Research Square

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Importance of Gross Type in Patients With T2 Gallbladder Cancer

In Sik Shin
Yonsei University Wonju College of Medicine, Wonju Severance Christian Hospital
Ji Woon Choi
Yonsei University Wonju College of Medicine, Wonju Severance Christian Hospital
Deok Gie Kim
Yonsei University Wonju College of Medicine, Wonju Severance Christian Hospital
Sung Whan Cha
Yonsei University Wonju College of Medicine, Wonju Severance Christian Hospital
Sung Hoon Kim (drgskim01@gmail.com)
Yonsei University Wonju College of Medicine, Wonju Severance Christian Hospital
Mee-Yon Cho
Yonsei University Wonju College of Medicine, Wonju Severance Christian Hospital

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Abstract

The 8th edition of the American Joint Committee on Cancer (AJCC) guidelines categorize T2 gallbladder cancer (GBCA) according to pathologic tumor location; peritoneal- and hepatic-side tumors are categorized as T2a and T2b, respectively. We hypothesized that the gross type of GBCA is more important and aimed to investigate their importance in the T2 stage GBCA. Eighty-six patients with GBCA underwent operation from February 2008 to December 2017. We retrospectively reviewed the medical records of 30 patients with pathologically confirmed T2-stage GBCA. There were 8 peritoneal-side and 22 hepatic-side GBCAs. Regarding gross types, 21 and 9 patients had infiltrative- and exophytic-type tumors. Mean disease-free survival (DFS) of T2a and T2b was 38 vs 36 months (p=0.48), respectively, and overall survival (OS) was 50 vs 52 months (p=0.312), respectively. However, patients with infiltrative-type tumors showed significantly worse DFS of 24 months (vs 67 months; p=0.003) and relative different OS of 48 months (vs 67 months; p=0.092). The gross type and lymph node metastasis were the only significant prognostic factor for DFS and OS, respectively. The gross types of T2 gallbladder cancer may be more important prognostic factor than tumor location.

Introduction

Although gallbladder carcinoma (GBCA) is a relatively rare neoplasm, it is considered to be a lethal malignancy with poor outcomes. Because of the vague symptoms and nonspecific radiologic findings, detecting GBCA remains a difficulty [1,2]. An effective systemic therapy for GBCA has not yet been established; therefore, its early detection and treatment is necessary but challenging. As laparoscopic cholecystectomy has emerged as the gold standard management for gallbladder-associated diseases, the diagnosis of GBCA is often made after surgery [3]. Pathologic staging is important to determine the treatment plan of GBCA. The National Comprehensive Cancer Network (NCCN) guideline [4] and American Joint Committee on Cancer (AJCC) tumor-node-metastasis (TNM) staging system recommends that patients who are diagnosed with T2 GBCA after laparoscopic cholecystectomy need to undergo extended cholecystectomy. However, there is some debate regarding T2 GBCA treatment [5-8]. The 8th AJCC TNM staging system for GBCA, which was issued on January 1, 2018, divided the original T2 stage in the 7th edition into T2a and T2b. T2a indicates that the cancer has invaded the peritoneal side of the gallbladder without invading the serosa and T2b indicates that the cancer is invading the hepatic side of the gallbladder without invading the liver [9]. This was based on evidence from a recent multi-country institutional study, which showed that tumor location was an important prognostic factor for recurrence and survival after resection [10]. Additionally, the histologic gross type of GBCA was reported to be an important prognostic factor [11,12]. Some studies emphasized cell type [13], invasion pattern [14] and histologic phenotype [12] as important prognostic factors. However, there was a few of evidences about the relationship between the gross type and disease progression and survival in GBCA patients. Therefore, in this study, we tried to validate the prognostic significance of tumor location in the 8th AJCC TNM stage and evaluate the impact of gross type of GBCA in T2-stage patients.

Results

Baseline and pathologic characteristics

Eighty-six patients with gallbladder cancer underwent surgical treatment and were reviewed in our institution during the study period. According to the criteria, we identified 30 patients with T2 gallbladder cancer who underwent R0 surgical treatment and were included in this study.

