Original Article

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Risk Factors for Malignant Gallbladder Polyps

Malign Safra Kesesi Polipleri için Risk Faktörleri

Serhan Yilmaz, Hakan Bolukbasi, Mehmet Abdussamet Bozkurt

University of Health Sciences, Kanuni Sultan Suleyman Research and Training Hospital, General Surgery Department

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ABSTRACT

Objective: *The aim of this study is to determine risk factors for malignancy in gallbladder polyps.*
Method: *92 patients who underwent laparoscopic cholecystectomy due to gallbladder polyp were retrospectively analyzed. Demographic data of the patients, size and number of polyp, the presence of gallstones and histopathological features of the polyps were recorded.*
Results: *92 patients were included. Mean age was 45.78±11.21 years (21-72). 59 of the patients (64.1%) were female and 33 (35.9%) were male. Mean polyp size was 8.17±2.19 mm and 35 patients (38.0%) had a single polyp, while 57 (62.0%) had multiple polyps (≥2). 47 of the patients (51.1%) had gallstone disease, while 45 (48.9%) had no stone disease. Benign polyps (Group 1) were found in 79 patients (85.9%) and adenocarcinomas (Group 2) were found in 13 (14.1%). Of the benign polyps, 71 (77.1%) were non-neoplastic polyps and 8 (8.8%) were neoplastic polyps (adenomas). Of the 13 patients with adenocarcinomas, 11 (11.9%) were T1a and 2 (2.2%) were T1b. Mean age was 44.32±11.03 years in Group 1 and 54.61±8.07 years in Group 2, the latter being significantly older (p=0.002). Mean polyp size was 7.47±5.51 mm in Group 1 and 12.46±1.89 mm in Group 2, with a significant difference (p<0.001). The cut-off value to detect malignant polyps was a polyp size of 10.5 mm with 92.3% sensitivity, 84.8% specificity, and 0.934 accuracy (p< 0.001). The cut-off value to detect malignant polyps was an age of 50.5 years with 76.9% sensitivity, 67.1% specificity, and 0.767 accuracy (p=0.002). Polyp size and age were important risk factors for malignant gallbladder polyps (p<0.001, OR=2.313; 95% CI: 1.502–3.561), (p=0.004, OR=1.100, 95% CI: 1.030–1.175).*
Conclusion: *We recommend cholecystectomy for asymptomatic patients aged above 50.5 years with gallbladder polyps larger than 10.5 mm due to the increased risk of malignancy.*

Keywords: *gallbladder adenocarcinoma, gallbladder polyp, surgical treatment*

ÖZ

Amaç: *Bu çalışmanın amacı safra kesesi poliplerinde malignite için risk faktörlerini belirlemektir.*
Yöntem: *Safra kesesi polipi nedeniyle laparoskopik kolesistektomi uygulanan 92 hasta geriye dönük olarak incelendi. Hastaların demografik verileri, polip boyutu ve sayısı, safra taşı varlığı ve poliplerin histopatolojik özellikleri kaydedildi.*
Bulgular: *92 hasta dahil edildi. Ortalama yaş 45,78 ± 11,21 yıl (21-72) idi. Hastaların 59'u (64.1%) kadın, 33'ü (35.9%) erkekti. Ortalama polip boyutu 8.17 ± 2.19 mm ve 35 hastada (38.0%) tek polip varken 57 hastada (62.0%) çoklu polip (≥2) vardı. Hastaların 47'sinde (51.1%) safra taşı hastalığı varken 45'inde (48.9%) taş hastalığı yoktu. Benign polipler (Grup 1) 79 hastada (85,9%), adenokarsinomlar (Grup 2) 13 (14,1%) hastada saptandı. Benign poliplerin 71'i (77,1%) neoplastik olmayan polip ve 8'i (8,8%) neoplastik polip (adenom) idi. Adenokarsinomlu 13 hastanın 11'i (11.9%) T1a ve 2'si (2.2%) T1b idi. Grup 1'de ortalama yaş 44,32 ± 11,03, Grup 2'de 54,61 ± 8,07 yıldı ve Grup 2'de anlamlı olarak daha yaşlıydı (p = 0,002). Ortalama polip boyutu Grup 1'de 7,47 ± 5,51 mm, Grup 2'de 12,46 ± 1,89 mm idi ve anlamlı bir farkla (p <0,001). Malign polipleri tespit etmek için kesme değeri, 92,3% duyarlılık, 84,8% özgüllük ve 0,934 doğrulukla 10,5 mm polip boyutuydu (p <0,001). Malign polipleri tespit etmek için kesme değeri, 76,9% duyarlılık, 67,1% özgüllük ve 0,767 doğruluk ile 50,5 yaş idi (p = 0,002). Polip boyutu ve yaş, malign safra kesesi polipleri için önemli risk faktörleriydi (p <0.001, OR = 2.313; 95% CI: 1.502–3.561), (p = 0.004, OR = 1.100, 95% CI: 1.030–1.175).*
Sonuç: *Malignite riskinin artması nedeniyle safra kesesi polipleri 10.5 mm'den büyük olan 50.5 yaş üstü asemptomatik hastalara kolesistektomi öneriyoruz.*

