



ORIGINAL ARTICLE

Reasonable cholecystectomy of gallbladder polyp – 10 years of experience

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KEYWORDS

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Summary *Background and objective:* Although the incidence of carcinoma is not high in gallbladder polyps, it is essential to diagnose gallbladder cancer at an early stage to achieve a good therapeutic outcome. Therefore, the aim of this study was to define the characteristics of gallbladder polyps to establish sound criteria for surgical indications.

Methods: In the current study, data from 516 patients with gallbladder polyps who underwent cholecystectomy were reviewed to correlate clinical features with histopathologic findings and identify risk factors with receiver-operating characteristic curves (ROCs).

Results: Among the 516 patients who underwent cholecystectomy, 24 patients (4.6%) had cancerous change. The cancer group was significantly older (65.5 years (median, range 35–85)) than the non-cancer group (42 years (median, range 23–82)) ($p < 0.001$). Among the cancer group, the preoperative polyp size on ultrasonography was significantly larger (14 mm (median, range 9–30)) than the polyps in the non-cancer group (10.4 mm (median, range 1.9–45)) ($p < 0.001$). Using the ROC curve and considering the sensitivity and specificity for predicting malignant polyps, 12 mm may be a reasonable cutoff for considering a malignant polyp.

Conclusions: Gallbladder polyps with 10–11 mm in asymptomatic young patients (less than 50 years old) have low risk of malignancy, and therefore, a careful “wait and see with follow up by using ultrasonography strategy” might be more appropriate than immediate cholecystectomy.

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1. Introduction

Gallbladder polyps are lesions that protrude from the wall to the inside of the gallbladder. They are classified as non-neoplastic and neoplastic polyps. Non-neoplastic polyps include cholesterol polyps, hyperplastic polyps, inflammatory polyps, adenomyomas, leiomyomas, fibromas, and lipomas. Neoplastic polyps include adenomas, adenocarcinomas, and squamous cell carcinomas.¹ According to the second edition of the WHO Histological Classification of Tumors of the Gallbladder and Extrahepatic Bile Ducts, cholesterol polyps, adenomyomatous hyperplasia, inflammatory polyps, and xanthogranulomatous cholecystitis are all classified as tumor-like lesions.²

Gallbladder polyps are found in 0.3%–12% of healthy individuals.³ The actual prevalence is unknown; however at present, gallbladder polyps are diagnosed more frequently because of the widespread use of abdominal imaging techniques. Gallbladder polyps are usually asymptomatic and are often diagnosed incidentally during radiological examinations performed for other reasons. Although most gallbladder carcinomas evolve from dysplasia and carcinoma in situ, the role of gallbladder adenomas in the pathogenesis of gallbladder carcinoma is still controversial. Most of these lesions are benign; however, due to the poor prognosis of gallbladder carcinoma, this diagnosis must not be missed. Although the incidence of carcinoma is not high in gallbladder polyps, it is essential to diagnose gallbladder cancer at an early stage to achieve a good therapeutic outcome.

In the current study, data from 516 patients with gallbladder polyps who underwent cholecystectomy were reviewed to correlate clinical features with histopathologic findings. The aim of this study was to define the characteristics of gallbladder polyps to establish sound criteria for cholecystectomy in these patients and to determine the differences between benign and malignant gallbladder polyps.

2. Material and methods

A total of 516 consecutive patients with polypoid lesions of gallbladder underwent laparoscopic cholecystectomy with curative intent at the Department of Surgery, Kangbuk Samsung Hospital between January 2005 and December 2014. Age, sex, clinical signs, laboratory results, preoperative ultrasonography (US), and histopathological diagnoses of patients were analyzed retrospectively.

The patients were categorized as having a non-neoplastic polyp or a neoplastic polyp according to their histopathologic results. Neoplastic gallbladder polyps were subcategorized as tumorous polyps if the pathological finding indicated that the polyps had a potential for malignant transformation, whereas non-neoplastic polyps were not regarded as precancerous lesions. The neoplastic polyps included adenomas, lymphoma, and cancer. The non-neoplastic polyps included cholesterol polyps, inflammatory polyps, cholelithiasis, and cholecystitis. This study protocol was approved by the ethics committee of Kangbuk Samsung Hospital Surgery.

The following standardized US criteria were used to identify polyps: immobile, hyperechoic compared to the surrounding bile, non-shadowing, and attached to the GB wall.^{5–7} US examinations were performed by an experienced certified radiologist using 3.5-MHz transducers (iU22 ultrasound system with a C5-1 convex transducer (Philips Medical Systems, Bothell, WA, USA)). The US examinations were interpreted by board certified radiologists who were trained in abdominal imaging and delineation of the number and size of gallbladder polyps. Patients with a preoperative ultrasound diagnosis of gallbladder polyps exceeding 10 mm, multiple polypoid lesions, those with disease progression, as well as those with painful polypoid lesions were indicated for surgery.

