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Surgical Indication for Advanced Gallbladder Cancer Considering the Optimal Preoperative Carbohydrate Antigen 19-9 Cutoff Value

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Keywords
Biliary surgery · Cancer of the gallbladder · Hepatobiliary surgery

Abstract
Background: Selecting patients who will benefit from resection among those with advanced gallbladder cancer (GBCa) having poor prognostic factors is difficult. ***Methods:*** One hundred twenty-one patients who underwent resection for stage II–IV GBCa and 19 unresected patients (unresectable group) were enrolled. The clinical impact of carbohydrate antigen 19-9 (CA19-9) and advanced surgical procedures for GBCa was evaluated. ***Results:*** The optimal CA19-9 cutoff value (based on the greatest difference in overall survival) was 250 U/mL. CA19-9 ≥250 U/mL was found to be an independent prognostic factor. Patients with CA19-9 <250 U/mL who developed jaundice (median survival time [MST], 49.1 months) or who required major hepatectomy (MST, 21.5 months) or pancreatoduodenectomy (PD; MST, 50.3 months) had a better prognosis than those with CA19-9 ≥250 U/mL who developed jaundice (MST, 16.1 months; $p = 0.061$) or who required major hepatectomy (MST, 9.2 months; $p = 0.066$) or PD (MST, 8.6 months; $p = 0.025$); their prognosis was comparable to that of the unresectable group (jaundice: $p = 0.145$, major hepatectomy: $p = 0.292$, PD: $p = 0.756$). ***Conclusions:*** Even if GBCa patients develop jaundice or require major hepatectomy, or combined PD, resection can be considered for those with CA19-9 <250 U/mL. However, surgical indication should be carefully determined in patients with CA19-9 ≥250 U/mL.

Introduction

Gallbladder cancer (GBCa) is the most common cancer of the biliary tract [1–4], and surgical resection is the only potentially curative treatment for GBCa. However, it can easily infiltrate adjacent organs, and the prognosis of GBCa after resection remains unsatisfactory [1–3]. Several prognostic factors – namely, the presence of jaundice [5], hepatic infiltration (H-inf) [6, 7], serosal invasion (Se-inv) [8, 9], and lymph node metastasis (LNM) [10] – have already been reported. In particular, in GBCa patients with jaundice, the National Comprehensive Cancer Network (NCCN) guideline still advocates that although surgical resection is a relative contraindication, resection with curative intent can be attempted in select patients [11].

Previous reports have suggested that major hepatectomy [5], combined pancreatoduodenectomy (PD) [12], and

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combined portal vein resection (PVR) [13] for GBCa do not result in long-term survival; however, some patients who require these advanced procedures sometimes achieve long-term survival after curative resection [1, 3, 14]. Unfortunately, it is difficult to preoperatively identify these select advanced GBCa patients who may benefit from surgical resection with long-term survival after surgery.

Carbohydrate antigen 19-9 (CA19-9) is a tumor-associated antigen whose level is increased in cases of pancreatic and biliary malignancy [15]. It is now promoted as a reliable test marker for the detection and prognostication of bile duct cancer [15–19]. Although some authors have discussed the utility of the preoperative CA19-9 level based on the upper limit in patients with GBCa [20–22], the optimal evidence-based cutoff value of CA19-9 in terms of prognosis or biological malignancy for detecting advanced GBCa patients who can avoid upfront surgery has not been clarified.

The aim of the present study was to determine the best CA19-9 cutoff value for GBCa based on overall survival (OS) and to classify advanced GBCa patients with various prognostic factors of a low or high CA19-9 level. The survival of those patients was then compared with that of patients with unresectable GBCa in order to examine the utility of CA19-9 for detecting the poor survival subset of advanced GBCa patients who can avoid upfront surgery and the subset of advanced GBCa patients who may actually benefit from extended resection.

Patients and Methods

Study Population

From a database containing all patients who underwent macroscopically curative resection for GBCa between November 2002 and September 2016 at the Division of Hepato-Biliary-Pancreatic Surgery, Shizuoka Cancer Center, patients with stage II, III, or IV GBCa according to the TNM classification (8th edition) of the American Joint Committee on Cancer [23] were enrolled in this study. The Shizuoka Cancer Center Institutional Review Board approved the retrospective collection and analysis of the data in this study.

Analysis of CA19-9

Serum CA19-9 values were examined using a radioimmunoassay kit (Abbott Laboratories, Chicago, IL, USA). The recommended upper limit of normal for CA19-9 is 37 U/mL. In principle, the CA19-9 value was measured within 2 days before surgery. In patients with icterus, the CA19-9 levels were measured before surgery at least 1 week after obtaining relief from jaundice by biliary stenting. Of note, individuals with a Lewis-negative blood group, lacking a Lewis antigen, not expressing glycosyltransferase, or unable to synthesize CA19-9 comprise approximately 5–10% of the general population of Japan [15, 16].

