5% in the EBD group [1/20] vs. 8.7% in the PTBD group [4/46], p = 1.0*).

Surgical mortality decreased from 4.6 to 0.8% in patients without jaundice and from 12 to 6.8% in patients with jaundice before and after 2000. All three surgical deaths of patients with jaundice since 2000 were in the early 2000s (2001, 2005,

Table 1 Details of all patients in the study

Variable		Without jaundice, $N = 281$	With jaundice, $N = 67$	*p value**
Age (year, median)		67	66	$^{\Phi}$0.20
Women		165 (59%)	43 (64%)	0.49
Major hepatectomy		36 (13%)	44 (66%)	< 0.001
With bile duct resection		69 (25%)	48 (72%)	< 0.001
With pancreaticoduodenectomy		66 (23%)	19 (28%)	0.43
Partial resection of the pancreas		3 (1%)	3 (4.5%)	0.088
Partial resection of the Du and/or St		12 (4.3%)	8 (12%)	0.034
Partial resection of the colon		16 (5.7%)	5 (7.5%)	0.57
Vascular resection		22 (8%)	21 (31%)	< 0.001
Blood loss > 1000 mL		107/280 (38%)	47 (70%)	< 0.001
Surgery time > 300 min		119/280 (43%)	58 (87%)	< 0.001
AJCC^{8th} T3/T4		113 (40%)	67 (100%)	< 0.001
AJCC^{8th} N1		83/270 (31%)	30/66 (45%)	0.029
AJCC^{8th} N2		42/270 (16%)	20/66 (30%)	0.008
AJCC^{8th} M1		59 (21%)	29 (43%)	< 0.001
R1		64 (23%)	41 (61%)	< 0.001
Adjuvant chemotherapy		37 (13%)	17 (25%)	0.022
Morbidity Clavien–Dindo grade ≥ 3	All cases	95 (34%)	34 (51%)	0.011
	From year 2000	30/121 (25%)	18/44 (41%)	0.053
Surgical mortality	All cases	13 (4.6%)	8 (12%)	0.040
	From year 2000	1/124 (0.8%)	3/44 (6.8%)	0.058

Du duodenum, *St* stomach

*2 × 2 Fisher exact test (two sided)

$^{\Phi}$ Wilcoxon rank sum test with continuity correction

and 2006). All patients who died postoperatively were included in the assessment for overall survival.

The 5-year overall survival rate was 21.9% in jaundiced M0 patients compared to 68.3% in M0 patients without jaundice (Fig. 1).

In multivariate analysis of all patients who underwent surgery for GBC, poorly differentiated histology, or others (vs. papillary/well/moderate differentiated, hazard ratio [HR] 1.80), the American Joint Committee on Cancer (AJCC), eighth edition (AJCC^{8th}) stages T3/4 (vs. T1/2, HR 2.65), AJCC^{8th} N1/2 (vs. N0, HR 1.98), and residual cancer (vs. R0, HR 1.94) were significantly associated with the overall survival (Supplemental Table 1). Preoperative jaundice was not an independent prognostic risk factor in the overall analysis.

Multivariate analysis of the prognostic factors of jaundiced patients separately showed that percutaneous transhepatic biliary drainage (PTBD, vs. endoscopic biliary drainage [EBD], HR 2.82), M1 stage (HR 1.85), and postoperative morbidity (Clavien–Dindo [CD] classification ≥ 3, HR 2.31) were significantly associated with patient prognosis, although the period factor was not significant (Table 2). Two- and 5-year overall survival and median survival time of GBCa patients with jaundice who underwent resectional surgery during the years 1985–1999 and 2000–2016 are shown in Supplementary Figures 1 and 2.

