International Journal of Advances in Medicine
Chung HH et al. Int J Adv Med. 2022 Mar;9(3):201-208
http://www.ijmedicine.com
pISSN 2349-3925 | eISSN 2349-3933
DOI: https://dx.doi.org/10.18203/2349-3933.ijam20220359

Original Research Article

Comparison between early gall bladder cancer and advanced gall bladder cancer in terms of clinicopathologic factors: large volume tertiary center experience

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Received: 17 January 2022
Revised: 01 February 2022
Accepted: 02 February 2022

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ABSTRACT

Background: Early diagnosis of gallbladder cancer (GBC) which enables to surgical resection is key for improve prognosis. Aim of this study was to investigate clinical features of early GBC patients compare to advanced ones.
Methods: We retrospectively reviewed medical records of all pathologically confirmed primary GBC patients between in single tertiary referral center.
Results: 250 patients (57.3%) were early GBC (stage I and II) and 186 (42.7%) were advanced GBC (stage III and IV). Less patients with early GBC had symptom at initial diagnosis (69.2% versus 90.8%, p<0.001). Large number of patients with early GBC were diagnosed GBC incidentally after surgical resection which initially suspected benign gallbladder polyp or symptomatic gallbladder stones (71/250, 28.4% versus 7/186, 3.8%) (p<0.001). Patients who initially diagnosed gallbladder stone or cholecystitis tended to more advanced than gallbladder polyp.
Conclusions: There were no definitive symptoms which can detect early GBCs. Large number of early GBCs were diagnosed incidentally and many of these initially diagnosed with or accompany with benign cholecystic disease. Careful examination should be performed before diagnosis and after treatment, even in patient with vague symptom or benign cholecystic disease without elevated tumor markers.

Keywords: Early GB cancer, Advanced GB cancer, Gallbladder polyp, Gallbladder stone

INTRODUCTION

GBC is an uncommon malignancy however, because of its high fatality, it is significant cause of death in selected area such as South Korea, Japan, India and Pakistan and South American countries-Chile, Bolivia and Ecuador.[1] The only chance for cure lying in early detection and complete surgical resection.[2] However, the majority of GBCs are presented in advanced stage which is already unsuitable for surgical resection.[3] Histologic characteristics which vulnerable to direct tumor invasion-thin and discontinuous muscularis propria, in the absence of muscularis mucosae and submucosa, lack of the serosal layer, in the area where the gallbladder is in direct contact with the liver and aggressive tumor biology enhances local and distant tumor spread of GBC.[4,5] Also, anatomical characteristics of gallbladder which is extensive venous and lymphatic drainage leads to rapid distant metastasis and adjacent structures which adjoining bile duct, portal vein, liver, duodenum and colon are become involved early, making radical surgical resection difficult.[6]

Currently, diagnosing GBC in time is challenging because most of patients have only vague and non-specific

symptoms in early stage and there is no known effective mass screening tool for GBC.[7,8] There also is no known high-risk group which sensitive and specific same time. Suggested risk factors known to related with GBC were demographic factors (advanced age, female gender, obesity, geography/ethnicity, genetic predisposition), gallbladder pathologies/abnormalities (cholelithiasis, porcelain gallbladder, gallbladder polyps, congenital biliary cysts, pancreaticobiliary malfunction anomalies), substance exposures (heavy metals, medications, smoking) and infection (salmonella, helicobacter).[8] However, some of these factors are too scares conditions and others are not specific to be used as a predictive marker for early GBC.

Rarity of GBC limits the capability to perform prospective, randomized studies to investigate proper tools for early detection of GBC. Still, more large data for clinical feature of GBC is needed to improve our ability to detect GBC at a respectable stage. Therefore, we investigated clinical features of early GBCs in comparison to advanced ones with large study population in tertiary referral center over 20-year period.

