Ahead of Print
Turk J Gastroenterol *2017; 28*

Predictive factors of neoplastic gallbladder polyps: Outcomes of 278 patients

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ABSTRACT

Background/Aims: Distinguishing between neoplastic and nonneoplastic gallbladder polyps (GBPs) in the preoperative workup is of great importance for appropriate treatment. The present study aimed to investigate the characteristics of GBPs and to determine potential predictive factors of neoplastic polyps.

Materials and Methods: The data of 278 patients who were confirmed to have GBPs through laparoscopic cholecystectomy were retrospectively analyzed. Polyps were classified as nonneoplastic and neoplastic GBPs, according to histopathological diagnoses. All clinicopathological characteristics were compared between these two groups.

Results: There were 264 (95%) nonneoplastic GBPs and 14 (5%) neoplastic GBPs. In univariate analysis, there were significant differences in age with a cutoff value of 60 years ($p=0.002$), polyp size ($p<0.001$), number of polyps ($p=0.014$), and polyp morphology ($p<0.001$) between the groups. Multivariate analysis showed that solitary polyp ($p<0.001$) and sessile morphology ($p<0.001$) were the independent predictors of neoplastic GBPs. Receiver-operating characteristic curve analysis of three cut-off values of polyp sizes (6, 10, and 15 mm) indicated that a polyp size of 10 mm had the highest area under curve (0.942).

Conclusion: Age above 60 years, solitary polyps larger than 1 cm, and sessile morphology are associated with an increased risk of neoplasia in GBP. Therefore, these characteristics should be considered in the management of GBPs to reduce the incidence of unnecessary surgeries and to prevent delays in the treatment of a possible cancer.

Keywords: Gallbladder polyp, management, neoplasia, predictive factor

INTRODUCTION

Gallbladder polyps (GBPs) are the mucosal lesions protruding into the lumen of the gallbladder, and they are found in up to 12% of the general population (1). These lesions are usually asymptomatic, and they are diagnosed as an incidental finding in the pathological examination of cholecystectomy for gallstones or on abdominal ultrasonography (US) for other reasons (2). GBPs are classified into various forms such as pseudo–true, benign–malignant, and neoplastic–nonneoplastic (2-4). Nonneoplastic polyps consist of cholesterol, inflammatory and hyperplastic polyps, adenomyomas, and mesenchymatous polyps including fibromas, leiomyomas, and lipomas, while neoplastic polyps include adenomas, adenocarcinomas, and squamous cell carcinomas (5). Cholesterol polyps are the most common type of all GBPs. However, carcinomas are rare malignancies with an overall survival rate of less than 5%. This poor survival rate increases up to 75% in the early stages of disease when treated appropriately (6). Therefore, distinguishing between neoplastic and nonneoplastic GBPs in the preoperative workup is of great importance. However, the management of GBPs detected by imaging modalities remains a controversial issue due to the lack of evidence-based clinical guidelines.

In this study, we aimed to investigate the characteristics of GBPs and determine the potential predictive factors of neoplastic polyps in one of the largest series from Turkey.

MATERIALS AND METHODS

Patients and Study Design

Between 2010 and 2016, medical records of 278 patients who were confirmed to have GBPs through laparoscopic cholecystectomy in a tertiary reference hospital were retrospectively analyzed. The study protocol

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Received: December 9, 2016 **Accepted:** February 10, 2017 **Available Online Date:** March 17, 2017

was approved by the Ethics Committee of Ankara Numune Training and Research Hospital, and informed consent was obtained from patients after the study was described in detail. GBP >1 cm was the primary indication for surgery. The surgical indications for smaller polyps were the presence of gallbladder stones, being symptomatic, suspicious sonographic findings such as vascularization pattern and sessile shape, rapid growth during follow-up, and personal request of the patient. Patients' age and gender, sonographic findings (presence of gallstones and number/shape of polyps), and histopathological types of polyps were recorded. Polyp size was determined on the preoperative US. Patients under 18 years old were excluded from the study.

According to the histopathological diagnoses, polyps were classified as nonneoplastic (cholesterol/inflammatory/hyperplastic polyps, adenomyomas, fibromas, leiomyomas, and lipomas) and neoplastic (adenomas and carcinomas) GBPs.

