Examination of The Characteristics of Long-Term Survivors Among Patients With Gallbladder Cancer With Liver Metastasis Who Underwent Surgical Treatment: A Retrospective Multicenter Study (ACRoS1406)

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Abstract

Background: Gallbladder cancer (GBC) with liver metastasis is considered unresectable. However, there have been infrequent reports of long-term survival in patients with GBC and liver metastases. Therefore, we examined the characteristics of long-term survivors of gallbladder cancer with liver metastasis.

Methods: A retrospective multicenter study of 503 patients with GBC (mean age, 68.6 years; female, 52%) was performed. Although patients with pre-operatively diagnosed GBC and liver metastasis were generally excluded from resection, some cases identified during surgery were resected.

Result: In patients with resected stage III/IV GBC (n = 228), the period 2007–2013 (vs. 2000–2006, hazard ratio 0.55), other type histology (vs. well/moderate histology, hazard ratio 2.34), ≥ 2 liver metastases (vs. one liver metastasis, hazard ratio 4.30), and positive margin resection (vs. complete resection with a negative margin, hazard ratio 1.57) were independent prognostic factors for overall survival, whereas one liver metastasis (vs. no liver metastasis) was not. The 5-year overall survival and median survival times in those with one liver metastasis with complete resection and a negative margin (40.9%, 28.3 months) were significantly better than those in patients with ≥ 2 liver metastases with complete resection and a negative margin (0%, 11.0 months, $p = 0.025$), and comparable to those in patients with liver metastasis with complete resection and a negative margin (37.0%, 33.0 months). According to the univariate analysis of resected patients with GBC and liver metastases (n=24), minor hepatectomy, less blood loss, less surgery time, papillary adenocarcinoma, T2, morbidity of Clavien–Dindo classification ≤ 2 , and adjuvant chemotherapy were significantly associated with longer survival. Long-term survivors (n = 5) had a high frequency of T2 tumors (4/5), had small liver metastases near the gallbladder during or after surgery, underwent minor hepatectomy without post-operative complications, and received post-operative adjuvant chemotherapy.

Conclusions: Although there is no surgical indication for GBC with liver metastasis diagnosed pre-operatively, minor hepatectomy and post-operative chemotherapy may be an option for selected patients with T2 GBC and liver metastasis identified during or after surgery who do not have other poor prognostic factors.

Background

Gallbladder cancer (GBC) is the most common biliary malignancy and the sixth most common gastrointestinal malignancy, with a prevalence rate ranging from 8.5 cases per 100,000 population in the United States (US) to 13.6 cases per 100,000 in Asian populations[1]. GBC occurs relatively often in certain geographic locations, such as Chile, North India, South Korea, Japan, and New Mexico (US)[2]. GBC is known to have a poor prognosis as it is often found during its early metastatic stage[3]. It is associated with fewer chemotherapy regimens than other cancers, and surgery is the only curative treatment that can be expected to confer long-term survival in patients with GBC[4]. In particular, the

median survival time of patients with stage IVB GBC and distant metastasis is very poor, at 2–7 months[3, 5, 6]. In clinical practice guidelines, stage IVB GBC is not indicated for resection[4].

However, in line with this concept, oligometastasis (defined as the intermediate state of spread, now synonymous with isolated distant metastases) in long-term survivors of other carcinomas with distant metastases has been reported[7-10]. There have also been infrequent reports of long-term survival in patients with GBC and distant metastases, including liver metastases[11-13]. However, there are no reports of oligometastasis in patients with GBC. The outcome of surgical resection in patients with GBC oligometastasis, especially liver metastasis, is not well understood. In patients in whom small liver metastases are found during radical resection and in the absence of other distant metastases, on pre-operative images, whether surgery should be performed is uncertain.

