담낭암 성차에 관한 절제가능성 및 조직병리학적 예후−국내 다기관 연구

[1]고려대학교 의과대학 내과학교실, [2]경북대학교 의과대학 내과학교실, [3]전북대학교 의과대학 내과학교실, [4]연세대학교 의과대학 내과학교실, [5]국립암센터 간담도췌장암센터, [6]한림대학교 의과대학 내과학교실, [7]가천대학교 의과대학 내과학교실

박양태[1] · 강진형[1] · 김재선[1] · 정민규[2] · 김성훈[3] · 조재희[4] · 우상명[5] · 이경주[6] · 김의주[7]* · 김효정[1]*

Multi-Center Study on Gender Difference in Resectability and Pathologic Prognosis of Gallbladder Cancer

Yang Tae Park[1], Jinhyong Kang[1], Jae Seon Kim[1], Min Kyu Jung[2], Seong Hun Kim[3], Jae Hee Cho[4], Sang Myung Woo[5], Kyong Joo Lee[6], Eui Joo Kim[7]*, Hyo Jung Kim[1]*

[1]Department of Internal Medicine, Korea University College of Medicine, Seoul; [2]Department of Internal Medicine, Kyungpook National University School of Medicine, Daegu; [3]Department of Internal Medicine, Chonbuk National University Medical School, Jeonju; [4]Department of Internal Medicine, Yonsei University College of Medicine, Seoul; [5]Center for Liver and Pancreatobiliary Cancer, National Cancer Center, Goyang; [6]Department of Internal Medicine, Hallym University College of Medicine, Chuncheon; [7]Department of Internal Medicine, Gachon University College of Medicine, Incheon, Korea

Background/Aim: In gallbladder cancer (GBC), gender differences in incidence and mortality rates have been reported with geographic variation. However, there is little known about sex-related difference in GBC prognosis. This study compares prognostic factors according to gender for GBC.

Methods: We searched clinicopathological factors in all stages of 952 GBC patients from seven medical centers in Korea. A total of 927 patients were enrolled and surgery with curative resection was performed in 499 patients.

Results: Carbohydrate antigen (≥37 U/mL) was a significant prognostic factor in both females and males (odd ratio [OR], 4.30; 95% confidence interval [CI], 3.13-5.89; $p<0.001$). Age was a significant factor only in female patients, elderly patients were associated with low resectability and the likelihood of T-stage >2; an independent predictor of poor prognosis via multivariate analysis (OR, 1.03; 95% CI, 1.01-1.05; $p=0.005$, OR, 1.05; 95% CI, 1.02-1.08; $p=0.002$). Body mass index (BMI) also showed gender difference, and lower BMI (≤25 kg/m^2) was the significant good indicator of multivariate analysis for lymph node metastasis in female patients (OR, 0.42; 95% CI, 0.23-0.77; $p=0.005$) but, the significant poor indicator of univariate analysis for advanced T-stage in male (OR, 2.79; 95% CI, 1.40-5.54; $p=0.003$).

Conclusions: These results suggest that there is a possibility of gender difference in GBC prognosis. Age and high BMI were poor prognostic factors for curative resection for female GBC patients.

Korean J Pancreas Biliary Tract 2022;27(3):121-127

Keywords: Gender; Age factors; Body mass index; CA-19-9 antigen; Bilirubin

Corresponding author : Eui Joo Kim

Division of Gastroenterology, Department of Internal Medicine, Gachon University Gil Medical Center, Gachon University College of Medicine, 21 Namdong−daero 774beon−gil, Namdong−gu, Incheon 21565, Korea
Tel. +82−32−460−3778 Fax. +82−32−460−3408
E−mail: imetkim@gilhospital.com
ORCID: https://orcid.org/0000−0001−5573−7083

Corresponding author : Hyo Jung Kim

Division of Gastroenterology, Department of Internal Medicine, Korea University Guro Hospital, Korea University College of Medicine, 148 Gurodong−ro, Guro−gu, Seoul 08308, Korea
Tel. +82−2−2626−1779 Fax. +82−2−2626−1770
E−mail: hjkimmd@korea.ac.kr
ORCID: https://orcid.org/0000−0003−3284−3793

*Eui Joo Kim and Hyo Jung Kim contributed equally to this work as corresponding authors.

