

Original Article

Impact of longitudinal tumor location on postoperative outcomes in gallbladder cancer: Fundus and body vs. neck and cystic duct, a retrospective multicenter study

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Backgrounds/Aims: Systematic investigations into the prognostic impact of the longitudinal tumor location in gallbladder cancer (GBC) remain insufficient. To address the limitations of our pilot study, we conducted a multicenter investigation to clarify the impact of the longitudinal tumor location on the oncological outcomes of GBC.

Methods: A retrospective multicenter study was conducted on 372 patients undergoing radical resections for GBC from January 2010 to December 2019 across seven hospitals that belong to the Daejeon–Chungcheong branch of the Korean Association of Hepato-Biliary-Pancreatic Surgery. Patients were divided into GBC in the fundus/body (FB-GBC) and GBC in the neck/cystic duct (NC-GBC) groups, based on the longitudinal tumor location.

Results: Of 372 patients, 282 had FB-GBC, while 90 had NC-GBC. NC-GBC was associated with more frequent elevation of preoperative carbohydrate antigen (CA) 19-9 levels, requirement for more extensive surgery, more advanced histologic grade and tumor stages, more frequent lymphovascular and perineural invasion, lower R0 resection rates, higher recurrence rates, and worse 5-year overall and disease-free survival rates. Propensity score matching analysis confirmed these findings, showing lower R0 resection rates, higher recurrence rates, and worse survival rates in the NC-GBC group. Multivariate analysis identified elevated preoperative CA 19-9 levels, lymph node metastasis, and non-R0 resection as independent prognostic factors, but not longitudinal tumor location.

Conclusions: NC-GBC exhibits more frequent elevation of preoperative CA 19-9 levels, more advanced histologic grade and tumor stages, lower R0 resection rates, and poorer overall and disease-free survival rates, compared to FB-GBC. However, the longitudinal tumor location was not analyzed as an independent prognostic factor.

Key Words: Gallbladder neoplasms; Neoplasms by site; Prognosis

INTRODUCTION

Even in the modern era of advanced surgical skills and chemotherapy, gallbladder cancer (GBC) is a devastating disease, due to its typically poor prognosis and late presentation [1]. Factors influencing the prognosis of GBC are widely known as the TNM stage, resection margin status, adjuvant therapy, histologic cell differentiation, and perineural invasion [2,3]. Recently, the anatomical tumor location within the gallbladder has been recognized as affecting the prognosis of GBC. In the 8th edition of the American Joint Committee on Cancer, T2

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GBC was subclassified according to transverse tumor location, based on several studies revealing that T2 tumors located on the hepatic side (T2b) exhibit a more aggressive tumor biology and higher invasiveness, and are associated with a relatively worse prognosis, compared to T2 tumors on the peritoneal side (T2a) [4-6].

Meanwhile, it is traditionally known that GBC in the neck/cystic duct (NC-GBC) has a better prognosis than GBC in the fundus/body (FB-GBC), due to the early manifestation of symptoms. However, systematic investigations into this aspect remain insufficient. In contrast, the authors have observed many cases where NC-GBC was diagnosed at a more advanced stage, and had a poorer prognosis. One of these reasons is thought to be that although tumor size is not large, the surrounding tissues including regional lymph nodes, and major vessels are vulnerable to invasion, due to the proximity of the tumor.

In the pilot study conducted at the Dankook University Hospital to investigate the impact of the longitudinal location of GBC, NC-GBC ($n = 19$) exhibited significantly more aggressive pathological features, a lower rate of radical resection, and a higher recurrence rate, compared to the FB-GBC group ($n = 58$). Survival outcomes of the NC-GBC group also showed poorer results, but there was no statistical significance. The pilot study had a significant limitation of a small number, with only 77 enrolled patients. To overcome these limitations, we conducted this multicenter study. This study aimed to examine the impact of the longitudinal tumor location on postoperative outcomes in patients undergoing radical resection for GBC. By elucidating the influence of tumor location on the clinicopathological parameters, the study sought to provide deeper insights into the prognostic factors of GBC, ultimately guiding more effective clinical management strategies.

MATERIALS AND METHODS

Ethical statement

The study protocol for this research at the Dankook University Hospital and all participating hospitals was reviewed and approved by the institutional review board (no. 2022-03-024). The protocol adhered to the Declaration of Helsinki, and due to the retrospective nature of the study, informed consent was waived.

Subjects and data collection

A total of 427 patients who underwent surgery with curative intent for GBC from January 2010 to December 2019 at seven hospitals belonging to the Daejeon–Chungcheong branch of the Korean Association of Hepato-Biliary-Pancreatic Surgery were enrolled (Fig. 1). Based on the exclusion criteria of palliative intent surgery ($n = 17$), existing other malignancy on surveillance, uncertain origin (cystic duct cancer vs. extrahepatic bile duct [EHBD] cancer, $n = 15$), rare histopathologic subtypes other than adenocarcinoma, Eastern Cooperative Oncology Group performance status ≥ 3 , in-hospital mortality ($n = 9$), and follow-up period of less than 1 month ($n = 14$), were excluded. Detailed clinicopathologic data covering the preoperative, operative, and postoperative course were retrospectively collected and analyzed.