Anahtar Kelimeler: *safra kesesi adenokarsinomu, safra kesesi polipi, cerrahi tedavi*

Corresponding Author:
drserhanyilmaz@gmail.com

S. Yilmaz 0000-0002-5612-5932
H. Bolukbasi 0000-0002-4904-9302
M.A. Bozkurt 0000-0003-3222-9363

INTRODUCTION

A gallbladder polyp (GP) is defined as a mucosal swelling that protrudes into the lumen. It occurs in nearly 5% of the general population. GPs are often detected incidentally during radiological imaging or by pathological examination following cholecystectomy [1]. GPs were first divided into two groups as non-neoplastic (cholesterol polyps, inflammatory polyps, and adenomyomatous hyperplasia) and neoplastic polyps (adenomas) by Christensen and Ishak [2] in 1970. Non-neoplastic polyps mostly consist of cholesterol polyps (60-70%), while neoplastic polyps are mostly gallbladder adenomas (1-5%) [1-3]. The literature reports that 0% to 27% of GPs are malignant [4-8]. Since gallbladder cancer (adenocarcinoma) has a poor prognosis [3], distinguishing between benign and malignant polyps is crucial. The increased malignancy risk of GPs is associated with various factors, although without any clear consensus on the matter. Most authors report increased polyp size (≥10 mm) and advanced age (>50) to be the most important risk factors for malignant transformation [1,5,6,8], while others suggest that polyps <10 mm should also be closely monitored due to their malignant potential [9,10].

Five -year survival rates have been reported as 95-99% in stage 1, and as 70% in stage 2 gallbladder cancers. This rate decreases to 5-12% for patients at stages 3 and 4 [11-13].

The aim of this study was to determine the risk factors for malignancy in gallbladder polyps.

MATERIALS and METHODS

Data belonging to 92 patients undergoing laparoscopic cholecystectomy for GP between 2015 and 2020 were analysed retrospectively. Approval for the research was obtained from the local ethics committee. Informed consent forms were signed by the patients. All patients were diagnosed by abdominal ultrasonography preoperatively. Surgical indication was decided as the presence of single polyp over ≥1 cm , multiple polyps and gallstone disease and symptoms for small ones. Patients over 18 years of age were included. Those with definite evidence of malignancy such as local organ invasion and metastasis by preoperative imaging were excluded.

Demographic data like age and sex were recorded. The size and number of polyps and the presence of gallstones were recorded based on the preoperative ultrasonography reports. The histopathological results of the polyps were also recorded.

The patients were categorized into two groups as benign (Group 1) and malignant (Group 2) according to histopathological findings. The benign group comprised non-neoplastic and neoplastic polyps (adenomas), and the malignant group consisted of adenocarcinomas. The malignant group was further classified as either T1a or T1b according to the TNM system. The T1a group did not undergo any additional surgical intervention after diagnosis, but the T1b group underwent segment 4b-5 resection and lymph node dissection.