A comparison of the EBD and PTBD groups in M0 GBC patients showed a difference in the proportions after 2000 (93% of all EBDs vs. 50% of PTBDs, $p = 0.001$). Patients who underwent EBD were more likely to receive adjuvant chemotherapy (47% vs. 10%, $p = 0.022$, Supplemental Table 2). Peritoneal recurrence (44% vs. 13%, $p = 0.07$, Supplemental Table 3) and poor outcomes (5-year overall survival: 16% vs. 39%, $p = 0.007$, Fig. 2) were more common in the PTBD group than in the EBD group.

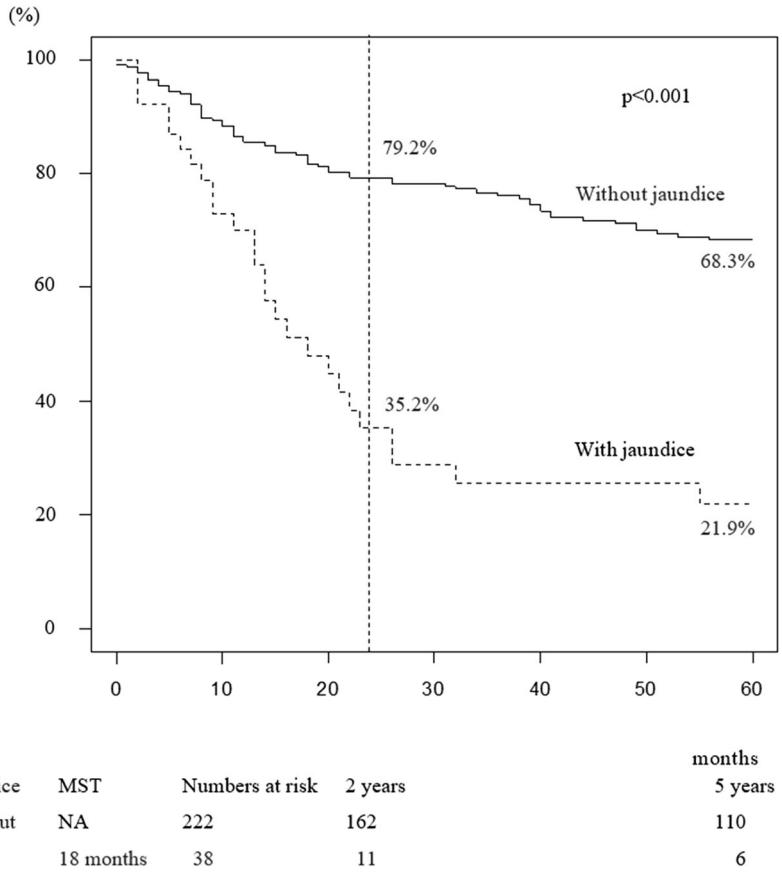
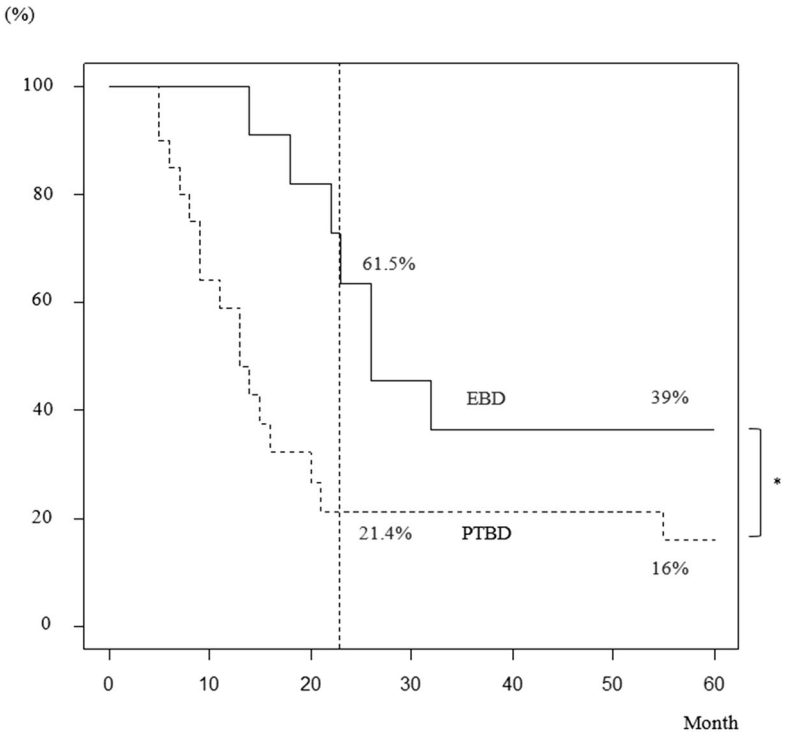