There were 8 peritoneal-side and 22 hepatic-side T2 gallbladder cancers. Two of the 8 patients with peritoneal-side cancer and 7 of the 22 patients with hepatic-side cancer underwent hepatic resection. Two patients with peritoneal-side cancer and 9 with hepatic-side cancer underwent adjuvant chemotherapy, and 3 with peritoneal-side cancer and 14 with hepatic-side cancer underwent adjuvant radiation therapy. During median 30 months (1-103 months) follow-up period, 2 patients with peritoneal-side cancer and 10 with hepatic-side cancer who were diagnosed with recurrence after resection. Tumor characteristics were similar between both groups. The baseline and pathologic characteristics according to the T2a and T2b stages are displayed in Table 1.

When the patients were compared with respect to gross type, there were 21 patients with infiltrative-type tumors and 9 with exophytic-type tumors. Six of the 21 patients with infiltrative-type tumors underwent hepatic resection, as 3 of the 9 patients with exophytic-type did. Ten of the patients with infiltrative-type tumors and 1 of the patients with exophytic-type patients underwent adjuvant chemotherapy. Additionally, 12 patients with infiltrative-type tumors and 5 with exophytic-type tumors underwent adjuvant radiation therapy. The patients with infiltrative-type tumors showed more aggressive tumor characteristics regarding lymphovascular invasion, perineural invasion, and lymph node metastasis. There were 11 patients with infiltrative-type tumors and 1 with exophytic-type tumors who were diagnosed with recurrence after resection. The characteristics according to the gross type are displayed in Table 2.

Surgical outcomes and prognostic factors

According to the T stage, the mean DFS and OS of T2a and T2b were 38 vs 36 months (p=0.48) and 50 vs 52 months (p=0.312), respectively. All values of DFS and OS did not show significant differences between T2a and T2b. However, patients with infiltrative-type tumors showed a significantly poor DFS (24 months vs exophytic 67 months; p=0.003). Although the comparison of OS did not demonstrate a statistically significant difference, the value of mean OS between exophytic- and infiltrative-type GBCA showed a relative difference (48 months vs exophytic 67 months; p=0.092). (Figure 2.)

The results of univariate and multivariate Cox regression analysis for identifying the prognostic factors of DFS and OS in patients with T2 GBCA are shown in Table 3 and 4. In the univariate analysis of DFS, lymph node metastasis [hazard ratio (HR) 4.751; p=4.751; 95% confidence interval (CI) 1.479–15.260], tumor differentiation (poorly differentiated, HR 2.082; p=0.038; 95% CI 1.369–15.483), gross type (infiltrative type, HR 10.537; p=0.026; 95% CI 1.325–83.771) and lymphovascular invasion (HR 4.603;

p=0.014; 95% CI 1.369–15.483) were significantly associated with poorer outcomes in patients with T2 GBCA. Gross type (infiltrative type, HR 9.709; *p*=0.031; 95% CI 1.231–76.586) was the only independent factor on multivariate Cox regression analysis. Regarding OS, age and lymph node metastasis were independent factors on univariate analysis; however, lymph node metastasis was the only independent factor associated with poorer outcomes in patients with T2 GBCA on Cox regression analysis (HR = 4.594; *p*=0.005; 9%% CI = 1.584-13.320).

Discussion

Recent studies have indicated that tumor location is an important prognostic factor in patients with T2 GBCA, and this result was reflected in the 8th AJCC TNM staging system [9]. Many GBCAs are diagnosed after simple cholecystectomy because the laparoscopic approach had become the golden standard treatment modality for gallbladder diseases. Current guidelines and studies recommend re-operation in incidental T2 GBCA because of residual cancer and survival benefit.[4,9,15-17] However, real clinical situations are much different from guidelines. In many studies, reoperation rate or liver resection rate are lower than those that we expected. The range of those rates is from 4% to 70%. Many patients usually use to be old age and have many co-morbidities and then refuse the further treatments or extended surgery.[5,8,10,17,18] Although T2b GBCA shows worse outcomes than T2a GBCA, the hepatic resection of T2b GBCA did not affect long-term survival in some studies.[6,19] This may have been an indication that there may be another method of classification for T2-stage GBCA. The decision to perform secondary operations such as extended cholecystectomy for T2 GBCA have also become important.