If gallbladder cancer was suspected during preoperative study or intraoperative surgery, we proceed with a frozen test to convert it to radical cholecystectomy in the case of stage T2 or higher. However, in T1 with frozen test, radical cholecystectomy is performed only for T1b according to the pathologic final result.

Statistical analysis of the data was performed by utilizing STATA version 14.0 (StataCorp LP, College Station, TX, USA). Continuous variables were presented as mean \pm SD. Intergroup comparisons were conducted using a Chi-Square test. In order to identify the risk factors for gallbladder cancer, the odds ratio was determined using multiple logistic regression analysis. The area under the curve (AUC) was calculated using the receiver-operating characteristic curve (ROC) to determine the sensitivity and specificity of the 10 mm size criteria for predicting malignant polyps. Further calculations were focused on determining an optimal size cut-off for predicting malignancy. Differences were considered significant when the P value was less than 0.05.

3. Results

3.1. Demographic findings and clinical characteristics

This study retrospectively obtained data for 516 patients who underwent laparoscopic cholecystectomy due to gallbladder polyps between January 2005 and December 2014. The demographic and clinical characteristics of all the 516 patients are listed in Table 1. The median age of the patients and the median size of polyps on US were 43 years (range 23–85) and 10.7 mm (range 1.9–45), respectively. Among the patients, 297 (57.6%) were male and 219 (42.4%) were female. The majority of patients (391 patients, 75.8%) underwent cholecystectomy because they had a polyp larger than 10 mm in size, indicating that the 10 mm size criteria may be the most important factor in making a decision regarding surgery in a clinical setting. Some of the patients had specific symptoms such as right upper quadrant pain or epigastric pain, but other patients complained of vague abdominal pain, dyspepsia, fatigue, or loss of body weight. While patients with gallbladder polyps had a high body mass index (BMI, kg/m²), total cholesterol, total bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), and cancer antigen 19-9 (CA 19-9) levels were normal.

Table 1 Demographic and clinical characteristics of patients (n = 516).

Characteristics	Number of patients (%)
Male/Female	297 (57.6)/219 (42.4)
Age (yr, median (range))	43 (23–85)
Type of surgery	Laparoscopic cholecystectomy 495 (95.9) Single incision robotic cholecystectomy 21 (4.1)
Inclusion criteria	Size >10 mm 391 (75.8) Others (increasing size, abnormal findings, etc) 125 (24.2)
Size (mm, median (range))	Ultrasonography 10.7 (1.9–45)
Number of polyps	<3 356 (69.0) 3 160 (31.0)
Body Mass Index (kg/m ² , median (range))	24.28 (16.68–35.87)
Body Surface Area (kg/m ² , median (range))	1.75 (0.92–2.33)
Total cholesterol (mg/dL, median (range))	185 (78–295)
Total bilirubin (mg/dL, median (range))	0.79 (0.16–5.21)
AST (U/L, median (range))	22 (9–147)
ALT (U/L, median (range))	21 (5–293)
Fasting glucose (mg/dL, median (range))	97.5 (63–259)
CA 19-9 (U/mL, median (range))	8.13 (0.5–42.81)
HBsAg positivity	25 (4.8)

Table 2 Pathologic results of gallbladder polyps which underwent cholecystectomy.

Pathologic results	Non-neoplastic polyp	Cholesterol polyp	289 (56.01%)
		Inflammatory polyp	1 (0.19%)
		Cholelithiasis	17 (3.29%)
		Cholecystitis	85 (16.48%)
	Neoplastic polyp	Adenoma	100 (19.38%)
		Adenocarcinoma	23 (4.46%)
		Lymphoma	1 (0.19%)
Total			516 (100%)

3.2. Pathologic examination

Among the 516 patients who underwent cholecystectomy, 392 patients (75.97%) had non-neoplastic polyps, and 124 patients (24.03%) had neoplastic polyps. In the patients with neoplastic polyp, 24 patients (4.64%) had a malignancy. Among all polyps, cholesterol polyps were the most common type and were found in 289 patients (56.01%). The pathologic results of all the 516 patients are listed in [Table 2](#).