Fig. 1 Overall survival in patients with gallbladder cancer (GBC) with and without jaundice

Table 2 Univariate and multivariate analyses of prognostic factors in patients with GBC with jaundice for overall survival

	Univariate			Multivariate	
	n	5y-OS, %	*p* value	HR (95% CI)	*p* value
Period 2000–2016 (vs.1985-1999)	44/23	11.5/19.0	0.70	1.72 (0.91–3.25)	0.092
Age ≥70 (vs. <70)	26/41	8.73/17.5	0.68		
Female (vs. Male)	43/24	12.3/17.1	0.65		
PTBD (vs. EBD)	46/20	9.33/26.1	0.002	2.82 (1.39–5.69)	0.004
Major hepatectomy (vs. none)	44/23	12.3/16.1	0.54		
PD (vs. bile duct resection)	19/48	6.5816.5	0.17		
Vascular resection (vs. none)	21/46	6.02/17.1	0.030	1.25 (0.67–2.33)	0.48
Vascular invasion (vs. none)	35/29	6.77/19.3	0.065		
Blood loss, mL ≥1000 (vs. <1000)	47/20	9.88/22.1	0.19		
Surgery time, min ≥300 (vs. <300)	58/9	12.0/22.2	0.87		
Histology G3/other (vs. pap/G1/G2)	20/46	10.7/14.6	0.17		
AJCC^{8th} N1 (vs. N0)	27/20	6.08/27.3	0.60		
AJCC^{8th} N2 (vs. N0)	20/20	12.4/21.5	0.50		
AJCC^{8th} M1 (vs. M0)	29/38	3.62/21.9	<0.001	1.85 (1.04–3.29)	0.036
Residual cancer R1 (vs. R0)	41/26	8.79/20.8	0.077		
CD classification ≥3 (vs. ≤2)	34/33	9.50/18.4	0.003	2.31 (1.28–4.16)	0.005
Adjuvant Chemotherapy (vs. none)	17/50	7.97/15.2	0.86		

OS, overall survival; *HR*, hazard ratio; *PTBD/EBD*, percutaneous transhepatic / endoscopic biliary drainage; *PD*, pancreaticoduodenectomy; pap, papillary; *G1/G2/G3*, well / moderate / poorly differentiated; *AJCC*, American Joint Committee on Cancer; *N1*, metastases 1-3 regional lymph node; *N2*, metastases ≥4 regional lymph node; *M*, Distant metastasis



Drainage	MST, month	Numbers at risk	2 years	5 years
EBD	26	15	7	3
PTBD	13	20	4	3

* 0.007

Fig. 2 Overall survival in M0 gallbladder cancer (GBC) patients with jaundice excluding surgical mortality depending on the type of preoperative biliary drainage

Discussion

The results of our study demonstrated the improvement in short-term surgical outcomes in recent years in patients with GBC with jaundice. Our findings emphasize the necessity for R0 resections and the possibility that the type of preoperative biliary drainage and the occurrence of postoperative morbidity significantly impact long-term survival.

This study also elucidated our institute protocol for the management of these patients and touched upon those reported in the literature.