Surgical Strategy and Surgical Procedures for GBCa

Regional lymph node dissection was usually performed in patients with stage II–IV GBCa. When tumors involving the hepatic hilus were noted, hemihepatectomy with caudate lobectomy and extrahepatic bile duct resection was performed. Macroscopic liver metastasis, peritoneal seeding, bulky LNM, para-aortic LNM, and tumors involving the common hepatic artery or causing occlusion of the portal vein were regarded as contraindications for surgery. Partial encasement of the portal vein was not considered a contraindication for surgery.

Postsurgical Management

All of the patients who were followed up in the outpatient clinic underwent abdominal ultrasound scans, CT, and measurement of carcinoembryonic antigen and CA19-9 levels every 3–6 months after surgery.

Unresectable Group

Patients brought into the operating room with suspected resectable disease in whom resection was not performed because laparotomy revealed occult unresectable disease were defined as the unresectable group. Patients with radiographically unresectable GBCa at diagnosis were not included in this study.

Statistical Analyses

Survival was estimated using the Kaplan-Meier method, and differences in survival were examined using the log-rank test. The optimal CA19-9 cutoff value was determined using the minimum p values calculated using the log-rank test. A Cox proportional hazards model was used to analyze the categorical clinicopathological variables that influenced the OS. Pearson's χ^2 test and Fisher's exact test were used to analyze the nominal variables. Continuous data were compared using the Mann-Whitney U test. All of the statistical analyses were performed using the Software Package for Social Sciences (version 19 for Windows; SPSS, Chicago, IL, USA). p values <0.05 were considered to indicate statistical significance.

Results

In total, 122 patients underwent macroscopically curative resection for GBCa during the study period. One patient who underwent S4a+5 resection, extrahepatic bile duct resection, and reconstruction died postsurgery; this patient was, therefore, excluded from the analysis and a total of 121 patients were analyzed. Thirty-five of the 121 patients were jaundiced and underwent biliary stenting (endoscopic biliary drainage, n = 20; percutaneous transhepatic biliary drainage, n = 15). The cause of jaundice was cancer infiltration in all patients. The remaining 86 patients were not jaundiced. Thirty-four patients underwent hemihepatectomy or more extended resection, while 87 underwent resection of <2 sections. Combined extrahepatic bile duct and vascular resection with reconstruction was performed in 76 and 13 patients, respectively.