Statistical Method

Categorical variables were presented as frequency and percentage and continuous variables as means and standard deviation. The normality of continuous variables was tested using the Shapiro-Wilk test. Student's T-test was used to compare normally distributed continuous variables, and Mann-Whitney U test to compare non-normally distributed continuous variables. Chi-square test was used to compare categorical variables. The ROC curve was used to determine the optimum cut-off values for the probability of malignancy. Variables that showed significant correlation in the univariate analysis were evaluated by multivariate binary logistic regression analysis to determine the risk factors for malignant gallbladder polyps, and to calsulate the odds ratio. All analyses were performed using the Statistical Package for the Social Sciences for Windows version 22.0 (SPSS Inc., Chicago, Illinois, USA). The level of statistical significance was set at $p<0.05$.

RESULTS

A total of 92 patients were included. Mean age was 45.78±11.21 years (21-72). Fifty-nine patients (64.1%) were female and 33 (35.9%) were male. Mean polyp size was 8.17±2.19 mm and 35 patients (38.0%) had a single polyp, while 57 (62.0%) had

Table 1. Demographic data.

Age (years)	45.78±11.21 (21-72)
Gender	
Female	59 (64.1%)
Male	33 (35.6,9%)
Polyp size (mm)	8.17±2.19
Presence of gallstones	
Yes	47 (51.1%)
No	45 (48.9%)
Number of polyps	
1	35 (38.0%)
≥2	57 (62.0%)
Histopathology	
Benign	79 (85.9%)
Non-neoplastic	71 (77.1%)
Neoplastic (adenoma)	8 (8.8%)
Malignant (adenocarcinoma)	13 (14.1%)
T1a	11 (11.9%)
T1b	2 (2.2%)

The categorical variables were presented as frequencies and percentages and the continuous variables were expressed as means and standard deviation.

multiple polyps (≥2). Forty-seven patients (51.1%) had, 45 (48.9%) had not gallstone disease. According to the pathology reports, benign polyps (Group 1) were found in 79 (85.9%) and adenocarcinomas (Group 2) in 13 (14.1%) patients. Histopathological examination of the benign polyps revealed the presence of non-neoplastic polyps in 71 (77.1%), and neoplastic polyps (adenomas) in 8 (8.8%) patients. Thirtreen patients with adenocarcinomas had stage T1a (n=11 :11.9%) and T1b (n=2 :2.2%) disease (Table 1.)

Mean age was 44.32±11.03 years in Group 1 and 54.61±8.07 years in Group 2, the latter being significantly older (p=0.002). Mean polyp size was 7.47±5.51 mm in Group 1 and 12.46±1.89 mm in Group 2, with a significant difference (p<0.001). In Group 1, the number of polyps ≥2 in size were significantly more (p=0.019). There was no difference between the groups in terms of gender (p=0.764) (Table 2).

Table 2. Comparison of groups.

	Group 1 (n=79)	Group 2 (n=13)	p value
Age (years)	44.32±11.03	54.61±8.07	**0.002 ***
Gender			
Female	50 (63.3%)	9 (69.2%)	0.764 †
Male	29 (36.7%)	4 (30.8%)	
Polyp size (mm)	7.47±5.51	12.46±1.89	**<0.001 ****
Presence of gallstones			
Yes	40 (50.6%)	8 (61.5%)	0.552 †
No	39 (49.4%)	5 (38.5%)	
Number of polyps			
1	27 (34.2%)	8 (61.5%)	0.059 †
≥2	52 (65.8%)	5 (38.5%)	

* Student T test ** Mann Whitney U test † Chi-square test was used for statistical analysis. p <0.005 was considered significant.

Table 3. Risk factors for malignant gallbladder polyps.

	S.E	Exp (β) (95% CI)	p value
Gender	0.645	1.305 (0.369-4.617)	0.680
Polyp size (mm)	0.220	2.313 (1.502-3.561)	**<0.001**
Age	0.034	1.100 (1.030-1.175)	**0.004**
Number of polyps	0.617	3.081 (0.919-10.336)	0.068
Presence of gallstones	0.762	1.667 (0.374-7.424)	0.503

Multivariate binary logistic regression analysis was performed for variables that showed a significant relationship in univariate analysis. SE: standard error; Exp (β): odds ratio; CI: confidence interval. p <0.005 was considered significant.