Based on the depth of invasion, tumor grade, resection margin status, and risk of nodal involvement, patients with incidentally identified GBC who had simple cholecystectomy for non-cancerous reasons might undergo a second operation that included regional lymphadenectomy and/or liver resection. Liver resection involving more than three hepatic segments was classified as a major liver resection. Tumor stage was determined according to the eighth edition of the American Joint Committee on Cancer staging system [4]. In-hospital mortality was defined as the case of death within 30 days after surgery.

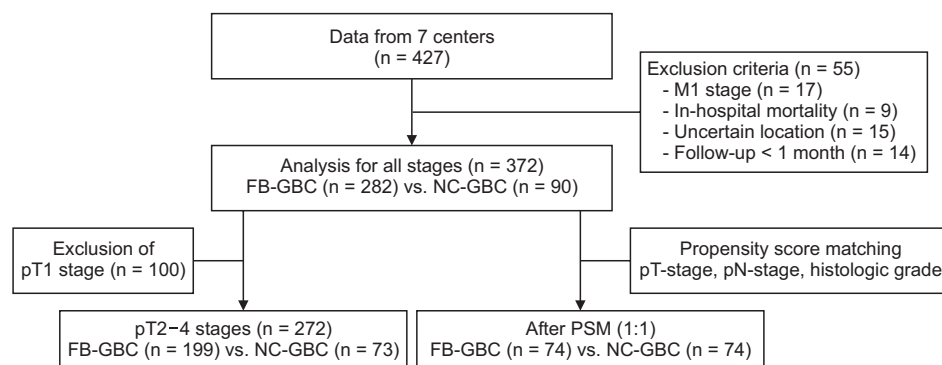


Fig. 1. Flow diagram of the analysis. A total of 427 patients were enrolled in this study. Based on the exclusion criteria, 55 patients were excluded for several reasons, and ultimately, data on 372 patients were analyzed. Because pT1 stage exhibits a low recurrence rate and good prognosis, further analysis was conducted on the patients with pT2–4 stages, excluding these 100 pT1 stage patients. Propensity score matching for pT-stage, pN-stage, and histologic grade was used to correct the imbalance in this study, and resulted in the creation of 74 patient pairs. FB-GBC, gallbladder cancer in the fundus/body; NC-GBC, gallbladder cancer in the neck/cystic duct; PSM, propensity score matching.

Division of longitudinal location of GBC

Patients were classified into two groups, based upon the longitudinal location of GBC: FB-GBC and NC-GBC groups. The gallbladder was divided into three sections, namely the fundus, body, and neck. We chose the guidelines of the Japanese Society of Hepato-Biliary-Pancreatic Surgery established in 2015 [7] as criteria for the anatomical division of the longitudinal tumor location. This division occurs along a horizontal line that starts from the top of the pear-shaped organ, and extends to the transitional region of the cystic duct (Fig. 2). Location of the tumor was determined based on pathological reports and radiologic findings, excluding uncertain locations. Patients with a diffuse tumor involving both locations were included in the NC-GBC group, because it was assumed that the NC portion of diffuse tumor, compared to the FB portion, would have a more critical impact on the postoperative prognosis, which was a point of interest of this study.

Statistical analysis

All statistical analyses were performed using SPSS software, version 27.0 (IBM Corp.). Categorical variables were evaluated using the chi-square or Fisher's exact tests. Continuous variables were summarized as the mean and standard deviation, and were compared using the Student t-test or analysis of variance. Statistical analysis using propensity score matching (PSM) was performed by accounting for the covariates that predicted patient prognosis. A 1:1 match was performed according to three related covariates, namely T-stage, N-stage, and histologic grading, to generate propensity scores.

Primary endpoints of this study were long-term oncological outcomes including disease-free survival (DFS), overall survival

(OS), and recurrence rate. DFS and OS were analyzed using Kaplan–Meier estimates, and survival curves were calculated using the log-rank test. Cox-proportional hazards models were

Table 1. Demographic and clinicopathological characteristics of all the patients (n = 372)

	FB-GBC (n = 282)	NC-GBC (n = 90)	p-value
Age (yr)	68.0 ± 11.3	68.8 ± 9.7	0.477
Female sex	138 (48.9)	53 (57.8)	0.144
BMI	24.1 ± 3.5	23.9 ± 3.6	0.713
ASA class < 3 ^{a)}	211 (85.8)	77 (89.5)	0.376
ECOG status < 2 ^{a)}	199 (87.7)	76 (91.6)	0.337
Acute cholecystitis	65 (23.0)	26 (28.6)	0.279
PTGBD insertion	24 (8.5)	11 (12.1)	0.304
Symptomatic GBC ^{a)}	160 (76.9)	67 (84.8)	0.142
CA 19-9 ≥ 37.0 (U/mL) ^{a)}	34 (14.6)	30 (39.0)	< 0.001
Laparoscopic approach	200 (70.9)	45 (50.0)	0.013
2nd look operation	54 (19.1)	19 (21.1)	0.707
Bile duct resection	26 (9.2)	29 (32.2)	< 0.001
Surgical extent			0.002
SC only	96 (34.0)	22 (24.4)	
SC + LND	37 (13.1)	13 (14.4)	
Wedge resection	107 (37.9)	29 (32.2)	
S4b + 5 segmentectomy	38 (13.5)	17 (18.9)	
Major liver resection ^{b)}	4 (1.4)	9 (10.0)	
ICPN ^{a)}	16 (8.7)	1 (1.3)	< 0.001
Tumor size (mm)	28.6 ± 17.7	35.0 ± 25.1	0.034
Histologic grade, WHO ^{a)}			< 0.001
G1	101 (37.5)	13 (15.5)	
G2	137 (50.9)	49 (58.3)	
G3	30 (11.2)	21 (25.0)	
G4	2 (0.7)	2 (2.4)	
pT-stage			0.001
T1	82 (29.2) ^{a)}	17 (18.9)	
T2	163 (58.0) ^{a)}	48 (53.3)	
T3	34 (12.1) ^{a)}	22 (24.4)	
T4	2 (0.7) ^{a)}	3 (3.3)	
pN-stage			0.004
Nx or N0	231 (81.9)	61 (67.8)	
N1–2	51 (18.1)	29 (32.2)	
R0 resection	265 (94.3) ^{a)}	68 (75.6)	< 0.001
Lymphovascular invasion ^{a)}	79 (28.4)	37 (42.0)	0.029
Perineural invasion ^{a)}	48 (18.0)	34 (39.1)	< 0.001
Adjuvant treatment	76 (27.0)	40 (44.4)	0.002
Recurrence ^{a)}	70 (25.9)	49 (55.7)	< 0.001

