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Gallbladder polyps growth rate is an independent risk factor for neoplastic polyps

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Abstract

Background: The size of gallbladder (GB) polyps is a representative risk factor for neoplastic polyps. However, whether growth rate during follow-up is associated with neoplastic polyps remains unclear.

Methods: From 2009 to 2019, a cohort of patients with GB polyps who underwent cholecystectomy was enrolled. We included only patients who underwent at least two abdominal ultrasonography procedures at least 6 months apart prior to cholecystectomy. Performance and optimal cutoff value of polyp growth rate for predicting neoplastic polyps were estimated using receiver operating characteristic (ROC) analysis. In addition to growth rate, several other variables considered suitable for predicting neoplastic polyps were also investigated. A nomogram was created to predict neoplastic polyps.

Results: A total of 239 patients with neoplastic polyps (n = 27, 11.3%) and non-neoplastic polyps (n = 212, 88.7%) were included. The median follow-up period was 28.5 months. The area under the ROC curve (AUROC) of polyp growth rate for neoplastic polyps was 0.66 (95% confidence interval, 0.59–0.72). The growth rate cutoff value for prediction of neoplastic polyps was 3 mm/year (sensitivity, 37.0%; specificity, 86.3%). Multivariate analysis identified several factors predicting neoplastic polyps: polyp size ≥10 mm (odds ratio [OR], 3.74, p = 0.041), solitary polyp (OR, 3.92, p = 0.004), and polyp growth rate ≥ 3 mm/year (OR, 2.75, p = 0.031). The AUROC of the nomogram using these three significant factors in multivariate analysis was 0.71.

Conclusion: GB polyps with a growth rate of over 3 mm per year on ultrasonography during follow-up should be considered a risk factor for neoplastic polyps.

KEYWORDS

gallbladder polyp, growth rate, neoplastic polyp, risk factor, ultrasonography

INTRODUCTION

Gallbladder (GB) polyps are lesions in which the GB wall protrudes into the lumen, and affect 4%–5% of the adult population.[1,2] Most GB polyps are benign non-neoplastic polyps, but neoplastic polyps, including adenomas and early cancers, can mimic non-neoplastic polyps on imaging and therefore require differentiation.[3] Since these polyps cannot be distinguished by preoperative biopsy, the risk factors for neoplastic polyps known from previous studies are taken into account when deciding whether to perform cholecystectomy. The most well-known risk factor for neoplastic polyps is size; the larger it is, the more likely it is to be a neoplastic polyp, especially when the size is larger than 1 cm.[4,5] An increase in GB polyp size during the follow-up period is also considered a risk factor for neoplastic polyps, but few studies have explored this. A systematic review of the growth rate and malignant potential of GB polyps reported that it was difficult to draw definitive conclusions as there were few reports of growth rates in the studies included in analysis.[6] In addition, the latest guidelines for GB polyps, the joint guidelines of European groups, considered 2 mm in growth during follow-up a risk factor for malignancy, but the evidence was weak.[7] Therefore, we sought to evaluate whether the growth of GB polyps on ultrasound follow-up is a risk factor for neoplastic polyps.

Key summary

Summarize the established knowledge on this subject

- The size of gallbladder polyps is a well-known risk factor for neoplastic polyps.
- It is not yet clear whether growth rate of gallbladder polyps during follow-up is related to neoplastic polyps.

What are the significant and/or new findings of this study?

- We found that gallbladder polyp growth rate ≥ 3 mm/year on ultrasonography during follow-up was an independent risk factor for neoplastic polyps.

METHODS

Patients and data collection

Data from patients with GB polyps who underwent cholecystectomy at Seoul St. Mary's Hospital between January 2009 and April 2019 were retrospectively reviewed. Among these, we enrolled patients who underwent at least two abdominal ultrasonography examinations at least 6 months apart before cholecystectomy.

Demographic and clinical data including age, sex, body mass index, underlying diabetes mellitus, ultrasonographic reports, and pathologic reports of cholecystectomy were obtained from electronic medical records. From ultrasonographic reports, data on the size, shape and number of GB polyps, fatty liver grade, and the presence or absence of GB stones were gathered. Using pathologic reports, adenoma and adenocarcinoma were classified as neoplastic polyps, and cholesterol, inflammatory, and hyperplastic polyps were classified as non-neoplastic polyps. The growth rate of GB polyps was defined as the difference in polyp size between the last and first ultrasound examinations divided by the time interval between examinations.

