

Pre-operative factors that can predict neoplastic polypoid lesions of the gallbladder

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Abstract

AIM: To investigate the preoperative factors that can predict neoplastic polypoid lesions of the gallbladder (PLGs) as well as malignant PLGs.

METHODS: A retrospective analysis was conducted on the 210 consecutively enrolled patients who underwent cholecystectomy due to a PLG larger than 10 mm, as was determined by preoperative trans-abdominal ultrasonography or endoscopic ultrasonography. We ana-

lyzed the medical, laboratory, radiologic data and the pathologic results.

RESULTS: In 210 cases, 146 had non-neoplastic polyps (69.5%) and 64 cases were neoplastic polyps (30.5%). An older age (≥ 65 years), the presence of diabetes mellitus (DM) and the size of polyp (≥ 15 mm) were revealed to be independent predictive variables for neoplastic polyps with odd ratios (OR) of 2.27 ($P = 0.044$), 2.64 ($P = 0.021$) and 4.94 ($P < 0.01$), respectively. Among the neoplastic PLGs, an older age (≥ 65 years), the presence of DM and polyp size (≥ 15 mm) were associated with malignancy with ORs of 4.97 ($P = 0.005$), 6.13 ($P = 0.001$) and 20.55 ($P < 0.001$), respectively.

CONCLUSION: Among patients with PLGs larger than 10 mm in size, higher risk groups such as elderly patients more than 65 years old, those with DM or a large polyp size (≥ 15 mm) should be managed by cholecystectomy.

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Key words: Gallbladder; Polyp; Neoplastic; Cholecystectomy; Diabetes; Pre-operative factors

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INTRODUCTION

A polypoid lesions of the gallbladder (PLGs) is defined

as any elevated lesion of the mucosal surface of the gallbladder wall. Sonographers have described PLGs as an image with similar echogenicity as that of the gallbladder wall; the lesion projects into the lumen and it is fixed, lacks displacement, it may or may not have a pedicle and it shows no acoustic shadow on ultrasonography^[1-3]. The prevalence of PLGs varies from 0.3% to 12% in healthy adults who undergo abdominal ultrasonography (US)^[4-11]. Although the exact prevalence of PLGs is not clear, the detection of PLGs has been increasing according to the more frequent use of abdominal imaging. Most of the PLGs that are without symptoms are non-neoplastic lesions, but a small portion of them are found to be malignant or premalignant neoplasms. The incidence of malignant polyps has varied from 1% to 20% of the resected PLGs among diverse study populations in previous reports^[2,12-17]. The largest PLG series was a review of 172 surgically resected cases, and this showed that the most common type of PLG was the cholesterol polyp (62.8%). They also reported that 7% were inflammatory polyps, 7% were hyperplasia, 5.9% were adenoma, 9.6% were miscellaneous and 7.7% were malignant polyps in the study population^[18]. Due to the considerable incidence of malignant polyps among the PLGs, surgical resection, including laparoscopic cholecystectomy, is widely accepted as the treatment of choice for PLGs that are more than 10 mm in size^[18]. This surgical treatment guideline has been supported by many previous published reports^[14,15,19]. However, the number of non-neoplastic polyps that are unnecessarily resected exceeds more than 3 times the number of neoplastic polyps when the resected polyps are in accordance with the above mentioned guideline^[20]. For this reason, some clinicians hesitate to recommend an operation based on this guideline.

Over the last 10 years, several interesting small trials have attempted to determine the endoscopic or transabdominal ultrasonographic features of neoplastic gallbladder polyps, as compared with those of nonneoplastic polyps^[10,11,21-23]. However, these sonographic findings have several limitations such as a mixed component of a benign nature, the lack of standardization and interobserver discrepancy^[20].

With this background, this study aimed to reveal the clinical and sonographic predictive findings of neoplastic PLGs, including malignant PLGs, in patients who have PLGs larger than 10 mm. We also tried to demonstrate the guidelines for the decision making for the surgical management of incidentally diagnosed gallbladder polyps.

MATERIALS AND METHODS

Patients

We performed a retrospective analysis of the consecutively enrolled patients who were diagnosed with a PLG larger than 10 mm by preoperative trans-abdominal ultrasonography or endoscopic ultrasonography (EUS) between March 1, 2003 and April 30, 2009 at Seoul National University Bundang Hospital. The study protocol

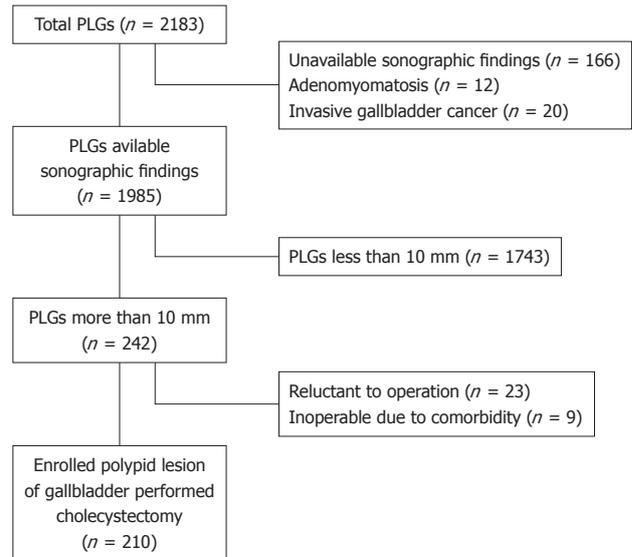


Figure 1 A diagram of the patients' enrollment. PLGs: Polypoid lesions of the gallbladder.