Methods

We investigated the characteristics of patients and long-term survivors of GBC and oligometastases, especially liver metastases. Patients aged 20 years or older with pathologically diagnosed GBC were included. We did not consider the stage of the disease, previous treatment, or tumor resection. The exclusion criterion was the patient's refusal to participate in the research through opportunities provided for refusal during information disclosure. We also excluded patients with insufficient clinical and/or histopathologic data (n = 6).

We identified 503 patients with pathological GBC diagnosed between 2000 and 2013 at five university hospitals: Tokyo Medical and Dental University (Tokyo, Japan [n = 92]), Yokohama City University (Kanagawa, Japan [n = 90]), Keio University (Tokyo, Japan, [n = 66]), St. Marianna University (Kanagawa, Japan [n = 27]), and Tokyo Women's Medical University (Tokyo, Japan [n = 218]). We included all the patients with GBC diagnosed during the target period. The median age of this patient sample (n = 593) was 70 years (range 35–91), and 262 (52%) patients were female.

Surgical approach

Multidisciplinary clinical approaches, including pre-operative and post-operative indications, varied by institution. However, the basic surgical strategy was as follows. Patients with distant metastases based on pre-operative diagnosis were generally excluded from resection. Furthermore, when pre-operative examination showed suspected GBC, and complete resection with negative margin (R0) resection was considered possible, surgical resection was indicated. The number of liver metastases found intra-operatively was based on macroscopic findings and intra-operative ultrasonography. Successful R0 resection was defined as hepatectomy, bile duct resection, lymph node dissection, and additional resection of the surrounding organs in order to secure a surgical margin. Decisions regarding hepatectomy, the extent of lymph node dissection, and resection of surrounding organs were made based on the policy of each institution. In some cases, small liver and/or distant lymph node metastases revealed during surgery were resected at the discretion of the surgeon at each institution, based on the extent of the surgical resection, the degree of invasiveness of the surgery, and the safety of surgical

treatment. For incidental GBC, additional resections, such as additional liver resection and/or bile duct resection or pancreaticoduodenectomy and/or lymph node dissection, were considered, either intra-operatively or in two stages based on the extent of GBC. Gallbladder bed resection and resection of segments 4a and 5 of the liver were defined as minor hepatectomy, and hepatectomy of three or more segments, such as right hepatectomy, was defined as major hepatectomy.

Pathological examination

All specimens were assessed for tumor progression by pathologists at each institution (rather than centralized). Formalin-fixed paraffin-embedded tissue sections were examined histologically according to the 8th edition of the American Joint Committee on Cancer (AJCC 8) staging system[14], and the 6th edition of the General Rules for Surgical and Pathological Studies on Cancer of the Biliary Tract of the Japanese Society of Biliary Surgery[15]. This included observations regarding primary tumor status, lymph node involvement, and histopathological grade (Supplemental Table 1). Liver metastases were defined as follows: H0, no liver metastases; H1, one liver metastasis; and H2, two or more liver metastases. The metastatic site was pathologically confirmed.

Small liver metastasis was defined as liver metastasis measuring less than 5 mm in size. This was done since most metastases that cannot be identified using current diagnostic imaging are 5 mm or less in size. Other types of histology included adenosquamous cell carcinoma, mixed neuroendocrine-non-neuroendocrine neoplasm, squamous cell carcinoma, carcinosarcoma, mucinous carcinoma, neuroendocrine carcinoma, and undifferentiated carcinoma.

Neoadjuvant and adjuvant chemotherapy and follow-up

Neoadjuvant and adjuvant chemotherapy were administered based on facility standards (Supplemental Table 2). Post-operative recurrence was evaluated using regular computed tomography (CT) scan and ultrasonography (performed once every 3 months for 2 years, and once every 6 months for years 2–5) and by the detection of tumor markers (once every 1–3 months for 2 years, and once every 6 months for years 2–5 years). Appropriate chemotherapy was considered if tumor recurrence was confirmed. The time of recurrence and death were assessed. Loss to follow-up was defined as a case in which the patient's vital status (alive/dead) could not be confirmed for more than 2 years, except for patients who lived for more than 5 years, or who were known to have died by the time of study data collection in March 2019.