Statistical Analysis

Statistical analyzes were performed using Statistical Package for the Social Sciences 17.0 (SPSS Inc.; Chicago, IL, USA). The normality of data distribution was assessed by the Kolmogorov–Smirnov test. All values are expressed as mean±standard deviation (SD) or counts (percentage), unless otherwise specified. Comparisons were made by using chi-square test or Fisher's exact test for categorical data and Mann–Whitney U test for continuous variables. Multivariate analysis was performed using binary logistic regression for variables with p≤0.5 on univariate analysis. Receiver-operating characteristic (ROC) curves analysis was used to identify the optimal cutoff value for polyp size.

Table 1. Demographic, clinical, and pathological characteristics of patients (n=278)

Characteristics	n (%)
Age (y)	48.9±13.3 (18-83)
Gender (F/M)	187 (67.3)/91 (32.7)
Presence of gallstone	182 (65.5)
Size of polyp (mm)	4.6±5 (0.3-45)
Number of polyps	
Solitary	149 (53.6)
Multiple	129 (46.4)
Morphology of polyps	
Pedunculated	253 (91)
Sessile	25 (9)
Presence of neoplasia	
Nonneoplastic	264 (95)
Neoplastic	14 (5)
Type of polyp	
Cholesterol	256 (92.1)
Adenocarcinoma	8 (2.9)
Adenoma	6 (2.2)
Hyperplastic	4 (1.4)
Adenomyoma	3 (1.1)
Inflammatory	1 (0.4)

Data are presented as mean±SD for age and polyp size; n (%) for other variables. y: year; mm: millimeter

RESULTS

A total of 278 patients with GBPs were included in this study, of whom 187 (67.3%) were female and 91 (32.7%) were male. All the patients underwent laparoscopic cholecystectomy for a preoperative diagnosis of GBPs and/or cholelithiasis. There were 14 (5%) neoplastic polyps, of which 8 (2.9%) were adenocarcinoma and 6 (2.2%) were adenoma. All the clinical and pathological characteristics are presented in Table 1.

All demographic, clinical, and pathological characteristics were compared between patients with nonneoplastic GBPs and those with neoplastic GBPs. There were significant differences in categorical age (p=0.002), polyp size (p<0.001), number of polyps (p=0.014), and polyp morphology (p<0.001) between the groups (Table 2). In multivariate analyses, polyp size (p<0.001) and polyp morphology (p<0.001) were found to be independent predictive factors of neoplastic GBPs (Table 3).

Table 2. Comparison of clinicopathological characteristics between nonneoplastic and neoplastic GBPs

Characteristics	Nonneoplastic GBPs (n=264)	Neoplastic GBPs (n=14)	p
Age (y)	48.6±13 (18-83)	54.9±18.6 (22-77)	0.158
Age (categorical)			0.002
<60	214 (81.1%)	6 (42.9%)	
≥60	50 (18.9%)	8 (57.1%)	
Gender			0.777
Female	178 (67.4%)	9 (64.3%)	
Male	86 (32.6%)	5 (35.7%)	
Presence of gallstone	172 (65.2%)	10 (71.4%)	0.777
Size of polyp (mm)	3.9±3.2 (0.3-30)	18±11.8 (6-45)	<0.001
Number of polyps			0.014
Solitary	137 (51.9%)	12 (85.7%)	
Multiple	127 (48.1%)	2 (14.3%)	
Morphology of polyps			<0.001
Pedunculated	251 (95.1%)	2 (14.3%)	
Sessile	13 (4.9%)	12 (85.7%)	

Data are presented as mean±SD for age and polyp size; n (%) for other variables. y: year; mm: millimeter

Finally, polyp size was compared between nonneoplastic and neoplastic GBPs using 3 different cutoff values (6, 10, and 12 mm). All the cutoff values were found to be significantly different between the two groups (Table 4). ROC curve analysis was used to compare the predictive ability of these 3 cutoff values of polyp sizes. A cutoff value of 10 mm had the highest area under curve (AUC: 0.942) when compared with the others (Figure 1).

DISCUSSION

Gallbladder polyps have been increasingly diagnosed in recent years due to the widespread use of imaging methods. To date, several factors such as advanced age, male gender, ethnicity, genetics, diabetes mellitus, hypertension, and obesity have been identified as risk factors associated with the occurrence of GBPs (2,3,7). Although there are conflicting reports about sex predominance and average age, two-third patients were female and the mean age was about 50 years in our study, similar to the majority of previous studies (8-11). Further, a close relationship between fat metabolism and GBP formation has been reported in the literature (2). Similarly, studies by Lee et al. (7) and Cantürk et al. (12) have shown that the formation of GBPs is significantly associated with the serum level of cholesterol. In our opinion, the high incidence of cholesterol polyps among all the types of polyps supports this theory.

