ORIGINAL ARTICLE

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Is Routine Histopathological Gallbladder Examination Necessary After Cholecystectomy? Evaluation of the Results of 1366 Cholecystectomy Specimens in Single Center

ABSTRACT

Objective: It was aimed to evaluate the results of routine histopathological examination after cholecystectomy and to investigate the necessity of routine histopathologic examination after cholecystectomy.

Methods: The study was designed retrospectively. One thousand three hundred sixty six patients who underwent laparoscopic and open cholecystectomy at Private Sani Konukoglu Hospital with pre-diagnosis of benign gallbladder disease between November 2011 and May 2017 were included in the study. Patients' demographic data, pathologic results, macroscopic appearance of the specimen, and cancer staging were recorded. The distribution and frequency of pathologic diagnoses and the prevalence of incidental gallbladder cancer (GBC) were evaluated. Pathologic findings were compared in terms of age groups and gender relations.

Results: The number of patients included in the study was 1366. Diagnosed with chronic cholecystitis patients were 1,303 (95%), 39 (3%) with acute cholecystitis, 7 (0.5%) with gallbladder cancer, and 17 (1.5%) with other diagnoses of the patients. Statistical significance was found between the groups in terms of the mean age ($p = 0.0002$). Comparisons between groups in terms of cholesterolysis were statistically significant ($p = 0.0003$). There was a significant relationship between mucosa atrophy and gender ($p = 0.001$).

Conclusions: The histopathological spectrum of gallbladder is quite extensive. Incidental GBC may not be detected by preoperative imaging methods. Incidental GBC are usually asymptomatic. T_2, T_3 and T_4 GBC were also encountered in our study. All of these patients need additional operations. In the absence of routine histopathologic examination, metastatic advanced GBC may be encountered because no treatment plans could make. Thus, we do recommend routine histopathological examination.

Keywords: Cancer, Cholesterolysis, Dysplasia, Gallbladder, Histopathologic, Metaplasia.

Kolesistektomi Sonrası Rutin Histopatlojik Safra Kesesi İncelemesi Gerekli Mi? Tek Merkezdeki 1366 Kolesistektomi Spesmeninin Sonuçlarının Değerlendirilmesi

ÖZET

Amaç: Kolesistektomi sonrası rutin olarak yapılan histopatolojik inceleme sonuçlarının değerlendirilmesi, kolesistektomiler sonrası rutin histopatolojik incelemenin gerekliliğini araştırmak amaçlanmıştır.

Gereç ve Yöntem: Çalışma retrospektif olarak dizayn edilmiştir. Bening safra kesesi hastalığı ön tanısı ile Kasım 2011- Mayıs 2017 yılları arasında Özel Sani Konukoğlu Hastanesinde laparaskopik ve açık kolesistektomi uygulanan 1366 hasta çalışmaya dahil edildi. Hastaların demografik verileri, patoloji sonuçları, spesmenin makroskopik görünümü, kanser evrelemesi kayıt edildi. Patolojik tanıların dağılımı ve sıklığı, incidental safra kesesi kanseri prevalansı değerlendirildi.

Bulgular: Çalışmaya dahil edilen hasta sayısı 1366 idi. Hastaların 1303 (%95)'ü kronik kolesistit, 39 (%3)'u akut kolesistit, 7 (%0.5)'i safra kesesi kanseri, 17 (%1.5) hastada diğer tanılar tespit edildi. Gruplar arasında yaş ortalaması açısından istatistiksel anlamlılık saptandı ($p=0.0002$). Kolesterolizis açısından gruplar arasında yapılan karşılaştırmalarda istatistiksel olarak anlamlılık bulundu ($p=0.0003$). Mukoza atrofisi ile cinsiyet arasında anlamlı ilişki tespit edildi ($p=0.001$).