Values are presented as mean ± standard deviation or number (%).

FB-GBC, gallbladder cancer in the fundus/body; NC-GBC, gallbladder cancer in the neck/cystic duct; BMI, body mass index; ASA, American Society of Anesthesiologists; ECOG, Eastern Cooperative Oncology Group; PTGBD, percutaneous transhepatic gallbladder drainage; SC, simple cholecystectomy; LND, lymph node dissection; ICPN, intracholecystic papillary neoplasm; WHO, World Health Organization.

^{a)}The total sample size may not equate to the breakdown because of missing data.

^{b)}Major liver resection is defined as liver resection ≥ 3 hepatic segments.

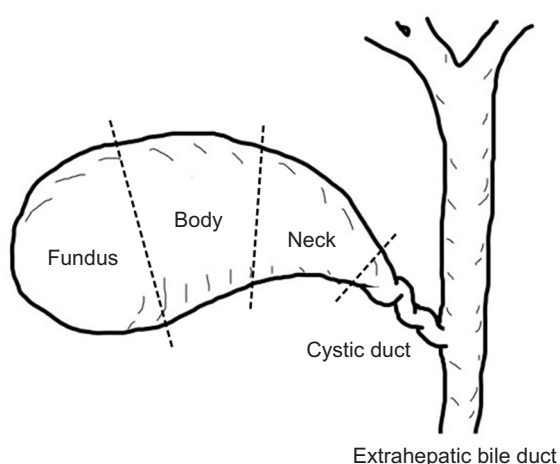


Fig. 2. The anatomical division of the gallbladder. We chose the guidelines of the Japanese Society of Hepato-Biliary-Pancreatic Surgery as the division criteria. Patients were classified into gallbladder cancer in the fundus/body and gallbladder cancer in the neck/cystic duct groups, based on the longitudinal tumor location.

used to create univariate and multivariate models for factors predictive of OS, and were reported as the hazard ratio (HR) with 95% confidence interval (CI). A p -value of < 0.05 was considered statistically significant.

RESULTS

Clinicopathologic features and oncological outcomes of all patients

A total of 372 consecutive patients underwent resection with curative intent for GBC. Of the total cases, 282 (75.8%) had tumors in the FB, while 90 cases (24.2%) were located at the NC. Table 1 presents the demographic and clinicopathological characteristics. There were no significant differences between the two groups with respect to the demographics and preoperative parameters. Only patients with preoperative serum carbohydrate antigen (CA) 19-9 levels above normal were significantly more in the NC-GBC group (14.6% vs. 39.0%, $p < 0.001$). In contrast, most surgical and histopathological results were significantly different in both groups. More extensive surgical procedures were required, and intracholecystic papillary neoplasm was less frequently found (8.7% vs. 1.3%, $p < 0.001$) in the tumors of NC. Further, in the NC-GBC group, histologic grade and tumor stages were more advanced, lymphovascular and perineural invasions were more frequent, and accordingly, the R0 resection rate was significantly lower (75.6% vs. 94.3%, $p < 0.001$).

The patients with NC-GBC had a significantly higher recurrence rate (55.7% vs. 25.9%, $p < 0.001$), despite receiving adjuvant treatment more frequently (44.4% vs. 27.0%, $p = 0.002$). Fig. 3 illustrates the survival analysis between the two groups. The NC-GBC group showed a significant difference in the 5-year OS (76.7% vs. 45.0%, $p < 0.001$) and DFS (68.7% vs. 25.0%, $p < 0.001$) compared to the other group, indicating a

poor prognosis.

Clinicopathologic features and oncological outcomes of patients with pT2–4 stages

Based on several studies, it appears that GBC patients in the pT1 stage generally exhibit a significantly lower recurrence rate and better oncological prognosis (10-year survival of 90%) following curative resection, compared to those with advanced GBC [8-10]. For this reason, the analysis was carried out excluding the 100 patients with pT1 stage (Table 2, Fig. 4). The comparative results of the patients with pT2–4 stages were similar to those of all the patients, except for only two parameters; the frequency of symptomatic GBC, and the tumor size. The patients with NC-GBC complained of symptoms more frequently (86.2% vs. 73.9%, $p = 0.047$), while the tumor size did not differ between the groups.

