

RESEARCH ARTICLE

Comparison of Clinical Outcomes of Incidental and Non-Incidental Gallbladder Cancers: A Single-Center Cross-Sectional Study

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Abstract

Background: Gallbladder cancer (GBC) is a rare malignancy characterized by high invasiveness and poor survival. In a nation-wide cancer survey, the age-standardized incidence rate of GBC was the highest in Jeju Island compared to 15 other provinces in Korea. The purpose of this study was to compare the clinical outcomes of GBC according to the nature of diagnosis, that is, incidental versus non-incidental. **Materials and Methods:** Consecutive patients who were newly diagnosed with GBC at the Digestive Disease Center and Department of Internal Medicine, Cheju Halla General Hospital, between November 2008 and November 2011, were enrolled and divided into 2 groups: incidental gallbladder cancer (IGBC) and non-incidental gallbladder cancer (NIGBC). Clinical outcomes were retrospectively compared between the two groups. **Results:** Seventy-nine patients were enrolled and analyzed in our study. Thirty-three (41.8%) and 46 (58.2%) were identified as IGBC and NIGBC, respectively. The proportions of patients with gallstone disease, gallbladder polyp, and cholecystectomy were significantly different between the two groups. Additionally, the median survival rate was significantly higher for patients with IGBC than for those with NIGBC (11.4, 95% confidence interval, 5.6-13.7 vs 4.0, 95% confidence interval 3.03-5.96 months; $p=0.01$) during a median follow-up period of 5.7 months. **Conclusions:** Patients with IGBC showed better clinical prognosis than those with NIGBC. Therefore, patients with gallstone disease or gallbladder polyps, major predictive risk factors for IGBC, should undergo advanced work-up for chelecystectomy.

Keywords: Gallbladder cancer - incidental - non-incidental - descriptive epidemiology

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Introduction

Gallbladder cancer (GBC) is a rare but highly invasive disease compared to other gastrointestinal malignancies. First described by Maximilian Stoll in 1777, GBC is still considered a highly malignant disease with a poor survival rate (Nevin et al., 1976).

The incidence of GBC varies widely among different geographic regions and ethnic groups, ranging from 1 to 23 per 100,000 individuals (Lazcano-Ponce et al., 2001), and (Randi et al., 2006). India, Pakistan, and Korea are among the countries with the highest incidence of GBC (Randi et al., 2006; Bae, 2012). Because the clinical presentation of early GBC is non-specific, a diagnosis is generally made when patients are at an advanced stage of disease (Henson et al., 1992). The overall mean survival rate associated with advanced GBC is less than 4 months, whereas the 5-year survival rate ranges from 0% to 10% (Misra et al., 2003).

Recently, however, due to a higher number of

laparoscopic cholecystectomies performed, GBC is being detected at earlier stages. Incidental gallbladder cancer (IGBC), which is diagnosed during or after cholecystectomy, has better prognosis than non-incidental gallbladder cancer (NIGBC) (D'Hondt et al., 2013). We examined the clinical characteristics and outcomes of IGBC and compared them to those of NIGBC in patients of Jeju Island where the incidence of GBC is the highest among all provinces in Korea (Bae, 2012).

Materials and Methods

Consecutive patients newly diagnosed with GBC at the Digestive Disease Center and Department of Internal Medicine, Cheju Halla General Hospital, Jeju City, Jeju Special Self-Governing Province, Korea, between November 2007 and November 2011 were enrolled in this study. The diagnosis of GBC was established on the basis of radiologic findings and was further confirmed by histopathology. The radiologic evidence

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of GBC was based on abdominal ultrasonography, contrast-enhanced computed tomography, and magnetic resonance cholangiopancreatography or positron emission tomography-computed tomography, if clinically needed. Pathologic specimens were obtained by ultrasonography-guided needle biopsy or resection of the primary tumor. Cases in which a pathologic confirmation was not possible were diagnosed on the basis of radiologic results and associated clinical follow-up data indicative of GBC.

IGBC was defined as a carcinoma originating from the gallbladder mucosa that was detected during or after cholecystectomy on microscopic observation without suspicion of malignancy before surgery. All other GBCs were defined as NIGBC. Surgery was recommended for all patients with asymptomatic gallstones of more than 1 cm, symptomatic gallstone disease, and calculous cholecystitis. Those with a gallbladder polyp of a large size (≥ 1 cm), sessile shape, or changes in the number, shape, or size during follow-up imaging studies were recommended to undergo prophylactic cholecystectomy.