was approved by the Institutional Review Board of our hospital. According to our institution's policy, we recommended cholecystectomy to all patients who had a PLG that was more than 10 mm in size if they were in an operable condition. During the study period, a total of 2281 cases of PLG were diagnosed. Among them, 12 definite adenomyomatosis lesions with a sonographic "comet tail sign" and 20 lesions that were suspected of being gallbladder cancer that had invaded the liver or other adjacent organs were excluded. The 166 cases that did not have sonographic findings available or where polyps were measured by different sonographic equipment were excluded. Among the remaining cases, 1743 patients with small polyps (smaller than 10 mm) and 31 patients who did not undergo an operation were also excluded. Therefore, 210 patients who underwent cholecystectomy were ultimately analyzed in this study (Figure 1).

Based on the final diagnosis of the pathologic reports, all the polyps were divided into 2 groups: the non-neoplastic polyps (chronic cholecystitis, inflammatory polyps, adenomyomatosis, cholesterosis or cholesterol polyps) and the neoplastic polyps (adenomatous polyps with low grade dysplasia, adenomatous polyps with high grade dysplasia, adenocarcinoma)^[24].

The following parameters of all patients were recorded and analyzed: the demographic features, including age, gender, a smoking history, a history of drinking alcohol, the presence of diabetes mellitus (DM), the presence of hypertension, clinical symptoms, measurements of obesity, a complete blood count, a routine chemistry panel, the fasting glucose level and the lipid profiles. The body mass index (BMI) was calculated by dividing the weight in kilograms by the square of the height in meters. Obesity was defined as a BMI > 25 kg/m² according to the Asian-Pacific criteria for obesity^[25]. Clinical symptoms were defined as abdominal pain that was compatible with biliary colic, such as right upper quadrant pain with or

without radiation pain that becomes aggravated with eating a fatty meal.

The radiologic reports were retrospectively reviewed by one experienced radiologist to describe and record the polyp size, the echogenicity, the echo pattern, the number of lesions, the location of lesion, lesion combined with gallbladder stones, the size change of the lesion and the duration of the size change. The histologic findings of all the resected specimens were retrospectively reviewed by one experienced pathologist.

Equipment and the definition of the sonographic findings

Abdominal sonography was performed by well trained sonographers who used 6-2 MHz curvilinear transducers with IU 22 or HDI 5000 units (Phillips). An EUS (endoscopic ultrasonogram) was obtained with 7.5-MHz or 12-MHz radial sector scan transducers (EUS-2000, Olympus Optical Co.), and these procedures were performed by 2 well-trained endosonographers. The EUS probe was advanced to the second portion or bulb of the duodenum and the gallbladder was scanned *via* the water-filled balloon method. All the sonographic findings of the patients were reviewed by two experienced radiologists.

The size of the polypoid lesion was measured by assessing the long diameter of the largest polypoid lesion. The echogenicity was determined on the ultrasonogram by comparing it with the echogenicity of the adjacent liver. For some cases that had a severe fatty liver, the echogenicity of the lesion was compared with the echogenicity of the kidney in same ultrasonographic series of the case. We classified the echogenicity into 3 categories: “hypoechoic”, “isoechoic” and “hyperechoic”. The surface pattern of the polypoid lesions was divided into 2 groups: “smooth” and “nodular”^[26]. The internal echo pattern of the polypoid lesions was divided into 2 categories: “homogeneous” and “inhomogeneous”. The number of polyps was divided into 2 categories: “multiple” and “solitary”. The patients with multiple polyps that consisted of both neoplastic and non-neoplastic polyps in one specimen were classified as having neoplastic polyps. The shape of the polypoid lesions was classified to 2 categories: “pedunculated” and “sessile”. Hyperechoic spots were defined “a single 1-5 mm, highly echogenic dot”, or “partial aggregates of 1-3 mm sized, multiple, highly echogenic spots”^[26].

Statistical analysis

Continuous variables are presented as the mean \pm SD, and categorical variables are summarized as frequencies and percents. The variables were compared assuming a 95% probability for rejection of the null hypotheses. Fisher’s exact test, Pearson’s χ^2 test and student’s *t*-test were used, when appropriate, to calculate the statistical significance of the different demographic and clinical variables. Multivariate binary logistic regression analysis was performed to determine the significance of the various predictive variables that were found to be significant by univariate

analysis. *P* values of < 0.05 were deemed as significant. All the statistical analyses were carried out using SPSS 15.0 software (SPSS, Chicago, Illinois, USA).