INTRODUCTION

Gallbladder cancer (GBC) is one of the common biliary tract cancer and the worldwide occurrence of GBC is less than 2/100,000 individuals and there is considerable variation in this number based on geographic distribution and gender.[1] The lowest rates of GBC incidence are found in the United States, Western, and Mediterranean European countries, while the highest incidence rates are found in India, Pakistan, Latin America, and Asia.[2,3] Age-standardized incidence and mortality rates are higher in females worldwide (1.4 and 1.0 per 100,00 females, and 0.9 and 0.7 per 100,000 males).[4] The Korea Central Cancer Registry (KCCR), a nationwide, hospital-based cancer registry reported that GBC incidence increased exponentially with age and the age-standardized incidence rate (ASR) was similar in both sexes (2.57 per 100,000 in 2017 annual report). However, ASR by age group has been higher in women for younger age groups less than 60 years old.[5] Furthermore, the 5-year cancer relative survival rate was lower in female compared to male patients (25% vs. 26.4%, respectively)

Known risk factors for GBC include the female sex, age >65 years, and longstanding gallstones.[6] Gallstone is one of the strongest risk factors for the development of GBC, and 70% to 90% of GBC patients have gallstones.[7,8] It is well known that estrogens increase the formation of gallstones, mainly by elevating cholesterol levels of bile.[9,10] Therefore, women have a higher incidence of gallstones than males, and have higher incidence of GBC.

Furthermore, in certain regions and countries, female-to-male incidence ratios were generally around 3, but ranged from 1 in Far East Asia to over 5 in Spain and Colombia.[3] However, the gender impact in GBC is not well understood. Although the risk factors for GBC and environmental, genetic factors are known and studied,[6,10-12] direct comparative studies according to gender have not been conducted well. Thus, this study aimed to study the gender difference in surgical ascpects of GBC prognosis.

METHODS

Patients who were diagnosed with GBC at seven centers in Korea (Korea University Guro Hospital, National Cancer Center, Gachon University Gil Medical Center, Yonsei University Gangnam Severance Hospital, Wonju Severance Christian Hospital, Kyungpook National University Hospital, Chonbuk National University Hospital) between January 2006 and January 2020 were included retrospectively. Clinical data of patients at the time of diagnosis including sex, age, body mass index (BMI), bilirubin, carbohydrate antigen 19-9 (CA 19-9), and surgical treatment were retrieved by reviewing electronic medical records.

To identify independent prognostic factors, each factor (Age, BMI, CA 19-9, Bilirubin) was categorized. BMI category was classified into BMI >25 kg/m^2 or $\leq$25 kg/m^2. Normal reference values for CA 19-9 were less than 37 U/mL and it was categorized CA 19-9 <37 U/mL vs. 37 U/mL $\leq$CA 19-9. Bilirubin was categorized bilirubin <2 mg/dL vs. 2 mg/dL $\leq$Bilirubin.

In patients where surgery with curative intent was possible, T stage, and N stage were also reviewed. T stage was categorized T-stage $\leq$2 vs. T-stage >2 to reflect the clinical outcome of patients with surgically treated GBC. The N category was classified into N0 or node metastases.

Unresectability was defined as the cases who are not eligible for curative-intent surgery because of advanced tumor extent. Cases who surgery was not performed due to refusal of surgery for severe comorbidity were excluded. Cases who surgery was not performed due to refusal of surgery for severe comorbidity were excludedThis study was approved by the Institutional Review Board of KUGH (Accession No. 2020GR1781).