Statistical analysis

Between-group differences in the qualitative and quantitative variables were determined using two-tailed Fisher's exact and Wilcoxon rank sum tests, respectively. Survival analyses were performed using the Kaplan-Meier method, log-rank tests, and Cox proportional hazards models. Only factors that were significant in the univariate analysis were included in the multivariate analysis. In the multivariate analysis, we used reference values for carbohydrate antigen (CA) 19.9 and carcinoembryonic antigen

(CEA) levels, and for the surgery time and blood loss, the median was used as the cut-off value. Due to the advancement in medical care year on year, the year of surgery was divided into two periods and analyzed as one of the factors. All statistical analyses were performed using R, version 3.6.1 (R Foundation for Statistical Computing, Vienna, Austria). A p-value ≤ 0.05 was considered statistically significant.

Results

Resection was performed in 369 patients (73%), and 15% of resection cases were incidental GBC, which we defined as diagnosis during surgery or pathological examination. The surgical mortality rate in patients was 1.9%. In terms of hepatic margins, gallbladder bed resection was performed in 110 (30%), resection of segment 4a plus 5 of the liver (S4aS5 resection) in 60 (16%), major hepatectomy in 70 (19%), other liver resections in 11 (3%), and cholecystectomy in 119 (32%) patients. In terms of bile duct margins or lymph node dissection, bile duct resection was performed in 141 (38%) and PD in 36 (10%) patients. The numbers and proportions of Tis or 1/T2/T3/T4 in T stage was 76 (19%)/122 (33%), 125 (34%), and 47 (13%), respectively. Those of N0/N1/N2 in N stage was 215 (58%), 117 (32%), and 38 (10%), respectively, and with distant metastasis (M1) in M stage was 70 (19%). The overall R0 resection rate was 79%. Details of the clinical and pathological findings are summarized in Supplemental Table 2, and details of non-resected cases are summarized in Supplemental Table 3.

Overall survival at each stage (Fig.1)

There were 264 deaths from cancer (52.5%), 25 deaths from other diseases (5.0%), 133 survivors (26.4%), and 81 lost to follow-up (16.1%). The median follow-up period was 36 months for the resected cases and 6 months for the non-resected cases. Five-year survival was 90.7%, 80.0%, 51.0%, 32.4%, 23.5%, 17.1% and 0% in patients with stage I/II/IIIA/IIIB/IVA/IVB/unresected GBC, respectively. Comparing the adjacent stages, the difference in survival between patients with stages II and IIIA GBC and between patients with stage IVB and non-resected GBC, were statistically significant but there were no significant differences in survival in comparisons between patients in the other adjacent stages.

Prognostic factors for overall survival in patients with stage III or IV GBC

The surgery period 2007–2013 (vs. 2000-2006, hazard ratio [HR] 0.55), other type histology (vs. tub1.2, HR 2.34), two or more liver metastases (H2, vs. one liver metastasis [H1], HR 4.30), and R1/2 resection (vs. R0, HR 1.57) were independent prognostic factors for overall survival. However, one liver metastasis (vs. no liver metastasis [H0]) was not an independent prognostic factor for overall survival (Table 1).

Table 1 Uni- and multivariate analyses of overall survival in patients with resected stage III-IV GBC