METHODS

Patients

This was a retrospective COHORT study. We enrolled all the patients who have diagnosed primary GBC by searching WHO diagnostic code for GBC in electronic medical registry at Samsung medical center, tertiary large volume center from 1997 to 2020. We only included pathologically confirmed cases and excluded patients who diagnosed only by clinical presentations without pathologic documentation, who had other accompanying malignancies and who had insufficient or inaccurate medical record.

Electronic medical records were reviewed and following clinical and laboratory parameters were obtained; patient's demographic data, initial presenting symptoms, performance status, serum concentration of CA 19-9, CEA and total bilirubin, initial diagnosis, tumor stage, result of surgical resection, treatment modalities, tumor recurrence, patients' survival and accompanied gallbladder polyp, gallbladder stone, anomalous union of pancreaticobiliary duct, and choledochal cyst. Annually, approximately 500 to 700 simple cholecystectomy was performed in our institution and GBC which revealed after simple cholecystectomy for initially suspected benign cholecystic disease were classified as an incidental GBC. Pathologic features were obtained by reviewing pathologic reports of surgical or biopsy specimen. The study protocol was approved by the ethics committee of the Samsung medical center (IRB No.2014-10-075). This study was conducted in accordance with the principles of the Declaration of Helsinki. As this study used only de-identified data routinely collected during hospital visits, the requirement to obtain informed patient consent was waived.

Comparisons of clinical features of early GBC and advanced GBC

Included patients were categorized by initial cancer stage. The 8th edition of the tumor-node-metastasis system for GBC from the American joint committee on cancer was used to determine the clinical stage of the study patients.[9] We divided the patients into two groups which was early GBC group (stage I and II) and advanced GBC group (stage III and IV). Clinical characteristics, laboratory parameters and pathologic diagnosis and differentiation were compared between two groups and subgroup analysis was performed for incidental GBCs to compare early stage and advanced stage GBCs.

Statistical analysis

The data were shown as the number (%) for categorical variables and the mean±standard deviation for continuous variables. Overall survival (OS) was shown as the median and 95% confidence interval. Chi squared test and Fisher's exact test (when appropriate) were used to compare the frequencies of nominal variables and an independent t test was used to compare the continuous quantitative variables. The Kaplan-Meier method and log-rank test were used to compare the OS. Two-sided p values of <0.05 were defined as statistically significant. All analyses were performed using SPSS 21.0 (IBM Corp., Armont, New York, USA).

RESULTS

Clinical characteristics of included patients

A total of 444 patients were pathologically confirmed as a GBC during the study period. Among them, 4 patients had other primary malignancy simultaneously and 4 patients had insufficient medical information. Total 436 patients were included in the analysis and detailed characteristics of included patients were described in Table 1. Among the 436 of study population, 197 (45.2%) were male and 239 (54.8%) were female. 250 (57.3%) patients were early-stage GBC and 186 (42.7%) were advanced stage. Curative surgical resection (R0 resection) was available in 205 (47.0%) of patients. Most of GBC were adenocarcinomas (415/436, 95.2%) and others were adenosquamous carcinoma (9/436, 2.1%), neuroendocrine tumor (5/436, 1.1%), sarcomatoid tumor (2/436, 0.5%) and squamous cell carcinoma (5/43, 1.1%).

Comparisons of early GBC group and advanced GBC group

Between the early GBC group and advanced GBC group, there were no difference in proportion of male and female. Patients in early GBC group were significantly older than in advanced GBC group but the difference was small (63.2±11.50 versus 60.2±10.63) ($p=0.005$). Less patients in early cancer had symptoms in initial diagnosis (69.2% versus 90.8%) ($p<0.001$) however, fever was more

frequently observed in early cancer group (32/247, 13.0% versus 11/185, 5.9%) (p=0.016). Jaundice (20/247, 8.1% versus 26/185, 14.1%) (p=0.047), dyspepsia (20/247, 8.1% versus 32/185, 17.3%) (p=0.004) and palpable mass (0/247, 0.0% versus 10/185, 5.4%) (p<0.001) were symptoms which presented more in advanced GBC group than early GBC group.