We performed a univariate and multivariate logistic regression analysis. For the univariate analyses, the categorical variables were compared using the Wald chi square tests and the Fisher's scoring test, and those variables with p-values. Statistical analysis was performed using SAS version 9.3 (SAS Institute, Cary, NC, USA) and statistical significance was set at p<0.05.

RESULTS

1. Baseline characteristics of GBC patients

A total of 927 patients were enrolled and 521 patients (56.2%)

were female. Two hundred ninety two patients (31.5%) of 927 patients less than 65 years old. Baseline characteristics were mostly similar for female and male patients, except for BMI (p=0.034). Median BMI at the time of diagnosis was 23.6 kg/m^2, and females and males were 23.8 kg/m^2 and 23.3 kg/m^2, respectively. 281 patients (30.3%) had BMI over 25 kg/m^2; females and males in this group numbered 175 (34.1%) and 106 (26.4%), respectively, more females than males were overweight. As for normal bilirubin (less than <2), normal CA 19-9 (less than 37 U/mL), there was no statistical difference between females and males (Table 1).

2. Predicting factors of unresectability

In total 927 patients, four cases refused the surgery for severe comorbidity and surgical resection was possible in 499 patients, 53.5% (279/521) in female and 54.2% (220/406) in male. In multivariate analysis of total 927 patients, age (OR, 1.02 [1.00-1.03]; p=0.007), Bilirubin of 2 mg/dL or more (OR, 3.58 [2.37-5.41], p<0.001), CA 19-9 of 37 U/mL or more (OR, 4.30 [3.13-5.89], p<0.001) were identified as independent factors predicting unresectability (Table 2).

In male patients, abnormal bilirubin (OR, 2.36 [1.32-4.20], p=0.003) and CA 19-9 (OR, 4.69 [2.92-7.52], p<0.001) were

Table 1. Baseline characteristics of gallbladder cancer

Variable	Total (n=927)	Male (n=406)	Female (n=521)	*p*-value
Age (years)	69.6±10.5	69.1±9.8	70.0±11.0	0.163
Height (cm)	157.9±8.9	164.9±6.2	152.4±6.5	<0.001
Weight (kg)	59.0±10.7	63.7±10.3	55.3±9.6	<0.001
BMI (kg/m^2)	23.6±3.4	23.3±3.0	23.8±3.7	0.034
BMI (≤25 kg/m^2)	281 (30.3)	106 (26.4)	175 (34.1)	0.014
Normal bilirubin	723 (78.0)	313 (77.9)	410 (80.2)	0.492
Normal CA 19-9	422 (45.5)	178 (50.4)	244 (52.2)	0.720

Values are presented as number (%) or mean±standard deviation.
BMI, body mass index; CA 19-9, carbohydrate antigen 19-9.

Table 2. Univariate and multivariate analysis of the factors predicting unresectability (total)

Variable	Univariate analysis		Multivariate analysis	
	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
Age	1.02 (1.01-1.03)	<0.001	1.02 (1.00-1.03)	0.007
BMI (≤25 kg/m^2)	1.70 (1.27-2.27)	<0.001	1.34 (0.95-1.89)	0.087
Bilirubin (≥2 mg/dL)	5.07 (3.52-7.29)	<0.001	3.58 (2.37-5.41)	<0.001
CA 19-9 (≥37 U/mL)	5.25 (3.89-7.07)	<0.001	4.30 (3.13-5.89)	<0.001

OR, odds ratio; CI, confidence interval; BMI, body mass index; CA 19-9, carbohydrate antigen 19-9.