This study was conducted in accordance with the Declaration of Helsinki and the need for informed consent was waived by the Institutional Review Board of Seoul St. Mary's Hospital (IRB No. KC20RISI0862).

Statistical analysis

Continuous data are presented as mean ± standard deviation and median (interquartile range [IQR]) whereas categorical data are presented as frequency (percentage). Comparisons of baseline characteristics between neoplastic and non-neoplastic groups were performed using the Student's *t*-test, Fisher's exact test, and chi-square test as deemed appropriate. The optimal cut-off value of polyp growth rate for predicting neoplastic polyp was determined using the receiver operating characteristic (ROC) curve and Youden index. Univariate and multivariate logistic regression analyses were performed to determine factors predicting neoplastic polyps. Variables with *p* values less than 0.1 in univariate analysis were included in multivariate analysis. A nomogram was built to predict the probability of neoplastic polyps using factors that were significant in multivariate analysis. Statistical analyses were performed using SPSS version 24.0 (IBM Corp., Armonk), MedCalc Statistical Software version 19.6.1 (MedCalc Software Ltd), and R version 3.2.3 (https://www.r-project.org) A *p* value less than 0.05 was considered statistically significant.

RESULTS

Baseline characteristics of patients

During the study period, there were 594 patients with GB polyps who underwent cholecystectomy at our institution. Among them, 239 patients who underwent follow-up abdominal ultrasounds at least 6 months apart before cholecystectomy were enrolled in this study. The median follow-up duration was 28.5 months (IQR, 13.2–58.6 months). Baseline characteristics of patients are shown in Table 1. There were 27 patients with neoplastic GB polyps and 212 patients with non-neoplastic GB polyps. The neoplastic polyp group was older than the non-neoplastic group (54.0 ± 13.4 years vs. 48.8 ± 11.3 years, $p = 0.029$). Mean polyp size was significantly larger in the neoplastic polyp group compared to the non-neoplastic polyp group (14.0 ± 5.2 mm vs. 10.2 ± 3.2 mm, $p = 0.001$). The proportion of solitary polyp was higher in the neoplastic polyp group (74.1% vs. 42.5%, $p = 0.002$). Polyps with hyperechoic spots were fewer in the neoplastic polyp group (29.6% vs. 86.8%, $p = 0.041$). Mean polyp growth rate was higher in the neoplastic polyp group, but this was not statistically significant (4.2 ± 7.9 mm/year vs. 1.5 ± 1.9 mm/year,

TABLE 1 Baseline characteristics of patients

Variables	Neoplastic polyp (n = 27)	Non-neoplastic polyp (n = 212)	p value
Age, years	54.0 ± 13.4	48.8 ± 11.3	0.029
Sex (male)	15 (55.6%)	111 (52.4%)	0.754
Body mass index, kg/m^2	25.0 ± 3.3	24.2 ± 3.3	0.229
Diabetes mellitus	2 (7.4%)	19 (9.0%)	0.788
Size, mm	14.0 ± 5.2	10.2 ± 3.2	0.001
Number			0.002
Solitary	20 (74.1%)	90 (42.5%)	
Multiple	7 (25.9%)	122 (57.5%)	
Shape			0.143
Sessile	16 (59.3%)	94 (44.3%)	
Pedunculated	11 (40.7%)	118 (55.7%)	
Hyperechoic spot	8 (29.6%)	184 (86.8%)	0.041
Fatty liver			0.794
None	19 (70.4%)	140 (66.0%)	
Mild	5 (18.5%)	50 (23.6%)	
Moderate	3 (11.1%)	18 (8.5%)	
Severe	0 (0.0%)	4 (1.9%)	
Gallstone	2 (7.4%)	26 (12.3%)	0.750
Growth rate (mm/year)	4.2 ± 7.9	1.5 ± 1.9	0.098

Note: Data are given as n (%) or mean ± SD.

p = 0.098). Other clinical characteristics, including sex, body mass index, diabetes mellitus, polyp shape, fatty liver grade, and presence of gallstones were not significantly different between groups.