RESULTS

Clinical and sonographic characteristics of the patients

Of the 210 patients, 145 had non-neoplastic polyps (69.0%) and 65 had neoplastic polyps (31.0%). The histological diagnosis of the resected PLGs revealed that 54 cases (25.7%) were chronic cholecystitis, 3 cases (1.4%) were inflammatory polyps, 78 cases (37.1%) were cholesterol polyps, 10 cases (4.8%) were adenomatous, 29 cases (13.8%) were adenoma with low grade dysplasia, 6 cases (2.9%) were adenoma with high grade dysplasia and 30 cases (14.3%) were adenocarcinoma.

We compared the clinical and laboratory features between the non-neoplastic polyps group and the neoplastic polyps group. The results are described in Table 1. The mean age, the proportion of DM patients and the mean serum alanine transferase (ALT) level were higher in the neoplastic polyp group than that in the non-neoplastic group ($P < 0.001$, $P < 0.001$, $P = 0.041$, respectively). Yet no significant difference was found for gender, medical history and the other laboratory findings between the two groups.

For the sonographic findings, the mean sonographic diameters of the polyps were 13.5 ± 4.5 mm and 22.1 ± 11.1 mm for the non-neoplastic group and the neoplastic group, respectively ($P < 0.001$). In addition, the inhomogeneous echo pattern ($P = 0.019$), a solitary lesion ($P = 0.002$) and a nodular surface pattern of the polyps ($P < 0.001$) revealed significant correlation with neoplastic polyps (Table 1).

For the detailed analysis, maximum diameter was divided to 2 categories by use of receiver-operator characteristic (ROC) curves. At a cutoff value of 15 mm diameter of PLGs’ size, the area under the ROC curve (AUC) had the highest sensitivity and specificity. (70.8%, 75.9%, Figure 2).

Predictive variables for neoplastic PLGs

On the univariate analysis, we obtained several important predictive clinical and sonographic values such as an age > 65 years, the presence of DM, the ALT level, a larger sonographic size (≥ 15 mm), solitary lesions and a nodular sonographic surface pattern (Table 1). On multivariate analysis, an older age (≥ 65 years), the presence of DM and polyp size (≥ 15 mm) were found to be the independent predictive variables for neoplastic polyps [odds ratios (OR) = 2.27, $P = 0.044$, OR = 2.64, $P = 0.021$ and OR = 4.94, $P < 0.001$, respectively]. A nodular surface pattern was found to have an association with neoplastic polyps, with borderline significance (OR = 2.31, $P = 0.058$) (Table 2).

Predictive variables for malignant PLGs

In addition, we subdivided the neoplastic group into two

Table 1 Comparative data for the prevalence of the demographic, laboratory and sonographic findings between the non-neoplastic polyp group and the neoplastic polyp group (mean ± SD) *n* (%)

	Total (<i>n</i> = 210)	Non-neoplastic (<i>n</i> = 146)	Neoplastic (<i>n</i> = 64)	<i>P</i>
Age (yr)	51.8 ± 13.7	49.1 ± 12.3	57.9 ± 14.7	< 0.001
Age > 65 yr	49 (23.3)	22 (15.1)	27 (42.2)	< 0.001
Gender, male	109 (51.9)	77 (52.7)	32 (50.0)	0.785
BMI (kg/m ²)	24.0 ± 2.97	23.9 ± 3.01	24.1 ± 2.89	0.620
Obesity	79 (38.2)	53 (36.6)	26 (41.9)	0.465
Hypertension	34 (16.3)	20 (13.7)	14 (22.2)	0.126
Diabetes mellitus	46 (21.9)	21 (13.0)	27 (42.1)	< 0.001
Hypercholesterolemia	77 (36.7)	57 (39.0)	20 (31.3)	0.135
RUQ pain	37 (17.6)	24 (16.4)	13 (20.3)	0.498
Total bilirubin (g/dL)	1.22 ± 3.41	0.91 ± 0.41	1.93 ± 6.17	0.189
ALP (g/dL)	69.4 ± 60.9	62.5 ± 20.2	84.7 ± 104.7	0.097
AST (IU/dL)	33.2 ± 61.9	26.2 ± 21.4	49.2 ± 105.9	0.090
ALT (IU/dL)	34.5 ± 42.0	29.1 ± 23.3	47.0 ± 66.2	0.041
Size (mm)	16.1 ± 8.20	13.5 ± 4.5	22.1 ± 11.1	< 0.001
Size > 15 mm	78 (37.1)	33 (22.3)	45 (70.3)	< 0.001
Location				0.977
Fundus	156 (74.3)	109 (74.7)	47 (73.4)	
Body	44 (21.0)	30 (20.5)	14 (21.9)	
Neck	10 (4.8)	7 (4.8)	3 (4.7)	
No. of polyps				0.002
Multiple	76 (36.2)	63 (43.2)	13 (20.3)	
Solitary	134 (63.8)	83 (56.8)	51 (79.7)	
Hyperchoic spots				0.315
No	172 (81.9)	117 (80.1)	55 (85.9)	
Yes	38 (18.1)	29 (19.9)	9 (14.1)	
Echogenecity				0.125
Anechoic or hyperechoic	130 (61.9)	96 (65.8)	34 (53.1)	
Hypoechoic or isoechoic	80 (38.1)	50 (34.2)	30 (46.9)	
Echo pattern				0.093
Homogeneous	115 (52.9)	85 (58.2)	30 (46.9)	
Inhomogeneous	95 (45.2)	60 (41.1)	35 (54.7)	
Sonographic surface pattern				< 0.001
Smooth surface	174 (82.9)	131 (89.7)	43 (67.2)	
Nodular surface	36 (17.1)	15 (10.3)	21 (32.8)	