Sonuç: Safra kesesi spesmenlerinin histopatolojik incelenmesinde en sık görülen tanı kronik kolesistitdir. Ancak kolesistektomi sonrası, safra kesesinin histopatolojik spekturumu oldukça geniştir. İncidental safra kesesi tümörleri preoperative görüntüleme yöntemleri ile tespit edilemeyebilir. İncidental safra kesesi tümörleri genellikle asemptomtomatik seyretmektedir. Çalışmamızda T_2, T_3 ve T_4 safra kesesi tümörlerine de rastlanılmıştır. Bu hastaların tümüne ek girişimler gerekmiştir. Rutin histopatolojik inceleme yokluğunda, tedavi planı yapılamadığından metastatic ileri evre safra kesesi tümörleriyle karşılaşılabilir. Bu nedenle rutin histopatolojik incelemenin yapılmasını önermekteyiz.

Anahtar Kelimeler: Safra kesesi, Histopatoloji, Kanser, Kolesterolizis, Displazi, Metaplazi

INTRODUCTION

Cholecystectomy is performed electively or urgently in gallbladder diseases. The most important aspect in the histopathological examination of the gallbladder specimens is the malign tumors of the gallbladder. Although the malignant diseases of the gallbladder are rarely seen, they are quite aggressive. In one study, incidence in western societies was reported as 0.9 and 1.9 in 100,000 men and women, respectively (1). However, it is observed in northern India and Pakistan with a high incidence of 21.5 and 13.8 in 100,000 cases, respectively (2, 3).

Since there are no specific signs and symptoms of gallbladder cancer (GBC), they usually appear late stage of the cancer. Therefore, the diagnosis can usually be made in the advanced stage. While 5-year survival is below 5%, overall mean survival is 6 months (4).

Cholecystectomy is sufficient for curative therapy in the mucosa limited (Tis) and T1a GBCs (5, 6). Early stage GBCs are usually incidentally detected during histopathological evaluation of the pathologist's cholecystectomy specimen. GBC diagnosis are made as incidental in the histopathological examination of the gallbladder specimen which is thought to be benign in 60-80% of cases. Incidental primary GBC ratio was reported as 0.19-3.3% (7, 8). It has been reported that the prognosis is better in incidental GBC. It was shown that this is because of early diagnosis and fast definitive treatment (9, 10).

Histopathologic examination is very important when it comes to the confirmation of the clinical and radiological diagnosis. Histopathologic examination is also an important prognostic tool in advanced treatment of patients. Histopathological examination also plays an important role in medicolegal cases. Although histopathological examinations are routinely performed in many centers, they are performed selectively in some centers (9, 11). Routine histopathological examination of the gallbladder is still a controversial subject. In some publications, it was emphasized the importance of the routine histopathological examination in cancer diagnosis, whereas in some publications, selective histopathological examination is recommended (12, 13). It has been reported that in patients with macroscopically abnormal gallbladder, elderly, female, high-risk group with high alkaline phosphatase levels; selective histopathologic examinations have higher cost effective. In addition, selective histopathological examinations are thought to reduce the workload of pathologists (14). The College of American and the UK Royal College of Pathologists recommend selective histopathologic examination of surgical specimens (15).

In this study, it was aimed to evaluate the results of routine histopathological examination after cholecystectomy and to investigate the necessity of routine histopathologic examination after cholecystectomy.

MATERIAL AND METHODS

The study was designed retrospectively. One thousand three hundred sixty six patients who underwent laparoscopic and open cholecystectomy at Private Sani Konukoglu Hospital with pre-diagnosis of benign gallbladder disease between November 2011 and May 2017 were included in the study. Patients with imaging findings consistent with preoperative gallbladder cancer were not included in the study. Cholecystectomies made in addition to liver resection or pancreaticoduodenectomy were not included in the study as well. All gallbladder specimens were sent to the pathology department. Patient data were retrospectively obtained by recording the data in patients' files and electronic records based on the protocol created initially for this study. Patients' demographic data, pathologic results, macroscopic appearance of the specimen, and cancer staging were recorded. The distribution and frequency of pathologic diagnoses and the prevalence of incidental GBC were evaluated. Pathologic findings were compared in terms of age groups and gender relations. Staging of gallbladder tumors was performed according to the American Joint Committee on Cancer TNM system. In this research which is not invasive approval from the ethical committee was not requested. Retrospective file scanning was performed. The study was conducted in accordance with the Declaration of Helsinki. This study is registered at researchregistry.com by the number ID researchregistry 3114.