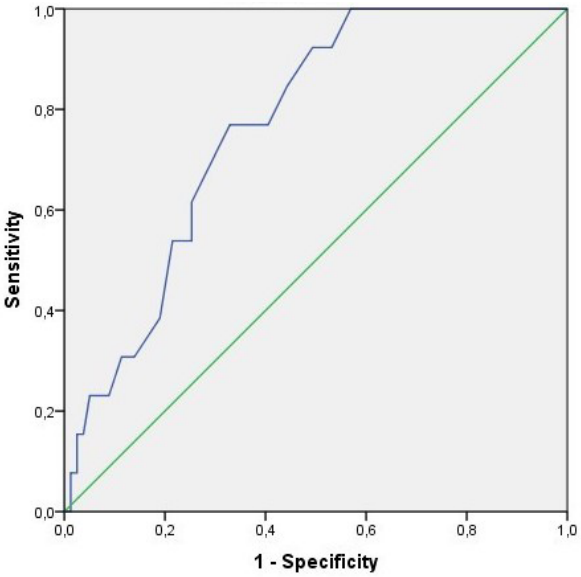

Figure 1. Receiver operating characteristic curves for 10.5 mm size of gallbladder polyp are shown. The area under the curve is 0.934 (95% CI: 0.881–0.987; p <0.001) for the polyp size. The cut-off value of 10.5 mm for gallbladder polyp size had 92.3% sensitivity and 84.8%, predictive value for detecting malignant polyps.

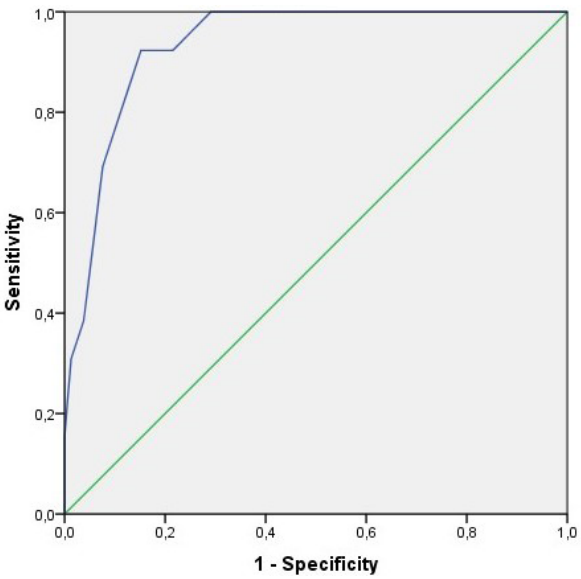

Figure 2. Receiver operating characteristic curves for 50.5 years of age are shown. The area under the curve is 0.767 (95% CI: 0.655–0.878; p= 0.002) for age. The sensitivity and predictive value of this cut-off value for age for detecting malignant polyps were 76.9% and 67.1%, respectively.

The cut-off value of 10.5 mm for polyp size in the prediction of malignant polyps had 92.3% sensitivity, 84.8% specificity, and 0.934 (95% CI: 0.881–0.987) accuracy (p< 0.001) (Figure 1). Similarly, the cut-off value of 50.5 years in the prediction of malignant polyps had 76.9% sensitivity, 67.1% specificity, and 0.767 (95% CI: 0.655–0.878) accuracy (p=0.002) (Figure 2).

Polyp size and patient's age were important risk factors for malignant gallbladder polyps (p<0.001, OR=2.313; 95% CI: 1.502–3.561), (p=0.004, OR=1.100, 95% CI: 1.030–1.175) (Table 3).

DISCUSSION

GPs are very important common lesions of the gallbladder, because of their association with malignancy. With the widespread use of imaging methods in recent years, they are being diagnosed at higher rates. The most common histopathological type of malignancies arising from GPs is adenocarcinomas. Survival rates for gallbladder cancer are very low. Thus, early detection of malignant polyps is of key importance for a better prognosis. To date, various clinical, radiological, and pathological characteristics have been suggested to be predictors for malignancy. Unfortunately, there is still a lack of evidence-based clinical guidelines on the correlation between GP and cancer regarding potential predictive malignancy factors. Similar to the literature, we found malignant GPs in 14.1% of our cases.