Large number of patients in early cancer group were diagnosed GBC incidentally after surgical resection, which initially suspected benign cholecystic disease such as simple gallbladder polyp or symptomatic gallbladder stones (71/25, 28.4% versus 7/186, 3.8%) (p<0.001). Early cancer group had significantly more accompanying gallbladder polyps (33/248, 13.3% vs. 0/180, 0.0%) (P < 0.001) and gallbladder stones (75/250, 30.0% versus 25/180, 13.9%) (p<0.001). There were no significant differences between two groups in mean serum concentration of CEA (4.0±6.84 versus 157.4±1059.9) (p=0.083) and total bilirubin at diagnosis (2.55±6.567 versus 3.03±5.656) (p=0.427). The elevation of CEA was more frequently observed in advanced GBC group than early GBC group (68 of 145, 46.9% versus 31 of 185, 16.8%) (p<0.001). The frequency of bilirubin elevation was not significantly different between two groups. The mean CA 19-9 level was significantly higher in advanced cancer group than early cancer group (4532.3±15600.44 versus 526.0±2726.73) (p=0.010). The more patients in advanced GBC group showed elevated CA 19-9 than early GBC group (68 of 186, 36.6% versus 43 of 250, 17.2%) (p<0.001). Curative resection was available in 204 of 250 patients in early cancer group however, only 1 of 186 patients in advanced cancer group (p<0.001). Adenocarcinoma was major histologic type in both groups. The median overall survival of patients was significantly longer in the patients of early GBC group than in the patients of advanced GBC group as shown in Figure 1 (135.3 months, 73.57-197.04 versus 9.0 months, 6.96-11.04) (p<0.001).

Table 1: Baseline characteristics of included patients.

Characteristics	N (%)
Total	436
Sex	
Male	197 (45.2)
Female	239 (54.8)
Age (mean±SD)	61.9±11.22
CA 19-9 (mean±SD)	2119.6±10226.70
CEA (mean±SD)	71.4±705.33
Total bilirubin (mean±SD)	2.8±6.19
Stage	
Carcinoma *in situ*	5 (1.1)
Stage IA or IB	121 (27.8)
Stage IIA	46 (10.6)
Stage IIB	78 (17.9)
Stage III	9 (2.1)
Stage IV	177 (40.6)
Curative resection	205 (47.0)
Histology	
Adenocarcinoma, not specified	180 (41.3)
Adenocarcinoma, well differentiated	60 (13.8)
Adenocarcinoma, moderately differentiated	120 (27.5)
Adenocarcinoma, poorly differentiated	55 (12.6)
Adenosquamous carcinoma	9 (2.1)
Neuroendocrine tumor	5 (1.1)
Sarcomatoid tumor	2 (0.5)
Squamous cell carcinoma	5 (1.1)

SD=standard deviation.

Table 2: Comparisons of early and advanced stage GBCs.

Parameters	Early (stage I and II)	Advanced (stage III and IV)	P value
	N (%)	N (%)	
Sex (male)	111/250 (44.4)	86/186 (46.2)	0.703
Age (mean±SD)	63.2±11.50	60.2±10.63	0.005

Continued.