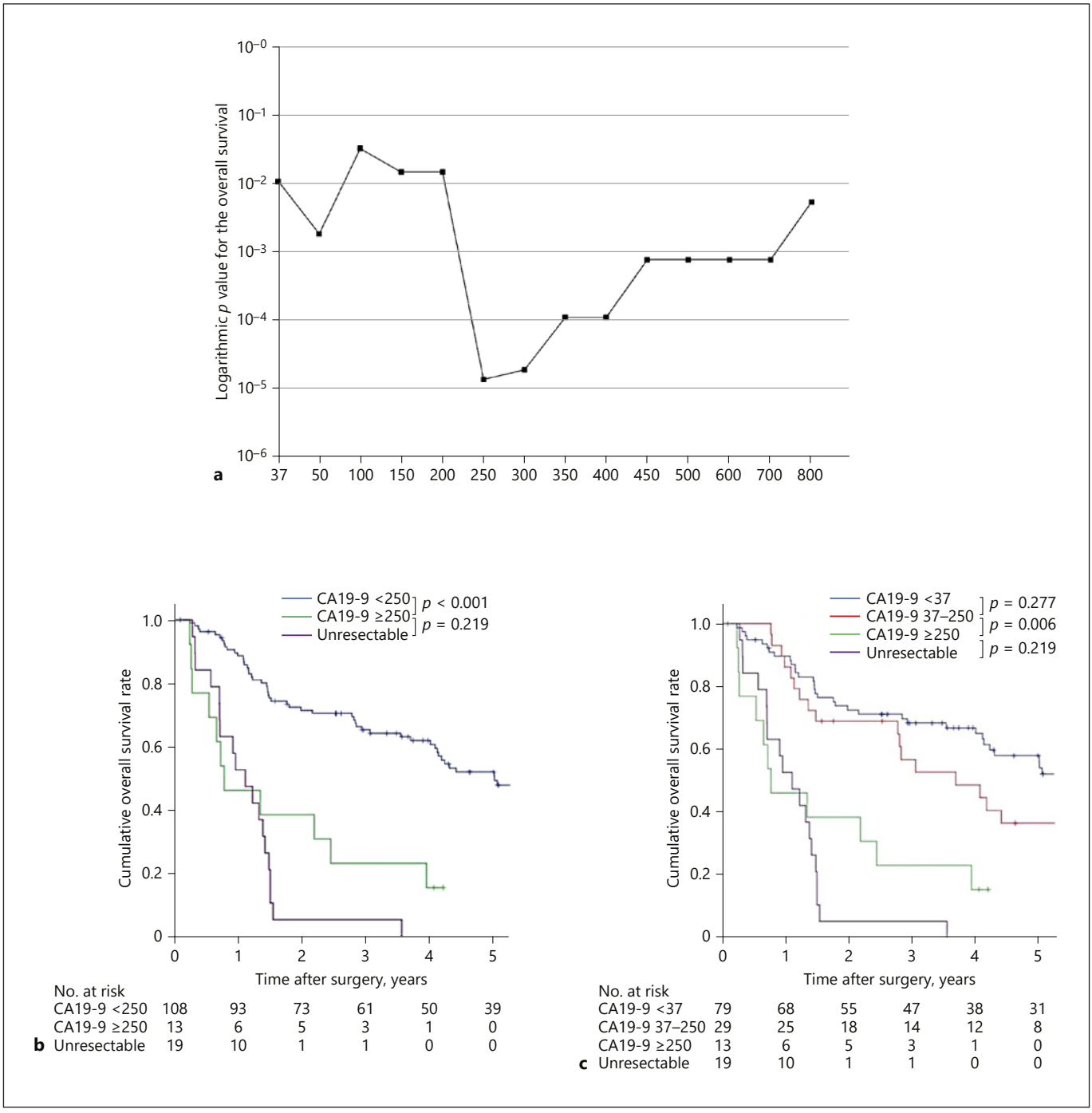

Fig. 1. a Optimal CA19-9 cutoff value based on the prognostic differences of the patients. **b** Overall survival curves of the CA19-9 ≥250 U/mL, CA19-9 <250 U/mL, and unresectable groups. **c** Overall survival curves of the CA19-9 <37 U/mL, CA19-9 = 37–250 U/mL, CA19-9 ≥250 U/mL, and unresectable groups. $p < 0.001$ (<250 U/mL vs. ≥250 U/mL), $p = 0.219$ (≥250 U/mL vs. unresectable) (**b**), $p = 0.277$ (<37 U/mL vs. 37–250 U/mL), $p = 0.006$ (37–250 U/mL vs. ≥250 U/mL), $p = 0.219$ (≥250 U/mL vs. unresectable) (**c**) (log-rank test).

Table 1. Results of univariate and multivariate analyses of the prognostic factors associated with overall survival in the patients who underwent resection for T2–T4 gallbladder carcinoma

	N	5 years OS, %	Median, months	Univariable *p**	Multivariable analysis†	
					Hazard ratio (95% CI)	*p* value
Age, years						
<70	51	56.5	66.7	0.088		
≥70	70	40.8	49.0			
Sex						
Male	71	43.2	49.5	0.339		
Female	50	55.2	74.6			
CA19-9, U/mL						
<250	108	51.9	60.3	<0.001	1 (reference)	0.001
≥250	13	15.4	9.2		3.125 (1.593, 6.132)	
Tumor size, mm						
<50	61	46.3	50.3	0.735		
≥50	60	49.4	51.8			
Portal vein invasion						
Absent	114	50.2	60.3	0.169		
Present	7	14.3	17.6			
Hepatic invasion						
Absent	63	56.8	69.9	0.030		
Present	58	37.9	33.4			
Bile duct invasion						
Absent	99	54.8	66.7	0.004		
Present	22	14.0	17.6			
Liver metastasis						
Absent	116	49.7	53.1	<0.001	1 (reference)	0.029
Present	5	0.0	13.6		2.977 (1.119, 7.918)	
Lymph node metastasis						
Absent	58	66.8	127.1	<0.001	1 (reference)	0.001
Present	63	30.1	29.3		2.563 (1.496, 4.392)	
Serosal invasion						
Absent	92	56.6	69.9	<0.001		
Present	29	19.3	17.7			
Perineural invasion						
Absent	50	71.7	91.7	<0.001	1 (reference)	0.009
Present	71	29.8	34.0		2.101 (1.202, 3.671)	
Venous invasion						
Absent	56	59.0	69.9	0.034		
Present	65	38.0	34.2			
Neural invasion						
Absent	29	73.3	127.1	0.013		
Present	92	39.8	49.1			

5 years OS, cumulative 5-year overall survival; MST, median survival time; CI, confidence interval; CA19-9, carbohydrate antigen 19-9. * Log-rank test. † Cox proportional hazards model.

Fig. 2. Influence of the CA19-9 value and icterus (**a**), serosal invasion (**b**), hepatic infiltration (**c**), and lymph node metastasis on overall survival after resection compared to the unresectable group (**d**). $p = 0.331$ (icterus− vs. icterus+ and CA19-9 <250 U/mL), $p = 0.061$ (icterus+ and CA19-9 <250 U/mL vs. icterus+ and CA19-9 ≥250 U/mL), $p = 0.145$ (icterus+ and CA19-9 ≥250 U/mL vs. unresectable) (**a**), $p = 0.007$ (Se-inv− vs. Se-inv+ and CA19-9 <250 U/mL), $p = 0.015$ (Se-inv+ and CA19-9 <250 U/mL vs. Se-inv+ and CA19-9 ≥250 U/mL), $p = 0.902$ (Se-inv+ and CA19-9 ≥250 U/mL vs. unresectable) (**b**), $p = 0.107$ (H-inf− vs. H-inf+ and CA19-9 <250 U/mL), $p = 0.010$ (H-inf+ and CA19-9 <250 U/mL vs. H-inf+ and CA19-9 ≥250 U/mL), $p = 0.603$ (H-inf+ and CA19-9 ≥250 U/mL vs. unresectable) (**c**), $p < 0.001$ (LNM− vs. LNM+ and CA19-9 <250 U/mL), $p = 0.002$ (LNM+ and CA19-9 <250 U/mL vs. LNM+ and CA19-9 ≥250 U/mL), $p = 0.640$ (LNM+ and CA19-9 ≥250 U/mL vs. unresectable) (**d**) (log-rank test). Se-inv, serosal invasion; H-inf, hepatic infiltration; LNM, lymph node metastasis.