Similar to the survival outcomes in patients with all stages, the 5-year OS (69.5% vs. 36.2%, $p < 0.001$) and DFS (58.4% vs. 19.8%, $p < 0.001$) were significantly higher in the FB-GBC patients with T2–4 stages.

Clinicopathologic features and oncological outcomes in the propensity score-matched cohort

Patients were not randomly assigned to the FB-GBC and the NC-GBC groups, resulting in significant imbalances in most parameters between the two groups. This caused significant obstacles in investigating the impact of the longitudinal tumor location of GBC on surgical outcomes. Therefore, we opted for PSM to correct the imbalance between the groups, and used 1:1 nearest neighbor matching without replacement to reduce conditional bias. After the 1:1 PSM for pT-stage, pN-stage, and histologic grade, known strong confounders of survivals, Table 3 compares the demographic and clinicopathological characteristics of the two groups. The analysis using PSM resulted in

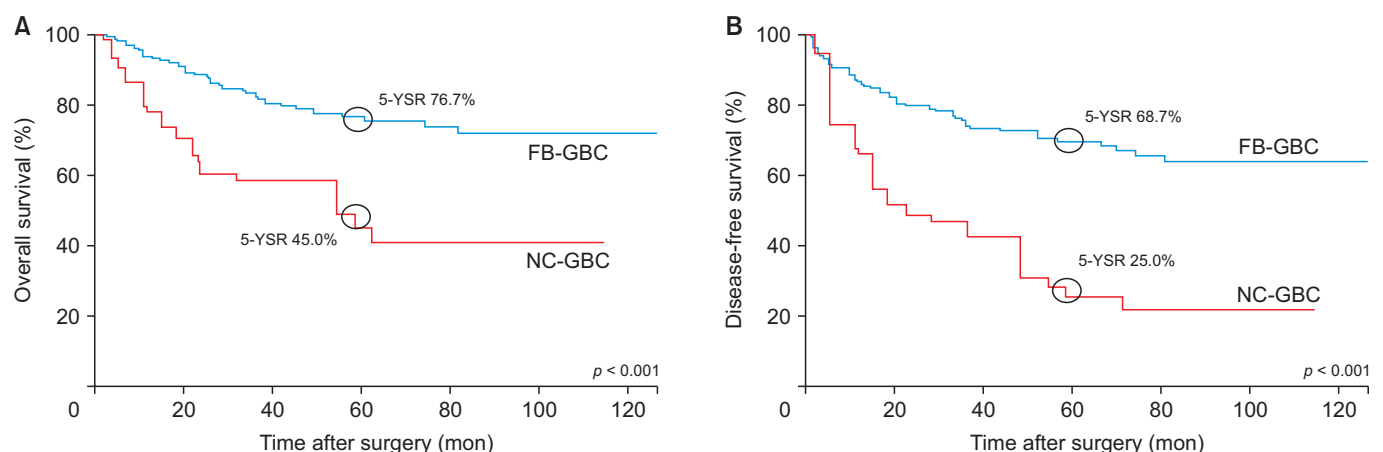


Fig. 3. Overall survival (A) and disease-free survival (B) of FB-GBC and NC-GBC for all patients ($n = 372$). The NC-GBC group showed a significant poor prognosis in the 5-year overall survival rate (76.7% vs. 45.0%, $p < 0.001$) and disease-free survival rate (68.7% vs. 25.0%, $p < 0.001$), compared to the FB-GBC group. FB-GBC, gallbladder cancer in the fundus/body; NC-GBC, gallbladder cancer in the neck/cystic duct; 5-YSR, 5-year survival rate.

Table 2. Demographic and clinicopathological characteristics of the patients with pT2–4 stages (n = 272)

	FB-GBC (n = 199)	NC-GBC (n = 73)	p-value
Age (yr)	69.1 ± 10.2	69.8 ± 8.9	0.621
Female sex	103 (51.8)	42 (57.5)	0.398
BMI	23.9 ± 3.9	23.9 ± 3.7	0.923
ASA class < 3 ^{a)}	146 (84.9)	63 (88.7)	0.419
ECOG status < 2 ^{a)}	145 (90.6)	62 (91.2)	0.887
Acute cholecystitis	49 (24.6)	19 (26.0)	0.909
PTGBD insertion	18 (9.0)	8 (11.0)	0.650
Symptomatic GBC ^{a)}	113 (73.9)	56 (86.2)	0.047
CA 19-9 ≥ 37.0 (U/mL) ^{a)}	29 (17.5)	27 (45.0)	< 0.001
Laparoscopic approach	132 (66.3)	33 (45.2)	0.002
2nd look operation	47 (23.6)	18 (24.7)	0.887
Bile duct resection	21 (10.6)	27 (37.0)	< 0.001
Surgical extent			0.003
SC only	49 (24.6)	12 (16.4)	
SC + LND	22 (11.1)	10 (13.7)	
Wedge resection	93 (46.7)	27 (37.0)	
S4b + 5 segmentectomy	34 (17.1)	15 (20.5)	
Major liver resection ^{b)}	1 (0.5)	9 (12.3)	
ICPN ^{a)}	7 (5.5)	1 (1.6)	0.222
Tumor size (mm)	32.9 ± 19.1	36.7 ± 26.1	0.319
Histologic grade, WHO ^{a)}			< 0.001
G1	52 (26.9)	5 (7.2)	
G2	114 (59.1)	42 (60.9)	
G3	25 (13.0)	20 (29.0)	
G4	2 (1.0)	2 (2.9)	
pT-stage			0.002
T2	163 (81.9)	48 (65.8)	
T3	34 (17.1)	22 (30.1)	
T4	2 (1.0)	3 (4.1)	
pN-stage			0.015
Nx or N0	150 (75.4)	44 (60.3)	
N1–2	49 (24.6)	29 (39.7)	
R0 resection	183 (92.4) ^{a)}	51 (69.9)	< 0.001
Lymphovascular invasion ^{a)}	72 (36.9)	35 (59.3)	0.040
Perineural invasion ^{a)}	47 (24.7)	34 (48.6)	< 0.001
Adjuvant treatment	68 (34.2)	39 (53.4)	0.005
Recurrence ^{a)}	63 (33.7)	45 (63.4)	< 0.001