Table 3. Univariate and multivariate analysis of the factors predicting unresectability (male)

Variable	Univariate analysis		Multivariate analysis	
	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
Age	1.01 (0.99-1.03)	0.206		
BMI (≤25 kg/m^2)	1.80 (1.13-2.85)	0.012	1.33 (0.77-2.28)	0.293
Bilirubin (≥2 mg/dL)	3.79 (2.27-6.31)	<0.001	2.36 (1.32-4.20)	0.003
CA 19-9 (≥37 U/mL)	5.59 (3.54-8.83)	<0.001	4.69 (2.92-7.52)	<0.001

OR, odds ratio; CI, confidence interval; BMI, body mass index; CA 19-9, carbohydrate antigen 19-9.

independent factors predicting unresectability. However, age was not associated with resectability in male (Table 3). Conversely, age (OR, 1.02 [1.00-1.04], p=0.031), bilirubin (OR, 5.47 [2.97-10.07], p<0.001) and CA 19-9 (OR, 3.81 [2.50-5.81], p<0.001) were factors of predicting unresectability in female patients (Table 4).

Furthermore comparison of two groups with age <65 years (292 patients) vs. 65 years ≤age (635 patients), age factor was not associated in both sex of younger group, but it was a predicting factor of unresectability only in elderly female group (OR, 1.05 [1.004-1.088], p=0.03).

3. Pathologic prognostic factors in resected patients

Subgroup analysis was done in 499 patients whose surgical resection was performed with curative intent. In all patients, multivariate analysis for the factors predicting T-stage >2 showed that age, abnormal bilirubin and CA 19-9 were statistically significant as independent factors, age (OR, 1.03 [1.01-1.05], p=0.005) and CA 19-9 (OR, 2.68 [1.71-4.19], p<0.001) (Table 5). In male patients, BMI, bilirubin and CA 19-9 were identified as predictive factors of T-stage >2 in univariate analysis. However, in multivariate analysis, only CA 19-9 (OR, 3.12 [1.59-6.13], p=0.001) was an independent factor predicting T state >2 (Table 6). In female patients, age, bilirubin and CA 19-9 were identified as

Table 4. Univariate and multivariate analysis of the factors predicting unresectability (female)

Variable	Univariate analysis		Multivariate analysis	
	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
Age	1.03 (1.01-1.04)	<0.001	1.02 (1.00-1.04)	0.031
BMI (≤25 kg/m^2)	1.65 (1.13-2.39)	0.008	1.39 (0.89-2.16)	0.147
Bilirubin (≥2 mg/dL)	6.73 (3.96-11.42)	<0.001	5.47 (2.97-10.07)	<0.001
CA 19-9 (≥37 U/mL)	5.00 (3.37-7.42)	<0.001	3.81 (2.50-5.81)	<0.001

OR, odds ratio; CI, confidence interval; BMI, body mass index; CA 19-9, carbohydrate antigen 19-9

Table 5. Univariate and multivariate analysis of the factors predicting T stage >2 (total)

Variable	Univariate analysis		Multivariate analysis	
	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
Age	1.03 (1.01-1.05)	0.004	1.03 (1.01-1.05)	0.005
BMI (≤25 kg/m^2)	1.47 (0.98-2.22)	0.061		
Bilirubin (≥2 mg/dL)	3.24 (1.74-6.01)	<0.001	2.08 (1.04-4.16)	0.038
CA 19-9 (≥37 U/mL)	2.97 (1.93-4.57)	<0.001	2.68 (1.71-4.19)	<0.001

OR, odds ratio; CI, confidence interval; BMI, body mass index; CA 19-9, carbohydrate antigen 19-9

Table 6. Univariate and multivariate analysis of the factors predicting T stage >2 (male)

Variable	Univariate analysis		Multivariate analysis	
	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
Age	1.02 (0.99-1.05)	0.201		
BMI (≤25 kg/m^2)	2.79 (1.40-5.54)	0.003	2.08 (0.99-4.38)	0.053
Bilirubin (≥2 mg/dL)	2.29 (1.00-5.25)	0.050	1.59 (0.64-3.95)	0.314
CA 19-9 (≥37 U/mL)	3.32 (1.73-6.40)	>0.001	3.12 (1.59-6.13)	0.001

OR, odds ratio; CI, confidence interval; BMI, body mass index; CA 19-9, carbohydrate antigen 19-9.

predictive factors of T-stage >2 in univariate analysis. However, age (OR, 1.05 [1.02-1.08], p=0.002) and CA 19-9 (OR, 2.44 [1.31-4.56], p=0.005) were identified in multivariate analysis (Table 7).

