



# Clinicopathologic characteristics of young patients with gallbladder cancer



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## ABSTRACT

Gallbladder cancer is the most common biliary tract cancer and the fifth most common cancer of the digestive system. However, the clinicopathologic features of gallbladder cancer in young Korean patients have not been studied. This study included 101 consecutive cases of gallbladder cancer that underwent cholecystectomy at Kangbuk Samsung Hospital from December 1990 to March 2011. The patients were divided into two groups by age at initial diagnosis of gallbladder cancer: a young patient group aged less than 45 years and an old patient group aged 45 or older. The young patient group included 10 patients with mean age of 38 (range, 29–44 years). Compared with the old patient group, the young patient group showed polypoid tumor appearance ( $p = 0.014$ ), lower pT stage ( $p = 0.023$ ), more frequent adenoma background ( $p = 0.009$ ), and less frequent dysplasia in remaining mucosa ( $p = 0.001$ ). The disease-related survival rate after 13.5 months was significantly more favorable for the young patients. Gallbladder cancers in young Korean patients have distinct clinicopathologic features of a high frequency of cancer arising in adenoma, rare association with intestinal metaplasia and dysplasia, and a favorable patient's prognosis. These findings suggest that the adenoma-carcinoma pathway could contribute more to gallbladder cancer carcinogenesis in young Korean patients than the metaplasia-dysplasia-carcinoma pathway.

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## 1. Introduction

Gallbladder cancer is the most common malignancy of the biliary tract and the fifth most common cancer of the digestive system [9,12]. Gallbladder cancer is generally known as a disease of elderly people and occurs rarely in younger patients, with an incidence of 0.1–1.0% in people aged less than 30 years [11,16].

Gallbladder cancer in young patients has typically been described in single case reports [3,8,13,14,18,20]. A few studies comparing gallbladder cancers that arise in young and old patients have been performed in India and Chile [4,5,10]. Kazmi et al. reported that the younger group aged less than 45 years showed higher expression of cholecystokinin type A receptor (CCKAR) and a more aggressive disease course compared to older patients, suggesting two possible variants of gallbladder cancer [10]. In the study

of Dutta et al., the presence of gallstones and low socioeconomic status were associated with early occurrence of gallbladder cancer [5].

Although Far East Asia, including Korea and Japan, is an endemic area of gallbladder malignancy, little is known about the pathogenesis and clinical course of gallbladder cancer in young patients. We examined 101 cases of gallbladder cancers in Korean patients and compared clinicopathologic features between young and old groups.

## 2. Methods

### 2.1. Patients and clinical data

This retrospective study was approved by the Institutional Review Board of Kangbuk Samsung Hospital. The study included 101 consecutive cases of gallbladder adenocarcinoma that underwent cholecystectomy at Kangbuk Samsung Hospital from December 1990 to March 2011. Patient information including age, sex, date of initial diagnosis, follow-up duration, and radiological findings was obtained from electronic medical records. Information about patient deaths was obtained from the medical record

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**Table 1**  
Clinical features of 101 cases of gallbladder adenocarcinoma.

	Entire patients (n = 101)	Age < 45 (n = 10)	Age ≥ 45 (n = 91)	P-value
Gender				0.518
male	49 (48.5)	6 (60)	43 (47.3)	
female	52 (51.5)	4 (40)	48 (52.7)	
Location				0.235
fundus	31 (30.7)	3 (30)	28 (30.7)	
body	41 (40.6)	7 (70)	34 (37.4)	
neck	10 (9.9)	0 (0)	10 (11.0)	
entire	17 (16.8)	0 (0)	17 (18.7)	
cystic duct	2 (2.0)	0 (0)	2 (2.2)	
Shape				<b>0.014</b>
papillary	14 (13.9)	2 (20)	12 (13.2)	
nodular	13 (12.9)	1 (10)	12 (13.2)	
flat	9 (8.9)	0 (0)	9 (9.9)	
infiltrative	37 (36.6)	0 (0)	37 (40.6)	
polypoid	28 (27.7)	7 (70)	21 (23.1)	
Cholelithiasis				>0.999
absent	79 (78.2)	8 (80)	71 (78)	
present	22 (21.8)	2 (20)	20 (22)	
pT stage				<b>0.023</b>
1	32 (31.7)	7 (70)	25 (27.5)	
2	44 (43.6)	2 (20)	42 (46.1)	
3	25 (24.8)	1 (10)	24 (26.4)	
Lymph node metastasis <sup>a</sup>				0.200
absent	29 (54.7)	0 (0)	29 (56.9)	
present	24 (45.3)	2 (100)	22 (43.1)	
Distant metastasis				0.088
absent	64 (63.4)	9 (90)	55 (60.4)	
present	37 (36.6)	1 (10)	36 (39.6)	