3.3. Comparison of the non-cancer group with the cancer group

Sex, number of polyps, BMI, body surface area (BSA), total cholesterol, total bilirubin, ALT, fasting glucose, CA 19-9, and HBsAg positivity were not different between the two groups ([Table 3](#)). However, patients in the cancer group (65.5 years (median, range 35–85)) were significantly older than those in the non-cancer group (42 years (median, range 23–82)) ($p < 0.001$). When comparing the preoperative polyp size on US, the cancer group had significantly larger polyps (14 mm (median, range 9–30)) than the non-cancer group (10.4 mm (median, range 1.9–45))

($p < 0.001$). Additionally, increasing size and an abnormal finding was found in only 1 patient (4.2%) in the cancer group compared to 124 patients (25.2%) in the non-cancer group with a statistically significant difference ($p = 0.019$).

Polyp size and patient age were significant risk factors for malignancy in patients with gallbladder polyps ($p < 0.046$, OR = 7.750; 95% CI: 1.036–57.982 for polyp size, $p < 0.001$, OR = 1.124; 95% CI: 1.084–1.166 for patient age). BSA, AST, and ALT were factors associated with a higher risk of malignant gallbladder polyps ($P < 0.05$) ([Table 4](#)).

3.4. Optimal size to predict malignant gallbladder polyps

Among the 24 patients with malignancy, only 1 (2.4%) patient had a polyp less than 10 mm in size and 2 patients had 10 mm polyps. In this group, the median polyp size on US was 14 mm (range 9–30). There was a statically significant difference in average polyp size between the benign and malignant groups ($p < 0.001$) and polyp size was found to be a prominent predictor of malignancy ($p = 0.046$). Therefore, this study calculated the AUC using the ROC curve to test the conventional size criteria for predicting the risk of malignancy ([Fig. 1](#)).

Table 3 Comparison of the non-cancer group with the cancer.

Characteristics	Total (%)	Non-cancer (%)	Cancer (%)	P-value	
Male/Female	297 (57.6)/219 (42.4)	285 (57.9)/207 (42.1)	12 (50.0)/12 (50.0)	0.443	
Age (yr, median, (range))	43 (23–85)	42 (23–82)	65.5 (35–85)	<0.001 ^a	
Type of surgery	Laparoscopic cholecystectomy Single site robotic cholecystectomy	495 (95.9) 21 (4.1)	472 (95.9) 20 (4.1)	23 (95.8) 1 (4.2)	>0.05
Inclusion criteria	Size 10 mm Others (increasing size, abnormal findings, etc)	391 (75.8) 125 (24.2)	368 (74.8) 124 (25.2)	23 (95.8) 1 (4.2)	0.019 ^a
Size (mm, median, (range))	10.7 (1.9–45)	10.4 (1.9–45)	14 (9–30)	<0.001 ^a	
Number of polyps	516 (100.0)	492 (95.3)	24 (4.7)	0.515	
<3	356 (69.0)	338 (68.7)	18 (75.0)		
≥3	160 (31.0)	154 (31.3)	6 (25.0%)		
Body Mass Index (median (range))	24.28 (16.68–35.28)	24.32 (16.68–35.28)	23.94 (17.48–33.97)	0.39	
Body Surface Area (median (range))	1.75 (0.92–2.33)	1.76 (0.92–2.33)	1.69 (1.39–1.94)	0.02 ^a	
Total cholesterol (mg/dL, median (range))	185 (78–295)	185 (78–295)	193.5 (91–248)	0.792	
Total bilirubin (mg/dL, median (range))	0.79 (0.16–5.21)	0.8 (0.16–2.35)	0.68 (0.2–5.21)	0.19	
AST (U/L, median (range))	22 (9–147)	21 (9–147)	23.5 (17–133)	0.045	
ALT (U/L, median (range))	21 (5–293)	21 (5–269)	18 (11–293)	0.364	
Fasting glucose (mg/dL, median (range))	97.5 (63–259)	97 (63–259)	103 (78–212)	0.402	
CA 19-9 (U/mL, median (range))	8.13 (0.5–42.81)	8.12 (0.5–42.81)	8.97 (3.8–21.26)	0.721	
HBsAg positivity	25 (4.8)	24 (4.9)	1 (4.1)	0.218	

^a Statistical significance.

When the size cut-off point was set at 10.05 mm, sensitivity and specificity for predicting malignant polyps was 82.4% and 49.4%, respectively. However, when the size cut-off point was set at 11.95 mm, the sensitivity remained equal to the sensitivity at a cutoff value of 10.05 mm, but the specificity increased (49.4% at 10.05 mm and 68.7% at 11.95). The sensitivity fell sharply when the cut-off point was increased to 12.05 mm. Therefore, after considering the sensitivity and specificity for predicting malignant

polyps, 12 mm might be an ideal cut-off point. When the size cut-off point was set at 12 mm, 3 patients were excluded (less than 12 mm) from cancer group. Two of these 3 patients were relatively older (65 and 75 years old) and 1 patient was comparatively young (56 years old) with

Table 4 Predictors of gallbladder cancer.