Statistical Analysis: Distribution of categorical factors (such as metaplasia and cholesterolosis groups) among the patients were compared by Chi-square tests. Age was analysed as continuous variable with a normal distribution and expressed as mean ± standard deviation. ANOVA was used to test the age difference between cholecystitis and other groups. P-values less than 0.05 were considered as statistically significant. All statistical analyses were conducted by SAS/STAT version 9.3 (SAS Institute, Inc, Cary, North Carolina, USA).

RESULTS

The number of patients included in the study was 1,366. Diagnosed with chronic cholecystitis patients were 1,303 (95%), 39 (3%) with acute cholecystitis, 7 (0.5%) with gallbladder cancer, and 17 (1.5%) with other diagnoses of the patients. Female and male patients were 954 (69.8%) and 412 (30.1%) respectively (Table 1). Statistical significance was found in gender comparison ($p = 0.0001$). The mean age in the chronic cholecystitis group was 49±15, 59±14 in the acute cholecystitis group and 52±18 in the other pathologic diagnosis group (Figure 1-2).

Table 1. Diagnosis and age groups distribution

Diagnosis	N (%)
Chronic cholecystitis	1303 (95%)
Acut cholecystitis	39 (3%)
Eosinophilic cholecystitis	4 (0.3%)
Gallbladder Cancer	7 (0.5%)
polyp	12 (0.9%)
Xanthogranulomatous cholecystitis	1 (0.1%)
Age Groups	
<25	67 (5%)
26 – 45	477 (35%)
46 – 50	153 (11%)
> 50	669 (49%)

Statistical significance was found between the groups in terms of the mean age (p = 0.0002). Histopathological examination of gallbladder revealed metaplasia in 16 (1.1%) patients. There was no statistical significance seen between the groups in terms of metaplasia (p = 0.92). There was no statistical significance between the metaplasia and age groups and gender (p = 0.99) (p = 0.81). Dysplasia was observed in 3 patients (0.2%) in the chronic cholecystitis group. Diffuse cholesterolysis was detected in 365 (26.7%) and cholesterol polyp in 28 (2%) of the examined gallbladder. Comparisons between groups in terms of cholesterolysis were statistically significant (p = 0.0003). Comparisons between cholesterolysis and age groups and gender were statistically significant (p = 0.0001) (p <0.0001). Mucosal atrophy was observed in 208 (15%) of the examined gallbladder (Table-2). There was no statistically significant difference between the groups in terms of mucosa atrophy (p = 0.32). However, there was a significant relationship between mucosa atrophy and gender (p = 0.001) (Table 3).

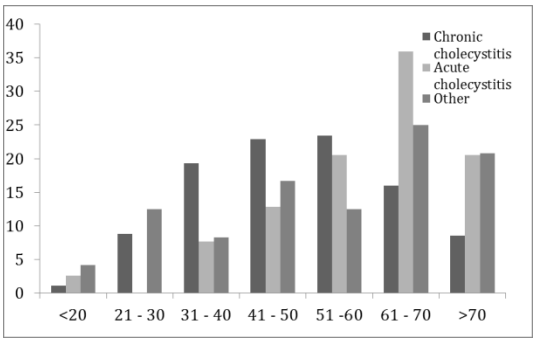

Figure 1. Distribution of gallbladder pathology among the age groups.

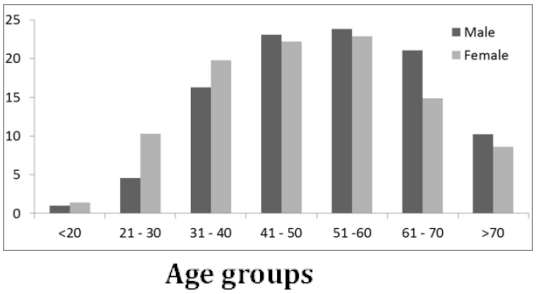

Figure 2- Distribution of male and female patients among the age groups.