<sup>a</sup> The lymph node dissection is performed in 53 patients.

department of Kangbuk Samsung Hospital and the Korea Central Cancer Registry.

## 2.2. Gross and microscopic evaluation of cholecystectomy specimens

All cholecystectomy specimens were fixed in 10% buffered formalin solution overnight after luminal opening. During the gross examination, the location and size of tumor, gross type, depth of invasion and resection margin status were recorded. After slicing tumor thinly, the tumor was examined meticulously and submitted with enough amount of tissue to determine the deepest layer of tumor invasion. The adjacent normal GB mucosa was also submitted. All cases were microscopically reviewed to determine histological classification according to the 2010 World Health Organization Tumor Classification [2]. Tumor differentiation, depth of wall invasion, resection margin status, lymphovascular invasion, perineural invasion, and concurrent dysplasia/adenoma were also evaluated. Tumor stage was assigned according to the 2010 AJCC Tumor Node Metastasis staging system [6].

## 2.3. Statistical analysis

Based on the most recent one among papers comparing age-specific features of GB cancer, the patients aged less than 45 were compared with those aged 45 or more [4,5,10]. Data were analyzed by PASW Statistics 18 (SPSS Inc., Chicago, IL, USA) software. Crosstabs, Pearson's chi-square test, and Fisher's exact test were applied as needed. Kaplan-Meier and Cox regression tests were used to analyze survival and metastasis data. Differences were regarded as statistically significant at  $p < 0.05$ .

## 3. Results

Clinical data for the entire group of 101 patients are shown in Table 1. The patients were diagnosed with gallbladder adenocarcinoma at a median age of 68 years (range, 29–89 years). About half

of patients (53.4%) were referred to our hospital as tumors within the gallbladder found on ultrasonography performed at local clinics and sixty one patients complained of gastrointestinal symptoms at the first visit. Nine (8.9%) patients presented with metastatic lesions at the time of initial diagnosis and 28 (27.7%) patients underwent distant metastasis of cancer at a mean of 10.4 post-operative months (range; 0.7–56.4 months). Tumors recurred in four patients (4%), and three of these were resection-margin positive cases. The mean follow-up period was 46.3 months (range, 0.5–276.5 months) and 46 patients (45.5%) died from gallbladder adenocarcinoma.

When we divided the total 101 patients into two groups according to the reference age of 45 years only 10 patients were included in the young patient group. The age of the young patient group ranged from 29 to 44 years with a mean age of 38 and the mean follow-up period was 67.8 months (range; 8.6–187.0 months). The remaining patients in the old patient group were diagnosed with gallbladder cancer at a mean age of 68.7 years (range; 46–89 years; median, 69 years) and were observed for a mean 44.0 post-operative months (range; 0.5–276.5 months). Compared with the old patient group, the young patient group showed lower pT stage and more frequent polypoid growth appearance (Table 1). Distant metastasis tended to occur more frequently in the old patient group, but this was not statistically significant. Tumors of the young patient group were mainly located in the fundus and body. The presence of gallstones was not correlated with age.

On microscopic examination, the tumors in the young patient group showed the characteristics of arising more frequently in adenoma and less frequent biliary intraepithelial neoplasia (BilIN) in the remaining mucosa compared with the old patient group (Table 2). Additionally, the young patient group tended to show more differentiated tumor histology and rare intestinal metaplasia in remaining mucosa (Table 2).

Although the survival curve according to age was not statistically significant, the disease-related survival rate was significantly different after 13.5 months (Fig. 1). Three patients in the young patient group died of gallbladder adenocarcinoma within a short post-operative time and shared the following clinicopathologic fea-

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