Regarding lymph node metastasis, among the all patients who were eligible for surgery, high BMI (OR, 0.56 [0.56-0.87], p=0.011), abnormal bilirubin (OR, 2.27 [1.12-4.58], p=0.022),

and CA 19-9 (OR, 2.26 [1.43-3.56], p<0.001) were significant factors in multivariate analysis (Table 8). These factors were significant in female, BMI (OR, 0.42 [0.23-0.77], p=0.005), Bilirubin (OR, 5.55 [1.56-19.67], p=0.008), and CA 19-9 (OR, 2.97 [1.60-5.53], p=0.001) (Table 9). Meanwhile there was no significant factor related to the possibility of lymph node metastasis

Table 7. Univariate and multivariate analysis of the factors predicting T stage >2 (female)

Variable	Univariate analysis		Multivariate analysis	
	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
Age	1.04 (1.01-1.06)	0.006	1.05 (1.02-1.08)	0.002
BMI (≤25 kg/m^2)	0.95 (0.56-1.61)	0.854		
Bilirubin (≥2 mg/dL)	4.93 (1.89-12.87)	0.001	2.65 (0.88-7.98)	0.082
CA 19-9 (≥37 U/mL)	2.75 (1.55-4.88)	0.001	2.44 (1.31-4.56)	0.005

OR, odds ratio; CI, confidence interval; BMI, body mass index; CA 19-9, carbohydrate antigen 19-9

Table 8. Univariate and multivariate analysis of the factors predicting N metastasis (total)

Variable	Univariate analysis		Multivariate analysis	
	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
Age	1.03 (1.01-1.04)	0.011	1.02 (1.0-1.04)	0.057
BMI (≤25 kg/m^2)	0.63 (0.43-0.94)	0.027	0.56 (0.36-0.87)	0.011
Bilirubin (≥2 mg/dL)	2.66 (1.44-4.92)	0.002	2.27 (1.12-4.58)	0.022
CA 19-9 (≥37 U/mL)	2.52 (1.63-3.88)	<0.001	2.26 (1.43-3.56)	>0.001

OR, odds ratio; CI, confidence interval; BMI, body mass index; CA 19-9, carbohydrate antigen 19-9.

Table 9. Univariate and multivariate analysis of the factors predicting N metastasis (female)

Variable	Univariate analysis		Multivariate analysis	
	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
Age	1.03 (1.00-1.05)	0.041	1.02 (1.00-1.05)	0.111
BMI (≤25 kg/m^2)	0.52 (0.31-0.87)	0.014	0.42 (0.23-0.77)	0.005
Bilirubin (≥2 mg/dL)	4.56 (1.75-11.90)	0.002	5.55 (1.56-19.67)	0.008
CA 19-9 (≥37 U/mL)	3.47 (1.96-6.13)	<0.001	2.97 (1.60-5.53)	0.001

OR, odds ratio; CI, confidence interval; BMI, body mass index; CA 19-9, carbohydrate antigen 19-9.

Table 10. Univariate and multivariate analysis of the factors predicting N metastasis (male)

Variable	Univariate analysis		Multivariate analysis	
	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
Age	1.02 (0.99-1.05)	0.127		
BMI (≤25 kg/m^2)	0.89 (0.47-1.67)	0.721		
Bilirubin (≥2 mg/dL)	1.86 (0.79-4.38)	0.154		
CA 19-9 (≥37 U/mL)	1.61 (0.82-3.17)	0.163		

OR, odds ratio; CI, confidence interval; BMI, body mass index; CA 19-9, carbohydrate antigen 19-9.

could be found in male patients (Table 10).