BMI: Body mass index; RUQ: Right upper quadrant; ALP: Alkaline phosphatase; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase. Obesity: BMI higher than 25 kg/m².

groups according their histologic results. The polyps that contained adenocarcinoma were classified as the malignant PLGs group and the other neoplastic polyps were classified as the benign PLGs group. We also compared the clinical and sonographic variables to discriminate the malignant PLGs group from the benign group. On univariate analysis, the important predictive clinical and sonographic values for malignant polyps were an older age (≥ 65 years, $P = 0.02$), the presence of DM ($P < 0.001$), the ALT level ($P = 0.033$), a larger sonographic size (≥ 15 mm, $P < 0.001$) and an inhomogeneous echo pattern ($P = 0.016$) (Table 3). But on multivariate analysis, it was observed that an older age (≥ 65 years), the presence of DM and polyp size (≥ 15 mm) had statistical significance

Table 2 Results of the multivariate logistic regression analysis for the factors that were significantly associated with neoplastic polypoid lesions of the gallbladder on univariate analysis

	Hazard ratio	95% CI	<i>P</i> -value
Age ≥ 65 yr old	2.27	1.02-5.06	0.044
Gender, male	1.08	0.57-2.51	0.617
DM	2.64	1.15-6.03	0.021
ALT level	1.008	0.99-1.02	0.168
Polyp size > 15 mm	4.94	2.43-10.02	< 0.001
Solitary polyp	0.59	0.26-1.33	0.205
Nodular surface pattern	2.31	0.97-5.50	0.058

DM: Diabetes mellitus; ALT: Alanine transaminase.

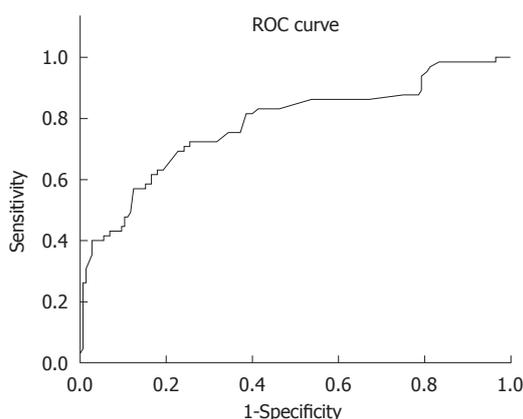


Figure 2 Receiver-operator characteristic curve of the sonographic size of the polypoid lesions of the gallbladder.

with the malignant PLGs group (OR = 4.97, $P = 0.005$, OR = 6.13, $P = 0.001$, OR = 20.55, $P < 0.001$, respectively) (Table 4).

For a more detailed analysis of the chronological change of the neoplastic polyps, we classified all the cases into three subgroups: the adenoma with low grade dysplasia group; the adenoma with high grade dysplasia group; and the adenocarcinoma group. After this subgroup analysis, we found a linear stepwise increase in the mean age of each groups; adenoma low grade dysplasia, high grade dysplasia and adenocarcinoma. The difference of the mean age was 18.9 years between the adenoma with low grade dysplasia group (46.4 ± 13.4 years) and the adenocarcinoma group (65.3 ± 18.0 years) ($P < 0.001$), and the difference of the mean age was 13.2 years between the high grade dysplasia group (52.1 ± 7.4 years) and the adenocarcinoma group ($P = 0.004$) (Figure 3).

DISCUSSION

GB polyps larger than 10 mm in size have generally been recommended for surgical resection despite of the large portion of non-neoplastic polyps among them. Because the current data for making the preoperative differentiation between neoplastic and non-neoplastic polyps is limited, a practical guideline was lacking to decide when to perform cholecystectomy. In this study, we tried to

Table 3 Comparative data for the prevalence of the demographic, laboratory and sonographic findings between the benign polyp group and the malignant polyp group for the 65 neoplastic polypoid lesions of the gallbladder (mean ± SD) *n* (%)