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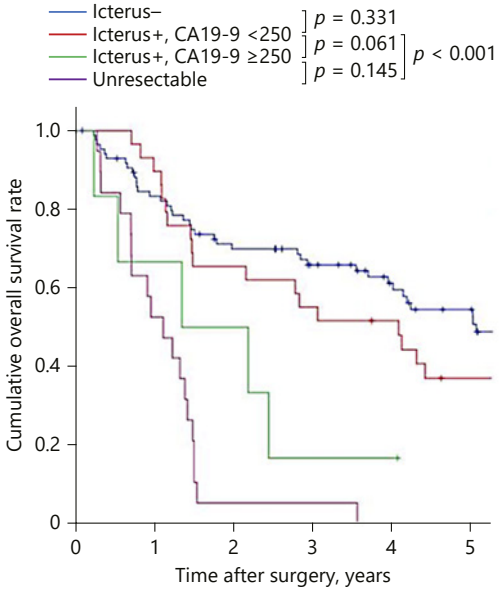
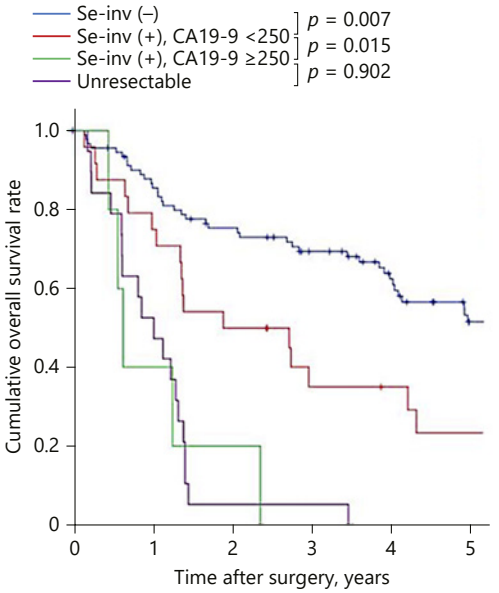


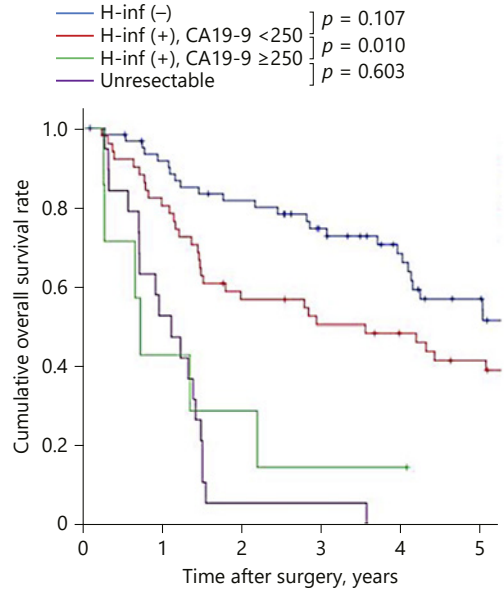
No. at risk						
Icterus–	86	69	56	47	37	30
Icterus+, CA19-9 <250	29	26	19	16	14	9
Icterus+, CA19-9 ≥250	6	4	3	1	1	0
Unresectable	19	10	1	1	0	0

a



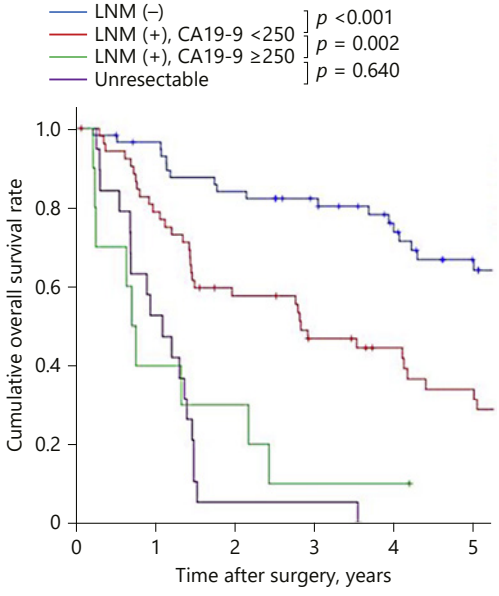
No. at risk						
Se-inv (–)	91	78	65	56	46	35
Se-inv (+), CA19-9 <250	24	19	12	8	6	4
Se-inv (+), CA19-9 ≥250	5	2	1	0	0	0
Unresectable	19	10	1	1	0	0