Parameters	Early (stage I and II) N (%)	Advanced (stage III and IV) N (%)	P value
Presence of symptom	171/247 (69.2)	168/185 (90.8)	<0.001
Weight loss, POI, GW	14 /247(5.7)	16/185 (8.6)	0.228
Jaundice	20/247 (8.1)	26/185 (14.1)	0.047
Abdominal pain	106/247 (42.9)	97/185 (52.4)	0.050
Dyspepsia	20/247 (8.1)	32/185 (17.3)	0.004
Fever	32/247 (13.0)	11/185 (5.9)	0.016
Palpable mass	0/247 (0.0)	10/185 (5.4)	<0.001
Initial diagnosis			
Incidental	71/250 (28.4)	7/186 (3.8)	<0.001
Suspected	179/250 (71.6)	179/186 (96.2)	
Accompanying condition			
GB polyp	33/248 (13.3)	0/180 (0)	<0.001
GB stone	75/250 (30.0)	25/180 (13.9)	<0.001
AUPBD	4/236 (1.7)	1/77 (1.3)	1.000
Choledochal cyst	4/234 (1.7)	1/77 (1.3)	1.000
CA 19-9 (mean±SD)	526.0±2726.73	4532.3±15600.44	0.010
CA 19-9 elevation (> 36 U/ml)	43/250 (17.2)	68/186 (36.6)	<0.001
CEA (mean±SD)	4.0±6.84	157.4±1059.9	0.083
CEA elevation (>4 ug/l)	31/185 (16.8)	68/145 (46.9)	<0.001
Total Bil (mean±SD)	2.55±6.567	3.03±5.656	0.427
Total Bil elevation (>1.2 mg/dl)	61/250 (24.4)	58/184 (31.5)	0.100
Curative resection	204/250 (81.6)	1/186 (0.5)	<0.001
Histology			
Adenocarcinoma, w/d	119/250 (47.6)	51/186 (27.4)	<0.001
Adenocarcinoma, m/d	91/250 (36.4)	39/186 (21.0)	
Adenocarcinoma, p/d	32/250 (12.8)	70 /186 (37.6)	
Adenosquamous carcinoma	5/250 (2.0)	10/186 (5.4)	
Neuroendocrine tumor	1/250 (0.4)	6/186 (3.2)	
Sarcomatoid tumor	1/250 (0.4)	3/186 (1.6)	
Squamous cell carcinoma	1/250 (0.4)	7/186 (3.8)	
Overall survival (median 95% CI, month)	135.3 (73.57-197.04)	9.0 (6.96-11.04)	<0.001

AUPBD=anomalous union of pancreaticobiliary duct; SD=standard deviation; POI=poor oral intake; GW=general weakness; GB=gallbladder; Bil=bilirubin; w/d=well differentiated; m/d=moderately differentiated; p/d=poorly differentiated; CI=confidence interval.

Table 3: Initial diagnosis and proportion in each stage of incidental GBC.

Parameters	CIS	Stage I	Stage IIA	Stage IIB	Stage III	Stage IV	Total
Proportion of incidental GBC	5/5 (100.0%)	43/121 (35.5%)	13/46 (28.3%)	10/78 (12.8%)	0/9 (0.0%)	7/177 (4.0%)	78/436 (17.6%)
Initial diagnosis							
GB stone	1	12	6	3	0	4	26
GB polyp	2	17	2	0	0	0	21
GB stone+polyp	2	4	0	1	0	0	7
GB stone+cholecystitis	0	7	4	4	0	2	17
Acalculous cholecystitis	0	2	0	1	0	1	4
Adenomyomatosis	0	1	1	1	0	0	3

GBC=gallbladder cancer; CIS=carcinoma *in situ*.

Table 4: Comparisons between stage I and stage II to IV in incidental GBC.

Parameters	Total=78	Stage I (n=48)	Stage II-IV (n=30)	P value
Sex (male)	32 (41)	20 (41.7)	12 (40.0)	0.884

Continued.