Values are presented as mean ± standard deviation or number (%).

FB-GBC, gallbladder cancer in the fundus/body; NC-GBC, gallbladder cancer in the neck/cystic duct; BMI, body mass index; ASA, American Society of Anesthesiologists; ECOG, Eastern Cooperative Oncology Group; PTGBD, percutaneous transhepatic gallbladder drainage; SC, simple cholecystectomy; LND, lymph node dissection; ICPN, intracholecystic papillary neoplasm; WHO, World Health Organization.

^{a)}The total sample size may not equate to the breakdown because of missing data.

^{b)}Major liver resection is defined as liver resection ≥ 3 hepatic segments.

the creation of 74 pairs of patients. After conducting PSM, both groups became more balanced, and there were no significant differences in parameters between the groups, except for the

rates of laparoscopic surgery (63.5% vs. 45.2%, $p = 0.026$) and bile duct resection (9.5% vs. 35.1%, $p < 0.001$). Further, the NC-GBC group showed a lower R0 resection rate (73.0% vs. 89.2%, $p = 0.012$), and a higher incidence of perineural invasion (42.3% vs. 24.6%, $p = 0.027$) and recurrence rate (66.7% vs. 36.4%, $p < 0.001$).

Even after adopting PSM, the survival outcomes between the two groups were still different; the 5-year OS rate was 74.3% (mean 103.0 ± 7.7 months) in the FB-GBC group and 44.1% (mean 61.7 ± 6.8 months) in the NC-GBC group, and the 5-year DFS rate was 58.3% (mean 84.6 ± 8.1 months) in the FB-GBC group and 21.6% (mean 41.0 ± 5.8 months) in the NC-GBC group. These OS and DFS differences had statistical significance ($p = 0.002$, $p < 0.001$) (Fig. 5).

Independent factors associated with survival in patients with GBC

Multivariate analysis was carried out to determine whether the tumor location of GBC was an independent prognostic factor, since we confirmed that the NC-GBC group had worse survival outcomes than the FB-GBC group. Table 4 shows the correlations between clinicopathological parameters and OS for all the patients. In univariate analysis, many parameters, including NC-GBC, were significantly associated with a worse prognosis. However, the tumor location of NC (HR: 1.03; 95% CI: 0.59–1.77; $p = 0.919$) was not a significant factor related to OS in the multivariate analysis of patients with all stages. Pre-operative elevated serum CA 19-9 (HR: 1.96; 95% CI: 1.21–3.18; $p = 0.006$), non-R0 resection (HR: 3.21; 95% CI: 1.85–5.57; $p < 0.001$), and lymph node metastasis (HR: 1.98; 95% CI: 1.16–3.39; $p = 0.012$) were identified as independent prognostic factors in multivariate analysis.

DISCUSSION

We chose criteria for the anatomical division of the gallbladder established by the Japanese Society of Hepato-Biliary-Pancreatic Surgery [7]. According to the guidelines of this society, the anatomical parts of the gallbladder are classified into the fundus, body, neck (including infundibulum), and cystic duct. Multicenter data on the prognostic impact of GBC location was collected from postoperative histopathologic reports. Histologically, the gallbladder neck is characterized by the presence of tubulo-alveolar mucus glands, and is located adjacent to the cystic duct [11]. The body division refers to the section distal to the neck, and does not contain mucus glands. The ratio of FB-GBC (n = 282) to NC-GBC (n = 90) in this multicenter dataset was approximately 3:1, which was similar to the ratios observed in the pilot study (FB-GBC, n = 58 vs. NC-GBC, n = 19). Until recently, it was believed that FB-GBC had a poorer prognosis than NC-GBC, due to delayed symptom manifestation. Contrary to expectations, the present study found that NC-GBC had a higher recurrence rate and worse survival rates, com-