Factors predicting neoplastic polyps

Figure 1 shows the ROC curve for polyp growth rate to predict neoplastic polyps. The area under the curve (AUROC) of polyp growth rate was 0.66 (95% confidence interval [CI], 0.59–0.72). According to the Youden index, the optimal cut-off value of polyp growth rate for predicting neoplastic polyps was 3 mm/year (sensitivity, 37.0%; specificity, 86.3%).

In univariate analysis, age ≥60 years, polyp size ≥10 mm, solitary polyp, polyp growth rate ≥ 3 mm/year, and absence of hyperechoic spot were significantly associated with neoplastic polyps. Multivariate analysis revealed three independent factors for predicting neoplastic polyps: polyp size ≥10 mm (odds ratio [OR], 3.19; 95% CI: 1.01–14.25; p = 0.046), solitary polyp (OR, 3.49; 95% CI: 1.43–9.43; p = 0.008), and polyp growth rate ≥ 3 mm/year (OR, 2.97; 95% CI 1.16–7.38; p = 0.020) (Table 2).

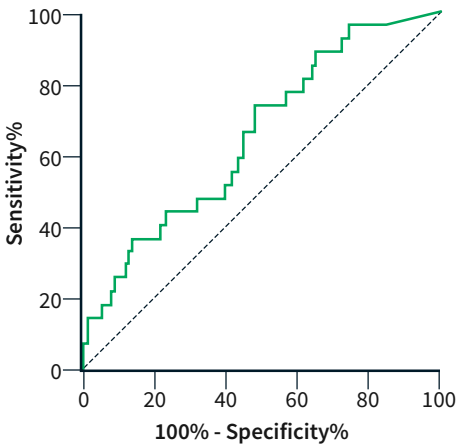


FIGURE 1 Receiver operating characteristic (ROC) curve analysis was performed to determine the power of polyp growth rate per year for predicting neoplastic polyps

TABLE 2 Univariate and multivariate logistic regression analysis of factors associated with neoplastic polyp

	Univariate		Multivariate	
Variables	**Odds ratio (95% CI)**	***p* value**	**Odds ratio (95% CI)**	***p* value**
Age ≥60 years	2.25 (0.96–5.25)	0.062		
Size ≥10 mm in ultrasonography	3.94 (1.15–13.55)	0.029	3.19 (1.01–14.25)	0.046
Solitary polyp	3.87 (1.57–9.55)	0.003	3.49 (1.43–9.43)	0.008
Shape, sessile	1.83 (0.81–4.12)	0.147		
Hyperechoic spot	0.36 (0.15–0.95)	0.030		
Gallstone	0.57 (0.13–2.56)	0.465		
Growth rate ≥ 3 mm/year	3.57 (1.49–8.53)	0.004	2.97 (1.16–7.38)	0.020

Abbreviation: CI, confidence interval

A nomogram predicting neoplastic polyps

Using factors such as polyp size ≥10 mm, solitary polyp, and polyp growth rate ≥ 3 mm/year which were significant factors in multivariate analysis, we developed a simple nomogram to predict the probability of neoplastic polyps (Figure 2). A score of 100 was obtained in cases of polyp growth rate ≥3 mm/year, and 24 in cases of polyp growth rate <3 mm/year. The score was 81 in cases of solitary polyps, and 0 in cases of multiple polyps. In addition, the score was 67 in cases of polyp size ≥10 mm, and 32 in cases of size <10 mm. We further investigated whether this model could improve the prediction of neoplastic polyp (Figure 3). The AUROC of the nomogram was 0.71 (95% CI, 0.60–0.82), which had better performance than the model using the polyp growth rate alone. According to the Youden index, the optimal cut-off point of the nomogram was 169.5 (sensitivity, 44.0%; specificity, 88.2%).