Parameters	Total=78	Stage I (n=48)	Stage II-IV (n=30)	P value
Age	66.9±11.91	65.0±12.07	69.8±11.23	0.083
Presence of symptom	48/77 (62.3)	26/48 (54.2)	22/29 (75.9)	0.057
Weight loss, POI, GW	0/77 (0.0)			
Jaundice	1/77 (1.3)	1/48 (2.1)	0/29 (0.0)	1.000
Abdominal pain	30/77 (39.0)	14/48 (29.2)	16/29 (55.2)	0.023
Dyspepsia	6/77 (7.8)	5/48 (10.4)	1/29 (3.4)	0.400
Fever	17/77 (22.1)	9/48 (18.8)	8/29 (27.6)	0.365
Palpable mass	0/77 (0.0)	0/48 (0.0)	0/29 (0.0)	
Operation type				
Laparoscopic cholecystectomy	44 (56.4)	30 (62.5)	14 (46.7)	0.170
Open cholecystectomy	34 (43.6)	18 (37.5)	16 (53.3)	
Curative OP	68 (87.2)	47 (97.9)	21 (70.0)	
Elevated CA19-9 (>36)	4 (5.1)	2 (4.2)	2 (6.7)	0.636
Elevated CEA (>4)	4 (5.1)	3 (9.7)	1 (4.5)	0.486
Accompaning condition				
GB polyp	28 (35.9)	25 (52.1)	3 (10.0)	<0.001
GB stone	50 (6.1)	26 (54.2)	24 (80.0)	0.021
AUPBD	2 (2.6)	1 (2.1)	1 (3.3)	1.000
Choledochal cyst	0 (0.0)	0 (0.0)	0 (0.0)	
Porcerline GB	0 (0.0)	0 (0.0)	0 (0.0)	
Histology				
ADC, not specified	14 (17.9)	10 (20.8)	4 (13.3)	0.043
ADC, well differentiated	33 (42.3)	24 (50.0)	9 (30.0)	
ADC, moderately differentiated	20 (25.6)	11 (22.9)	9 (30.0)	
ADC, poorly differentiated	11 (14.1)	3 (6.3)	8 (26.7)	
Overall survival (median 95% CI, month)		Not reached	24.6 (17.26-31.94)	<0.001

AUPBD=anomalous union of pancreaticobiliary duct; POI=poor oral intake; GW=general weakness; GB=gallbladder; CI=confidence interval.

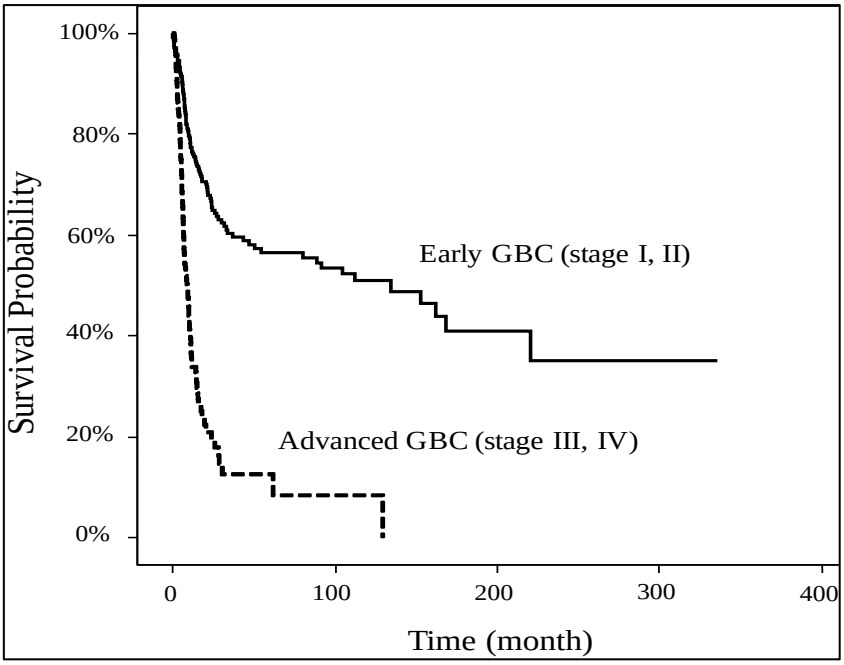

Figure 1: Kaplan-Meier estimation of overall survival of total GBC patients; the median overall survival of patients was significantly longer in patients with early GBC (stage I, II) than patients with advanced GBC (stage III, IV) [135.3 months (73.57-197.04) versus 9.0 months (6.96-11.04), p<0.001]; patients with early GBC (solid line); patients with advanced GBC (broken line).

