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ORIGINAL ARTICLE

Should jaundice preclude resection in patients with gallbladder cancer? Results from a nation-wide cohort study

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Abstract

Background: It is controversial whether patients with gallbladder cancer (GBC) presenting with jaundice benefit from resection. This study re-evaluates the impact of jaundice on resectability and survival.

Methods: Data was collected on surgically explored GBC patients in all Dutch academic hospitals from 2000 to 2018. Survival and prognostic factors were assessed.

Results: In total 202 patients underwent exploration and 148 were resected; 124 non-jaundiced patients (104 resected) and 75 jaundiced patients (44 resected). Jaundiced patients had significantly ($P < 0.05$) more pT3/T4 tumors, extended ($\geq$3 segments) liver- and organ resections, major postoperative complications and margin-positive resection. 90-day mortality was higher in jaundiced patients (14% vs. 0%, $P < 0.001$). Median overall survival (OS) was 7.7 months in jaundiced patients (2-year survival 17%) vs. 26.1 months in non-jaundiced patients (2-year survival 39%, $P < 0.001$). In multivariate analysis, jaundice (HR1.89) was a poor prognostic factor for OS in surgically explored but not in resected patients. Six jaundiced patients did not develop a recurrence; none had liver- or common bile duct (CBD) invasion on imaging.

Conclusion: Jaundice is associated with poor survival. However, jaundice is not an independent adverse prognostic factor in resected patients. Surgery should be considered in patients with limited disease and no CBD invasion on imaging.

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Introduction

Gallbladder (GBC) cancer is an aggressive malignancy with a notoriously poor prognosis.[1] Five-year survival is less than 5%.[2,3] The only curative treatment remains complete surgical resection.[1] Unfortunately, due to nonspecific symptoms and subsequent late detection, most patients present with advanced disease. GBC tends to grow rapidly and disseminates early to the surrounding hepatic parenchyma, lymph nodes, and peritoneum.[4] Extended liver resections are often necessary to achieve tumor-free margins.[5] Consequently, patients with GBC are frequently either unresectable or require extensive surgery with a high risk of morbidity and mortality to achieve potential cure.

Obstructive jaundice is one of the indicators for advanced disease since it implies infiltration of the hepatic hilum.[6] The first paper reporting on obstructive jaundice in GBC specifically consisted of a series of 107 jaundiced patients; only 6 (7%) patients were deemed resec' and no survival beyond two years was reported.[7] Based on these data the traditional consensus was that obstructive jaundice should preclude surgery.[8] However, recently published studies do report survival beyond 2 years in a small number of patients. Results from a recent meta-analysis show that surgery for GBC presenting with obstructive jaundice should be considered in medically fit patients where R0 resection appears feasible.[9] Nevertheless, most previous studies stem from single center series and generalizability may be limited. Moreover, none of the published studies focus on pre-operative factors associated with prolonged survival in jaundiced patients.

The aim of this study was therefore to analyze the prognostic impact of jaundice in GBC patients who underwent surgical exploration in a nation-wide setting.

Methods

Patient inclusion and data collection

Patients were identified from the Netherlands Cancer Registry (NCR). The NCR contains data on all newly diagnosed malignancies, including year of diagnosis, patient age and gender, tumor characteristics (histology and TNM stage), patient identification number and treatment hospital. The data from the NCR is based on data from the automated pathological archive (PALGA), the nation-wide network and registry of histo- and cytopathology in the Netherlands, and supplemented by data from the National Archive of Hospital Discharge Diagnosis.[10] Patients treated for GBC in any of the expert, tertiary referral centers in the Netherlands were included in a retrospective database. Patients diagnosed in community hospitals were not included because in the Netherlands patients with gallbladder cancer will be referred to and treated in an expert center.

All patients with pre-operatively diagnosed GBC from January 2000–September 2018 who underwent surgical exploration were included. Patients with GBC diagnosed during or after cholecystectomy for presumed benign disease (incidental GBC) were excluded from analysis. Data on patient medical history, pre-operative imaging and laboratory results, operative characteristics, histopathological characteristics, post-operative morbidity, mortality and recurrence were obtained from the medical records, which were available for all included patients. Data on follow-up was obtained through linkage with the automated Municipal Personal Records Database and was last accessed at 1/3/2018. The study was approved by the Medical Ethics Committee of the region Arnhem-Nijmegen (number 2017–3912).