In this study, the location of the tumor did not show any relation with the prognosis of patients with GBCA, but the growth pattern of the tumor showed strong relation with this prognosis. Although the patients with exophytic-type tumors underwent less adjuvant chemotherapy than those with infiltrative-type tumors, there was less tumor recurrence in the exophytic group. Regarding lymph node metastasis, patients with exophytic-type tumors had relatively fewer instances of lymph node metastasis than those with infiltrative-type tumors (p=0.091). The p-value may not be considered a meaningful result, but if the scale of patient groups is considered, a study with a larger population may show a more meaningful result.

The effectiveness of adjuvant or neoadjuvant therapy has been evaluating in bile duct carcinoma including gallbladder cancer and cholangiocarcinoma.[20,21] The similar effects were identified in both tumors and both tumors shared some characteristics like as lymph node metastasis, lymphovascular and perineural invasion. In intrahepatic cholangiocarcinoma, periductal infiltration type showed those aggressive characteristics and associated with poor prognosis. Recent one study analyzed the association between the histopathological type and growth pattern and elucidated the difference of behavior and prognosis according to the growth pattern.[22] Recently, many studies focused tumor microenvironments of GBCA including immune check point inhibitors. Programmed cell death ligand-1 (PD-L1) was well known to allow tumor cells escaping from host immune systems and associated with

tumor aggressiveness and poor prognosis in many cancers. The importance of PD-L1 has been investigating in GBCA and they suggested that PD-L1 was important prognostic factor and possibility to be a target for molecular therapy. The increased expression of PD-L1 was associated with aggressive pathological characteristics.[23,24] In our study, infiltrative growth pattern was relatively more associated with aggressive pathological characteristics than tumor location. In other cancers, infiltrative growth pattern shows more aggressive characteristics and poorer prognosis than other types.[25,26]

Gallbladder carcinoma usually spreads to the liver through the gallbladder bed in several pathways, and might be associated with the prognosis of the patients. According to Wakai et al, the mode of hepatic spread of GBCA shows several patterns of invasion such as intrahepatic, lymphatic, venous, and direct invasion through the gallbladder bed alone [27]. The definition of T2 GBCA is a tumor confined to the connective tissue of the gallbladder, which does not invade the liver, but the prognosis is poorer than that of T1 GBCA despite both being tumors confined to the gallbladder. For this reason, a proper surgical approach such as the extent of liver resection is still a matter of debate. We might hypothesize that the surgical strategy, including liver resection, did not show similar results in several studies because of the importance of gross type over tumor location. As observed in this study, the gross type was more closely related to the prognosis than the tumor location. Our study is a retrospective analysis of a small number of patients in a single institute, and this constitutes the main limitation in accepting the use of histologic description to evaluate effective prognostic indication and determine an effective surgical strategy. However, to our knowledge, a similar study about the relation of growth pattern and prognosis in GBCA has not been performed before; therefore, this study could be one of the milestones in the search for other clues to evaluate and predict the course of GBCA and determine the treatment strategy.

In conclusion, the histologic description of GBCA was more related to the prognosis when compared to tumor location. If patients show infiltrative GBCA on the pathologic report, we should recommend re-operation in incidental GBCA cases and consider adjuvant therapy. If we perform similar studies with a larger patient population from multiple institutions, we may be able to find more definitive evidence about the relationship and clues about the effectiveness of liver resection and adjuvant therapy. These could also suggest novel methods of treating and predicting the survival of patients with this disease.