Characteristics	GB cancer	
	OR (95%CI)	P value
Female/Male	1.377 (0.606–3.126)	0.445
Age (mean, yr)	1.124 (1.084–1.166)	<0.001 ^a
Size (>10 mm)	7.750 (1.036–57.982)	0.046 ^a
Number of polyps (>3)	0.732 (0.285–1.879)	0.516
Body Mass Index (BMI)	0.957 (0.847–1.082)	0.484
Body Surface Area (BSA)	0.103 (0.014–0.769)	0.027 ^a
Total cholesterol (mg/dL)	0.999 (0.986–1.012)	0.828
Total bilirubin (mg/dL)	1.487 (0.688–3.215)	0.313
AST (U/L)	1.042 (1.024–1.061)	<0.001 ^a
ALT (U/L)	1.016 (1.005–1.027)	0.004 ^a
Fasting glucose (mg/dL)	1.013 (0.9996–1.026)	0.057
CA 19-9 (U/mL)	1.002 (0.931–1.079)	0.956
HBsAg positivity	1.096 (0.138–8.736)	0.931

^a Statistical significance.

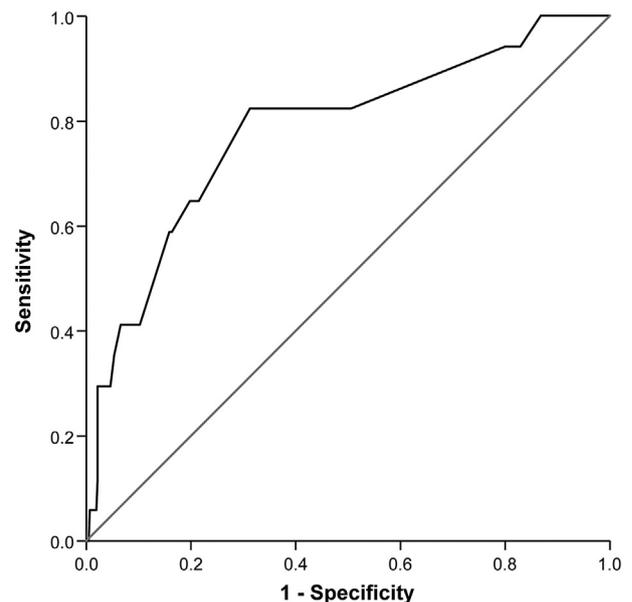


Figure 1 Receiver operating characteristic curves for the size of gallbladder polyps. The area under the curve is 0.781 (95% CI, 0.660–0.903; $p < 0.001$) for the polyp size.

high AST and ALT (133U/L, 95U/L). In the present study, the AUC for polyp size was 0.781 (95% CI, 0.660–0.903) ($p < 0.001$).

4. Discussion

Gallbladder polyps are common lesions that should not be ignored because of their association with malignancy. Previous studies have reported an incidence of gallbladder polyps between 0.3% and 12.0% in routine health examination of general population.^{4,5} Gallbladder polyps were first defined pathologically by Christense and Ishak.⁶ Generally, these lesions were categorized as benign or malignant. Benign lesions were further subdivided into neoplastic polyps (adenoma, hemangioma, lipoma) and non-neoplastic polyps (cholesterol polyps, inflammatory polyps, hyperplastic polyps). On other hand, malignant lesions included adenocarcinoma, squamous cell carcinoma and lymphoma.^{6,7} In our hospital, 3586 patients underwent laparoscopic cholecystectomy between January 2005 and December 2014. Gallbladder polyps were an indication for cholecystectomy in 14.3% (516 patients) of cases. 102 of these patients were postoperatively diagnosed with cholelithiasis or cholecystitis; therefore, the true incidence of gallbladder polyps was 11.5% (414 patients) and the true incidence of neoplastic gallbladder polyps was 3.4% (124 patients) in cholecystectomy patients, which was similar to the previous reported incidence.^{4,5}

Gallbladder cancer is an aggressive malignancy that carries an extremely poor prognosis. The only chance of cure comes from early detection and curative surgery.⁴ Risk factors that increase the likelihood of malignancy in a polypoid lesion are increased size, higher number, morphologic type and growth rate of polyp, advanced age (>50 years), and preoperative laboratory results.^{8,9}