Most GBC patients with jaundice have lesions in the gallbladder neck or body [18]. Thus, the hepatic duct, hepatic artery, and portal vein tend to be involved early in the disease due to their proximity. Bile duct resection is usually required. Major hepatectomy may be needed in cases with deep liver infiltration or vascular involvement at the hilum, provided the left hepatic artery and the left portal vein are not involved [2].

GBC patients with jaundice underwent major hepatectomies (> 30% in various series and 66% in our study), more combined resection of adjacent organs (CRAO), vascular resections (range of portal vein resections was 4–62% in various series and 31% in our study), and CBD resections (Tables 1 and 3) [3, 19, 24, 26]. Although we resected the CBD in all patients with jaundice, some series did not perform this procedure in all jaundiced patients (in 82%, 87.9%, and 93.6% of patients in the series by Regimbeau, Tran, and Yang, respectively) [3, 24, 25].

The reported resectability rate in GBC patients with jaundice is around 30–50% and is slightly lesser than that in patients without jaundice (49% in jaundiced patients versus 75% in those without jaundice, according to Nishio et al.) [23]. However, this rate can vary and a very recent study from India reported that only one out of seven patients having jaundice had resectable disease on clinical presentation, as opposed to every second person in the non-jaundiced group [6]. More patients with preoperative jaundice were of advanced T stage and node-positive. This finding was consistent across studies [2, 24].

Major liver surgeries have become safer with better patient selection, technique refinement, and critical care. Postoperative deaths (6.8% during 2000–2016 in our study vs. an average of 12% in the literature) and postoperative major morbidity (CD ≥ 3, 41% in our series from 2000 vs. an average of 56% reported in the literature) in the surgery for patients with GBC with jaundice have declined (Tables 1 and 3). The major causes of postoperative morbidity include intra-abdominal abscess caused by a biliary fistula or hepatico- or pancreaticojejunostomy leakage.

Table 3 A comparison of our study with previous studies on gallbladder cancer with jaundice (only includes patients who underwent resection)

Author	No of pts with jaundice	Morta-lity	Morbidity	Indication of PVE	Major Hep	Vascular resection	R1 resection	2 yr survival	5 yr survival	MST (months)	Preop biliary drainage	Poor prognostic factors (p<0.05)
Miyazaki [19] 1996	27 CBD+/-hep-atic involvement	27%	52%	-	74%	26% PVR	70%	-	-	-	-	CBD involvement; R1 resection
Kondo S [20] 2003	48	27%	-	Yes# but not enough data	43 pts (89%) hilar inv	PVR common	-	21%-3yr	-	-	100% PTBD	M1 disease; Right Hepatectomy in cholestatic liver; PVR; male sex (for hospital death)
Agarwal [21] 2007	14	7.14%	50%	-	7.14%	2 art	-	50%	1pt+	26 (DFS)	3 pts cholangitis	
D'Angelica M [22] 2009	?36 clinical CBD involvement	20%	-	-	-	-	-	-	21%	19	-	T stage; higher N stage; CBD involvement; poor differentiation
NishioH [8, 23] 2011	96	18.7%	-	-	82%*	36%*	16%*	41%-3yr	23.8% (R0)	18 (R0)	All pts, endoscopic	CRAO, R1 resection; Intraop blood loss>3000 ml (for hospital death)
Regimbeau [24] 2011	50	16%	62%	7pts	56%	9, art: 4	26%	19%-3yr	19%	11	56% (majority endoscopic)	T; N and M stage
Yang [25] 2014	47	6.4%	34%	none	8% (60% GB neck type)	2	23.4%	6%-3yr	6%	14	40% (10 PTBD, 9 endoscopic)	R1 resection; Jaundice for morbidity,
Nasu [26] 2016	37	5%	65%	Yes#	65%	23 PVR 8 art	11%	-	27%	1.9yrs	All pts, ENBD preferred	Lymph node (para-aortic); M1 disease
Tran TB[3] 2017	33	6.5%	69%	-	39.4%	4 PVR 12%	48.5%	23.5-3yr	9.4%	14	75.8%	Advanced stage; Blood transfusion; Jaundiced Pts with CA 19-9>50; lympho-vascular invasion
Mishra PK[6] 2017	23	21%	56%	-	39%	2pts	-	32%	Nil	12	Endoscopic/PTBD	T stage; adjacent organ involvement; Node positivity
Our study	67	9%	50.7%	18pts#	66%	21, 31%	61%	22.7%	16.7% (21.9% in M0 pts)	14	EBD-20 PTBD-46	Type of biliary drainage; Post-operative morbidity≥3; M1 disease