Variable and subgroup definitions

Patients were classified as jaundiced when yellow pigmentation of the skin or sclera was present at primary presentation or when serum bilirubin was $\geq$30 μmol/L.[11] Performance status was assessed using the ASA Physical Status Classification System.[12] All laboratory values were reported in μmol/L. All post-operative complications were classified according to the Clavien-Dindo Classification System and included complications up to 90-days after surgery.[13] Major complications were defined as Clavien-Dindo grade $\geq$ 3A. Post-operative mortality was defined as death due to any cause <90 days postoperatively. Radical (R0) resection was defined as distance margin to tumor $\geq$ 1 mm. TNM staging was reported according to the American Joint Committee on Cancer (AJCC) staging system, 7th edition.[14] Conversion to the 8th edition was not possible since the location of the tumor since the location of the tumor (i.e. on the liver- or peritoneal side of the gallbladder) was frequently unknown. Early GBC was defined as AJCC stage $\leq$ II and late stage GBC was defined as AJCC $\geq$ IIIA. Overall survival (OS) was defined as number of days between date of surgical exploration and death from any cause. Long-term survival was defined as survival beyond two years.

Statistical analysis

Categorical variables were reported as counts with percentages and continuous variables as median values with corresponding Interquartile Ranges (IQR). Differences in baseline variables were assessed using the student's *t*-test, Mann-Whitney-U test, Chi-Squared test or Fisher's exact test. Overall survival was analyzed using the Kaplan–Meier method. Differences in OS between jaundiced and non-jaundiced patients were analyzed across the entire cohort and in the subgroup of resected patients. Differences in survival between subgroups (N0 vs. N1) were assessed using log-rank testing. Multivariable Cox regression analysis with backward elimination was used to identify prognostic factors. Included potential prognostic factors were those with p-values < 0.10 in univariable analysis or those known from literature. Missing values were presumed to be not missing at random (related to the value itself, potentially related to the outcome). Imputation was not conduced since it may result in biased estimates and/or overestimation of test statistics.[15] Results

were reported as hazard ratio (HR) with 95% confidence interval (CI). All analyses were conducted using SPSS Statistics for Windows, version 25.0 (IBM Corporation, Armonk, NY, USA). P-values ≤ 0.05 were considered statistically significant.

Results

Patient inclusion and baseline characteristics

A total of 410 patients with GBC was identified through the NCR. Of those, 208 patients were excluded; 128 patients had incidental GBC and 80 did not undergo surgical exploration (Fig. 1).

The cohort consisted of 202 patients who underwent surgical exploration; 127 non-jaundiced patients (63%) and 75 (37%) jaundiced patients. Patient demographics and medical history were comparable in both groups (Table 1). Jaundiced patients presented more frequently with weight loss (36% vs. 14%, P < 0.001). Median bilirubin at presentation was 9 (IQR 5–12) µmol/L in non-jaundiced patients and 170 (IQR 88–229) µmol/L in jaundiced patients. Tumor location on imaging was significantly different between groups; non-jaundiced patients more frequently presented with a tumor in the gallbladder fundus/corpus (38% vs. jaundiced 13%) whilst jaundiced patients more frequently had a tumor in neck of the gallbladder (16% vs. non-jaundiced 8%) (P = 0.003).

(Pre-)operative treatment

Pre-operative biliary drainage was performed in 76% of patients who presented with jaundice (Table 2). Of non-jaundiced patients at time of presentation, 13 (10%) underwent pre-operative biliary drainage due to; development of jaundice after presentation (N = 6), cholangitis (N = 2) and diagnostic purposes (N = 5). In 54 (27%) patients unresectable or metastatic disease was discovered during surgical exploration and no resection was performed. Jaundiced patients had a higher rate of unresectable disease during surgical exploration (N = 31/75, 41%) compared to non-jaundiced patients (N = 23/124, 18%, P < 0.001).

A curative-intent resection was performed in 44 (59%) jaundiced and 104 (82%) non-jaundiced patients. Jaundiced patients had a higher rate of extended (≥3 segments) liver resection (14/