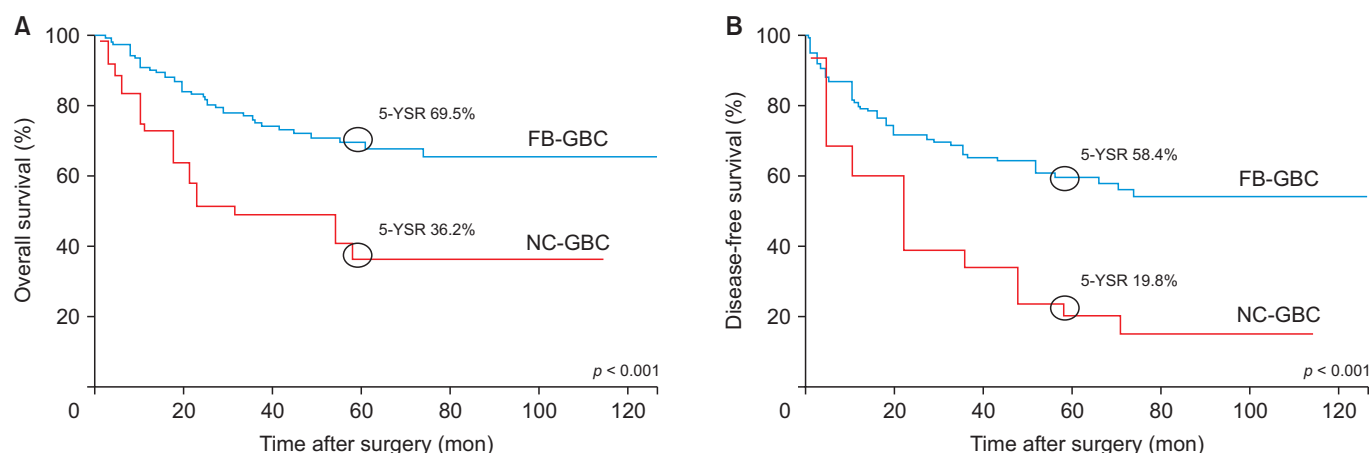


Fig. 4. Overall survival (A) and disease-free survival (B) of FB-GBC and NC-GBC for the patients with pT2–4 stages (n = 272). Similar to the survival outcomes in patients with all stages, the 5-year overall survival rate (69.5% vs. 36.2%, $p < 0.001$) and disease-free survival rate (58.4% vs. 19.8%, $p < 0.001$) were significantly higher in the FB-GBC patients. FB-GBC, gallbladder cancer in the fundus/body; NC-GBC, gallbladder cancer in the neck/cystic duct; 5-YSR, 5-year survival rate.

Table 3. Demographic and clinicopathological characteristics of the patients after propensity score matching (n = 148)

	FB-GBC (n = 74)	NC-GBC (n = 74)	p-value
Age (yr)	69.2 ± 10.4	68.8 ± 9.5	0.812
Female sex	43 (58.1)	43 (58.1)	> 0.999
BMI	24.1 ± 3.6	24.0 ± 3.7	0.995
ASA class < 3 ^a	61 (91.0)	64 (90.1)	0.856
ECOG status < 2 ^a	57 (86.4)	65 (91.5)	0.331
Acute cholecystitis	20 (27.0)	22 (29.7)	0.715
PTGBD insertion	7 (9.5)	9 (12.2)	0.597
Symptomatic GBC ^a	56 (75.6)	63 (85.1)	0.247
CA 19-9 ≥ 37.0 (U/mL) ^a	17 (26.2)	25 (38.5)	0.134
Laparoscopic approach	47 (63.5)	33 (45.2)	0.026
2nd look operation	16 (21.6)	15 (20.3)	0.840
Bile duct resection	7 (9.5)	26 (35.1)	< 0.001
Surgical extent			0.109
SC only	16 (21.6)	15 (20.3)	
SC + LND	10 (13.5)	11 (14.9)	
Wedge resection	39 (52.7)	26 (35.1)	
S4b + 5 segmentectomy	9 (12.2)	14 (18.9)	
Major liver resection ^b	0 (0.0)	8 (10.8)	
Tumor size (mm)	28.8 ± 14.6	33.3 ± 25.8	0.196
R0 resection	66 (89.2)	54 (73.0)	0.012
Lymphovascular invasion ^a	29 (39.7)	32 (44.4)	0.565
Perineural invasion ^a	17 (24.6)	30 (42.3)	0.027
Adjuvant treatment	24 (32.4)	34 (45.9)	0.092
Recurrence ^a	24 (36.4)	42 (66.7)	< 0.001

Values are presented as mean ± standard deviation or number (%).

FB-GBC, gallbladder cancer in the fundus/body; NC-GBC, gallbladder cancer in the neck/cystic duct; BMI, body mass index; ASA, American Society of Anesthesiologists; ECOG, Eastern Cooperative Oncology Group; PTGBD, percutaneous transhepatic gallbladder drainage; SC, simple cholecystectomy; LND, lymph node dissection.

^aThe total sample size may not equate to the breakdown because of missing data.

^bMajor liver resection is defined as liver resection ≥ 3 hepatic segments.

pared to FB-GBC. Not only that, the rate of symptomatic GBC was comparable between both groups in the analysis of all patients (76.9% vs. 84.8%, $p = 0.142$). The authors believe that the following two reasons indirectly contributed to these results. First, NC-GBC is anatomically close to major hepatic vascular structures and the EHBD, and adjacent to neural systems and lymphatic pathways [12,13]. Second, early detection of FB-GBC can be feasible through advanced radiological technology and proactive regular checkups, even in the absence of symptoms. Based on these factors, FB-GBC had a more favorable prognosis than previously believed.

Although a clear difference in oncological outcomes between the groups was identified, the longitudinal tumor location of GBC was not demonstrated to be an independent prognostic factor. On the other hand, elevated preoperative CA 19-9 levels, lymph node metastasis, and non-R0 resection were found to be independent prognostic factors in multivariate analysis, and these three were characteristics of the NC-GBC group. Therefore, the direct and strong cause of the poor prognosis of the NC-GBC group was not the longitudinal tumor location, but the low R0 resection rate, and the high frequency of lymph node metastasis. Moreover, after conducting PSM, low R0 resection rate was the most salient feature of the NC-GBC group.