Demographic data (age, sex, residence, body mass index (BMI), medical history, and underlying morbidities), laboratory and imaging findings, and clinical outcomes (date of death, last follow-up, disease stage, and treatment) were collected on review of our hospital records. Continuous variables are presented as means \pm standard deviation (SD) and categorical variables are presented as a frequency with percentage of RAWs. The Student's t-test was used to determine the statistical difference between groups for continuous variables, and the Pearson chi-square test was used for categorical variables. Cumulative survival was determined using the Kaplan-Meier method, and the difference between two groups was analyzed using the log-rank test. A p value of <0.05 was considered statistically significant. All statistical analyses were performed using SPSS 19.0 software (SPSS, Chicago, Illinois, USA).

This study protocol was approved by the Institutional Review Board of Cheju Halla General Hospital.

Results

Of the 79 patients with GBC, 33 (41.8 %) and 46 (58.2 %) were diagnosed as having IGBC and NIGBC, respectively. The preoperative diagnosis for each case of IGBC is listed in Table 1. The two main reasons for gallbladder resection were gallbladder polyps and gallstones with or without symptoms.

The two groups did not differ significantly in age, sex, medical history, and personal history (Table 2). The number of patients diagnosed at an early stage was higher in the IGBC group than in the NIGBC group. Using the

Table 1. Preoperative Diagnosis of IGBC

Preoperative diagnosis categories	Frequency	%
Acalculous cholecystitis	9	27.3%
Calculous cholecystitis	13	41.9%
Gallbladder polyp	11	41.9%
Total	33	100.00

*IGBC, Incidental Gallbladder Cancer

Table 2. Comparison of Clinical Characteristics and Outcomes between CGBC and NCGBC Groups

N, %	Total		IGBC		NIGBC		p value
	79	100%	33	41.8%	46	58.2%	
Age (year)							
Mean/SD	70.5	11.8	69.3	11.6	71.3	12	0.478
Sex							
Male	22	27.8%	9	27.3%	13	28.3%	0.923
Female	57	72.2%	24	72.7%	33	71.7%	
F:M	2.59		2.67		2.54		
Alcohol							
No	59	74.7%	24	72.7%	35	76.1%	0.369
Yes	17	21.5%	9	27.3%	8	17.4%	
smoking							
No	68	86.1%	30	90.9%	38	82.6%	0.721
Yes	8	10.1%	3	9.1%	5	10.9%	
BMI (Kg/m ²)							
Mean/SD	22.4	3.6	22.7	3.6	22.2	3.5	0.553
No. of Pregnancy							
Mean/SD	4.4	2.2	5.0	2.6	3.9	1.8	0.094
DM							
No	68	86.1%	29	87.9%	39	84.8%	0.695
Yes	11	13.9%	4	12.1%	7	15.2%	
HTN							
No	55	69.6%	23	69.7%	32	69.6%	0.990
Yes	24	30.4%	10	30.3%	14	30.4%	
CAOD							
No	77	97.5%	32	97.0%	45	97.8%	0.811
Yes	2	2.5%	1	3.0%	1	2.2%	
CHB							
No	47	59.5%	22	66.7%	25	54.3%	0.279
Yes	4	5.1%	3	9.1%	1	2.2%	
CHC							
No	45	57.0%	22	66.7%	23	50.0%	0.325
Yes	1	1.3%	1	3.0%	0	0.0%	
Biliary stone disease							
No	58	73.4%	20	60.6%	38	82.6%	0.017
Yes	20	25.3%	13	39.4%	7	15.2%	
Gallbladder polyp							
No	66	83.5%	22	66.7%	44	95.7%	0.001
Yes	13	16.5%	11	33.3%	2	4.3%	
Stage (TNM)							
0, I and II	27	34.2%	24	77.4%	3	6.3%	<0.001
III and IV	52	65.8%	7	22.6%	45	93.8%	
Operation							
No	40	50.6%	0	0.0%	34	73.9%	<0.001
Yes	36	45.6%	33	100.0%	10	21.7%	
Chemotherapy							
No	42	53.2%	18	54.5%	24	52.2%	0.597
Yes	30	38.0%	11	33.3%	19	41.3%	
Radiotherapy							
No	58	73.4%	23	69.7%	35	76.1%	0.577
Yes	8	10.1%	4	12.1%	4	8.7%	
Survival							
Yes	38	48.1%	24	72.7%	14	30.4%	<0.001
No	41	51.9%	9	27.3%	32	69.6%	
Survival time (months)							
Mean/SD	9.5	9.6	13.2	11.8	6.8	6.5	<0.001
Follow-up duration (months)							
Mean/SD	9.5	9.6	13.7	12	6.7	6.2	0.001