Methods

Patients

This retrospective study was approved by the Institutional Review Board of Yonsei University Wonju Severance Hospital (CR314023), which waived the obtainment of the informed consent due to the retrospective review of the medical records. All studies were conducted based on the principles of the Declaration of Helsinki. Eighty-six patients underwent surgical treatment for GBCA from February 2008 to December 2017. We reviewed their medical records retrospectively. Patients who were diagnosed and referred after surgery at other hospitals were excluded. Another exclusion criterion were double primary cancer and patients diagnosed with neuroendocrine tumor.

Definition of terminology

Pathologic staging followed the 8th AJCC TNM stage system.[9] We used the same definition like Shindoh classified GBCA into T2a and T2b. Briefly, T2a GBCA was defined as the tumor infiltrated the only the free serosal side of the gallbladder and T2b as at least part of tumor infiltrated the hepatic side of gallbladder. Extended cholecystectomy was defined as cholecystectomy, regional lymph node dissection, and liver resection, including wedge resection. Curative surgery was defined as the absence of microscopic residual cancer. The histopathologic reports included information about depth of invasion, lymph node metastasis, and lymphovascular and perineural invasion.

The Japanese society of hepato-biliary-pancreatic surgery (JSHBPS) published and updated the Japanese classification of the biliary tract cancer.[28] According to them, GBCA was categorized into three (papillary, nodular and flat) types and each type has two-subtypes (expanding and infiltrating). Actually, there are some overlap between those types in real-clinical situation. World Health Organization (WHO) and the result of autopsies descripted GBCA into two gross types, namely, infiltrative type and exophytic type.[29,30] The description of the tumor types refers to the growth pattern of the tumors. Infiltrative type is defined as GBCA that shows diffuse thickening and induration of the wall with possible fistula formation due to deep ulceration and exophytic type refers to an irregular, cauliflower mass that grows into the lumen and invades the wall[29]. However, it still has ambiguous part to define definitively one type. In ambiguous cases, if the height of papillary or nodular growth is 2 times more than that of adjacent mucosa, it is defined as exophytic type and the other is defined as infiltrative type. (Figure 1.)

Protocol of pre- and post-operative evaluation and policy of surgery

When the patient was referred to our hospital for suspicious GBCA, we performed computer tomography (CT) to identify the extent of tumor and positron emission tomography–computed tomography to evaluate the distant metastasis. When the patient received emergency cholecystectomy and was diagnosed as GBCA after laparoscopic cholecystectomy due to the symptom of acute cholecystitis, we performed only CT. Carbohydrate antigen 19-9 (CA19-9) was check before the operation. When the GBCA may be suspected, we performed extended cholecystectomy except cases that patients and families denied the extended cholecystectomy because of old age or morbidities. We also performed re-operation in cases that patients were diagnosed as T2 GBCA after laparoscopic cholecystectomy except denial cases. Patients were regular checked by CT scan and CA 19-9 every three month until postoperative 2 years. After then, we increased the interval as 4 or 6 months according to the status of patients. We recommend all patients adjuvant treatment. However, the patient and family decided finally whether they receive the adjuvant treatment after meeting oncologist.

Outcomes

We compared the baseline characteristics of patients and the pathologic characteristics of tumors according to their TNM stage and gross type. We analyzed disease-free survival (DFS) and overall

survival (OS) and compared those results between the classification by tumor location as well as that by gross type. We also analyzed the prognostic factors for DFS and OS.

Statistical analysis

Statistical analysis was performed using IBM SPSS software (version 23.0, SPSS Inc, Chicago, IL. USA). Categorical variables were compared using the chi-squared test. Continuous variables were compared using the Mann-Whitney U test. Survival was calculated using the Kaplan-Meier method from the date of surgical treatment. The univariate and multivariate analysis of DFS and OS were conducted by using the forward stepwise Cox's proportional hazard model to identify prognostic factors. A p-value < 0.05 was considered to be significant.