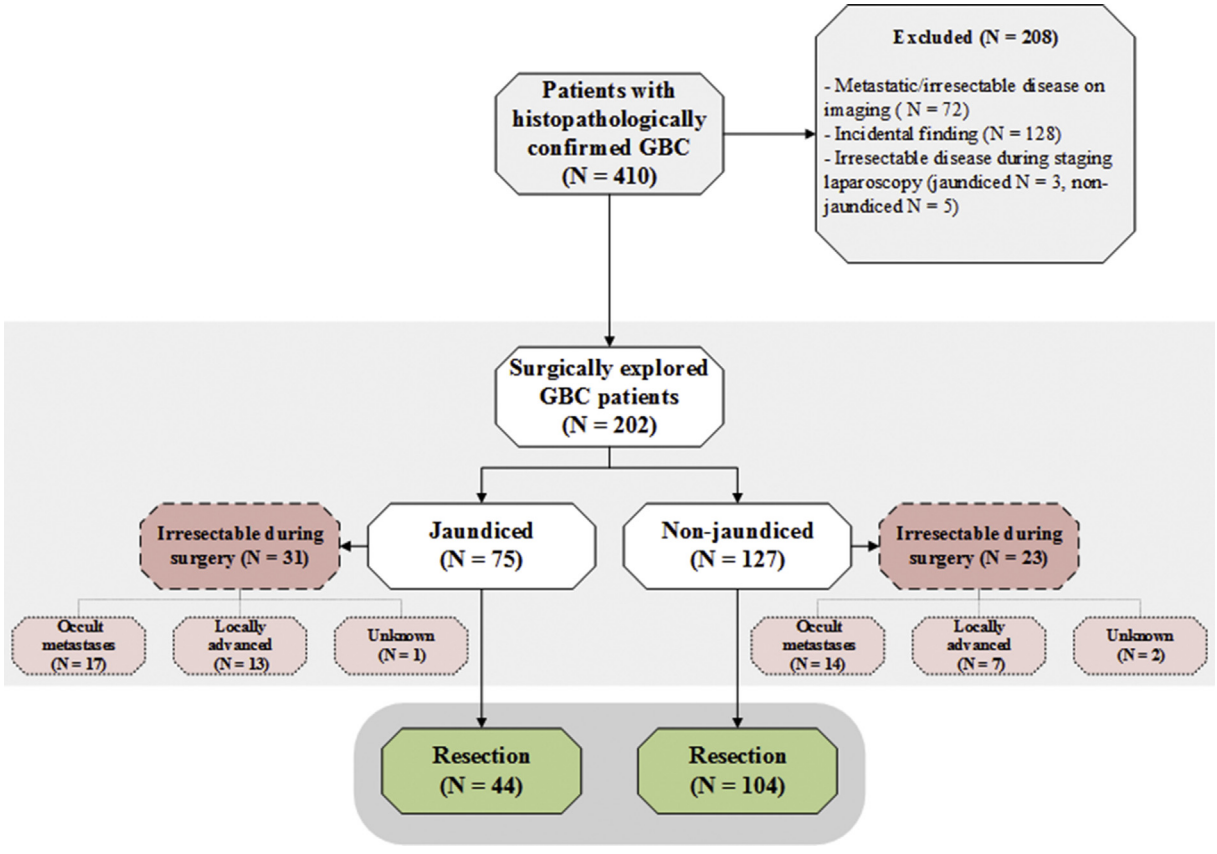

Figure 1 Patient inclusion flow diagram

Table 1 Baseline patient- and tumor characteristics

Characteristic	Non-jaundiced (N = 127)	Jaundiced (N = 75)	P value
Gender (male)	48 (38%)	33 (40%)	0.458
Age (years)	65 (57–74)	66 (60–76)	0.818
Medical history			
ASA >2	34 (28%)	15 (20%)	0.240
Previous malignancy	31 (24%)	10 (13%)	0.071
Gallbladder polyp	8 (6%)	3 (4%)	0.750
Cholecystitis	8 (6%)	2 (3%)	0.328
Cholelithiasis	29 (23%)	12 (16%)	0.280
Presenting symptoms			
Nausea/vomiting	32 (25%)	24 (32%)	0.331
Abdominal pain	74 (58%)	39 (52%)	0.463
Weight loss	18 (14%)	27 (36%)	<0.001
Bilirubin[a]	9 (5–12)	170 (88–229)	<0.001
CA 19.9[b]	57 (14–328)	152 (59–1951)	0.216
T stage (imaging)			
<T3	25 (19%)	8 (24%)	0.070
T3/T4	31 (23%)	25 (45%)	
Missing	71 (56%)	42 (56%)	
Gallstones (imaging)	8 (6%)	6 (8%)	0.764
Liver invasion (imaging)	35 (28%)	27 (36%)	0.262
N1/2 stage (imaging)	31 (24%)	26 (35%)	0.141
M1 stage (imaging)	8 (6%)	4 (5%)	0.326
Tumor location (imaging)			
Fundus/corpus	48 (38%)	10 (13%)	0.003
Neck	10 (8%)	12 (16%)	
Diffuse	20 (16%)	17 (23%)	
Unreported	49 (39%)	36 (48%)	

[a] Reported in 60/127 non-jaundiced patients and 60/75 jaundiced patients.
[b] Reported in 36/127 non-jaundiced patients and 34/75 jaundiced patients.