Medical conditions such as polyp size, advanced age, male gender, presence of gallstones, solitary and sessile polyps, rapid growth, ethnicity, diabetes mellitus, and primary sclerosing cholangitis have been identified as risk factors for malignant GPs [1,6,8,15,14-20]. The size of GP remains the most important risk factor. Studies have shown that malignant polyps often tend to be larger than benign polyps. Kubota K et al. [6] reported that 88% of malignant polyps were larger than 10 mm, and in adenocarcinoma patients, 75% of them were larger than 10 mm at diagnosis. Likewise, Terzi C et al. reported in their series of 100 cases that 88% of malignant polyps were larger than 10 mm [8]. One systematic review on risk factors for malignancy in gallbladder polyps found that 84.7% of malignant polyps were larger than 10 mm. It has also been found that, in polyps smaller than 4.15 mm, the

probability of malignancy is almost zero [14]. Kwon W et al. [16], Park JY et al. [18], and Sarkut P et al. [20] reported that a polyp size of 10 mm was a risk factor for malignancy. Some studies also argue that polyps smaller than 10 mm should also be considered due to their malignant potential [9], while Kasle D et al. [7] reported foci of carcinoma in 7 mm gall bladder polyps, and Zielinski MD [21] et al. recommended surgical resection for polyps larger than 6 mm due to a significant risk of malignancy. Wennmacker S et al. emphasized that 32% of patients with neoplastic polyps (18% of gallbladder cancers and 53% of precursor lesions) were deprived of surgery based on the 10 mm threshold criterion alone [22]. The ROC curve analysis in our research has showed that polyp size of 10.5 mm is the most appropriate cut-off value for distinguishing malignancy with 92.3% sensitivity and 84.8% specificity, with polyp size being an independent risk factor for malignant GPs. These results also support the international guidelines that advocate cholecystectomy for GPs larger than 10 mm [23,24].

In most cancers, risk increases with age, and a similar pattern should be expected in gallbladder cancer. Various age cut-off values as indicated in parentheses were considered risk factors for malignant GPs by Terzi C et al. [8] (60), Park JY et al. [18] (57), Sarkut P et al. [20] (50), and Cha BH et al. [25] (65). Despite the differences in age cut-off values in various studies, the consensus holds that malignant polyps are more common in patients aged between 50-65 years [8,14,16,18,20,25]. Here, similarly, we found a mean age of about 54.61 years in patients with malignant GPs at 76.9% sensitivity and 67.1% specificity, although the optimum cut-off value to detect malignant GPs was 50.5 years. Age was found to be a risk factor for malignant GP in our multivariate analysis.

Some studies suggest that GP is more common in men [21], while others report the opposite [14,18], with some suggesting lack of gender differences [8,12]. Thus, the effect of gender on malignant transformation has not been reported clearly [8,12,16,18-20]. We found no correlation specific to gender in the occurrence of malignant GPs, consistent with the findings of some studies in the literature. Data on the effect of presence of gallstone disease on malignant transformation remains controversial. Both Terzi C et al. [8] and Park JY et al. [18] reported presence of gallstone disease to be a risk factor for malignant GPs. Aldouri AQ et al. [19] revealed an increased risk of malignancy in the presence of gallstones in their large series including 71,000 patients, although findings on the contrary still exist in the literature [16,26,27]. In our study, we found no definite correlation between presence of gallstone disease and malignant GP. There are differing opinions regarding a correlation between the number of polyps and malignancy. Some data suggest that single polyps have more malignant potential [14,16,19], while others argue for a lack of difference between single and multiple polyps in terms of malignancy risk [8,21,25,26]. According to our findings, the presence of single or multiple polyps was not a risk factor for malignant GP. The gallbladder wall consists of a mucosa, lamina propria, thin muscle layer, intramuscular connective tissue, and serosa. Most surgeons agree that simple cholecystectomy is adequate to treat T1a, but when malignancy is diagnosed in the muscle layer after cholecystectomy (T1b), lymphadenectomy with segment 4b – 5 resections is recommended [11-13]. Similarly, we performed staged surgery on patients with T1b.