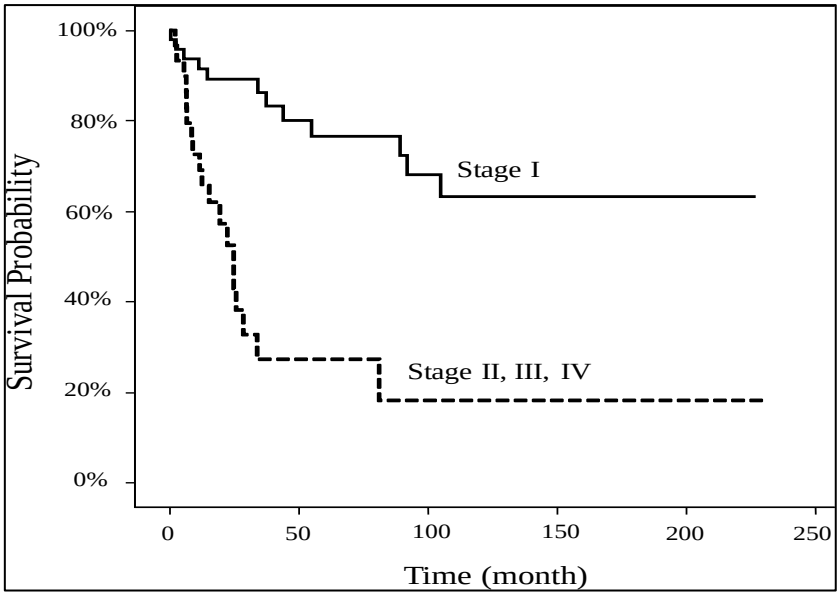

Figure 2: Kaplan-Meier estimation of overall survival of incidental GBC patients; the median overall survival of patients was significantly longer in patients with stage I GBC than patients with stage II, III or IV GBC [median survival not reached versus 24.6 months (17.26-31.94), p<0.001]; patients with stage I GBC (solid line); patients with stage II, III or IV GBC (broken line).

Characteristics of incidental GBCs

The proportion of incidental GBC in each tumor stage and indications of initial surgery in incidental GBC patients were described in Table 3. Proportion of incidental GBC tended to more frequent in early stage than later stage of cancer. Symptomatic gallbladder stone was the most common and gallbladder polyp was second most common initial diagnosis of incidental GBC. Besides, acalculous cholecystitis or adenomyomatosis were the initial diagnosis of some patients. Incidental GBC in patients initially received cholecystectomy for porcelain gallbladder or anomalous union of pancreaticobiliary duct was not reported. The comparisons between stage I and stage II to IV in incidental GBC were described in Table 4. The more patients with stage II to IV were presenting abdominal pain than patients with stage I (16/29, 55.2% versus 14/48, 29.9%) (p=0.023). Gallbladder polyps were significantly more frequent in patients with stage I than with stage II to IV (25/48, 52.1% versus 3/30, 10.0%) (p<0.001) and gallbladder stones were more frequent in patients with stage II to IV than with stage I (24/30, 80.0% versus 26/48, 54.2%) (p=0.021). Overall survival of patients was significantly longer in stage I than stage II to IV as shown in Figure 2 (median survival not reached versus 24.6 month, 17.26-31.94) (p<0.001).

DISCUSSION

GBC is aggressive cancer which showed poor prognosis. Surgical resection was only treatment modality expectable to cure thus early detection was the key to GBC treatment. However, early detection of GBC was hindered by several factors of GBC which were histologic characteristics of gallbladder and anatomic characteristics of gallbladder and surrounding structures. Also, vague clinical symptoms and absence of effective screening tool were obstacles to detect GBC in time.