44 vs. 7/104, P < 0.001), vascular reconstruction (8/44 vs. 3/104, P = 0.003), common bile duct (CBD) resection (30/44 vs. 11/104, P < 0.001) and peri-operative complications (6/44 vs. 3/104, P = 0.043). Adjuvant chemotherapy (capecitabine) was administered to one non-jaundiced patient. None of the jaundiced patients received (neo)adjuvant therapy.

Morbidity and mortality in patients with resection with curative intent

In all patients who received resection with curative intent, jaundiced patients (N = 44) had a higher rate of major (Clavien-Dindo grade ≥ 3A) complications after resection compared to non-jaundiced (104) patients (18/44 vs. 16/104, P < 0.001). In patients who underwent extended surgery (defined as resection of ≥3 liver segments or resection of adjacent organs) no differences in major complications occurred when comparing jaundiced (13/27) to non-jaundiced patients (9/18) (P = 0.852). Multivariable analysis including pre-operative T-stage, ASA classification, extent of resection, CBD resection (yes/no) and presence of jaundice showed that only resection of the CBD was an independent predictor for major complications (HR 26.51, 95%CI 2.94–239.02, P = 0.003).

Six patients died within 90 days postoperatively due to surgical complications; two due to liver failure, two due to leakage of the hepatoduodenal anastomosis and subsequent sepsis and multi-organ failure, one due to post-operative hemorrhage and one due to aspiration pneumonia. All postoperative mortality occurred in jaundiced patients (6/44 vs. 0/104, P < 0.001). In all deceased patients the CBD was resected. Two patients underwent a right hemihepatectomy, one received a radical cholecystectomy with CBD resection, one received a right hepatectomy with adjacent colon resection, one underwent a Whipple's procedure and one patient underwent a Whipple's procedure with portal vein reconstruction.

Histopathology of resected patients

Jaundice was associated with higher pT-stage (T3/T4 in 31/44 vs. 28/104, P < 0.001) and a higher rate of R1/R2 resection (25/44 vs. 28/104, P = 0.001) (Fig. 3). Histopathological characteristics also differed significantly between jaundiced

Table 2 Surgical procedures and complications

All patients (N = 202)	Non-jaundiced (N = 127)	Jaundiced (N = 75)	P-value
Pre-operative therapy			
No	113 (89%)	18 (24%)	**<0.001**
ERCP	12 (11%)	51 (68%)	
PTC	1 (1%)	0 (0%)	
ERCP + PTC	0 (0%)	7 (9%)	
PVE	1 (0%)	5 (7%)	
Diagnostic laparoscopy (yes)	19 (15%)	14 (20%)	0.437
Non-resectable during surgery	23 (18%)	31 (41%)	**<0.001**
Resected patients (N = 148)	Non-jaundiced (N = 104)	Jaundiced (N = 44)	
Hepatic resection			
Minor (≤2 segments)	39 (38%)	16	**<0.001**
Major (≥3 segments)	7 (7%)	14	
Vascular reconstruction	3 (3%)	8	**0.003**
CBD resection	11 (11%)	30	**<0.001**
Other organ resection[a]	12 (11%)	17	**0.001**
Perioperative complications[b]	3 (3%)	6	**0.043**
Postoperative complications CD ≥ 3A	16 (15%)	18	**0.001**

PVE: Portal Vein Embolization.
Bold: Significant values.
[a] Includes head of pancreas (jaundice = 11, no jaundice = 3), duodenum (jaundice = 10, no jaundice = 6), colon (jaundice = 2, no jaundice = 4) and other (jaundice = 5, no jaundice = 4).
[b] Includes bleeding (jaundice = 7, no jaundice = 2), bowel injury (jaundice = 0, no jaundice = 1) and SIRS reaction (jaundice = 1, no jaundice = 0).

and non-jaundiced patients; jaundiced patients more frequently had a tumor located in the neck (9/44 vs. 12/104, P = 0.001), a diffuse tumor (18/44 vs. 17/104, P = 0.001), perineural invasion (24/44 vs. 30/104, P = 0.005), liver invasion (20/44 vs. 21/104, P = 0.003) and CBD invasion (25/44 vs. 5/104, P < 0.001).