Table 2. Relationship betwen diagnosis and metaplasia, dysplasia, cholesterolosis, mucosa atrophy

	Diagnosis			
	Chronic cholecystitis (n=1303)	**Acut cholecystitis (n=39)**	**Other (n=24)**	**P**
Age (mean±SD)	49±15	59±14	52±18	**0.0002**
Sex (%)				**0.0001**
Male (n=412)	94	5	0.5	
Female (n=954)	96	2	2	
Metaplasia				0.92
• Yes (n=16) (%)	100	0	0	
• No (n=1346) (%)	95	3	2	
Dysplasia (n=3) (%)3	100	0	0	
Cholesterolosis				**0.0003**
• Yes (n=365) (%)	99	0.6	0	
• No (n=967) (%)	94	4	2	
• Cholesterol polyp (n=28) (%)	100	0	0	
Mucosa atrophy				0.32
• Yes (n=208) (%)	97	3	0.5	
• No (n=1156) (%)	95	3	2	

Table 3. Relationship betwen metaplasia, dysplasia, cholesterolosis, mucosa atrophy and sex, age groups.

	Metaplasia				Cholesterolosis				Mucosa atrophy		
	Yes (n=16) %	No (n=1346) %	Dysplasia + Metaplasia (n=3) %	P	Yes (n=365) %	No (n=967) %	Cholesterol polyp (n=28) %	p	Yes (n=208) %	No (n=1156) %	p
Sex				0.81				***0.0001***			***0.001***
Male	37	30	33		18	35	29		40	28	
Female	63	60	67		82	65	71		60	72	
Age Groups				0.99				***<0.0001***			0.16
<20	0	1	0		1	1	3		1	1	
20-30	6	9	0		12	7	11		5	9	
31-40	19	19	33		23	17	18		16	19	
41-50	19	22	33		23	22	32		26	22	
51-60	25	23	0		24	22	36		27	22	
61-70	19	16	33		3	13	0		16	17	
>70	12	9	0		4	11	0		8	9	

DISCUSSION

Routine histopathological examination of all gallbladder specimens is still a controversial issue (9, 15). Selective histopathologic examination is recommended for some publications (16). In selective histopathological examination, histopathologic examination is performed especially in case of macroscopic pathologies occurred in the perioperative gallbladder and > 60 years of age (6). Dix *et al*., Darmas *et al*., Ramraje SN *et al*. have proposed a selective approach. Thus, it has been argued that the workload of the pathologist will reduce and the cost will go down as well (4, 6, 15). In a study conducted in India, 47% of gallbladder specimens contained macroscopic abnormalities. It has been reported that 13 of these patients have GBC. In this study, histopathologic examination of gallbladder specimens containing only macroscopically abnormalities was proposed (14). The frequency of the GBC's in Asian countries and North Indiada is quite high. Selective histopathologic examination in areas with high susceptibility has not been found appropriate by some researchers (17). However, Chin KF *et al*. stated that demographic characteristics did not affect selective treatment (18).

Although there are some authors who recommend selective histopathological examination, there are also authors who do not recommend it. Siddiqui *et al.* reported in their study that the histopathological spectrum of gallbladder was quite variable. It is stated that the incidence of incidental GBC is not uncommon, and subclinical malignancies cannot be detected as a result of non-routinely histopathologic examinations and this situation will be catastrophic. Thus, Siddiqui *et al.* suggests routine histopathological examination of all gallbladder specimens (11). Agarwal *et al.* reported that late recurrences due to gallbladder specimens without histopathological examination may be seen and may cause poor prognosis due to unresectability. Therefore, it is recommended that all cholecystectomy specimens be sent to pathologic examination for histopathological examination (9). Our center has a policy to send all gallbladder specimens to a histopathological examination. However, macroscopic abnormalities of the mucosa were detected in all the specimens except for a specimen, which had 7 GBC diagnoses in our series. Moreover, the average age of the patients was 63.