		Univariate			Multivariate	
		n	OS 5 years	p value ^a	Hazard ratio (95% CI)	p value ^b
Period	07–13'/00–06'	111/117	35.4/20.0	<0.001	0.55 (0.38–0.80)	0.002
Age (year)	≥70/<70	110/118	30.7/24.8	0.50		
Gender	Female/Male	131/97	26.3/29.5	0.90		
Preop. Jaundice	Yes/No	65/161	11.7/34.1	<0.001	1.63 (0.99–2.66)	0.053
NAC	Yes/No	13/214	9.23/28.7	0.30		
CA19-9, U/L	>37/≤37	127/95	17.0/39.9	<0.001	1.09 (0.73–1.62)	0.68
CEA, ng/mL	>5/≤5	75/149	15.2/33.2	0.003	1.11 (0.74–1.66)	0.62
Incidental	Yes/No	20/208	16.0/28.5	0.30		
Hepatectomy	Ch/GB	37/60	31.8/40.0	<0.001	1.67 (0.88–3.17)	0.11
	S4aS5/GB	51/60	31.1/40.0	–	1.29 (0.77–2.17)	0.33
	R2.3/GB	69/60	12.4/40.0	–	1.74 (0.98–3.07)	0.057
	Others/GB	11/60	23.6/40.0	–	1.53 (0.58–4.03)	0.39
BDR.PD	Absent/ BDR	74/121	33.8/23.4	0.30		
	PD/ BDR	33/121	28.8/23.4	–		
Blood loss, mL	≥900/<900	109/105	12.1/40.6	<0.001	1.27 (0.80–2.02)	0.31
Surgery time, min	≥366/<366	107/107	18.8/33.8	0.004	0.81 (0.53–1.25)	0.34
Histology	pap/tub1.2	23/129	50.2/27.0	0.005	0.57 (0.28–1.17)	0.13
	tub3/tub1.2	47/129	23.9/27.0		1.21 (0.74–1.96)	0.45
	other/tub1.2	28/129	15.9/27.0		2.34 (1.32–4.12)	0.003
AJCC T 8 th	T3/T2	125/56	24.8/42.0	<0.001	1.33 (0.77–	0.30

					2.30)	
	T4/T2	47/56	17.3/42.0		1.78 (0.87–3.62)	0.11
AJCC N 8 th	N0/N1	74/90	37.6/25.5	0.03	0.53 (0.33–0.85)	0.009
	N2/N1	17/90	14.6/25.5		0.92 (0.45–1.88)	0.82
	Distant/N1	47/90	19.5/25.5		1.44 (0.91–2.29)	0.12
H	H0/H1	193/15	29.3/36.4	0.002	1.56 (0.71–3.41)	0.26
	H2/H1	20/15	5.26/36.4		4.30 (1.66–11.2)	0.003
P	P0/ P1	211/13	29.9/0	<0.001	0.51 (0.24–1.06)	0.072
	P2/ P1	4/13	0/0		1.11 (0.26–4.75)	0.88
Residual cancer	R1.2/R0	72/153	9.88/35.6	<0.001	1.57 (1.04–2.36)	0.031
Morbidity*	≥3/≤2	66/159	18.5/31.5	0.002	1.37 (0.92–2.05)	0.12
AC	with /without	98/119	30.5/27.0	0.10		

^aLog-rank test, ^bCox proportional hazards model. OS, overall survival; NAC, Neoadjuvant chemotherapy; CA, cancer antigen; CEA, carcinoembryonic antigen; CI, confidence interval; GB, gallbladder bed resection; Ch, cholecystectomy; S4aS5, resection of segment 4a plus 5 of the liver; R2, right hepatectomy; R3, right trisectionectomy; BDR, bile duct resection; PD, pancreatoduodenectomy; AJCC, American Joint Committee on Cancer; *Clavien–Dindo classification; AC, adjuvant chemotherapy. pap/tub1/tub2/tub3/other, T2/T3/T4, N0/N1/N2/Distant LNM, H0/H1/H2, P0/P1/P2, R0 (See Supplemental table 1). Other type histology includes adenosquamous cell carcinoma (n = 11), mixed neuroendocrine-non-neuroendocrine neoplasm (n = 3), squamous cell carcinoma (n = 4), carcinosarcoma (n = 2), mucinous carcinoma (n = 1), neuroendocrine carcinoma (n = 1), undifferentiated carcinoma (n = 1). Other than papillary, well differentiated, moderately differentiated, or poorly differentiated adenocarcinoma, but details are unknown (n = 5)

Overall and median survival in patients with stage III/IV R0 GBC with or without liver metastasis (Fig.2)

Five-year overall survival was significantly better in H1R0 patients (40.9%) than in H2 (0%) or unresected (0%) patients but equivalent to H0 (37.0%) patients. In terms of median survival, H1R0 patients showed comparable rates to H0R0 patients and significantly better rates than H2R0 or unresected patients.