Survival of all surgically explored GBC patients

Median OS was 15.9 months (95% CI 11.2–20.6). Median OS of jaundiced patients was 7.7 months and significantly worse than the median OS of 26.1 months in non-jaundiced patients (Fig. 2a, 3-year survival 14% vs. 42%, P < 0.001).

Survival of resected patients

In resected patients (N = 148), median OS in jaundiced patients was 16.7 months vs. 36.4 months in non-jaundiced patients (P < 0.001, Fig. 2b). In the subgroup of patients who underwent an extended resection (≥3 liver segments or adjacent organ resection), jaundiced patients also showed significantly reduced survival compared to non-jaundiced patients (16 vs. 26 months, P = 0.010). When analyzing survival according to pN status, jaundice was associated with worse median OS in pN0 patients (jaundiced 18.9 vs. non-jaundiced 112.5 months, P < 0.001), but not in pN1 patients (jaundiced 10.4 vs. non jaundiced 14.8 months, P = 0.365). In patients who received an R0 resection,

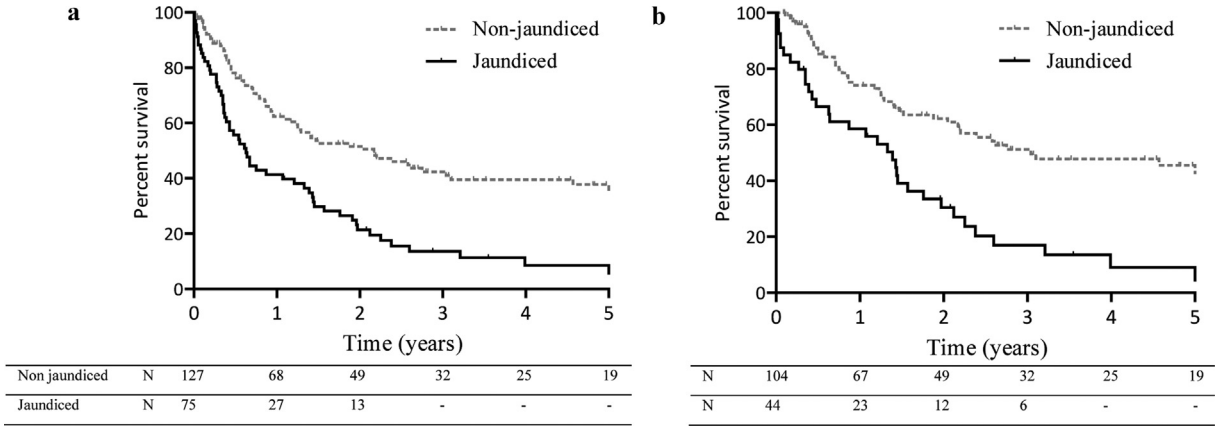

Figure 2 a: Survival of all jaundiced vs. all non-jaundiced patients. Log rank <0.001. b: Survival of resected jaundiced vs. resected non-jaundiced patients. Log rank <0.001