DISCUSSION

In this study, we demonstrated that an increase in GB polyp size was significantly associated with neoplastic polyps and proposed an optimal cut-off value for polyp growth rate to predict neoplastic polyps. To the best of our knowledge, this is the first study to propose an optimal cut-off for polyp growth rate that has a significant association with neoplastic polyps. Furthermore, to date this is the largest retrospective study related to GB polyp growth rate. There have been few studies on the association between the growth rate of GB polyps and neoplastic polyps. Cairns et al. reported that an increase in polyp size could predict neoplastic polyps, but there was no mention of follow-up interval or polyp growth rate.[8] Another study related to polyp growth conducted by Shin et al. showed that a polyp growth rate greater than 0.6 mm/month was associated with neoplastic polyps in univariate analysis; however, there was no significant association on multivariate analysis.[9] The study by Shin et al. had a total of 145 subjects, which was less than that of our study; this relatively small number of subjects could be the reason for not reaching statistical significance. The joint guidelines for GB polyp in the Europe group consider increased polyp size a risk factor for neoplastic polyps[7] and cholecystectomy is recommended for GB polyps with a size increase by 2 mm or more during the follow-up period. However, this recommendation was not based on research, but based on a hypothesis that an increase of 2 mm or more could be considered an actual size increase.[7,10] Therefore, the cutoff value of 3 mm/year polyp growth rate proposed for the first time in this study can be used as a good criterion for predicting neoplastic polyps once verified in a future large-scale study. Bao et al. reported that the growth rate was not significantly different between the cholesterol polyp and adenoma groups.[11] However, when their cohort was divided into ≤ 4 mm and > 4 mm in terms of size progression, the frequency of adenoma was tended to be higher in the > 4 mm group than ≤ 4 mm group (41/322, 12.7% vs. 38/198, 19.2%, $p = 0.058$), implicating the interval growth might have a role in the predicting neoplastic polyps. In addition, the short-term follow-up period in the study by Bao et al. may also have contributed to the absence of differences in growth rates between the two groups.

We also demonstrated in this study that polyp size greater than 10 mm and solitary polyps were independent risk factors for neoplastic polyps, consistent with previous studies.[1,12] Older age, which is associated with most neoplastic diseases, showed a significant trend in univariate analysis in this study, but not in multivariate analysis.[1,13] Sessile shape, which was a risk factor for neoplastic polyps in other studies, was more frequent in the neoplastic polyp group but not significantly so.[14,15] This difference from previous studies may be due to the retrospective nature of this study and the relatively small number of subjects.

Diep et al. recently described that the growth rate of GB polyps was not significantly different between the solitary and multi-polyp groups.[16] When we compared the growth rate between solitary and multi-polyp groups in the present study, there was no significant difference (mean 2.1 ± 4.4 mm/year, solitary polyp group, vs. 1.6 ± 1.8 mm/year, multi-polyp group, $p = 0.766$), which is consistent with the study by Diep et al.[16] These findings suggest that the number of GB polyps and growth rate of them might be independent factors for predicting neoplastic polyps, as we also showed in the multivariate analysis (showed in Table 2).

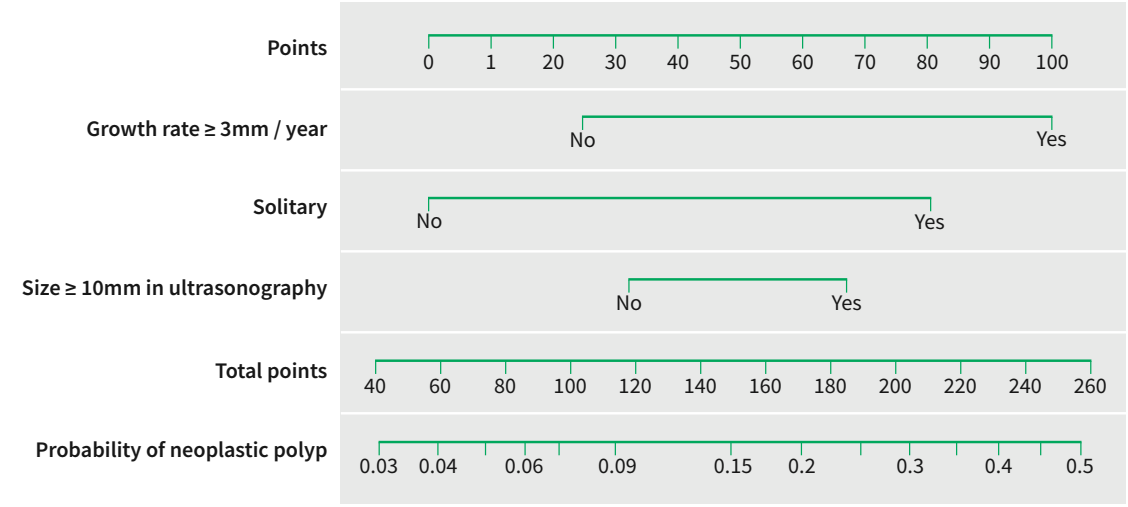
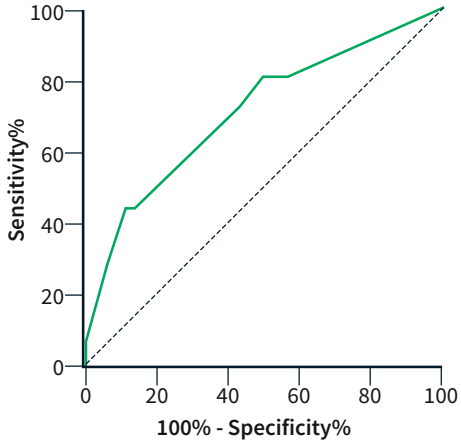