Larger polyp size increases the likelihood of malignancy.^{10,11} Terzi et al reported the histopathologic characteristics of polypoid lesions in 100 patients who underwent cholecystectomy.¹² Of the 74 patients with benign gallbladder polyps, only 11 (15%) had polyps larger than 10 mm. In contrast, 23 (88%) of the 26 malignant polyps were larger than 10 mm. A previous study reported that polyps larger than 5 mm had potential for malignancy and all polyps larger than 15 mm were malignant.¹³ In these above-mentioned studies, larger polyp size suggested a higher likelihood of malignancy. Based on these previous polyp size findings, this study examined the standard size for cholecystectomy of gallbladder polyps and determined how to predict early gallbladder cancer preoperatively using a simple standard such as polyp size.

The present study calculated the AUC using the ROC curve to test the conventional size criteria for predicting the risk of malignancy and cholecystectomy. Our method differed from existing methods used to predict significance. This study assumed that malignancy is closely connected to polyp size, and predicting significance could be estimated with AUC. AUC is a measure of the overall performance of a diagnostic factor.^{14,15} It can be any value between 0 and 1 since both the x- and y-axes range from 0 to 1. The closer the AUC is to 1, the better the overall diagnostic performance of the factor. A factor with an AUC value of 1 is

perfectly accurate. The practical lower limit for the AUC of a diagnostic factor is 0.5 with a 95% CI. In the present study, the AUC for polyp size was 0.781 (95% CI, 0.660–0.903; $p < 0.001$). This could be considered a good score with good predictive value and statistical significance. In this study, there is a significant difference in the average polyp size between the cancer group (14 mm (median, range 9–30)) and non-cancer group (10.4 mm (median, range 1.9–45)) ($p < 0.001$). The ROC curve shows that 12.05 mm is the optimal point for predicting malignancy. Therefore, this size might be an acceptable size to consider cholecystectomy for preventive and curative treatment of malignant polyps.

Based on the above results, this study does not give definite guidelines on the management of 10–11 mm polyps. Previous studies reported a 10 mm cutoff value for considering cholecystectomy in patients with gallbladder polyps.^{10–12} However, using the ROC curve in this study, 10–11 mm polyps had identical sensitivity (82.4%) with very low specificity (49.4%–68.7%) and the size of non-cancer polyps with low malignant potential was similar with a mean value of 11.23 ± 4.07 . Therefore, in the absence of other risk factors, suggesting cholecystectomy to patients with only 10–11 mm polyps might need to be careful.

Many studies have demonstrated that malignant gallbladder polyps are significantly more common in patients over 50 years of age.^{3,16,17} This study identified that patient age is associated with the risk of developing malignant polyps (OR; 1.124 CI; 1.084–1.166, $p < 0.001$). Additionally, there was a significant difference in the mean age of patients with malignant gallbladder polyps (65.5 years (median, range 35–85)) compared to those with non-cancer gallbladder polyps (42 years (median, range 23–82)) ($p < 0.001$). Only one patient in the cancer group was less than 50 years old (36 years) with a large polyp (27 mm). This finding might be considered that there is a low possibility of gallbladder carcinoma in patients younger than 49 years old with polyps smaller than 12 mm.

Previous studies suggested that high BMI, fasting glucose, total cholesterol, total bilirubin, and CA-19-9 were risk factors of gallbladder cancer.^{18,19} The study of Lin et al demonstrated that the rate of hepatitis B surface antigen positivity was greater in patients with malignant gallbladder polyps compared to the general population²⁰. However, the above mentioned factors did not show any evidence as predictive factors for gallbladder cancer in this study. Although AST, ALT, and high BSA were determined to be predictors of malignant gallbladder polyps in this study, other previous studies had not shown these factors to be predictors. Therefore, the validity of these factors is questionable.

This study had several limitations. The study was a retrospective study from a single center despite the large number of cases. Furthermore, the number of patients in the neoplastic group was relatively small. Therefore, prospective multicenter studies will be needed to validate this study.

In conclusion, gallbladder polyps measuring more than 12 mm in size should clearly be treated with immediate cholecystectomy. 10–11 mm polyps with old age (>50 years), or with abnormal ultrasound findings, or with symptom might also need cholecystectomy. However,

asymptomatic young patients (less than 50 years old) with 10–11 mm sized gallbladder polyps have a low risk of malignancy, and therefore, a careful “wait and see with follow up by using ultrasonography strategy” might be more appropriate than immediate cholecystectomy.

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Conflict of interest

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Appendix A. Supplementary data

Supplementary data related to this article can be found at <https://doi.org/10.1016/j.asjsur.2018.03.005>.

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