Declarations

Author contribution

Concept design: SHKim, MYCho

Data acquisition: ISShin, DGKim, SWCha, JWChoi

Data analysis: ISShin, DGKim, JWChoi

Writing draft: ISShin, JWChoi, SHKim

Revision draft: DGKim, SWCHa, SHKim, MYCho

Declarations of interest: none

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Tables

Table 1. Baseline characteristics of patients according to pathologic staging

Variable		T2a (n=8)	T2b (n=22)	*p*
Sex	Female	n=5 (62.5%)	n=10 (45.5%)	0.341
	Male	n=3 (37.5%)	n=12 (55.5%)	
Age, years		69.1 (52-82)	70.1 (40-88)	0.910
Operation type	Simple	6 (75%)	15 (68.2%)	0.719
	Extended	2 (25%)*	7 (31.8%)†	
Pathology	Adenocarcinoma	7 (87.5%)	20 (91.0%)	0.629
	Adenosquamous	1 (12.5%)	1 (4.5%)	
	Mixed type	0	1 (4.5%)	
Gross type	Exophytic	3 (37.5%)	6 (27.3%)	0.292
	Infiltrative	5 (62.5%)	16 (72.7%)	
LN metastasis	Retreived LN	1 (0-49)	2 (0-17)	0.534
	Nx	2 (25%)	8 (36.4%)	
	N0	4 (50%)	7 (31.8%)	0.529
	N1	2 (25%)	7 (31.8%)	
LVI	No	7 (87.5%)	11 (50%)	0.064
	Yes	1 (12.5%)	11 (50%)	
PNI	No	6 (75%)	14 (63.6%)	0.682
	Yes	2 (25%)	8 (36.4%)	
Differentiation	well	2 (28.6%)	10 (50.0%)	0.300
	moderate	2 (28.6%)	7 (35.0%)	
	poor	3 (42.8%)	3 (15.0%)	
Adjuvant CTx		2 (25%)	9 (41.0%)	0.424
Adjuvant RTx		3 (37.5%)	14 (63.6%)	0.201
Recurrence	No	6 (75%)	12 (54.5%)	0.419
	Yes	2 (25%)	10 (45.5%)	

LN, lymph node; LVI, lymphatic vessel invasion; PNI, perineural invasion; CTx, chemotherapy; RTx. Radiotherapy

*One and †six patients received re-operation after laparoscopic choleycstectomy

Table 2. Baseline characteristics of patients according to gross type

Variable		Exophytic (n=9)	Infiltrative (n=21)	*p*
Sex	Female	n=4 (44.4%)	n=11 (52.4%)	0.69
	Male	n=5(55.6%)	n=10 (47.6%)	
Age, year		68.0 (40-82)	70.7 (43-88)	0.141
Operation type	Simple	6 (66.7%)	15 (52.4%)	0.794
	Extended	3 (33.3%)*	6 (28.6%)†	
Location	T2a	3 (33.3%)	5 (23.8%)	0.589
	T2b	6 (66.7%)	16 (76.2%)	
LN metastasis	Retreived LN	2 (0-15)	1 (0-19)	0.727
	Nx	2 (22.2%)	8 (38.1%)	
	N0	6 (66.7%)	5 (23.8%)	0.169
	N1	1 (11.1%)	8 (38.1%)	
LVI	No	9 (100%)	9 (42.9%)	0.342
	Yes	0 (0%)	12 (57.1%)	
PNI	No	8 (88.9%)	12 (57.1%)	0.091
	Yes	1 (11.1%)	9 (42.9%)	
Differentiation	well	8 (88.9%)	19 (90.5%)	0.203
	moderate	0 (0%)	2 (9.5%)	
	poor	1 (11.1%)	0 (0%)	
Adjuvant CTx		1 (11.1%)	10 (47.6%)	0.057
Adjuvant RTx		5 (55.6%)	12 (57.1%)	0.936
Recurrence	No	8 (88.9%)	10 (47.6%)	0.034
	Yes	1 (11.1%)	11 (52.4%)	

LN, lymph node; LVI, lymphatic vessel invasion; PNI, perineural invasion; CTx, chemotherapy; RTx. Radiotherapy

* Two and †five patients received re-operation after laparoscopic choleycstectomy