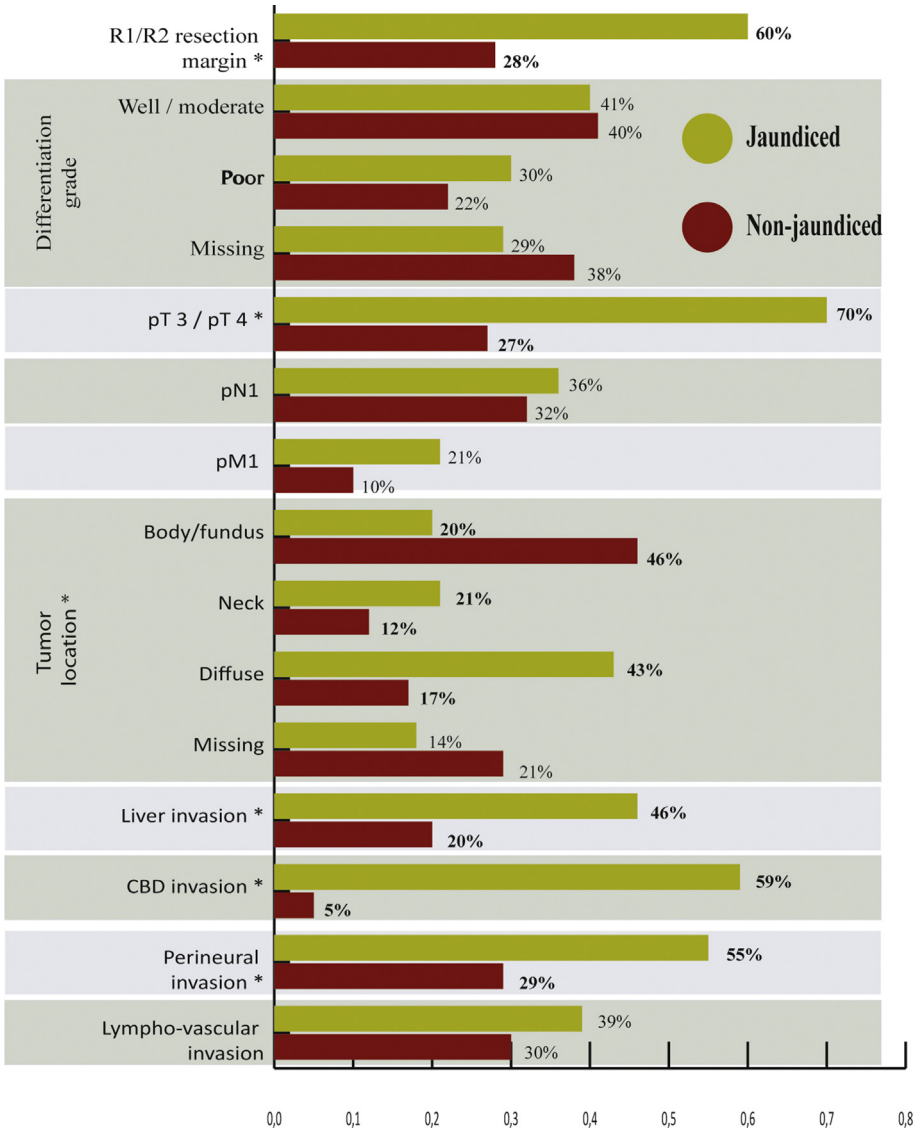

Figure 3 Comparison of histopathological characteristics of jaundiced vs. non-jaundiced patients that underwent resection. * Chi squared P-values <0.05

survival was worse in jaundiced compared to non-jaundiced patients (23.6 months vs. 104 months, P = 0.001). In patients with an R1 resection, no differences in survival were found between jaundiced and non-jaundiced patients (13.7 vs. 8.2 months, P = 0.888).

Prognostic factors for OS in surgically explored patients

Age, jaundice, weight loss, T3/T4 disease on imaging and a diffuse tumor or a tumor located in the gallbladder neck on imaging were all associated with a poor prognosis on univariate analysis in all surgically explored patients (N = 202, Supplementary Table 1A). In multivariable Cox regression analysis, jaundice (HR 1.89, 95% CI 1.01–3.53, P = 0.049) and T3/T4 disease on imaging (HR 2.02, 95% CI 1.03–3.97, P = 0.041) remained significant poor prognostic factors for OS.

Prognostic factors for OS in resected patients

Jaundice, extent of resection (non extended vs. extended resection), pT-stage (pT1/2 vs. pT 3/4), pN-stage, CBD-invasion, perineural invasion, liver invasion and resection margin were predictive for prognosis on univariate analysis in resected patients (N = 148, Supplementary Table 1B). In multivariate analysis, only pN1 stage (HR 1.84, 95%CI 1.08–3.12, P = 0.025),

Table 3 Characteristics of long-term (≥2 years) survivors of patients with GBC and jaundice