Table 3. Multivariate analysis (binary logistic regression test) of neoplastic GBPs

Variables	β (SE)	p	Exp (β)	95% CI of Exp (β)
Age (categorical)	0.827 (1.115)	0.458	2.288	0.257-20.354
Size of polyp	0.302 (0.076)	<0.001	1.352	1.166-1.568
Number of polyps	-1.275 (1.224)	0.297	0.279	0.025-3.074
Morphology of polyp	-5.094 (1.381)	<0.001	0.006	0-0.092
Constant	2.346 (1.432)			

SE: standard error; Exp (β): odds ratio; CI: confidence interval

Table 4. Comparison of polyp sizes with different cut-off values between nonneoplastic and neoplastic GBPs

Cut-off values	Nonneoplastic GBPs (n=264)	Neoplastic GBPs (n=14)	p
Cut-off value of 6 mm			<0.001
<6	216 (81.8%)	0 (0%)	
≥6	48 (18.2%)	14 (100%)	
Cut-off value of 10 mm			<0.001
<10	252 (95.5%)	1 (7.1%)	
≥10	12 (4.5%)	13 (92.9%)	
Cut-off value of 15 mm			<0.001
<15	259 (98.1%)	8 (57.1%)	
≥15	5 (1.9%)	6 (42.9%)	

A majority of patients with GBPs are asymptomatic or have nonspecific symptomatology. Therefore, these lesions are usually detected as an incidental finding on imaging methods (3). Additionally, most patients with GBPs have synchronous gallstones, and it is often difficult to determine which one is the main cause of symptoms. Similarly, two-third patients in our study had gallstones.

Most GBPs are benign nonneoplastic lesions, of which cholesterol polyps represent the most common type with a ratio of 60%–90% (2). Neoplastic GBPs are infrequent lesions and include adenomas and carcinomas. In the present study, cholesterol polyps were found in 92% patients, while neoplastic polyps accounted for approximately 5% of all GBPs. Adenomas are mostly benign in nature; however, approximately 4% of these lesions have premalignant behavior (13). On the other hand, adenocarcinomas are the most common histological type of malignant GBPs, as in our study. Malignant GBPs have a fairly poor survival rate; therefore, the early detection of neoplastic polyps is of great importance for a better prognosis of patients. To date, various clinical, radiological, and pathological characteristics have been suggested as the predictors of malignancy. Unfortunately, there is a lack of evidence-based clinical guidelines on the potential predictive factors of malignancy and the association between GBPs and cancer. In routine practice, polyps >10 mm or symptomatic lesions are surgically treated, while smaller asymptomatic polyps are followed-up by serial sonographic examinations (14). The guideline of the Society of American Gastrointestinal and Endoscopic Surgeons (SAGES) recommended watchful waiting strategy for small (<5 mm) asymptomatic polyps and laparoscopic cholecystectomy for larger, especially single, polyps or those with associated symptoms. (15). Our approach was also along this direction, and it included surgery for polyps >1 cm and symptomatic lesions.

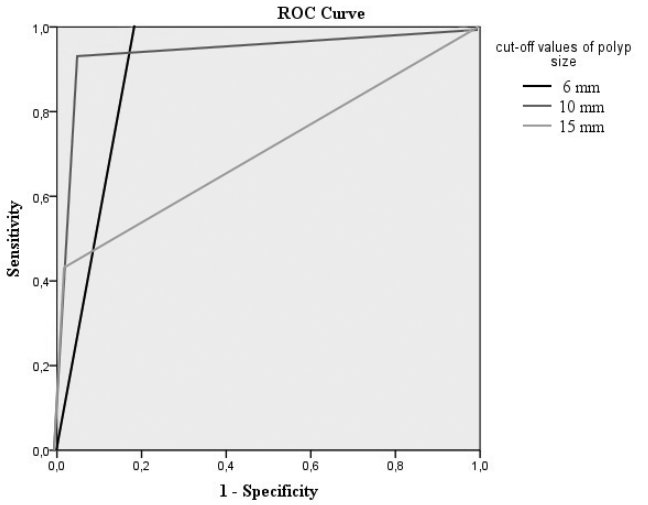

Figure 1. ROC curves of the predictive ability of 3 cut-off values of polyp sizes. The 10-mm cut-off value of polyp size had the highest area under curve [AUC: 0.942, 95% CI: 0.862–1.000, p<0.001], in comparison to the 6-mm cut-off value [AUC: 0.909, 95% CI: 0.870–0.948, p<0.001] and 15-mm cut-off value [AUC: 0.705, 95% CI: 0.532–0.878, p=0.01]