Pts, patients; *PVE*, portal vein embolization; *Hep*, hepatectomy; *yr*, year; *CBD*, Common Bile Duct; *PVR*, Portal Vein Resection; art, arterial; *MST*, median survival time; *DFS*, disease free survival; *ENBD*, endoscopic nasal biliary drainage; *PTBD*, Percutaneous transhepatic biliary drainage; *CRAO*, Combined Resection of Adjacent Organs; *GB*, Gall Bladder;

[#] when extended right hepatectomy was planned;

*percentages are for patients with pathological invasion of CBD [23]

There is no consensus regarding when biliary drainage should be performed and how long to wait before scheduling the patient for surgery. Yang et al. [25] performed surgery 1 week after biliary drainage. We generally waited for 2 weeks or more after biliary drainage, when the bilirubin levels had decreased to 2 mg/dL when a major hepatectomy was planned (median 1.8 [0.4–8.1] mg/dL). Nishio et al. [8, 23] also waited for the serum bilirubin level to drop to 2 mg/dL. Some authors only performed preoperative biliary drainage if the serum bilirubin level was > 10 mg/dL or if the patient had cholangitis [21]. The Japanese guidelines for the management of biliary cancer recommend preoperative biliary drainage for all such patients with obstructive jaundice. Our data suggested that endoscopic drainage may be better than PTBD, with superior overall survival, although the number of cases was small. A decrease in cholestasis improves hepatic function and chances of liver failure postoperatively if major liver resection is performed [13].

For the above-described reasons, we performed PVE in patients with GBC with jaundice stipulated to undergo an extended major hepatectomy with small future remnant liver. Many authors perform PVE in patients with GBC, although the reported studies do not discuss further details [20, 24, 26]. Many institutes perform PVE for biliary cancers when the future remnant liver is < 40% [27]; we performed PVE if the future remnant liver was < 30%, and < 35% in high-risk patients. In these cases, surgeons face the prospect of delaying surgery in a patient who has already waited for 1–2 weeks following biliary drainage. We waited for approximately 3 weeks after PVE. Thus, the appropriate waiting period remains debatable.

The R1 resection rate is reportedly higher in patients with jaundice, ranging from 11 to 70% (Table 3) [8, 19, 26]. Sixty-one percent of patients in our study also had residual tumor, mostly in those who underwent surgery during the earlier part of the study period. High R1 rates could be explained by the inclusion of patients with margin-positive disease, para-aortic nodes, or liver metastasis discovered later in the final pathology report. Second, the definition of what exactly constitutes an R1 resection in GBC invading the hepatoduodenal ligament needs to be examined. Technically, even when we remove the CBD, the very act of dissecting the right hepatic artery off this anatomically challenging area renders the patient prone to R1 resection, unless the spread of the tumor is intramural.