b



No. at risk						
H-inf (–)	63	55	48	39	30	22
H-inf (+), CA19-9 <250	51	41	28	24	21	17
H-inf (+), CA19-9 ≥250	7	3	2	1	1	0
Unresectable	19	10	1	1	1	0

c



No. at risk						
LNM (–)	58	54	47	42	34	26
LNM (+), CA19-9 <250	53	43	28	22	17	13
LNM (+), CA19-9 ≥250	10	4	3	1	1	0
Unresectable	19	10	1	1	0	0

d

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Adjuvant Chemotherapy and Systemic Therapy after Recurrence

Adjuvant chemotherapy was administered to 6 patients (gemcitabine, $n = 1$ and S1, $n = 5$). Sixty-five patients developed recurrence after surgery, and 44 of them received nonsurgical treatments: gemcitabine-based chemotherapy ($n = 34$), S1-based chemotherapy ($n = 7$), irinotecan + cisplatin ($n = 1$), and 5-fluorouracil-based chemotherapy ($n = 2$). Five patients underwent resection for local recurrence, 2 underwent resection for liver metastasis after chemotherapy, and 16 did not undergo anticancer treatment.

Treatment in the Unresectable Group

Nineteen patients were included in the unresectable group. The median CA19-9 value of the unresectable group was 113 (6-225199) U/mL. These patients had unsuspected macroscopic liver metastases ($n = 2$), peritoneal dissemination ($n = 7$), para-aortic LNM ($n = 8$), bulky LNM ($n = 1$), or nerve plexus invasion around the common hepatic artery ($n = 1$). Fourteen of these patients underwent nonsurgical treatment: chemotherapy with gemcitabine ($n = 3$), S-1 + cisplatin ($n = 3$), gemcitabine + cisplatin ($n = 7$), and irinotecan + cisplatin ($n = 1$). Five patients did not undergo anticancer treatment.

Optimal CA19-9 Cutoff Value Based on the Prognostic Differences among Patients

The cumulative 5-year OS and median survival time of the patients were 59.7% and 50.9 months, respectively. The optimal CA19-9 cutoff value for dividing patients into 2 groups based on the greatest difference in the OS was 250 U/mL ($p = 0.000018$) when using the minimum p value approach (Fig. 1a, b). There were no significant differences in the OS between the CA19-9 <37 U/mL and 37–250 U/mL groups ($p = 0.277$); however, the OS of the CA19-9 37–250 U/mL group was significantly better than that of the CA19-9 ≥250 U/mL group ($p = 0.006$, Fig. 1c). Furthermore, there were no significant differences between the CA19-9 ≥250 U/mL group and the unresectable group ($p = 0.219$).

Analysis of the Prognostic Factors in GBCa after Curative Resection

The Cox proportional hazards analysis showed that a CA19-9 value ≥250 U/mL ($p = 0.001$), microscopic liver metastasis ($p = 0.029$), LNM ($p = 0.001$), and perineural invasion ($p = 0.009$) were independent prognostic factors that were associated with the OS (Table 1). GBCa patients with CA19-9 <250 U/mL who developed icterus tended to have better OS than those with CA19-9 ≥250 U/mL who developed icterus ($p = 0.061$, Fig. 2a) and were significantly better than those in the unresectable group ($p < 0.001$). There were no significant differences in the OS between patients with CA19-9 ≥250 U/mL who developed icterus and the unresectable group ($p = 0.145$). Patients with CA19-9 <250 U/mL who developed H-inf, Se-inv, and LNM had a significantly better prognosis than those with CA19-9 ≥250 U/mL who developed H-inf ($p = 0.010$, Fig. 2b), Se-inv ($p = 0.015$, Fig. 2c), and LNM ($p = 0.002$, Fig. 2d), and their prognosis was comparable to that of the unresectable group (H-inf: $p = 0.603$, Se-inv: $p = 0.902$, and LNM: $p = 0.640$).

Regarding major hepatectomy, patients with CA19-9 <250 U/mL who required major hepatectomy tended to have a better prognosis than those with CA19-9 > 250 U/mL who required major hepatectomy ($p = 0.066$, Fig. 3a), and they had a significantly better prognosis than those in the unresectable group ($p < 0.001$, Fig. 3a). There were no significant differences in the OS between patients with CA19-9 <250 U/mL who required major hepatectomy and the unresectable group ($p = 0.292$, Fig. 3a). Regarding combined PD or combined PVR, patients with a CA19-9 level of <250 U/mL and combined PD or PVR had a significantly better prognosis than those with GBCa with a CA19-9 level of ≥250 U/mL and combined PD ($p = 0.025$, Fig. 3b) or combined PVR ($p = 0.002$, Fig. 3c), and their prognosis was comparable to that of the unresectable group ($p = 0.756$, Fig. 3b and $p = 0.370$, Fig. 3c).