Table 3. Univariate and multivariate analysis for disease free survival

Variable		Univariate analysis			Multivariate analysis		
		HR	*p*	95% CI	HR	*p*	95% CI
CEA, ng/mL		1.711	0.099	0.905-3.237			
CA 19-9, U/mL		1.001	0.216	1-1.002			
Operation type	Extended	2.486	0.115	0.800-7.724			
GB perforation	Yes	0.042	0.463	0-200.754			
Reoperation	Yes	2.219	0.169	0.713-6.91			
LN metastasis	Positive	4.751	0.009	1.479-15.260			
T stage	T2b	2.454	0.249	0.533-11.289			
Gross type	Infiltrative	10.537	0.026	1.325-83.771	9.709	0.031	1.231-76.586
Differentiation	Moderate	2.924	0.143	0.696-12.279			
	Poor	2.082	0.038	1.010-4.292			
LVI	Positive	4.603	0.014	1.369-15.483			
PNI	Positive	2.875	0.081	0.873-9.464			
Adjuvant therapy	CTx	1.254	0.699	0.397-3.961			
	RTx	1.233	0.733	0.370-4.107			

HR, hazard ratio; CI, confidential interval; CEA, carcinoembryonic antigen; CA 19-9, carbohydrate antigen 19-9 GB, gall bladder, LN, lymph node; CTx, chemotherapy; RTx. Radiotherapy; LVI, lymphatic vessel invasion; PNI, perineural invasion

Table 4. Univariate and multivariate analysis for overall survival

Variable		Univariate analysis			Multivariate analysis		
		HR	*p*	95% CI	HR	*p*	95% CI
Age, year		1.082	0.021	1.012-1.157			
CEA, ng/mL		1.059	0.871	0.529-2.119			
CA 19-9, U/mL		1.001	0.186	1-1.002			
Operation type	Extended	0.616	0.454	0.173-2.192			
GB perforation	Yes	2.331	0.195	0.649-8.375			
Reoperation	Yes	0.828	0.747	0.263-2.606			
LN metastasis	Positive	4.594	0.005	1.584-13.32	4.594	0.005	1.584-13.32
T stage	T2b	1.892	0.324	0.533-6.725			
Gross type	Infiltrative	2.852	0.109	0.792-10.269			
Differentiation	Moderate	1.529	0.505	0.438-5.331			
	Poor	2.059	0.286	0.546-7.758			
LVI	Positive	2.773	0.058	0.965-7.966			
PNI	Positive	2.071	0.174	0.725-5.92			
Adjuvant therapy	CTx	1.164	0.775	0.412-3.283			
	RTx	0.715	0.518	0.259-1.977			

HR, hazard ratio; CI, confidential interval; CEA, carcinoembryonic antigen; CA 19-9, carbohydrate antigen 19-9 GB, gall bladder, LN, lymph node; CTx, chemotherapy; RTx. Radiotherapy; LVI, lymphatic vessel invasion; PNI, perineural invasion