Many studies have reported that preoperative jaundice, per se, does not independently affect survival after adjusting for advanced disease stage [3, 25, 26, 28, 29]. While findings were consistent with these reports, other authors have reported contrary findings (Table 3) [22, 30, 31]. CBD involvement or pathologic extrahepatic bile duct invasion are reportedly strong independent prognostic factors, predicting poor survival in patients undergoing liver resection [22, 23]. However, survival was still better for patients who underwent resection compared to that in patient who did not [23]. Studies have also reported much worse prognosis in jaundiced patients with GBC requiring CRAO other than liver and CBD, compared to the prognosis in patients who did not [8, 23]. Serum carbohydrate antigen (CA) 19-9, lymphovascular invasion and perioperative blood transfusions were independently associated with a poor prognosis in patients with GBC with jaundice [3, 8, 32]. In our study, preoperative PTBD, M1 stage, and postoperative morbidity (CD grade ≥ 3) were significantly associated with poor survival in jaundiced patients (Table 2).

The median survival times range from 11 to 26 months and are generally longer in studies from Asia compared to those from Western countries. While more patients have survived for 2 years, there are few 5-year survivors (Table 3). While our study had seven 5-year survivors (Supplemental Table 4), Nishio et al. [8, 24] and Nasu et al. [26] reported higher 5-year survival rates of 23% and 27% respectively.

Patients with M0 disease who underwent preoperative EBD survived longer than those who underwent PTBD or those with M1 disease (detected on final HPE), with a 5-year survival rate of 36.4% (Fig. 2). Although M1 disease implies a poor prognosis, data in the literature indicate that the percutaneous drainage of bile in obstructed biliary malignancies leads to increased rates of recurrence [33–35]. PTBD induces bile leakage into the abdominal cavity, which may lead to an increased rate of peritoneal dissemination, leading to a poorer outcome as opposed to patients in the EBD group (Supplemental Table 3). However, this was not statistically significant, as the number of patients was small.

Comparisons of patients with GBC with jaundice who underwent resectional surgery but were stated to be R1 or M1 on final histopathology, with patients who underwent potentially curative resections showed significantly better survival in the latter group. Many authors have emphasized that aggressive surgery should only be undertaken for these patients if R0 resection is possible [8, 26, 29, 36]. Studies have emphasized the oncological completeness of resection with R1 status independently being predictive of a poor prognosis [19, 23]. However, authors have insisted on parenchyma preserving strategies vis-à-vis extended resection provided R0 is achieved [21, 23, 25]. A larger remnant would result in fewer postoperative complications.

Thus, the judicious selection of surgical patients along with preoperative optimization to reduce the chance of postoperative hepatic failure may yield a better survival [37]. Therefore, our philosophy should be to opt for endoscopic drainage vis-à-vis PTBD, avoid resections in metastatic patients, and perform surgery only if R0 resection is possible.

Our study has some limitations. During the 30-year study period, patients underwent different diagnostic and treatment modalities with the development of technological advances. These could have skewed the outcomes of patients treated

during different study periods. Our survey was conducted at a single institution; thus, it is difficult to completely rule out bias. Postoperative adjuvant chemotherapy, which is now the standard, was not administered consistently across the study. This could be because the study recruited patients over a long period and practice guidelines have changed considerably. Prolonged postoperative morbidity not only delays but may also prevent the start of adjuvant therapy.

However, the literature regarding patients undergoing resection for GBC and with jaundice is scarce, and no reports have described the impact of the mode of preoperative drainage and recurrence in patients with GBC. Thus, our study is valuable in this regard.

Conclusion

Opting for EBD instead of PTBD may be better; however, due to the small number of cases reported, further studies are needed. Surgery in patients with GBC should be performed only when there is a reasonable chance of R0 resection.

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Authors' contributions RKC, RH, and MY conceptualized the study design and wrote the article. TY, SU, WI, YM, EN, and TO helped with data collection and surgeries, along with RH, MY, and RKC. TF helped with pathology. YS provided advice on the statistics.

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Code availability Not applicable

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethics approval This study was approved by the institutional review board of Tokyo Women's Medical University (approval number: 4328-R). The study was a retrospective analysis of a prospectively maintained database. The procedures followed were in accordance with the ethical standards of the institutional research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

Consent to participate The need for informed consent was waived because this was a retrospective chart review analysis.

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