In this study, we compared clinical features of patients with early-stage GBC and advanced stage GBC which expected to provide us a clue for early detection of GBC. Among the all included patients, the most common initial presenting symptom was abdominal pain which was similar to previous studies.[10-13] However, actual proportion of patients who had symptom was much lower in our study. We speculated that the cause of less symptoms in our study was due to larger proportion of early GBC in our study compared to previous studies (57.3% versus 15.2%, 12.7%, 14%, 23.2%).[10-13] Abdominal pain was more frequently observed in advanced tumor group though it was not statistically significant (p=0.050). In regard of symptoms like jaundice, dyspepsia and palpable mass, it was more frequently observed in advanced GBC group than early GBC group and it was statistically significant. It was quite understandable since GBC in stage I or II, the tumor was confined to gallbladder and not invade biliary tree or gastrointestinal tract which can cause jaundice or dyspepsia.[9,14] The volume of tumor also generally considered smaller in early cancer than advanced one which explained none of patients had palpable mass in initial diagnosis. For a similar reason, the more patients in early GBC group than advanced GBC group tended to discover GBC incidentally after surgical resection and this tendency was also shown in previous studies.[15,16] Early tumors which confined to gallbladder (T1 or T2) often not visible or difficult to differentiate from wall thickening of cholecystitis with ultrasonography or conventional

tomographic images.[17,18] It can be diagnosed only after the surgical resection of other reasons. In our study, significantly more patients in early cancer group initially diagnosed simple gallbladder polyp or gallbladder stones with or without cholecystitis before they received surgical resection.

It was already known that the tumor markers such as CA 19-9 and CEA was frequently elevated in GBC patients19,20. In our study, both CA 19-9 and CEA was more frequently elevated in advanced GBC group than early GBC group which possibly reflected smaller tumor volume of early GBC patients.

Cholelithiasis was well acknowledged as an important risk factor for GBC and according to the earlier study, up to 95% of GBC were related with cholelithiasis.[21,22] Gallbladder polyp also was well known condition which related with GBC and some of features in gallbladder polyp such as large size (>1 centimeter), solitary, sessile shape and associated gallstones were known to indicate malignancy.[23] Also, in our study, gallbladder stones and gallbladder polyps were frequently accompanied with GBC and both of it were more frequent in early GBC group than advanced GBC group. It was possible that gallbladder stones or gallbladder polyps were under reported in patients with more advanced tumor since more than half patients in advanced tumor group did not receive surgical resection and presence of gallbladder stones or polyps were evaluated only by imaging study (computed tomography, magnetic resonance image or endoscopic/abdominal ultrasonography).

In this study, we could not find any definitive clinical feature or symptom to diagnose GBC in early stage. Instead, GBC patients in early stage had less symptoms or signs and larger portion of patients were diagnosed incidentally. Most of patients who diagnosed GBC incidentally was initially diagnosed as benign cholecystic disease such as gallbladder polyp or gallbladder stone and which possibly the opportunity to detect GBC in earlier stage. We have performed further analysis which comparison of early stage (stage I) and advanced stage (stage II to IV) in incidental GBCs. Among patients who was diagnosed GBC incidentally, the more patients in advanced stage presented abdominal pain and accompanying gallbladder stone than patients in early stage. It may suggest that gallbladder stone and cholecystitis more often mask advanced GBCs than other benign cholecystic conditions. Careful assessment of such benign cholecystic disease may lead to early diagnosis of GBC in more patients.

The limitations of our study were that that it was conducted retrospectively. Some of symptoms or clinical features could be missed in medical record and gallbladder polyp and gallbladder stone could be under reported in patients who did not receive surgical resection. Also, there were some missing data on accompanying conditions and laboratory findings. However, we reviewed the medical record carefully including radiologic findings and pathologic which minimized these limitations. Also, our study may have significance in regard of relatively large study population over long period.

CONCLUSION

In conclusion, large number of early GBC were diagnosed incidentally and many of these initially diagnosed with or accompany with benign cholecystic disease such as gallbladder stone or polyp. There were no definitive symptoms or clinical presentation which can detect early GBCs. Careful examination should be performed before diagnosis and after treatment, even in patient with vague symptom or benign cholecystic disease, especially without elevated tumor markers.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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Cite this article as: Chung HH, Kim JE, Chung KH, Park JK. Comparison between early gall bladder cancer and advanced gall bladder cancer in terms of clinicopathologic factors: large volume tertiary center experience. Int J Adv Med 2022;9:201-8.