Gallbladder diseases are more common in women than in men (19). In our study, 69.8% of the patients were female. Our findings were compatible with the literature.

Chronic cholecystitis was found to be the most common diagnosis in our study. Siddiqui FG *et al.* (11) reported that the diagnosis of chronic cholecystitis was 92.3% and Basak F *et al.* (12) stated that it was 96.3%. In our study, the diagnosis of chronic cholecystitis was found to be 95% in agreement with the literature.

Histopathological examination of gallbladder revealed a mucoceles incidence of approximately 3% (11). No mucoceles were found among the specimens examined in our study. Xanthogranulomatous cholecystitis is an inflammatory disease characterized by the accumulation of lipid-laden macrophages, fibrous tissue, acute and chronic inflammatory cells. It may mimic gallbladder cancer as involvement in neighboring organs (20). It has also been reported that there is a relationship between xanthogranulomatous cholecystitis and carcinoma of the gallbladder cancer (21). In our study,

xanthogranulomatous cholecystitis was detected in a specimen. Eosinophilic cholecystitis is a rare form of Cholecystitis. Histopathologically, it is characterized by transmural leukocyte infiltration with more than 90% eosinophil. Although etiology is uncertain, it has been reported that it can be associated with allergies, parasites, hypereosinophilic syndromes, eosinophilic gastroenteritis, cholelithiasis, and acalculous cholecystitis (22). In our study, eosinophilic cholecystitis was detected in 3 specimens.

The incidence of gallbladder polyps varies between 4.6-12% (23, 24). Gallbladder polyps are often asymptomatic and are usually detected incidentally during ultrasonography. Non-neoplastic or neoplastic polyps can be seen in the gallbladder. Neoplastic polyps can be seen as adenomas, adenocarcinomas and squamous cell carcinomas (25). The most common polyps are cholesterol polyps as the rate of 60-90% (26).

In our study, the cholesterol polyp ratio was 70%. Neoplastic polyps are seen rarely. Adenomas and carcinomas are involved in neoplastic polyps. Although adenomas are usually benign, they exhibit premalignant behavior at 4% (23). In our study, adenomatous polyp was detected in 10 specimens. One of the specimens was reported as a tubulovillous adenomatous polyp. The other two specimens were reported as fibromas, while the other one was adenomyomas. American Gastrointestinal and Endoscopic Surgeons recommends the follow-up of asymptomatic polyps <5 mm, and treatment of larger single and symptomatic polyps with cholecystectomy (27). The approach in our center is in the same direction as laparoscopic cholecystectomy was suggested with gallbladder polyps > 1 cm and symptomatic disease.

Although cholesterolosis of the gallbladder is common, it is a rarely reported subject. Cholecystectomy is seen in about 20% of the specimens (28). Cholesterolosis rate was reported as 25% by Ozgur T *et al.* (29). In our study, Cholesterolosis of the gallbladder was seen in 26%. Gallbladder cholesterolosis can be correlated with elevated serum cholesterol. In addition, cholesterol that accumulates in the gallbladder wall causes gallbladder dysfunction. . Cholesterolosis can also cause idiopathic pancreatitis (28, 30, 31). Yaylak F *et al.* reported that cholesterolosis of the gallbladder might be associated with metaplasia at the gallbladder (32). Roa I *et al.* reported that cholesterolosis was significantly lower in specimens with gallbladder cancer (33). In our study, cholesterolosis was not seen in specimens with gallbladder cancer. Studies conducted by Dairi S *et al.* and Yaylak F *et al.* showed that cholesterolosis was significantly higher in women (28, 32). In our study, histopathological examination of gallbladder specimens revealed that cholesterolosis was significantly higher in females compared to males. This may be due to the difference in cholesterol metabolism between male and female (34). The clinical significance of cholesterolosis of the gallbladder is still unclear (32). Therefore, wider series of studies are needed.