Figures

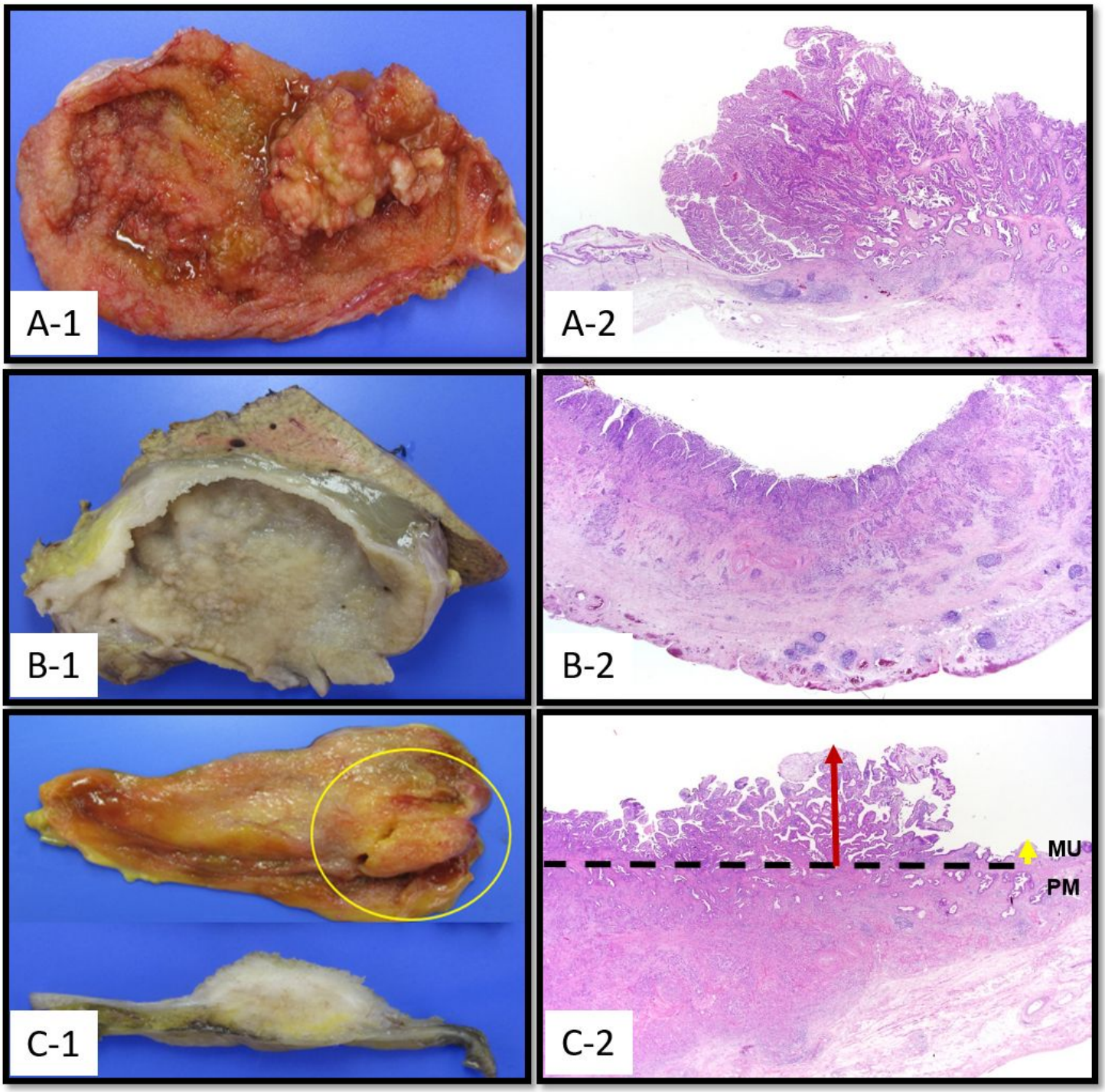

Figure 1

Photomicrographs show gross image (labeled 1) and low-power magnification (×100, labeled 2). Immunohistochemical (IHC) staining is shown for each gross type of gallbladder cancer (GBCA): Exophytic GBCA (A1-2), infiltrative GBCA (B1-2), and intermediate-type GBCA (C1-2). Exophytic GBCA is defined as papillary or nodular growth patterns that protrude into the lumen of gallbladder. Infiltrative GBCA is defined as growth pattern that it is not obvious to protrude into the lumen of gallbladder. Some cases showed intermediate-type that have papillary or nodular and infiltrative growth pattern. In this

cases, if the height of papillary or nodular growth is 2 times more than that of adjacent mucosa, it is defined as exophytic type and the other is defined as infiltrative type.