Age, gender, ASA	Ca 19.9	Gallstones, imaging	Liver/lymph node invasion, imaging	Tumor location, imaging	Procedure	pTNM	Resection margin, grade, PNVI	Organ invasion	Follow-up (months)	Vital status (+COD)
64, F, ASA 2	–	Yes	Yes (regional lymph nodes)	Unspecified	Right hepatectomy	T2 N0 Mx	R1, GR x, PNVI+	None	25	Alive without recurrence
81, F, ASA 2	–	Yes	No	Unspecified	Classic cholecystectomy	T3 Nx Mx	Rx, GR 2, PNVI -	None	25	Dead, tumor progression
68, M, ASA 1	–	Yes	No	Unspecified	Radical cholecystectomy + Extended right hemihepatectomy due to recurrence (26 months later)	T2 N0 M0	R0, GR 2, PNVI -	None	26	Dead, liver failure after extended right hemi hepatectomy
79, F, ASA 2	–	Yes	Yes (liver)	Diffuse	Radical cholecystectomy, bile duct excision, Whipple	T2 N1 M0	R1, GR 2, PNVI +	None	29	Dead, tumor progression
62, F, ASA 1	234	Yes	Yes (liver and regional lymph nodes)	Diffuse	Radical cholecystectomy and bile duct excision	T4 N1 M0	R0, GR 2, PNVI +	None	31	Dead, other malignancy
63, M, ASA 2	–	No	No	Unspecified	Whipple/PPPD	T4 N1 M0	R1, GR 1, PNVI +	Pancreas	38	Dead, tumor progression
82, F, ASA 2	–	No	No	Corpus	Classic cholecystectomy	T2 N0 M0	R0, GR 2, PNVI -	None	42	Alive without disease
46, M, ASA 2	90	No	No	Diffuse	Right hemihepatectomy, bile duct excision and PPPD	T3 N1 M0	R0, GR 2, PNVI +	Extrahepatic bile duct	48	Dead, tumor progression
77, F, ASA 2	–	No	No	Unspecified	Radical cholecystectomy	T2 N0 M0	R0, GR 1, PNVI -	None	53	Alive without recurrence
69, F, ASA 3	28	No	No	Unspecified	Right hemihepatectomy, bile duct excision and PPPD	T4 N1 M1	R1, GR 1, PNVI +	Pancreas	70	Dead, tumor progression
60, M, ASA 3	–	No	No	Fundus	Cholecystectomy, local excision bile ducts	T1B N0 M0	R0, GR x, PNVI -	None	100	Dead, liver cirrhosis (PSC)
62, M, ASA 2	–	No	No	Fundus	Classic cholecystectomy	T2 NX M0	R0, GR 2, PNVI -	None	166	Alive without recurrence

GR = tumor differentiation grade. 1 = good differentiation, 2 = moderate differentiation, 3 = poor differentiation, x = missing differentiation. PNVI = Perineural or lymphovascular invasion.

liver invasion (HR 2.23, 95% CI 1.29–3.88, P = 0.004) and R1 resection (HR 2.76, 95% CI 1.58–4.84, P < 0.001) were significant poor prognostic factors for OS. pT3/4 stage was borderline significant (HR 1.95, 95% CI 0.99–3.81, P = 0.055). In multivariate regression analyses excluding all patients with peri-operative mortality <90 days (data not shown).and in patients with gallstones on imaging (supplementary table 1C) jaundice was also not a significant prognostic factor for survival.

Characteristics of jaundiced, long-term survivors

After resection, 12/44 (27%) jaundiced patients lived beyond two years; their characteristics are summarized in Table 3. Five patients died due to tumor progression after a mean follow-up of 42 months. One patient died due to complications related to end-stage liver cirrhosis and PSC, one patient died due to another malignancy, one patient died from postsurgical liver failure after extended right hemihepatectomy for a recurrence. Four patients were still alive at the time this study was conducted. Notably, all patients who remained free of recurrence (N = 6) had a tumor located in the body or the fundus of the gallbladder and showed no liver invasion on pre-operative imaging. Additionally, five out of six patients had a pT1b or pT2 tumor and four patients did not have any perineural or lymphovascular invasion. Gallstones were present in three out of six patients without a recurrence. CBD invasion was not present in any of the patients without a recurrence.

Discussion

Jaundice as a presenting symptom for GBC is significantly associated with irresectability or extensive surgery. In resected GBC patients, jaundice is associated with significant post-operative morbidity, mortality and poor histopathological features. Median OS in jaundiced patients was 7.7 months versus 26.1 months in non-jaundiced patients. Pre-operative jaundice was significantly correlated with poor OS in surgically explored patients. However, multivariate analysis showed that jaundice was not an independent predictor of poor outcome in patients who underwent resection when adjusting for N status, liver invasion and resection margin. All jaundiced patients who remained free of recurrence had a tumor located outside of the gallbladder neck and did not show liver invasion on pre-operative imaging. The present study is the first to assess imaging characteristics of GBC long-term survivors who presented with jaundice.

Previous studies investigating surgery in jaundiced GBC patients report dismal median survival and virtually no survival beyond two years.[7,16–18] In the present series median OS was

7.7 months and 12/44 resected jaundiced patients survived beyond two years. Major postoperative complications occurred in 41% of jaundiced patients in our study, which is less than other studies; complication rates in literature range from 52% to 83%.[9,11,19–24] These results support the notion that long-term survival in jaundiced patients is achievable after surgical resection.