	Total (<i>n</i> = 65)	Benign (<i>n</i> = 35)	Malignant (<i>n</i> = 30)	<i>P</i>
Age (yr)	49.8 ± 13.5	47.2 ± 12.4	65.6 ± 7.39	< 0.001
Age > 65 yr	51 (24.3)	31 (17.2)	20 (66.7)	0.002
Gender, male	109 (51.9)	95 (52.6)	14 (46.7)	0.535
BMI (kg/m ²)	23.9 ± 2.97	24.0 ± 3.03	23.8 ± 2.66	0.835
Obesity	79 (38.2)	67 (37.2)	12 (40.0)	0.583
Hypertension	34 (16.3)	25 (13.8)	9 (30.0)	0.244
Diabetes mellitus	46 (21.9)	25 (13.8)	21 (70.0)	< 0.001
Hypercholesterolemia	19 (29.2)	10 (28.6)	7 (10.9)	0.830
RUQ pain	13 (6.2)	6 (4.1)	7 (10.9)	0.534
Total bilirubin (g/dL)	1.22 ± 3.41	0.89 ± 0.41	3.2 ± 6.17	0.166
ALP (g/dL)	69.3 ± 60.9	63.4 ± 20.0	104.9 ± 150.5	0.142
AST (IU/dL)	33.2 ± 61.9	26.6 ± 20.9	72.8 ± 151.3	0.106
ALT (IU/dL)	34.5 ± 42.0	29.2 ± 23.3	67.3 ± 9.09	0.033
Size (mm)	16.1 ± 8.20	14.3 ± 6.3	26.7 ± 10.0	< 0.001
Size >15 mm	45 (69.2)	17 (48.6)	28 (93.3)	< 0.001
Location				0.705
Fundus	40 (61.5)	21 (60.0)	20 (66.7)	
Body	18 (27.7)	10 (28.6)	8 (26.7)	
Neck	3 (6.0)	2 (4.2)	1 (1.5)	
No. of polyps				0.534
Multiple	13 (20.0)	8 (22.9)	5 (16.7)	
Solitary	52 (80.0)	27 (77.1)	25 (83.3)	
Hyperechoic spots				0.912
No	56 (86.2)	30 (85.7)	26 (86.7)	
Yes	9 (13.8)	5 (14.3)	4 (13.3)	
Echogenicity				0.180
Hyperechoic	34 (52.3)	21 (60.0)	13 (43.3)	
Hypoechoic or isoechoic	31 (47.7)	14 (40.0)	17 (56.7)	
Echo pattern				0.016
Homogeneous	30 (46.2)	21 (60.0)	9 (30.0)	
Inhomogeneous	35 (53.8)	14 (40.0)	21 (70.0)	
Sonographic surface pattern				0.135
Smooth surface	45 (69.2)	27 (77.1)	18 (60.0)	
Nodular surface	20 (30.8)	8 (22.9)	12 (40.0)	

BMI: Body mass index; RUQ: Right upper quadrant; ALP: Alkaline phosphatase; AST: Aspartate aminotransferase; ALT: Alanine transaminase; Obesity: BMI higher than 25 kg/m².

determine the predictive values for neoplastic PLGs. We evaluated a total of 210 cases of resected GB polyps larger than 10 mm in size and we found that an older age (> 65 years), a history of DM and a large size were the significant predictive values for neoplastic PLGs. We also found that an older age (> 65 years), a history of DM and a large size were significant predictive values for malignant PLGs.

In our study, older patients more than 65 years showed a statistical relation with neoplastic or malignant PLGs, as compared to that of the younger patients (*P* = 0.021, *P* = 0.005, respectively). This result corresponds with previous studies about the correlation between age and neoplastic PLGs^[12,13,18,27,28]. With this background, we tried to determine a more detailed correlation of age with the

Table 4 Results of the multivariate logistic regression analysis for the factors that were significantly associated with the malignant gallbladder polyps for the 65 neoplastic polypoid lesions of the gallbladder on univariate analysis

	Hazard ratio	95% CI	<i>P</i> -value
Age ≥ 65 yr old	4.97	1.58-15.61	0.005
Gender, male	1.19	0.38-3.73	0.764
DM	6.13	1.98-18.94	0.001
ALT level	1.01	0.99-1.02	0.075
Polyp size > 15 mm	20.55	4.25-99.39	< 0.001
Inhomogeneous echo pattern	1.60	0.50-5.09	0.418

DM: Diabetes mellitus; ALT: Alanine aminotransferase.

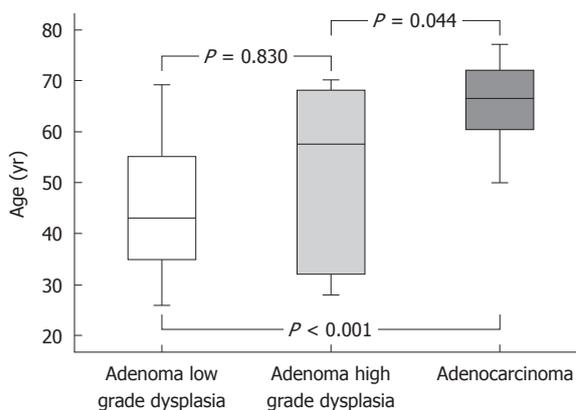


Figure 3 The age distribution according to the pathology subgroups with neoplastic polypoid lesions of the gallbladder.

subdivided groups among the neoplastic PLGs. According to pathologic results, the neoplastic PLGs were sorted into three subgroups; adenomatous polyp with low grade dysplasia, adenomatous polyp with high grade dysplasia and adenocarcinomas. We then compared the mean ages of each subgroup. After this detailed analysis, we found out a trend for a stepwise increase of mean age in the different neoplastic groups.