Cumulative recurrence rate and pattern in patients with stage III/IV GBC with or without liver metastasis (Fig.3)

The cumulative 5-year recurrence rate was 66.7% for H1R0 patients, which was equivalent to that of H0R0 patients (62.6%) and better than that of H2R0 patients (100%) ($p = 0.01$). The time to recurrence and recurrence patterns in the H1R0 group were similar to that in the H0R0 group and better than that in the H2R0 group (Table 2). There were no differences in clinical or pathological factors between the H1 and H0 groups (Supplemental Table 4).

Table 2 The pattern of recurrence in resected GBC patients with liver metastasis and R0 resection

	Liver metastasis		
	H0R0	H1R0	H2R0
Number of patients	135	11	10
Recurrence	86 (64%)	5 (45%)	9 (90%)
Time to recurrence (months, median)	*18.0	21.0	*9.0
Liver	*36/133 (27%)	4 (36%)	*8 (80%)
Lymph node	*26/133 (20%)	1 (9%)	*5 (50%)
Local	15/133 (11%)	0	1 (10%)
Dissemination	27/133 (20%)	1 (9%)	2 (20%)
Others	11/133 (8%)	0	0

* $p < 0.05$ between two group, H0, no liver metastasis; H1, one liver metastasis; H2, Two or more liver metastasis; The p-value between for recurrence between the H1R0 and H2R0 groups was not statistically significant ($p = 0.063$).

Univariate analyses of overall survival in patients with resected GBC and liver metastasis

According to the univariate analysis of resected patients with GBC with liver metastases ($n = 24$), those who underwent minor hepatectomy; had less blood loss, less surgery time, papillary adenocarcinoma (vs. other type of adenocarcinoma), T2 (vs. T3 and 4), and morbidity of Clavien–Dindo classification ≤ 2 (vs. ≥ 3); and received adjuvant chemotherapy (vs. did not receive adjuvant chemotherapy) exhibited significantly prolonged survival (Table 3).

Table 3 Univariate analyses of overall survival in patients with resected GBC and liver metastasis

		n	3 years OS	p value ^a
Period	2000–2006'/2007–2013'	13/11	9.38/45.5	0.09
Age (year)	<70/≥70	16/8	18.8/50.0	0.50
Gender	Male/ Female	11/13	36.4/18.3	0.40
Preop. jaundice	No/Yes	18/6	37.8/0	0.10
Neoadjuvant chemotherapy	No/Yes	21/3	26.6/33.3	0.80
CA19-9, U/L	≤37/>37	9/14	37.5/23.4	0.70
CEA, ng/mL	>5/≤5	14/9	28.6/28.6	0.70
Surgical procedure	minor/major	11/13	60.0/0	0.002
Blood loss, mL	<900/≥900/	10/14	75.0/0	<0.001
Surgery time, min	<366/≥366/	13/11	54.5/0	<0.001
Histology	Pap/other than pap	4/20	75.0/16.8	0.03
AJCC T 8 th	T2/ T3,4	8/16	85.7/0	<0.001
AJCC N 8 th	N0/N1/N2	9/12/3	33.3/30.7/0	0.40
Residual cancer	R0/R1,2	18/6	31.7/16.7	0.90
Morbidity*	≤2/≥3	18/6	37.6/0	0.05
Adjuvant chemotherapy	with/without	14/10	35.7/0	0.05

^aLog-rank test. OS, overall survival; CA, cancer antigen; CEA, carcinoembryonic antigen; AJCC, American Joint Committee on Cancer; *Clavien–Dindo classification. pap/tub1/tub2/tub3/other, T2/T3/T4, N0/N1/N2, R0/R1,2 (See Supplemental table 1).