Changes caused by lymphocytes and plasma cells during inflammatory processes that occur in the mucous membranes of chronic cholecystitis result in mucosal atrophy. Mucosa atrophy was detected in 15% of the specimens in our study. Hassan *et al.* found that there was no significant association between mucosal atrophy and Helicobacter pylori in their study conducted on helicobacter pylori and gallbladder mucosal changes (35).

GBC is a very aggressive malignant disease although that is rarely seen. It especially affects the elderly population. It has a poor prognosis in the absence of early diagnosis and treatment. GBC is more common in women relative to men. It shows peak incidence in seventh decade of life (8). Approximately 0.3-2% of patients with benign cause of cholecystectomy have GBC (36, 37). This rate was 0.5% in our study. Basak F *et al.* found this rate as 0.23%, whereas the rate in Asian countries and North India is higher than in western countries (12, 38). The most important reason for this depends on variables of the GBC incidence based on the geographical region.

There are two important sequences in gallbladder carcinogenesis. One of them is metaplasia-dysplasia and carcinoma development and the other one is adenoma-carcinoma development. Metaplasic changes cause precancerous changes in gallbladder epithelium (39). The relationship between gallbladder cancer and metaplasia-dysplasia has been shown in studies (8). Basak F *et al.* showed that metaplasia is associated with carcinoma in 2 of 4 patients whose gallbladder cancer was detected in their study (12). In our study, cancer and metaplasia associations were not seen in the reports. In our study, 16 (1.1%) metaplasias were found in histopathological examinations of gallbladder. Dysplasia was observed in only 3 (0.2%) specimens.

It has long been believed that there is a relationship between GBC and chronic inflammation, which is the cause of gallbladder stones (40). Gallstones are present in 54-97% of GBCs (12). It has been reported that gallstones may cause long-term chronic inflammation of the gallbladder (41). The association between chronic inflammations, gallstones and GBC is still controversial. In our study, the mass was accompanied by gallstones in 4 (57%) gallbladder diagnosed with GBC. Our findings were consistent with the literature. GBC and acute cholecystitis have also been reported (42). However, acute cholecystitis and GBC association did not observed in our study.

In their meta-analysis, Swank *et al.* reported that tumors of the Tis or T_1 stage were the rate of 42.4% (43). Deng *et al*. have shown that 61.4% of gallbladder tumors are in T1a or T1b (42). Basak F *et al.* reported T_2, T_3, and T_4 gallbladder tumors as 26.4%, 24%, and 7.2%, respectively (12). In our study, Tis gallbladder tumor was found in two patients (28%), T_1 in one patient (14%), T_2 in two patient (28%), T_3 in one patient (14%) and T_4 in one patient (14%). Cholecystectomy is curative in Tis and T1a biliary cancer, which is limited in the mucosa (5, 6). Five-year survival in these tumors was reported as 100% (44). Cholecystectomy by itself is not sufficient in T_2, T_3 and T_4 tumors. New surgical interventions and adjuvant treatments involving hepatic resection and lymph node dissection targeting the tumor-free surgical margin should be planned (12, 45).

There are some limitations in our study. Although our study did not include a large series, it was difficult to reach some data due to the fact that it is retrospective and some patients taking additional surgical procedures and adjuvant treatment at other centers. These findings are from a single region of Turkey. The results in regions with high incidence of gallbladder cancer may differ. Therefore, there is a need for multicenter studies from different regions and countries.

CONCLUSION

The most common diagnosis in the histopathological examination of gallbladder specimens is chronic cholecystitis. However, after cholecystectomy, the histopathological spectrum of gallbladder is quite extensive. Incidental gallbladder tumors may not be detected by preoperative imaging methods. Incidental gallbladder tumors are usually asymptomatic. T_2, T_3 and T_4 gallbladder tumors were also encountered in our study. All of these patients need additional operations. In the absence of routine histopathologic examination, metastatic advanced gallbladder tumors may be encountered because no treatment plans could make. Thus, we do recommend routine histopathological examination.

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