Fig. 3. Influence of the CA19-9 value and major hepatectomy (**a**), combined PD (**b**), and combined portal vein resection on the overall survival after hepatectomy compared to the unresectable group (**c**). $p = 0.029$ (minor hepatectomy vs. major hepatectomy and CA19-9 <250 U/mL), $p = 0.066$ (major hepatectomy and CA19-9 <250 U/mL vs. major hepatectomy and CA19-9 ≥250 U/mL), $p = 0.292$ (major hepatectomy and CA19-9 ≥250 U/mL vs. unresectable) (**a**), $p = 0.681$ (PD− vs. PD+ and CA19-9 <250 U/mL), $p = 0.025$ (PD+ and CA19-9 <250 U/mL vs. PD+ and CA19-9 ≥250 U/mL), $p = 0.756$ (PD+ and CA19-9 ≥250 U/mL vs. unresectable) (**b**), $p = 0.610$ (PVR− vs. PVR+ and CA19-9 <250 U/mL), $p = 0.002$ (PVR+ and CA19-9 <250 U/mL vs. PVR+ and CA19-9 ≥250 U/mL), $p = 0.370$ (PVR+ and CA19-9 ≥250 U/mL vs. unresectable) (**c**) (log-rank test). Min Hx, minor hepatectomy; Maj Hx, major hepatectomy; PD, pancreatoduodenectomy; PVR, portal vein resection.

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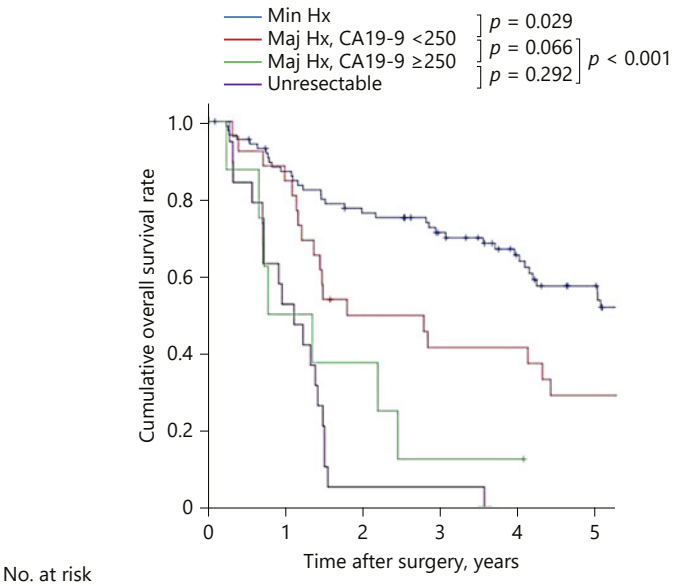
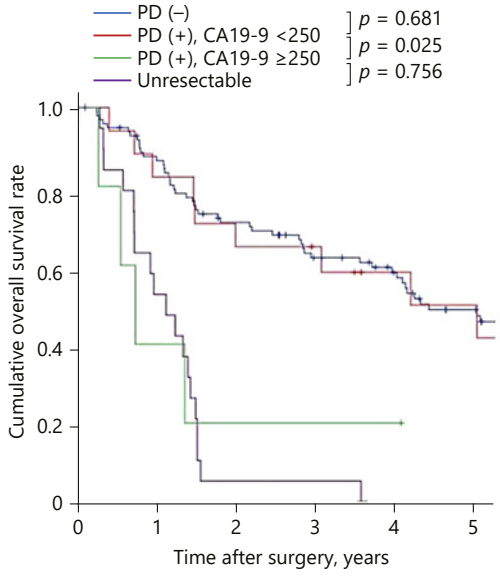


No. at risk

Min Hx	87	73	63	53	41	32
Maj Hx, CA19-9 <250	26	22	12	10	10	7
Maj Hx, CA19-9 ≥250	8	4	3	1	1	0
Unresectable	19	10	1	1	0	0

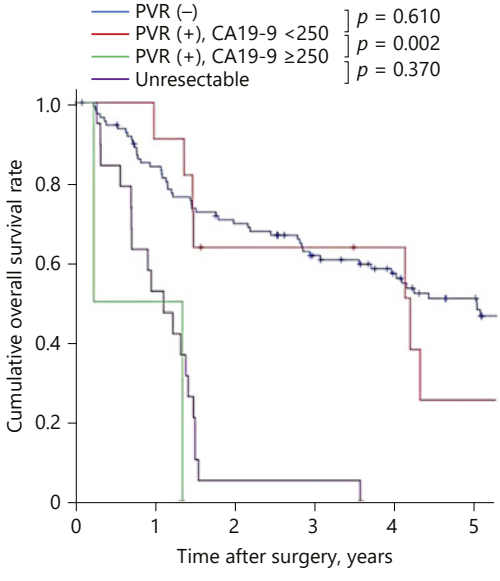
a



No. at risk

PD (–)	99	83	66	53	44	33
PD (+), CA19-9 <250	17	14	11	10	7	6
PD (+), CA19-9 ≥250	5	2	1	1	1	0
Unresectable	19	10	1	1	0	0

b



No. at risk

PVR (–)	108	89	72	58	47	37
PVR (+), CA19-9 <250	11	10	6	6	5	2
PVR (+), CA19-9 ≥250	2	1	0	0	0	0
Unresectable	19	10	1	1	0	0

c

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Table 2. Histopathological and immunohistochemical features in the CA19-9 <250 U/mL and CA19-9 ≥250 U/mL groups