Histopathological results: size, number, and distribution of liver metastases in the resected specimens

The median maximum size of resected liver metastases was 9 mm, and the number of liver metastases was 1 in 11 (46%) of the 24 cases and 2 in 8 (33%) cases (Table 4). Additionally, 18 of the 24 cases with a confirmed metastatic portion were in segment 4/5.

Table 4 Histopathological results: actual size, number, and distribution of liver metastases in the resected specimens

		N = 24
Number of liver metastasis	1	11 (46%)
	2	8 (33%)
	3	5 (21%)
Maximum size of liver metastasis (mm)		9 (1.9-38)
Distribution of liver metastases*	Segment 4 or 5	18 (75%)
	Segment 3	1 (4%)
	Segment 6	5 (21%)
	Segment 7	1 (4%)
	Segment 8	3 (13%)
	Right liver**	3 (13%)

*There are duplications. **Details of metastasis site unknown

Long-term survival in patients with GBC and liver metastases

Liver metastases found during surgery or pathological examination were relatively common, and 4 out of 5 patients had T2 disease (Supplemental Table 5). These metastases were resected via minimally invasive minor hepatectomy without major post-operative complications, and patients received post-operative adjuvant chemotherapy.

Discussion

This study suggests that minimally invasive minor hepatectomy and adjuvant chemotherapy may achieve long-term survival in patients with GBC with small liver metastases found during surgery or in a post-operative specimen.

Hellman et al.[16] proposed the concept of oligometastasis as a state in which some metastases exist before malignant cells acquire widespread metastatic potential[16]. The concept of oligometastasis suggests that if the number of metastases and organ sites are limited, radiation therapy or surgery may cure the condition. Oligometastasis has been reported in various carcinomas[7-10] but not in biliary cancer.

In general, surgery is the only curative treatment for biliary tract cancer that achieves long-term survival. The 5-year overall survival rate for GBC according to the AJCC 8 version is 62.5–78.4% for stage I, 50.2–68.7% for stage II (IIA 68.7%, IIB 81.6%), 25.7–39.7% for stage IIIA, 20.0–22.1% for stage IIIB, 15.7% for stage IVA, and 6.7–12.5% for stage IVB, respectively [17, 18]. This study showed better surgical outcomes at all stages compared to the reported data.

In addition, the prognostic factors for resected advanced GBC have been reported to include excessive blood loss[19], poor histology[19], N stage[20], ≥ 4 regional lymph node metastases[19], liver invasion[20], and R1 resection[20]. However, the multivariate analyses of these reports did not include prognostic factors for distant metastasis. In recent years, surgery has been contraindicated in patients with GBC and distant metastases; therefore, the multivariate analyses in these reports[20] rarely included cases of distant metastases.

Patients with biliary cancer who develop distant metastases are considered to have widespread disease and to be incurable. Most studies report a 5-year survival rate of 0–6.7%, and long-term survival is rare[21, 22]. Large-scale studies in patients with GBC and distant metastases treatment with chemotherapy have reported a median survival of around 7 months[3]. Few patients with GBC and distant metastases achieve 5-year survival after chemotherapy [3, 23]. The median overall survival of patients with locally advanced or metastatic biliary tract cancer receiving chemotherapy with cisplatin and gemcitabine is 11.2–11.7 months[24, 25]. Wakai et al.[26] classified hepatic spread from GBC into three categories: direct invasion through the gallbladder bed, portal tract invasion, and hepatic metastatic nodules. They also reported that direct invasion through the gallbladder bed and portal tract invasion were the main forms of progression of hepatic spread from GBC, and patients with hepatic metastatic nodules had poor outcomes after resection.