Our research may have limitations in terms of the generalization of our findings, given the small number of patients in the sample and the retrospective and single-center nature of the study. Despite all these limitations, we believe that our findings will contribute to the literature in the assessment of risk factors for malignancy and shaping the treatment for gallbladder polyps.

CONCLUSION

According to the results of our study, we recommend cholecystectomy for asymptomatic patients aged above 50.5 years with gallbladder polyps larger than 10.5 mm due to the increased risk of malignancy, regardless of gender and the number of polyps or the presence of gallstone disease. These risk factors should be taken into consideration to prevent delayed diagnosis or treatment in potential cancer cases.

Ethics Committee Approval: İstanbul S.B.Ü. Kanuni Sultan Süleyman Training and Research Hospital Clinical Research Ethics Committee (25.11.2020, 204).

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Informed Consent: Written consent was obtained from all patients participating in the study.

REFERENCES

1. Myers RP, Shaffer EA, Beck PL. Gallbladder polyps: epidemiology, natural history and management. Can J Gastroenterol. 2002;16(3):187-94. doi: 10.1155/2002/787598.
2. Christensen AH, Ishak KG. Benign tumors and pseudotumors of the gallbladder. Report of 180 cases. Arch Pathol. 1970;90(5):423-32. PMID: 4319984.
3. Lee KF, Wong J, Li JC, Lai PB. Polypoid lesions of the gallbladder. Am J Surg. 2004;188(2):186-90. doi: 10.1016/j.amjsurg.2003.11.043.
4. Wan YL, Wang WZ, Li T, Tang XY. Polypoid lesions of the gallbladder. Chin J Surg. 1989;27(8):450-3. PMID: 2695314.
5. Koga A, Watanabe K, Fukuyama T, Takiguchi S, Nakayama F. Diagnosis and operative indications for polypoid lesions of the gallbladder. Arch Surg. 1988;123(1):26-9. doi: 10.1001/archsurg.1988.01400250028003.
6. 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(5):481-7. doi: 10.1016/s0039-6060(05)80245-4.
7. Csendes A, Burgos AM, Csendes P, Smok G, Rojas J. Late follow-up of polypoid lesions of the gallbladder smaller than 10mm. Ann Surg. 2001;234(5):657-60. doi: 10.1097/00000658-200111000-00011.
8. Terzi C, Sokmen S, Seckin S, Albayrak L, Uğurlu M. Polypoid lesions of the gallbladder: report of 100 cases with special reference to operative indications. Surgery. 2000;127(6):622-7. doi: 10.1067/msy.2000.105870.
9. Lu D, Radin R, Yung E, Tchelepi H. Malignant transformation of a 5-mm gallbladder polyp over 2 years: a case report and review of current literature. Ultrasound Q. 2015;31(1):66-8. doi: 10.1097/RUQ.0000000000000094.
10. Kasle D, Rahnemai-Azar AA, Bibi S, Gaduputi V, Gilchrist BF, Farkas DT. Carcinoma in situ in a 7 mm gallbladder polyp: time to change current practice. World J Gastrointest Endosc. 2015;7(9):912-5. doi: 10.4253/wjge.v7.i9.912.
11. Amin MB, Greene FL, Edge SB, Compton CC, Gershenwald JE, Brookland RK, et al. The Eighth Edition AJCC Cancer Staging Manual: Continuing to build a bridge from a population-based to a more "personalized" approach to cancer staging. CA Cancer J Clin. 2017;67(2):93-99. doi: 10.3322/caac.21388.
12. Goetze TO. Gallbladder carcinoma: Prognostic factors and therapeutic options. World J Gastroenterol. 2015;21(43):12211-7. doi: 10.3748/wjg.v21.i43.12211.
13. Ito H, Matros E, Brooks DC, Osteen RT, Zinner MJ, Swanson RS, et al. Treatment outcomes associated with surgery for gallbladder cancer: a 20-year experience. J Gastrointest Surg. 2004;8(2):183-90. doi: 10.1016/j.gassur.2003.10.006.