DISCUSSION

We compared the predicting factors for curative resection for GBC in each gender. CA 19-9 was a significant prognostic factor in both sexes, but age factor showed a gender difference. Age was not a significant factor in male patients but elderly female patients more than 65 years old showed the risk for surgical resection.

In this study, we analyzed pathologic data, liver involvement (T-stage >2) and lymph node metastases as known for significant prognostic factors. Age in female patients was also poor prognostic factors predicting T-stage >2 (OR, 1.05), however, 0.2-3.0% of GBCs are incidentally detected at an early stage via pathologic review of gallbladder resections performed for benign diseases such as gallstones, and have a good prognosis.[13-15] Thus incidental GBC could be common in relatively young female patients, less than 65 years old and old aged female GBC patiwnts might showed the poor prognostic factor, unresectability and advanced T-staging.

Meanwhile, BMI showed conflicting results in both sexes. A lower BMI (≤ 25 kg/m^2) was the significant factor for N0 staging in female patients, but lower BMI was the significant factor for advanced T staging in male, although it was significant only in univariate analysis. Even if it was judged that a patient could be operated on, a lower BMI at the time of diagnosis, was associated with a less possibility of having lymph node metastasis after operation in female patients, but high possibility of having T-stage >2 in male patients. These results suggest that there is a possibility of gender difference in GBC prognosis.

It is known that incidence rates have heterogeneity in geographic distribution and gender. Therefore, a study on the clinical factors associated with prognosis are required for survival improvement. A recent study reported the trend of GBC incidence and survival in Korea, but there has been no large study evaluating the prognosis and gender difference in GBC until now. Thus, this study provides a foundation for future GBC studies.

This study has several strengths. First, this is a large multi-center study including over nine-hundred patients and about five-hundred surgical patients. Third, multi-center results were obtained from six provinces for the bias of geographical variation within Korea.

Lastly, there are a few limitations in this study. First, there was no data for survival evidence. It was very difficult to obtain past information retrospectively, because the last follow-up date or the date of death concludes the personal information. Second, there was no data on gallstone as a risk factor for GBC. Gallstone could be best detected via US (ultrasound) exam, but imaging methods used in GBC diagnosis were computed tomography or magnetic resonance imaging in this study. In conclusion, age and high BMI were poor prognostic factors for curative resection for female GBC patients and these results suggest that there is a possibility of gender difference in GBC prognosis.

요 약

배경/목적: 담낭암의 발생률 및 암사망률에 있어서 성차(gender difference)가 지역적 차이를 보인다고 보고되어 있으나 담낭암 예후에서의 성차 연구는 잘 알려져 있지 않다. 본 연구는 담낭암의 절제 가능성과 수술 병리학적 예후를 성차에 따라 비교해 보고자 하였다.

방법: 7개 국내 다기관 총 927명의 담낭암 환자들을 대상으로 진단 당시 나이, BMI, CA 19-9, bilirubin, 영상 검사 판독 소견 및 499명의 수술 병리 결과를 후향적으로 분석하였다.

결과: CA 19-9 (≥37 U/mL)는 남녀 모두에서 절제가능성에 대한 의미 있는 예후 인자였다(odd ratio [OR], 4.30; 95% confidence interval [CI], 3.13-5.89; $p<0.001$). 나이는 남성에서는 통계적 유의성은 없었으나 여성에서는 절제불가능과 T-stage >2의 병리 결과의 통계적으로 유의한 예측 인자였다(OR, 1.03; 95% CI, 1.01-1.05; $p=0.005$, OR, 1.05; 95% CI, 1.02-1.08; $p=0.002$). BMI는 남녀에서 상반된 결과를 보였으며 25 kg/m2 이하의 낮은 BMI는 여성에서는 LN metastasis가 없을 가능성에 대한 예후 인자였으나(OR, 0.42; 95% CI, 0.23-0.77; $p=0.005$) 남성에서는 univariate analysis에서만 T-stage >2 이상의 예후를 예측하는 인자였다(OR, 2.79; 95% CI, 1.40-5.54; $p=0.003$).