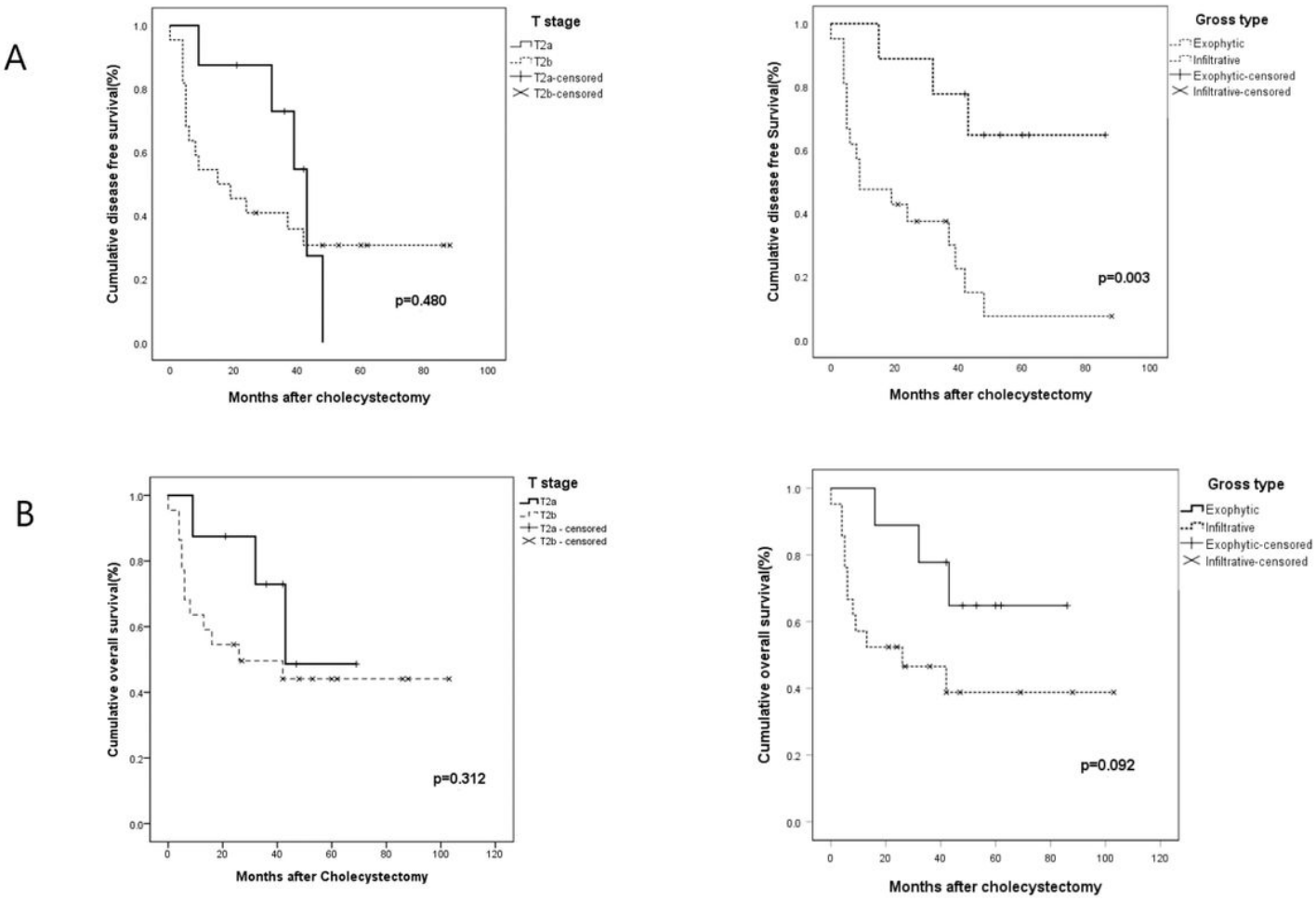

Figure 2

Disease-free and overall survival according to tumor location and gross type A. The difference of disease-free survival between T2a and T2b was not significant (p=0.048). However, that between exophytic and infiltrative type was significant (p=0.003). B. There was no significant difference regarding overall survival in tumor location (p=0.312) and histologic description (p=0.092). The mean overall survival of patients with exophytic-type gallbladder cancer was 67 months, and it was much longer than that of patients with infiltrative-type gallbladder cancer (48 months).