R0 resection rates were significantly different between the two groups (94.3% FB-GBC vs. 75.6% NC-GBC in all patients, $p < 0.001$). Surgical radicality for GBC is a well-known prognostic factor, and this study also proved it. R1 resection, indicating the presence of microscopic residual tumor, may occur more frequently in cases of NC-GBC, due to various causes. Positive resection margins, including radial and vascular margins, were more frequently identified in NC-GBC, due to the anatomical proximity of the NC of the gallbladder to the EHBD, right hepatic artery, and portal vein. Most surgeons

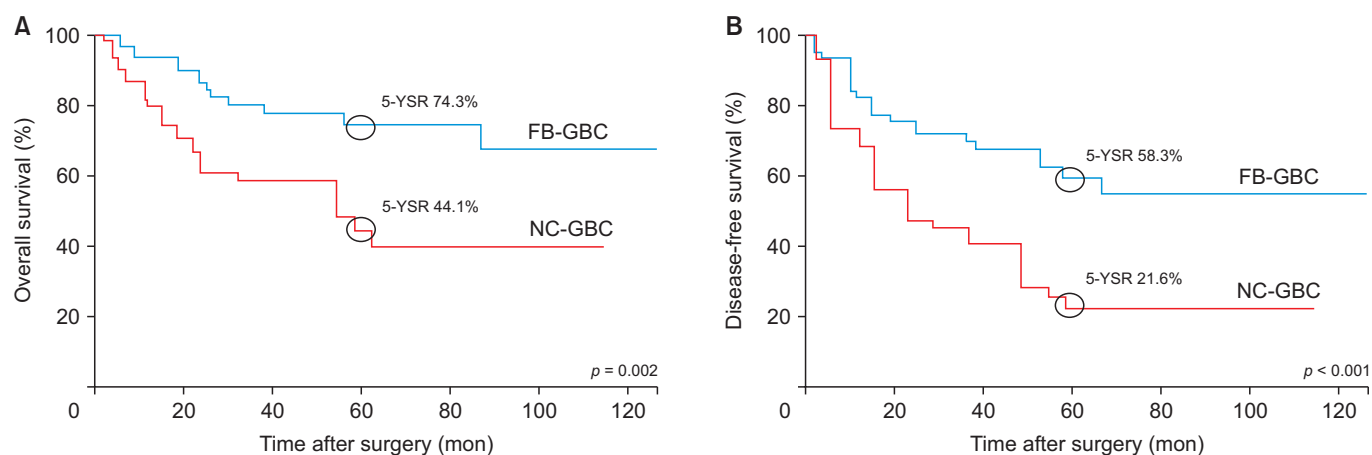


Fig. 5. Overall survival (A) and disease-free survival (B) of FB-GBC and NC-GBC after propensity score matching ($n = 148$). Even after adopting propensity score matching, the survival outcomes between the two groups were still significantly different; the 5-year overall survival rate (74.3% vs. 44.1%, $p = 0.002$) and disease-free survival rate (58.3% vs. 21.6%, $p < 0.001$) were lower in the NC-GBC group. FB-GBC, gallbladder cancer in the fundus/body; NC-GBC, gallbladder cancer in the neck/cystic duct; 5-YSR, 5-year survival rate.

Table 4. Univariate and multivariate Cox regression model analysis of the OS for all the patients ($n = 372$)

Variable	Univariate analysis			Multivariate analysis		
	HR	95% CI	p -value	HR	95% CI	p -value
NC-GBC	2.51	1.72–3.64	< 0.001	1.03	0.59–1.77	0.919
Age ≥ 70 yr	1.57	1.08–2.26	0.017	1.06	0.65–1.70	0.819
Female sex	1.31	0.91–1.89	0.142			
ASA class ≥ 3	1.64	1.04–2.60	0.034	0.70	0.31–1.53	0.689
ECOG performance state ≥ 2	1.27	0.76–2.12	0.348			
Preoperative CA 19-9 ≥ 37.0 (U/mL)	3.55	2.35–5.35	< 0.001	1.96	1.21–3.18	0.006
Acute cholecystitis (+)	1.17	0.78–1.75	0.442			
Tumor size ≥ 30 mm	1.60	1.11–2.30	0.011	0.97	0.59–1.60	0.928
Poor histologic grade, G3–4	2.34	1.48–3.72	< 0.001	1.72	0.98–3.01	0.059
Non-R0 resection	5.75	3.66–9.01	< 0.001	3.21	1.85–5.57	< 0.001
Advanced pT-stage, T3–4	3.53	2.35–5.30	< 0.001	1.55	0.87–2.78	0.135
Lymph node metastasis (+)	2.56	1.70–3.87	< 0.001	1.98	1.16–3.39	0.012
Lymphovascular invasion (+)	2.51	1.74–3.61	< 0.001	1.05	0.56–1.95	0.883
Perineural invasion (+)	2.88	1.94–4.29	< 0.001	0.74	0.41–1.31	0.300
Adjuvant treatments (+)	2.44	1.70–3.51	< 0.001	1.54	0.93–2.57	0.095

OS, overall survival; HR, hazard ratio; CI, confidence interval; NC-GBC, gallbladder cancer in the neck/cystic duct; ASA, American Society of Anesthesiologists; ECOG, Eastern Cooperative Oncology Group.

routinely perform a frozen section examination of the resection margin of the cystic duct stump during the operation. While frozen biopsy exhibits high sensitivity and specificity, its accuracy is not 100%, due to factors such as chronic/acute inflammation, skipped lesions, and contamination from carcinomatous tissue.