In the present study, jaundice was no longer significantly associated with poor survival in resected patients in multivariate analysis. This finding implies that jaundice in itself does not preclude resection. Rather, jaundice in GBC is indicative of advanced disease. When considering surgery one should be aware of the limited survival benefit of surgery for advanced GBC in general.[25]

Multiple explanations arise for the correlation between jaundice, advanced GBC and poor survival. Tumors growing in the neck of the gallbladder rapidly result in obstructive jaundice by either direct invasion in the hepatic hilum or compression of the CBD. In contrast, tumors arising from the fundus or corpus of the gallbladder are more likely to invade the hepatic parenchyma. Gallbladder neck tumors frequently require an (extended) hemihepatectomy to obtain tumor-free surgical margins, whereas fundus or corpus type tumors may be entirely resected by a non-anatomical wedge resection. The difference in morbidity and mortality between extended resections and wedge resections may account for the difference in survival between jaundiced and non-jaundiced patients.

Another explanation may be that jaundiced patients represent a biologically more aggressive subset of tumors. In our cohort jaundiced patients showed higher rates of perineural and hepatic invasion; known poor prognostic factors.[16,26] Additionally, malignant biliary obstruction and hyperbilirubinemia are associated with increased risks in liver surgery due to hepatic and systemic inflammation.[27]

Although patient selection appears to be key when considering surgery in jaundiced patients, no reported pre-operative selection criteria are definitive. In our cohort, resected patients with jaundice who did not develop recurrent disease did not show liver invasion or lymph node metastases on pre-operative imaging and did not have a tumor located in the gallbladder neck[28] All of these patients had R0 resection margins and did not have lymph node metastases. In case jaundiced patients do not show liver involvement on pre-operative imaging, have a tumor that is confined to the fundus or corpus of the gallbladder and no lymph node metastases are detected, surgery may provide favorable survival outcomes.

In addition to pre-operative imaging, staging laparoscopy (SL) is a helpful tool for pre-operative evaluation and patient selection.[29] Although 41% of jaundiced patients had unresectable disease during surgical exploration, only 20% underwent SL. SL could have potentially prevented several futile laparotomies and should be recommended in jaundiced GBC patients.

This study has several limitations that need to be considered when interpreting results. First and foremost, all pitfalls of retrospective data are applicable to this study; selection bias may significantly influence our results. Propensity score matching to adjust for bias was attempted but the number of available matches was too low to draw any conclusions. Additionally, many pre-operative characteristics potentially associated with prognosis could not be investigated due to missing data. Imputation would not have been feasible since these data were most likely not missing at random. Finally, in some included patients with small (T1/T2) tumor, jaundice may not have been caused by CBD invasion but rather by proximity of the tumor to the CBD, nodal metastases or even Mirizzi syndrome and inflammation. Because it is difficult to identify the cause of jaundice retrospectively, we chose to include all jaundiced patients as this an accurate reflection of clinical practice.

Strengths of this study include the nation-wide design. Previous studies stem from high-volume single center experiences or expert center collaborations. Our results reflect actual, nation-wide outcomes in a low incidence country with per center less experience in the treatment of GBC and generalizability is likely high. Additionally, patients in whom unresectable disease was discovered during surgical exploration were included in our survival analysis. Some studies excluded these patients from analysis since they did not undergo resection.[9] However, we feel that the inclusion of these patients provides a more realistic reflection of the median survival of all patients with jaundice and GBC. Analyzing only resected patients may induce treatment-selection bias because patients with smaller tumors (and thus a more favorable prognosis) are more likely to receive a resection.

In summary, jaundice primarily indicates the presence of advanced GBC; a disease for which the benefit of resection is questionable in general. Moreover, jaundice is associated with increased postoperative morbidity, mortality and poor overall survival. In cases with limited disease, a tumor located outside of the gallbladder neck and no lymph node metastases on pre-operative imaging, long-term survival may be achieved. When considering surgery for patients with jaundice, careful pre-operative evaluation is required. Multiple pathways may result in biliary obstruction and not all these mechanisms are directly associated with the presence of unresectable disease. Identifying the root cause of jaundice is key when selecting patients for surgery.

Author contribution

EdSL, PdR, RV and TvG contributed to the design of the study. All authors (EdSL, HK, MvD, RV, JE, BGK, AB, JH, FD, RvD, TvG, MdB, PdR) contributed to data collection. EdSL, MvD, HK, RV and LvG were responsible for data analysis. EdSL prepared the first draft of the manuscript. All authors (as stated above)

critically reviewed the paper. EdSL and HK revised and finalized the manuscript. All authors have read and approved the final manuscript.

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Conflicts of interest

None declared.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.hpb.2020.03.015.