14. Bhatt NR, Gillis A, Smoothey CO, Awan FN, Ridgway PF. Evidence based management of polyps of the gall bladder: A systematic review of the risk factors of malignancy. Surgeon. 2016;14(5):278-86. doi: 10.1016/j.surge.2015.12.001.
15. Sung JE, Nam CW, Nah YW, Kim BS. Analysis of gallbladder polypoid lesion size as an indication of the risk of gallbladder cancer. Korean J Hepatobiliary Pancreat Surg. 2014;18(1):9-13. doi: 10.14701/kjhbps.2014.18.1.9.
16. Kwon W, Jang JY, Lee SE, Hwang DW, Kim SW. Clinicopathologic features of polypoid lesions of the gallbladder and risk factors of gallbladder cancer. J Korean Med Sci. 2009;24(3):481-7. doi: 10.3346/jkms.2009.24.3.481.
17. Lee KF, Wong J, Li JC, Lai PB. Polypoid lesions of the gallbladder. Am J Surg. 2004;188(2):186-90. doi: 10.1016/j.amjsurg.2003.11.043.
18. Park JY, Hong SP, Kim YJ, Kim HJ, Kim HM, Cho JH, et al. Long-term follow up of gallbladder polyps. J Gastroenterol Hepatol. 2009;24(2):219-22. doi: 10.1111/j.1440-1746.2008.05689.x.
19. Aldouri AQ, Malik HZ, Waytt J, Khan S, Ranganathan K, Kummaraganti S, et al. The risk of gallbladder cancer from polyps in a large multiethnic series. Eur J Surg Oncol. 2009;35(1):48-51. doi: 10.1016/j.ejso.2008.01.036.
20. Sarkut P, Kilicturgay S, Ozer A, et al. Gallbladder polyps: factors affecting surgical decision. World J Gastroenterol. 2013;19(28):4526-30. doi: 10.3748/wjg.v19.i28.4526.
21. Zielinski MD, Atwell TD, Davis PW, Kendrick ML, Que FG. Comparison of surgically resected polypoid lesions of the gallbladder to their pre-operative ultrasound characteristics. J Gastrointest Surg. 2009;13(1):19-25. doi: 10.1007/s11605-008-0725-2.
22. Wennmacker S, Dijk A, Raessens J, Laarhoven C, Drenth J, Reuver P, et al. Polyp size of 1 cm is insufficient to discriminate neoplastic and non-neoplastic gallbladder polyps. Surg Endosc. 2019;33(5):1564-71. doi: 10.1007/s00464-018-6444-1.
23. European Association for the Study of the Liver. EASL Clinical Practice Guidelines on the prevention, diagnosis and treatment of gallstones. J Hepatol. 2016;65(1):146-181. doi: 10.1016/j.jhep.2016.03.005.
24. Wiles R, Thoeni RF, Barbu ST, Vashist YK, Rafaelsen SR, Dewhurst C, et al. Management and follow-up of gallbladder polyps: Joint guidelines between the European Society of Gastrointestinal and Abdominal Radiology (ESGAR), European Association for Endoscopic Surgery and other Interventional Techniques (EAES), International Society of Digestive Surgery- European Federation (EFISDS) and European Society of Gastrointestinal Endoscopy (ESGE). Eur Radiol. 2017;27(9):3856-66. doi: 10.1007/s00330-017-4742-y.
25. Cha BH, Hwang JH, Lee SH, Kim JE, Cho JY, Kim H, et al. Pre-operative factors that can predict neoplastic polypoid lesions of the gallbladder. World J Gastroenterol. 2011;17(17):2216-22. doi: 10.3748/wjg.v17.i17.2216.
26. Park JK, Yoon YB, Kim YT, Ryu JK, Yoon WJ, Lee SH, et al. Management strategies for gallbladder polyps: is it possible to predict malignant gallbladder polyps? Gut Liver. 2008;2(2):88-94. doi: 10.5009/gnl.2008.2.2.88.
27. Choi SY, Kim TS, Kim HJ, Park JH, Park DI, Cho YK, et al. Is it necessary to perform prophylactic cholecystectomy for asymptomatic subjects with gallbladder polyps and gallstones? J Gastroenterol Hepatol. 2010;25(6):1099-104. doi: 10.1111/j.1440-1746.2010.06288.x.