Positive regional lymph nodes were more frequent in the NC-GBC group (32.2% vs. 18.1%, $p = 0.004$) before PSM, and were an independent prognostic factor. Many authors have studied lymphatic pathways around the gallbladder: the cholecysto-ret-

ropancreatic, cholecysto-celiac, and cholecysto-mesenteric pathways [12,14]. The cystic and pericholedochal lymph nodes serve as important sentinel stations for the spread of cancer to distant regional lymph nodes through the cholecysto-celiac pathway. NC-GBC, near these sentinel nodes, may have a higher risk of recurrence and a worse prognosis, compared to FB-GBC.

In this study, elevated serum CA 19-9 level was an independent factor for prognosis, and more frequent in the NC-GBC group. Several authors have described associations between

elevated CA 19-9 and poor prognosis in bile duct or other malignancies, using a variety of value criteria or measurement techniques [15,16]. Hatzaras et al. [16] explained that CA 19-9 was an independent predictor of survival, and elevated levels above the upper limit of normal (> 35 U/mL) were correlated with poor survival, even after surgical resection.

In the present study, the rates of bile duct resection (35.1% vs. 9.5%, $p < 0.001$) and positive perineural invasion (42.3% vs. 24.6%, $p = 0.027$) were higher in the NC-GBC group. Invasion into the EHBD in GBC is associated with a poorer survival, and is commonly observed in advanced T- and N-stage tumors with perineural invasion [11,17,18]. While the neural network in the hepatoduodenal ligament is complicated, and has not been extensively characterized, it includes abundant autonomic nerve networks, particularly around the hepatic artery and portal vein [12]. Lv et al. [13] mentioned that postoperative adjuvant chemotherapy clearly improves survival in GBC patients with positive perineural invasion who have undergone resection. Kaneoka et al. [19] suggested that when GBC has spread to the cystic duct, there is a potential risk of infiltration into the hepatoduodenal ligament. Finally, direct involvement of the hepatoduodenal ligament or jaundice in advanced GBC predicts a poor prognosis, despite aggressive curative intent surgery [18,20].

In the current study, adjuvant treatments were administered more frequently after surgery for NC-GBC than for FB-GBC. The recent guidelines from the National Comprehensive Cancer Network recommend adjuvant chemotherapy and/or chemoradiation for patients with margin positive disease or lymph node metastases. A consensus statement for GBC suggests that patients with preoperatively staged T3–4 and/or N1 GBC should be considered as potential candidates for clinical trials investigating the effectiveness of neoadjuvant chemotherapy [10]. Leigh et al. [11] recommend that adjuvant treatments should be considered for all neck GBC, regardless of margin status or TNM stage. Many authors have concurred that adjuvant treatments can improve survival in GBC patients [8,10]. In our study, 31.2% of all enrolled cases underwent adjuvant treatments, and the rate of chemoradiation was 19.9%. The rate of chemoradiation in the NC-GBC group was significantly higher than in the FB-GBC group (30.7% vs. 17.0%, $p = 0.002$). This result was attributed to the higher frequency of positive resection margins and lymph node metastasis in the NC-GBC group. To date, there is no established evidence regarding neoadjuvant treatment for advanced GBC; even in this study, there was only one patient in the NC-GBC group.

In another scenario, the obstructive hydropic change of the gallbladder, or the necessity of stent insertion through endoscopic retrograde cholangiopancreatography for Mirizzi syndrome, may lead to pericholecystic inflammation. The likelihood of encountering these situations can be higher in the NC-GBC patients, where acute inflammation results in fragile conditions of tumor spread.

Our study had a few limitations. First, due to the retrospective design and data collection from multiple centers, surgical procedures, such as the extent of lymph node dissection and liver resection, varied among surgeons at different hospitals with their own protocols. Also, adjuvant treatment types, regimens, and durations seem to be heterogeneous among the participating hospitals. In addition, the decision on tumor location may have included subjective opinions from researchers representing each institution. Second, the study included data from seven hospitals in the central region of South Korea only, resulting in a smaller sample size after PSM, despite being a multicenter study. To overcome these limitations of the current study, further prospective research at large scale will be required.

This study showed that NC-GBC had more frequent elevation of preoperative CA 19-9 levels, requirement for more extensive surgery, more advanced histologic grade and tumor stages, more frequent lymphovascular and perineural invasion, lower R0 resection rates, higher recurrence rates, and worse 5-year overall and DFS rates, compared to FB-GBC. While the longitudinal location was not identified as an independent factor associated with the oncological prognosis of GBC, elevation of preoperative serum CA 19-9 levels, lymph node metastasis, and R1 resection were proven to be associated factors. It is advisable for surgeons to strive to achieve R0 resection for NC-GBC by adopting more aggressive surgery. Prospective research on a large scale, such as a national cohort, is needed to assess the correlation between the longitudinal location of GBC, and long-term oncological outcomes.

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CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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