A new finding we discovered in this study was the relationship between DM and neoplastic polyps. Our results showed that patients with DM have a strong probability of having neoplastic and malignant polyps, as compared to that of the patients without DM, on univariate (*P* < 0.001, *P* < 0.001, respectively) and multivariate analyses, which were adjusted by age and gender (OR = 2.64, *P* = 0.021, and OR = 6.13, *P* = 0.001, respectively). There has been one document which reported the relation between diabetes and gallbladder cancer^[29]. But the exact mechanism or pathogenesis is not known. There have been a few reports that have found DM or hyperglycemia to be an independent risk factor for gastrointestinal or endocrine malignancies, such as colorectal^[30] or pancreatic cancers^[31]. Some recent researchers have proposed that the insulin resistance associated with hyperinsulinemia plays an important role as an oncogenic factor^[32,33]. According to many etiologic studies, it has become evident that the insulin-like growth fac-

tor (IGF) system plays a permissive role in cancer development and tumor progression^[34-38]. But, none of them mentioned any evidence of the IGF-I receptor pathway being involved in the development of gallbladder cancer. So we think that well designed trials are warranted in order to prove that this IGF signal pathway system plays a leading role in developing gallbladder cancer.

We found that the size of polyps (≥ 15 mm) is a powerful predictor for neoplastic polyps (OR = 4.94, $P < 0.001$). There was also a similar trend for malignant polyps (OR = 20.55, $P < 0.001$). Many studies have reported on the size criteria of PLGs as one of the predictive values for neoplastic lesions. The majority of them insisted that a size of gallbladder polyps more than 10 mm may be the most reliable predictor of malignant neoplasm^[12,13,18,27,28]. In a retrospective analysis of 354 subjects with resected PLGs, the authors suggested increasing the size criteria for cholecystectomy from 10 to 12 mm^[39]. Our study result showed a larger size than the previous noted criteria because small polyps less than 10 mm were not included in the analysis.

For the sonographic findings, solitary polyps ($P = 0.001$), an inhomogeneous echo pattern ($P = 0.019$) and a nodular surface pattern ($P < 0.001$) had a significant correlation with neoplastic PLGs on univariate analysis. However, only one variable, the nodular surface pattern, showed borderline statistical correlation with neoplastic polyps on the multivariate analysis. In addition, a nodular surface pattern did not show statistical significance with malignant polyps. The other sonographic parameters failed to show correlation with neoplastic or malignant PLGs. Many sonographers and endosonographers have recently tried to determine the sonographic characteristics that can reliably predict premalignant polypoid lesions in the gallbladder^[20,21,23,40]. They have suggested various sonographic findings as having predictive value for neoplastic lesions; the echo pattern, marginal irregularity, the shape, solitary lesion and preservation or loss of the GB wall layer structure. In spite of vigorous efforts to standardize these ultrasonographic features, inter-observer discrepancy is still the main concern to utilize these values to differentiate malignant polyps from benign polyps.

On the contrary, among 110 cases, which were lower risk groups for neoplastic polyps, such as those younger than 65 years old, those without DM and those with polyps less than 15 mm in sonographic diameter, 15 cases (13.6%) were reported as neoplastic polyps and the remaining 95 cases (86.4%) were non-neoplastic polyps.

The major limitations of this study include the following; first, this is not prospective study, rather, it is a cross-sectional study. There was no additional follow up data about the unresected PLGs more than 10 mm in size. However, because this study included patients who were consecutively enrolled during the study period, we could rule out a common selection bias. To the best of our knowledge, this study is the largest study that has enrolled patients with pathologically confirmed PLG larger than 10 mm in size. Thus, this data might be valuable when

making decisions on how to manage such patients with PLGs.

In conclusion, among patients with PLGs more than 10 mm in size, the higher risk groups, such as elderly patients who are more than 65 years, those with DM and those with a large sized polyp (≥ 15 mm) should be recommended cholecystectomy more seriously than other groups.

COMMENTS

Background

Some neoplastic polypoid lesions of the gallbladder (PLGs) including early cancer show similar appearances to the non-neoplastic PLGs. But there have been no definite guidelines except size criteria (more than 10 mm diameter) for the recommendation of surgical resection.

Research frontiers

Many studies have investigated the relationship between the neoplastic nature of PLGs and their morphological characteristics such as the number of polyps, the polyp shape, the diameter of the largest polyp, the echo level and internal echo pattern, and the polyp margin. But previously published documents showed a lack of case number, pathologic results, and long term follow up data. Also reports about the relationship between other clinical parameters and neoplastic PLGs were rare.

Innovations and breakthroughs

The authors performed the study using the consecutively enrolled pathologic data of patients with PLGs more than 10 mm in size to eliminate selection bias. This study demonstrated old age and diabetes history are added to the size criteria for predictive values of neoplastic PLGs for the decision about surgical resection.

Applications

Among patients with PLGs more than 10 mm in size considering surgical resection, the higher risk groups such as elderly patients who are more than 65 years, those with diabetes mellitus (DM) and those with a large sized polyp (≥ 15 mm) should be recommended cholecystectomy more seriously than other groups.

Terminology

Neoplastic PLGs: PLGs which have the features of the neoplasm including adenoma and adenocarcinoma. Non-neoplastic PLGs: PLGs which do not have the features of the neoplasm including cholesterol polyps, adenomyomatosis and inflammatory polyps.

Peer review

The authors described that older age, DM and polyp size > 15 mm were independent predictors of neoplasia as well as malignancy. Over all, this paper is well written, concise and information.