	CA19-9 <250 group (n = 108)	CA19-9 ≥250 group (n = 13)	p value[†]
Preoperative parameters			
Age, years, median (range)	72 (66–76)*	73 (61–75)*	0.651[‡]
Sex (male/female)	62/46	9/4	0.413
CEA, ng/mL, median (range)	2.7 (1.8–4.3)*	7.0 (1.8–7.1)*	0.028[‡]
CA19-9, U/mL, median (range)	15 (5–37)*	1,015 (370–1,423)*	<0.001[‡]
Surgical parameters			
Major hepatectomy	26 (24)	8 (62)	0.005
Major hepatopancreatoduodenectomy	6 (6)	3 (23)	0.023
Combined PD	17 (16)	5 (38)	0.045
Hepatic artery resection	3 (3)	0	0.543
Portal vein resection	11 (10)	2 (15)	0.567
Bile duct resection	66 (61)	10 (77)	0.265
Operation time, min, median (range)	190 (121–264)*	270 (211–308)*	0.058[‡]
Blood loss	812 (424–1,455)*	1,513 (1,083–2,348)*	0.021[‡]
Blood transfusion	23 (21)	5	0.166
Pathological parameters			
Tumor size, mm, median (range)	50 (35–75)*	60 (35–76)*	0.611[‡]
Serosal invasion	24 (22)	5 (38)	0.195
Portal vein invasion	6 (6)	1 (8)	0.755
Bile duct invasion	15 (14)	7 (54)	<0.001
Hepatic invasion	51 (47)	7 (54)	0.652
Liver metastasis	4 (4)	1 (8)	0.495
Lymph node metastasis	53 (49)	10 (77)	0.058
Perineural invasion	60 (56)	11 (85)	0.044
Venous invasion	56 (52)	9 (69)	0.235
Lymphatic invasion	79 (73)	13 (100)	0.032
Surgical margin	1 (1)	2 (15)	0.002

Values in parentheses are percentages, unless indicated otherwise. CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen 19-9. * Values are median (interquartile range). [†] χ^2 test, except. [‡] Mann-Whitney U test.

Histopathological Features of the CA19-9 <250 U/mL (n = 108) and ≥250 U/mL (n = 13) Groups

Regarding the histopathological features, incidence of bile duct invasion ($p < 0.001$), and lymphatic invasion ($p = 0.032$), a positive surgical margin ($p = 0.002$) and the frequency of major hepatectomy ($p = 0.023$) or PD ($p = 0.045$) were significantly higher in the CA19-9 ≥250 U/mL group than the CA19-9 <250 U/mL group (Table 2).

Discussion

Only a few reports have revealed the clinical usefulness of the preoperative CA19-9 level in GBCa alone [20–22]. Wen et al. [20] compared the survival of GBCa patients using a cutoff value of 37 U/mL, which is the upper limit of normal CA19-9. However, this value may not be the best cutoff point in terms of the influence on survival or biological malignancy. Yamashita et al. [24] mentioned that a preoperative CA19-9 level >37 U/mL in cases of bile duct cancer was not an independent predictor of worse survival; however, non-normalization of the CA19-9 level after resection was associated with worse OS. In addition, a preoperative CA19-9 level of ≥100 U/mL was a predictor of non-normalization of the CA19-9 level after resection [24]. Their data indicate that the upper limit of the normal CA19-9 level is not the best cutoff value in terms of the influence on survival or tumor aggressiveness; however, a markedly increased preoperative CA19-9 level can identify patients likely to have a poor outcome.

In the present study, we analyzed the CA19-9 cutoff values based on the minimum p value approach and found that the best cutoff value was 250 U/mL. There

were no significant differences in the OS between patients with a CA19-9 level of 37–250 U/mL and those with a CA19-9 level of <37 U/mL, and patients with a CA19-9 level of 37–250 U/mL had a significantly better prognosis than those with a CA19-9 level of ≥250 U/mL. Patients with a CA19-9 level of <250 U/mL exhibited lower rates of important prognostic factors for GBCa than those with CA19-9 levels of ≥250 U/mL. These results suggest that the cutoff value of 250 U/mL, which reflects the best prognosis after surgery, is an important cutoff value for patients undergoing resection for GBCa.