FIGURE 2 A nomogram was built for predicting neoplastic polyps



AUROC = 0.714 (0.603-0.824)
P = 0.0003
Cut-off: 169.5 points
Sensitivity = 44.4%
Specificity = 88.2%

FIGURE 3 Receiver operating characteristic (ROC) curve analysis was performed to determine the power of the nomogram for predicting neoplastic polyps

For polyps larger than 7 mm, the question may be raised whether a growth rate of 3 mm/year would have additional clinical utility beyond the 10 mm size criterion. This is because if a polyp with a size of 7 mm or more exceeds the growth rate of 3 mm/year, the size will inevitably exceed the 10 mm size criterion at follow-up after 1 year. However, there was a report that the 10 mm size criterion might be imperfect to discriminate neoplastic GB polyps, with a sensitivity of 68.1%.[17] Therefore, it is necessary to examine in more detail whether there is an additional clinical utility of growth rate. Our data also suggested the low proportion of neoplastic polyps in patients with ≥10 mm polyps at the initial evaluation, implicating that 10 mm size alone might be insufficient to discriminate neoplastic polyps. Among patients (≥10 mm in size) without prompt cholecystectomy, 33% of patients with a growth rate over 3 mm/year had neoplastic polyps in the surgical specimens, suggesting the growth rate might be helpful in the increased sensitivity to finding neoplastic polyps. We showed that a nomogram combining the risk factors would increase the predictive ability of neoplastic polyps, and it would be useful in deciding whether and when to perform the surgery. Nevertheless, the adjustment of this useful tool is needed for further studies to use in the real clinical practice.

Sugiyama et al. showed that internal echogenic pattern in addition to the morphology might be helpful to predict neoplastic polyps.[18] Internal hyperechoic spot suggests the cholesterol polyp, whereas hypoechoic foci are helpful to predict neoplastic polyps.[19] In this study, we found that the absence of hyperechoic spots was a significant factor for predicting neoplastic polyps in the univariate analysis, but did not reach statistical significance in the multivariate analysis. These results might be due to the small sample size of total study patients or neoplastic polyps, but also suggest that future studies should consider the hyperechoic spot as an associated factor for non-neoplastic polyps.

There are some limitations in this study. First, this is a retrospective study conducted at a single institution. Second, there may be selection bias in this study because it was performed in a retrospective design and only included patients who underwent cholecystectomy.

In conclusion, our study showed that a GB polyp growth rate of 3 mm or more per year is a significant predictor of neoplastic polyps. In addition to the previously established risk factors for neoplastic GB polyps, cholecystectomy should be considered if the GB polyp growth rate is 3 mm/year or more.

AUTHOR CONTRIBUTIONS

Young Hoon Choi designed the study. Tae Ho Hong, Young Kyoung You, In Seok Lee, Young Hoon Choi and Ho Joong Choi provided clinical data. Ji Won Han and Young Hoon Choi collected and analyzed the data. In Seok Lee and Young Hoon Choi supervised the analyses and the manuscript. Ji Won Han and Young Hoon Choi wrote and edited the manuscript.

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CONFLICT OF INTEREST

The author declares no conflict of interest.

INSTITUTIONAL REVIEW BOARD STATEMENT

The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Institutional Review Board of Seoul St. Mary's Hospital (IRB No. KC20RISI0862).

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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