REFERENCES

- 1 Ozdemir A, Ozenc A, Bozoklu S, Coskun T. Ultrasonography in the diagnosis of gallbladder polyps. *Br J Surg* 1993; **80**: 345
- 2 Csendes A, Burgos AM, Csendes P, Smok G, Rojas J. Late follow-up of polypoid lesions of the gallbladder smaller than 10 mm. *Ann Surg* 2001; **234**: 657-660
- 3 Jones-Monahan KS, Gruenberg JC, Finger JE, Tong GK. Isolated small gallbladder polyps: an indication for cholecystectomy in symptomatic patients. *Am Surg* 2000; **66**: 716-719
- 4 Jørgensen T, Jensen KH. Polyps in the gallbladder. A prevalence study. *Scand J Gastroenterol* 1990; **25**: 281-286
- 5 Segawa K, Arisawa T, Niwa Y, Suzuki T, Tsukamoto Y, Goto H, Hamajima E, Shimodaira M, Ohmiya N. Prevalence of gallbladder polyps among apparently healthy Japanese: ultrasonographic study. *Am J Gastroenterol* 1992; **87**: 630-633
- 6 Chen CY, Lu CL, Chang FY, Lee SD. Risk factors for gallbladder polyps in the Chinese population. *Am J Gastroenterol* 1997; **92**: 2066-2068
- 7 Ozmen MM, Patankar RV, Hengirmen S, Terzi MC. Epide-