The NCCN guideline now describes surgical resection for advanced GBCa patients with jaundice as a relative contraindication [11]. Hawkins et al. [5] reported that jaundice is an indicator of advanced malignancy and did not encourage routine operative exploration of patients with jaundice secondary to GBCa. However, several authors recently mentioned that the presence of jaundice does not preclude resection [2, 3, 25]. In our study, the median survival time of patients with CA19-9 <250 U/mL who developed icterus was 49.1 months, which was significantly better than that in the unresectable group. The preoperative CA19-9 value seems able to identify advanced GBCa patients with jaundice who will benefit from upfront surgery.

LNM has been established as an important prognostic factor for GBCa [7, 9, 26]. However, not all patients with regional LNM have uniformly poor outcomes after resection [27]. Some authors have found that high metastatic lymph node numbers [27, 28] or a high metastatic lymph node ratio [29] was associated with a dismal prognosis in patients with GBCa who had LNM. However, it is difficult to preoperatively evaluate these factors in patients with LNM. In contrast, the preoperative CA19-9 value can readily be obtained. The survival of GBCa patients with LNM and a preoperative CA19-9 level of ≥250 U/mL was shown to be dismal, similar to that of unresectable GBCa patients. In addition to these prognostic factors, GBCa patients developing H-inf or Se-inv, which are known to be important prognostic *T* factors, and who had a CA19-9 level of ≥250 U/mL had a similar prognosis to the unresectable group. The chemotherapy regimen of cisplatin plus gemcitabine, developed in the late 2000s, has notably improved the survival rate [30]. However, even if these prognostic factors are present, select patients with a preoperative CA19-9 level of <250 U/mL may be considered suitable for surgical treatment, although adjuvant chemotherapy should be performed due to the reduced rate of long-term survival in such patients compared with others [31].

The indications of major hepatectomy and combined PD or PVR for advanced GBCa patients remain controversial [1–3, 5, 12, 14]. Some authors have recently advocated that these advanced procedures may be acceptable in patients with otherwise unresectable GBCa involving the hepatic hilum or pancreas [2, 3, 14, 25]. In the present study, the OS of patients with a CA19-9 level <250 U/mL and who required PD or PVR was comparable to that of such patients who did not require PD or PVR. Furthermore, the OS of patients with major hepatectomy and a CA19-9 level <250 U/mL was better than that in those with a CA19-9 level ≥250 U/mL or in the unresectable group. In contrast, the OS of patients with a CA19-9 level ≥250 U/mL who required major hepatectomy, PD, or PVR was comparable to that of patients in the unresectable group. The CA19-9 cutoff value of 250 U/mL appears to be a useful indicator of the need for intervention in advanced GBCa patients, including stage IV local disease without any distant metastasis. Moreover, preoperative laparoscopy would be reasonable for staging of patients with high CA19-9 levels due to the high rate of the presence of other prognostic factors in these patients.

In this study, we did not routinely perform neoadjuvant or adjuvant therapy for GBCa. However, some researchers recently reported improved patient survival with adjuvant chemotherapy or chemoradiation therapy for GBCa [31, 32]. Considering the recent improvements in gemcitabine-based chemotherapy for biliary cancer, prompt adjuvant chemotherapy after resection without major morbidity would be required. If prompt adjuvant chemotherapy after surgery is considered to be difficult in GBCa patients with high CA19-9, surgical resection should be abandoned, as the survival of GBCa patients with prognostic factors and a preoperative CA19-9 level ≥250 U/mL was shown to be unsatisfactory, as noted for unresectable GBCa patients.

Several limitations associated with the present study warrant mention. First, this was a retrospective analysis, and it was limited by the single-center aspect. Second, our sample size had inadequate power to allow for a broad interpretation; therefore, our findings must be verified in larger cohorts to ensure generalizability. Third, Lewis antigen status was not measured in this series. Further prospective studies will be required to precisely evaluate the clinical significance of CA19-9 in the treatment of GBCa.

In the clinical setting, the CA19-9 cutoff value of 250 U/mL was shown to be important for patients undergoing resection for GBCa in terms of prognosis and biological malignancy. Even if GBCa patients develop jaundice, H-inf, Se-inv, or LNM or require major hepatectomy and

combined PD or PVR, surgical treatment can be considered for select patients who have a CA19-9 level <250 U/mL. However, the surgical indication should be carefully determined in patients with CA19-9 ≥250 U/mL.

Statement of Ethics

This study received approval from the Ethics Committee of the Shizuoka Cancer Center (Approval No. J2019-3-2019-1-3).

Disclosure Statement

The authors have no conflicts of interest to disclose.

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Author Contribution

Substantial contributions to the conception or design of the work: Y. Yamamoto, T. Sugiura, and K. Uesaka. Drafting the work or revising it critically for important intellectual content: Y. Yamamoto and T. Sugiura. Final approval of the version to be published: Y. Yamamoto, T. Sugiura, Y. Okamura, T. Ito, R. Ashida, K. Ohgi, and K. Uesaka. Agreement to be accountable for all aspects of the work: Y. Yamamoto, T. Sugiura, Y. Okamura, T. Ito, R. Ashida, K. Ohgi, and K. Uesaka.

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