결론: 진단 당시 나이와 high BMI는 여성에서 담낭암의 절제가능성 및 수술병리 결과의 나쁜 예후 인자였으며 이러한 남녀 차이는 국내 담낭암 환자의 예후에 성차가 있음을 제시한다.

국문 색인: 성차; 나이; 체질량지수; CA 19-9; 빌리루빈

Conflicts of Interest

The authors have no conflicts to disclose.

ORCID

Yang Tae Park   https://orcid.org/0000-0003-3588-8073

Jinhyong Kang   https://orcid.org/0000-0002-9404-1537

Jae Seon Kim   https://orcid.org/0000-0002-2012-6781

Min Kyu Jung   https://orcid.org/0000-0001-8749-408X

Seong Hun Kim   https://orcid.org/0000-0002-7592-8060

Jae Hee Cho   https://orcid.org/0000-0003-4174-0091

Sang Myung Woo   https://orcid.org/0000-0003-3786-4403

Kyong Joo Lee   https://orcid.org/0000-0002-9175-9164

Eui Joo Kim   https://orcid.org/0000-0001-5573-7083

Hyo Jung Kim   https://orcid.org/0000-0003-3284-3793

REFERENCES

1. Shaffer EA. Gallbladder cancer: the basics. Gastroenterol Hepatol (N Y) 2008;4:737-741.

2. Hundal R, Shaffer EA. Gallbladder cancer: epidemiology and outcome. Clin Epidemiol 2014;6:99-109.

3. Randi G, Franceschi S, La Vecchia C. Gallbladder cancer worldwide: geographical distribution and risk factors. Int J Cancer 2006;118:1591-1602.

4. Ferlay J, Colombet M, Soerjomataram I, et al. Cancer statistics for the year 2020: an overview. Int J Cancer 2021;149:778-789.

5. Korea National Cancer. KNCI (Korea National Cancer Incidence) Database.

6. Lazcano-Ponce EC, Miquel JF, Muñoz N, et al. Epidemiology and molecular pathology of gallbladder cancer. CA Cancer J Clin 2001;51:349-364.

7. Hsing AW, Gao YT, Han TQ, et al. Gallstones and the risk of biliary tract cancer: a population-based study in China. Br J Cancer 2007;97:1577-1582.

8. Paraskevopoulos JA, Dennison AR, Ross B, Johnson AG. Primary carcinoma of the gallbladder: a 10-year experience. Ann R Coll Surg Engl 1992;74:222-224.

9. Everson GT, McKinley C, Kern F Jr. Mechanisms of gallstone formation in women. Effects of exogenous estrogen (Premarin) and dietary cholesterol on hepatic lipid metabolism. J Clin Invest 1991;87:237-246.

10. Sharma A, Sharma KL, Gupta A, Yadav A, Kumar A. Gallbladder cancer epidemiology, pathogenesis and molecular genetics: recent update. World J Gastroenterol 2017;23:3978-3998.

11. Goetze TO. Gallbladder carcinoma: prognostic factors and therapeutic options. World J Gastroenterol 2015;21:12211-12217.

12. Wang F, Wang B, Qiao L. Association between obesity and gallbladder cancer. Front Biosci (Landmark Ed) 2012;17:2550-2558.

13. Romano F, Franciosi C, Caprotti R, et al. Laparoscopic cholecystectomy and unsuspected gallbladder cancer. Eur J Surg Oncol 2001;27:225-228.

14. Toyonaga T, Chijiiwa K, Nakano K, et al. Completion radical surgery after cholecystectomy for accidentally undiagnosed gallbladder carcinoma. World J Surg 2003;27:266-271.

15. Smith GC, Parks RW, Madhavan KK, Garden OJ. A 10-year experience in the management of gallbladder cancer. HPB (Oxford) 2003;5:159-166.