Rapid growth and coexisting gallstones were also other surgical indications for small GBPs. However, this approach is still controversial, and many different cutoff values of polyp sizes for the differentiation of benign and malignant GBPs have been reported to date. Zielinski et al. (3) recommended surgical resection for GBPs ≥6 mm due to the significant risk of neoplasm, while a polyp size ≥15 mm was determined as the strongest predictor of neoplasia by other authors (1,13,14). However, a polyp size of 10 mm has been generally accepted as a surgical indication (4,8,16,17). In our study, size was found to be one of the independent factors of neoplastic GBPs. We also investigated the predictive abilities of 3 cutoff values of polyp sizes, namely, 6, 10, and 15 mm. Among all the neoplastic GBPs in our study, only 1 had a polyp size <10 mm. Additionally, the cutoff value of 10 mm was the best size limit indicating the risk of neoplasia.

Polyp size has not been considered as an adequate exclusion criteria for neoplasia or malignancy (18). Advanced age, male gender, associated gallstones, solitary and sessile polyps, rapid growth, and presence of various medical conditions such as diabetes mellitus and primary sclerosing cholangitis have been demonstrated as risk factors of neoplastic or malignant GBPs (1,9,16,19-21). No patient with neoplastic GBPs had primary sclerosing cholangitis in our study population, while diabetes mellitus was detected in only 1 patient.

In most studies, neoplastic/malignant GBPs were found to be more common in patients above 50–60 years (11,13,17,20-22). Similarly, the mean age of patients with neoplastic GBPs was approximately 55 years, whereas that of patients with nonneoplastic GBPs was 48 years in our study. However, mean age was not an associated factor for neoplastic GBPs in the present study. Instead, being 60 years or older was found to be associated with neoplastic GBPs in univariate analyses.

Polyp morphology is another indicator of neoplasia. Generally, neoplastic GBPs tend to be solitary and sessile. This may be explained by the hypothesis that most gallbladder cancers arise *in situ* from flat and dysplastic epithelium (20). In a study by Liu et al. (23), more than 80% of neoplastic GBPs were solitary and sessile, whereas half of the patients in the nonneoplastic group had multiple and pedunculated polyps. Similarly, in this study, we found that a majority of neoplastic GBPs were solitary and sessile. These 2 morphological characteristics were also found to be associated factors for neoplastic histology in univariate analyses. However, multivariate analyses showed that sessile morphology, in addition to size, was an independent factor for neoplasia.

Rapid growth in polyp size is usually accepted as an associated factor indicating malignancy. However, the correlation between polyp growth and development of malignancy cannot be established using currently available evidence (24). Additionally, the definition of rapid growth is unclear. In a survey study by Marangoni et al. (25), most of the surgeons gave extremely variable answers for the question "What growth rate of polyps prompts consideration of laparoscopic cholecystectomy?" We also did not analyze the association between growth rate and malignancy risk in our study, due to the uncertain definition of growth rate.

Gallstone is a frequent finding in patients with GBP, as observed in our study. Some authors reported that gallstone is more common in patients with neoplastic GBPs than in those with nonneoplastic lesions, while others reported no association between gallstones and malignancy risk (4,16). In our study, gallbladder stone was slightly more common in the neoplastic group than in the nonneoplastic group, without a statistically significance.

This study has several limitations. First, it was conducted in a single center, which may limit the generalizability of the results. A relatively small sample size is another limitation of this work, which makes it difficult to interpret subgroup findings. Finally, its retrospective nature may be considered as a limitation. However, having the potential to contribute to an evidence-based guideline for the management of GBPs can make this work valuable.

In summary, this study showed that the risk of neoplasia in GBPs increases in patients above 60 years, solitary and sessile lesions larger than 10 mm. These risk factors should be considered in the management of GBPs to reduce the incidence of unnecessary surgeries and to prevent delays in the treatment of a possible cancer.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Ankara Numune Training and Research Hospital.

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Consept – S.G.T., M.Ö.K.; Design: – S.G.T., M.Ö.K.; Supervision – M.Ö.K., A.S.K.; Data collection and/or Processing – S.G.T., A.S.; Analysis and/or interpretation – M.Ö.K., A.S.; Literature Review – S.G.T., M.Ö.K.; Writer – M.Ö.K.; Critical Review – A.S., A.S.K.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study has received no financial support.

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