- miology of gallbladder polyps. *Scand J Gastroenterol* 1994; **29**: 480
- 8 **Hayashi Y**, Liu JH, Moriguchi H, Takenawa H, Tazawa J, Nakayama E, Marumo F, Sato C. Prevalence of polypoid lesions of the gallbladder in urban and rural areas of Japan: comparison between 1988 and 1993. *J Clin Gastroenterol* 1996; **23**: 158-159
 - 9 **Pandey M**, Khatri AK, Sood BP, Shukla RC, Shukla VK. Cholecystosonographic evaluation of the prevalence of gallbladder diseases. A university hospital experience. *Clin Imaging* 1996; **20**: 269-272
 - 10 **Okamoto M**, Okamoto H, Kitahara F, Kobayashi K, Karikome K, Miura K, Matsumoto Y, Fujino MA. Ultrasonographic evidence of association of polyps and stones with gallbladder cancer. *Am J Gastroenterol* 1999; **94**: 446-450
 - 11 **Lin WR**, Lin DY, Tai DI, Hsieh SY, Lin CY, Sheen IS, Chiu CT. Prevalence of and risk factors for gallbladder polyps detected by ultrasonography among healthy Chinese: analysis of 34 669 cases. *J Gastroenterol Hepatol* 2008; **23**: 965-969
 - 12 **Yeh CN**, Jan YY, Chao TC, Chen MF. Laparoscopic cholecystectomy for polypoid lesions of the gallbladder: a clinicopathologic study. *Surg Laparosc Endosc Percutan Tech* 2001; **11**: 176-181
 - 13 **Terzi C**, Sökmen S, Seçkin S, Albayrak L, Uğurlu M. Polypoid lesions of the gallbladder: report of 100 cases with special reference to operative indications. *Surgery* 2000; **127**: 622-627
 - 14 **Koga A**, Watanabe K, Fukuyama T, Takiguchi S, Nakayama F. Diagnosis and operative indications for polypoid lesions of the gallbladder. *Arch Surg* 1988; **123**: 26-29
 - 15 **Kubota K**, Bandai Y, Noie T, Ishizaki Y, Teruya M, Makuuchi M. How should polypoid lesions of the gallbladder be treated in the era of laparoscopic cholecystectomy? *Surgery* 1995; **117**: 481-487
 - 16 **Ito H**, Hann LE, D'Angelica M, Allen P, Fong Y, Dematteo RP, Klimstra DS, Blumgart LH, Jarnagin WR. Polypoid lesions of the gallbladder: diagnosis and followup. *J Am Coll Surg* 2009; **208**: 570-575
 - 17 **Park JK**, Yoon YB, Kim YT, Ryu JK, Yoon WJ, Lee SH, Yu SJ, Kang HY, Lee JY, Park MJ. Management strategies for gallbladder polyps: is it possible to predict malignant gallbladder polyps? *Gut Liver* 2008; **2**: 88-94
 - 18 **Yang HL**, Sun YG, Wang Z. Polypoid lesions of the gallbladder: diagnosis and indications for surgery. *Br J Surg* 1992; **79**: 227-229
 - 19 **Mainprize KS**, Gould SW, Gilbert JM. Surgical management of polypoid lesions of the gallbladder. *Br J Surg* 2000; **87**: 414-417
 - 20 **Akatsu T**, Aiura K, Shimazu M, Ueda M, Wakabayashi G, Tanabe M, Kawachi S, Kitajima M. Can endoscopic ultrasonography differentiate nonneoplastic from neoplastic gallbladder polyps? *Dig Dis Sci* 2006; **51**: 416-421
 - 21 **Sadamoto Y**, Oda S, Tanaka M, Harada N, Kubo H, Eguchi T, Nawata H. A useful approach to the differential diagnosis of small polypoid lesions of the gallbladder, utilizing an endoscopic ultrasound scoring system. *Endoscopy* 2002; **34**: 959-965
 - 22 **Numata K**, Oka H, Morimoto M, Sugimori K, Kunisaki R, Nihonmatsu H, Matsuo K, Nagano Y, Nozawa A, Tanaka K. Differential diagnosis of gallbladder diseases with contrast-enhanced harmonic gray scale ultrasonography. *J Ultrasound Med* 2007; **26**: 763-774
 - 23 **Choi WB**, Lee SK, Kim MH, Seo DW, Kim HJ, Kim DI, Park ET, Yoo KS, Lim BC, Myung SJ, Park HJ, Min YI. A new strategy to predict the neoplastic polyps of the gallbladder based on a scoring system using EUS. *Gastrointest Endosc* 2000; **52**: 372-379
 - 24 **Christensen AH**, Ishak KG. Benign tumors and pseudotumors of the gallbladder. Report of 180 cases. *Arch Pathol* 1970; **90**: 423-432
 - 25 **Kanazawa M**, Yoshiike N, Osaka T, Numba Y, Zimmet P, Inoue S. Criteria and classification of obesity in Japan and Asia-Oceania. *World Rev Nutr Diet* 2005; **94**: 1-12
 - 26 **Sugiyama M**, Xie XY, Atomi Y, Saito M. Differential diagnosis of small polypoid lesions of the gallbladder: the value of endoscopic ultrasonography. *Ann Surg* 1999; **229**: 498-504
 - 27 **Shin SR**, Lee JK, Lee KH, Lee KT, Rhee JC, Jang KT, Kim SH, Choi DW. Can the growth rate of a gallbladder polyp predict a neoplastic polyp? *J Clin Gastroenterol* 2009; **43**: 865-868
 - 28 **Sun XJ**, Shi JS, Han Y, Wang JS, Ren H. Diagnosis and treatment of polypoid lesions of the gallbladder: report of 194 cases. *Hepatobiliary Pancreat Dis Int* 2004; **3**: 591-594
 - 29 **La Vecchia C**, Negri E, Decarli A, Franceschi S. Diabetes mellitus and the risk of primary liver cancer. *Int J Cancer* 1997; **73**: 204-207
 - 30 **Larsson SC**, Orsini N, Wolk A. Diabetes mellitus and risk of colorectal cancer: a meta-analysis. *J Natl Cancer Inst* 2005; **97**: 1679-1687
 - 31 **Huxley R**, Ansary-Moghaddam A, Berrington de González A, Barzi F, Woodward M. Type-II diabetes and pancreatic cancer: a meta-analysis of 36 studies. *Br J Cancer* 2005; **92**: 2076-2083
 - 32 **Becker S**, Dossus L, Kaaks R. Obesity related hyperinsulinaemia and hyperglycaemia and cancer development. *Arch Physiol Biochem* 2009; **115**: 86-96
 - 33 **Vigneri P**, Frasca F, Sciacca L, Pandini G, Vigneri R. Diabetes and cancer. *Endocr Relat Cancer* 2009; **16**: 1103-1123
 - 34 **Allen NE**, Roddam AW, Allen DS, Fentiman IS, Dos Santos Silva I, Peto J, Holly JM, Key TJ. A prospective study of serum insulin-like growth factor-I (IGF-I), IGF-II, IGF-binding protein-3 and breast cancer risk. *Br J Cancer* 2005; **92**: 1283-1287
 - 35 **Stattin P**, Bylund A, Rinaldi S, Biessy C, Déchaud H, Stenman UH, Egevad L, Riboli E, Hallmans G, Kaaks R. Plasma insulin-like growth factor-I, insulin-like growth factor-binding proteins, and prostate cancer risk: a prospective study. *J Natl Cancer Inst* 2000; **92**: 1910-1917
 - 36 **Yu H**, Spitz MR, Mistry J, Gu J, Hong WK, Wu X. Plasma levels of insulin-like growth factor-I and lung cancer risk: a case-control analysis. *J Natl Cancer Inst* 1999; **91**: 151-156
 - 37 **Palmqvist R**, Hallmans G, Rinaldi S, Biessy C, Stenling R, Riboli E, Kaaks R. Plasma insulin-like growth factor 1, insulin-like growth factor binding protein 3, and risk of colorectal cancer: a prospective study in northern Sweden. *Gut* 2002; **50**: 642-646
 - 38 **Renahan AG**, Zwahlen M, Minder C, O'Dwyer ST, Shalet SM, Egger M. Insulin-like growth factor (IGF)-I, IGF binding protein-3, and cancer risk: systematic review and meta-regression analysis. *Lancet* 2004; **363**: 1346-1353
 - 39 **Lee JS**, Lee KT, Jung JH, Ok SW, Choi SC, Lee KH, Lee JK, Heo JS, Choi SH, Rhee JC. [Factors associated with malignancy in gallbladder polyps without gallbladder stone]. *Korean J Gastroenterol* 2008; **52**: 97-105
 - 40 **Cheon YK**, Cho WY, Lee TH, Cho YD, Moon JH, Lee JS, Shim CS. Endoscopic ultrasonography does not differentiate neoplastic from non-neoplastic small gallbladder polyps. *World J Gastroenterol* 2009; **15**: 2361-2366

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