However, if pre-operative diagnosis determines that there is no distant metastasis, small liver metastasis is evident around the gallbladder during surgery. In addition, when R0 resection without post-operative morbidity is highly possible using less invasive resection, it is unclear whether it is better to perform resection. Shimizu et al. [27] examined the outcomes of the aggressive surgical management of stage IV GBC. In their study, limited hepatic metastases were resected with the primary tumor only if complete tumor resection was possible. The 5-year survival rate in patients with liver metastasis ($n = 16$) was 14.4%. However, they mentioned the necessity of clarifying the indications to be considered when performing radical surgery on patients with liver metastasis because of the very limited sample size of their study. In a study of 1526 patients with metastatic gallbladder adenocarcinoma, Yang et al. [5] reported that, while 51.6% of patients had isolated liver metastases, only 5.2% had isolated distant lymph node metastases. Their multivariate analysis showed that not performing surgery at the primary site and not receiving chemotherapy were associated with poor overall survival for patients with isolated liver (HR 1.8 and 2.7, respectively) or distant lymph node metastases (HR 3.6 and 3.7, respectively). Patients who underwent surgery at the primary site showed significantly better overall survival compared to patients not undergoing surgery in both the groups with liver (7 vs. 2 months, $p = 0.01$) or distant lymph node (12 vs. 6 months, $P = 0.01$) metastases. The results of the multivariate analysis in this study are consistent with our results.

In recent years, conversion surgery has been gradually reported in biliary cancer. Kato et al. [28, 29] reported that, in patients with initially unresectable locally advanced biliary cancer who received chemotherapy with either gemcitabine ($n = 22$) or gemcitabine and cisplatin ($n = 36$), 36.4% and 25.6% of patients, respectively, unresectable has changed to resectable over time and two patients survived for 5

years [28, 29]. Noji et al. [30] described the disease course of 24 patients with biliary cancer, including 12 patients with distant metastases, who were initially ineligible for resection but underwent resection after chemotherapy. Following initial therapy, the 5-year overall survival in these patients was 43.2%. These studies suggest that advances in chemotherapy have led to improved outcomes for unresectable biliary tract cancer.

Liver invasion of 5 mm or more, invasion of the left margin or the entire area of the hepatoduodenal ligament, and four or more regional lymph node metastases are poor prognostic factors for GBC, even in patients without distant metastasis[19, 31]. In our univariate analyses of patients with resected GBC and liver metastasis, those who underwent minor hepatectomy, those who had less blood loss, those with less surgery time, those with papillary type histology, those with T2 stage, those with post-operative morbidity of Clavien–Dindo classification ≤ 2 , and those who received adjuvant chemotherapy showed more favorable outcomes (Table 3). Four of five patients with liver metastases who survived for 5 years did not have the abovementioned poor prognostic factors at T2 (Supplemental Table 5). In addition, four cases were found to have liver metastases during the operation, one case was found to have liver metastases due to postoperative pathology, four cases had a single metastasis (8 mm or less), and one case had two metastases. Therefore, patients with T2 GBC with small liver metastases, first diagnosed during surgery and free of other poor prognostic factors, may be in the oligometastatic state of GBC. Furthermore, in these patients, long-term survival may be expected with minimally invasive minor hepatectomy and R0 with post-operative adjuvant chemotherapy. The next important step will be to conduct a study with a higher number of GBC resections with small liver metastasis that result in R0 resection (in a minor hepatectomy) with chemotherapy and to enroll more long-term survivors.

This study has several limitations. It is a retrospective study, and there were very few H1/H2 cases and multidisciplinary clinical approaches, including pre-operative or post-operative indications. The number of liver metastases was determined intra-operatively through macroscopic findings and ultrasonography; however, it is difficult to accurately determine the number of micro-hepatic metastases using these methods. Furthermore, the surgical procedure and surgical indication to be selected may differ depending on the institution and the surgeon. There may also be different choices of preoperative and adjuvant chemotherapy.