*CGBC, Cholecystectomy detected Gallbladder Cancer; NCGBC, Non-cholecystectomy detected Gallbladder Cancer; SD, Standard Deviation; BMI, Body Mass Index; DM, Diabetes Melitus; HTN, Hypertension; CAOD, Coronary Artery Occlusive Disease; CHB, Chronic Hepatitis B; CHC, Chronic Hepatitis C

Table 3. Multivariate Analysis of Risk Factors Correlated with Overall Survival Rates Using by Cox Regression Model

	p	Exp(B)	95% CI	
			Lower	Upper
Age	0.604	1.007	0.98	1.036
Sex (Male vs Female)	0.831	1.078	0.54	2.154
Diagnostic Prediction (IGBC vs NIGBC)	0.016	0.26	0.087	0.777
Early Stage (\leq II vs \geq III)	0.042	0.288	0.087	0.955

IGBC, Incidental Gallbladder Cancer; NIGBC, Non-Incidental Gallbladder Cancer

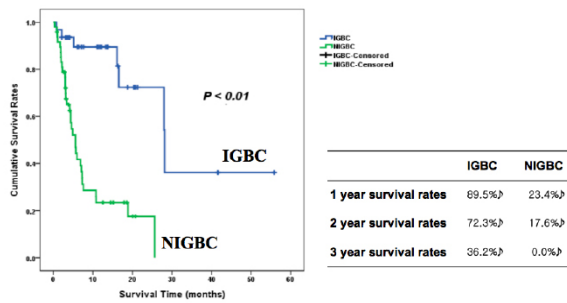


Figure 1. Kaplan-Meier Survival Curves of IGBC and NIGBC Groups. Abbreviation: IGBC, Incidental gallbladder cancer; NIGBC, Non-incidental gallbladder cancer

Kaplan-Meier method, we found a significant difference in the survival rate between the two groups (Figure 1). Multivariate analysis using the Cox regression model showed that an incidental versus non-incidental diagnosis of GBC and disease stage were significant factors affecting the survival rates of patients with GBC (Table 3).

Discussion

GBC is a malignant disease, which is prevalent in certain geographic areas. Early diagnosis with curative surgical resection is the only management strategy that ensures good prognosis. However, most patients with GBC are diagnosed at advanced stages (Henson et al., 1992).

In our study, we compared the clinical outcomes of IGBC and NIGBC and found significant differences in disease stage and overall survival between these groups. We also found that the two main reasons for cholecystectomy in the IGBC group were gallbladder polyps and gallstones, with or without cholecystitis.

Previous epidemiological studies have suggested that a history of gallstones is a potential risk factor for GBC (Maringhini et al., 1987; Chow et al., 1999). Recent studies have shown that gallstone disease is the main reason for cholecystectomy in patients with IGBC Koshenkov et al., 2013). However, the incidence of IGBC among patients undergoing cholecystectomy was very low (0.25%, 67 of 26,572 patients) in these studies. Further, there is no evidence to support the performance of prophylactic cholecystectomy for asymptomatic gallstone disease to prevent GBC. Thus, the clinical conditions or radiologic clues that could predict early GBC or benign premalignant lesions in patients with gallstones are still unknown. In contrast, gallbladder polyps, especially adenomatous polyps, are well known as potential pre-cancerous lesions. Many researchers have attempted to determine the demographic and radiologic factors that differentiate the malignant potential from the benign nature of a polyp. Typically, prophylactic cholecystectomy is recommended for high-risk groups, which include patients with diabetes, polyps larger than 1 cm, and certain sonographic findings (Kwon et al., 2009; Cha et al., 2011).

There are important implications to our finding that IGBC has better clinical outcomes than NIGBC. Higher proportion of earlier stages included in IGBC group might be considered to contribute the better prognosis, but we cannot exactly assess the patients with GB stone and GB

polyp at the time of cholecystectomy because they were not suspicious as cancer. Even if the physicians did not recommend the patients to undergo cholecystectomy, they would have been discovered as advanced GBC later. Therefore we need to make efforts to differentiate the patients with high risks for IGBC from benign diseases before the decision of operation regardless of symptoms. Determination of valid predisposing risk factors for early GBC among patients with gallbladder polyps and gallstone disease can help improve the clinical outcomes of GBC by establishing more strict or advanced guidelines for cholecystectomy. Despite the limitations of our study, including the retrospective observational study design and small sample size, due to the relative rarity of GBC, we compared two different GBC patient populations and found significantly better clinical outcomes in patients with IGBC than in those with NIGBC.

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