Conclusions

For GBC patients with small liver metastases that are initially diagnosed during or after surgery and in the absence of other poor prognostic factors, minimally invasive minor hepatectomy with R0 resection and postoperative chemotherapy may be considered as an option.

Abbreviations

ACRoS1406: Association for Clinical Research on Surgery Group

AJCC 8: American Joint Committee on Cancer

CA 19.9: carbohydrate antigen 19.9

CEA: carcinoembryonic antigen

CT: computed tomography

H0: no liver metastasis

H1: one liver metastasis

H2: two or more liver metastases

HR: hazard ratio

GBC: gallbladder cancer

No at risk: number at risk.

M1: with distant metastasis

R0: complete resection with negative margin

R1/2 resection: grossly negative but microscopically/grossly and microscopically positive margin of resection

T2: Tumor invades the peri-muscular connective tissue on the peritoneal side without involvement of the serosa or on the hepatic side with no extension into the liver

T3: Tumor perforates the serosa and/or directly invades the liver and/or one other adjacent organ or structure, such as stomach, duodenum, colon, pancreas, omentum, or extrahepatic bile ducts

T4: Tumor invades the main portal vein or hepatic artery or invades two or more extrahepatic organs or structures

Tub1.2: well or moderately differentiated adenocarcinoma

Declarations

Ethics approval and consent to participate: This study was approved by the institutional review board of Tokyo Women's Medical University (acceptance number 3839). The requirement to obtain written informed consent from each patient was waived due to the study's retrospective design.

A Consent for publication: This article does not contain any personally identifiable data.

Availability of data and materials: The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Figures

$p < 0.001$

No at risk	0month	24 months	60 months
Stage 0/1	76	68	50
Stage 2	65	55	34
Stage 3a	42	25	16
Stage 3b	55	37	16
Stage 4a	29	8	5
Stage 4b	102	23	9
Unresected	134	4	0

		MST	5y survival		MST	5y survival
MST	Stage 1	NA	90.7	Stage 3b	36.0	32.4
	Stage 2	NA	80.0	Stage 4a	19.1	23.5
	Stage 3a	NA	51.0	Stage 4b	11.0	16.3
	Unresected	6.8	0			

Figure 1

Overall survival rate according to the AJCC 8th stage in patients with gallbladder cancer

Median survival time for stage 0/1, 2, 3a, 3b, 4a, 4b and unresected were "not reached", "not reached", "not reached", 36.0, 19.1, 11.0 and 6.0 months, respectively. No at risk, number at risk.

No at risk	0 month	24 months	60 months
H0R0	135	73	39
H1R0	11	5	3
H2R0	10	1	0
Unresected	134	3	0

MST	5y survival				
33.0	37.0				0.84
28.3	40.9	*	*	*	0.025
11.0	0				0.47
6.8	0				

Figure 2

Overall survival with or without liver metastasis in patients with stage 3,4 R0 and gallbladder cancer

Median survival time for H0R0, H1R0, H2R0 and unresected were 33.0, 28.3, 11.0 and 6.8 months, respectively. *< 0.001, **<0.05, R0, complete resection with negative margin; H0, no liver metastasis; H1, one liver metastasis; H2, two or more liver metastasis, Not at risk, number at risk

No at risk	0 month	24 months	60 months
H0R0	0	71	96
H1R0	0	7	8
H2R0	0	9	10

	Median time to recurrence	5y recurrence %		
H0R0 (n = 135)	21	62.6	] NS]	<0.001]
H1R0 (n = 11)	40.5	66.7		
H2R0 (n = 10)	11	100		

Figure 3

Cumulative recurrence rate in stage 3,4 gallbladder cancer patients with or without liver metastasis

Median time to recurrence for H0R0, H1R0 and H2R0 were 21.0, 40.5 and 11 months, respectively. R0, complete resection with negative margin; H0, no liver metastasis; H1, one liver metastasis; H2, two or more liver metastasis; No at risk, number at risk

Supplementary Files

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