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A retrospective evaluation of the epitelial lesions / neoplasms of the gallbladder in Uşak city and determination of the visual frequency

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Abstract

Cholecystectomy is one of the most common types of surgical operations and includes many pathologies ranging from the most common cholecysistitis to randomly detected dysplasia and cancer. In this study, it is aimed to obtain a general regional incidence by documenting gallbladder pathology data in Usak province and to contribute to literature in this field. Between 2015 and 2019, 1712 cholecystectomy specimens were analyzed retrospectively in the Department of Pathology, Usak University Training and Research Hospital; adenocarcinoma (primary invasive carcinomas), low and high grade dysplasias (Biliary intraepithelial neoplasia - BillN1,2), neoplasms / adenomas, intestinal – pyloric metaplasia, reactive atypia and other lesions were re-evaluated with Olympus CX41 light microscope and based on recent diagnoses. Epithelial changes / lesions were reported in 11.3% of cholecystectomy materials. Of these epithelial lesions, 6.18% had adenocarcinoma, 4,6% had high-grade dysplasia, 29,3% had low-grade dysplasia, 27,3% reactive / regenerative atypia and 2,06% - 14,9% - 15,4 %, neoplastic polyps, intestinal metaplasia and intestinal + pyloric metaplasic respectively. Of the cases with dysplasia and carcinoma, 39.3% and 33.4% were male, 60.7% and 66% female, respectively. The mean age was 57 in dysplasia and 66 in carcinoma. The female / male ratio in carcinoma cases was 2/1 and 41.6% of these cases had stones. The remaining lesions (88,7%) were non-neoplastic polypoid / hyperplastic leions and pyloric metaplasia. According to our findings, we suggest that, even in the absence of clinical symptoms, an adequate number of samples should be taken from the specimen during histopathological examination, especially in elderly women with long-standing stones due to the risk of developing precancerous lesions.

Keywords: Gallbladder, cholecystectomy specimens, epithelial changes, sampling

Introduction

Gallbladder diseases are one of the most common medical conditions requiring surgical intervention. Cholelithiasis and chronic cholecystitis affect approximately 10% of the adult population in the United States. Cases of chronic cholecystitis often affect women and the disease peaks in the 5th-6th decades. Gallbladder stones accompany in 95% of cases [1,2]. Histopathological examination of cholecystectomy materials includes chronic cholecystitis, cholesterolosis, muscle hypertrophy, polypoid and adenomatous proliferation of mucous glands - adenoma, metaplasia, hyperplasia - atypical hyperplasia, dysplasia, carcinoma in situ and malignancy. Histomorphologically, the gallbladder epithelium is monolayered, with columnar epithelium, contains sulphomucine, does not contain mucous gland and goblet cells. Two major types of metaplasia occur in the biliary tract: gastric (pyloric) and intestinal. Pyloric gland metaplasia is the most common type of metaplasia and is found in about 66-84 % of gallbladders removed for chronic cholecystitis or cholelithiasis . Also squamous metaplasia can be seen in rarely [3].

Metaplasia, hyperplasia - atypical hyperplasia and dysplasia are considered as precancerous lesions. Malignant tumors are rarely seen in the gallbladder and most of them are adenocarcinomas. A significant number of tumors are asymptomatic and detected incidentally during postoperative histopathological examination. Although there are different results in the literature, 0.19-3.3% of cancer cases are found after cholecystectomy. Although the pathogenesis is not fully elucidated, genetically dysplasia-carcinoma sequence and to a lesser extent adenoma-carcinoma sequence is held responsible for the development of gallbladder carcinoma. [4]. It is known that demographic features such as age, gender, obesity and clinical findings such as chronic cholecystitis and cholelithiasis play a role in this process. [4]. Early diagnosis is very difficult in patients with gallbladder carcinomas with

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cholelithiasis and chronic cholecystitis, due to masking of specific symptoms. Therefore, routine histopathological examination of cholecystectomy materials is important. [2].

The aim of our study was to document the gallbladder pathology data in Usak to obtain a general local incidence, to review pathological lesions and clinical findings and to compare them with the literature findings.

Materials and Methods

Study design and data Sources

Slides of 1712 cholecystectomy specimens sampled between 2015 and 2019 in the Department of Pathology, Uşak University Training and Research Hospital were re-evaluated retrospectively. Adenocarcinoma (primary invasive carcinomas), histhological grade, pathologic stage, lymphovascular and perineural invasion in adenocarcinoma cases were recorded. Low and high grade dysplasias (Biliary intraepithelial neoplasia BillN1,2 and 3), neoplasms / adenomas, metaplasias, reactive atypia, cholelithiasis, cholesterolosis and the other lesions were re-evaluated with the Olympus CX41 light microscope and based on recent diagnoses. In addition, diagnosis rates, age and sex distributions were determined. Pathological staging of the tumor was done based on American Joint Committee on Cancer (AJCC) criteria.

Ethical considerations

The study was in accordance with the principles outlined in the Declaration of Helsinki. Ethical approval was received from the local Human Non-invasive Clinical Research Ethics Committee. The informed consent was not requested, since the study was retrospective and the data were analyzed anonymously.

Results

Of the 1712 cases, 1252 (73.1 %) were female and 460 (26.9%) were male. The female / male ratio was 2.8. The ages of the patients ranged between 11-84 and the mean age was 50.7 for females and 54.8 for males. There was no significant difference in the mean age of female and men.

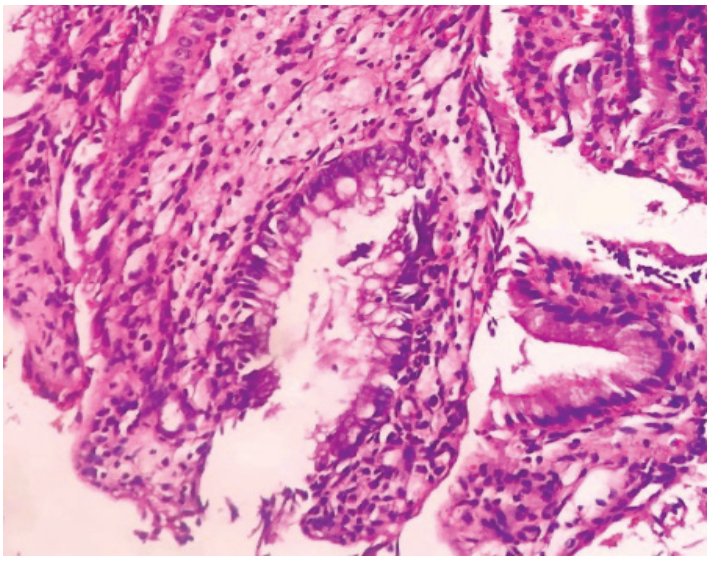

Figure 1. İntestinal metaplasia of the gallbladder (H&E; x400)

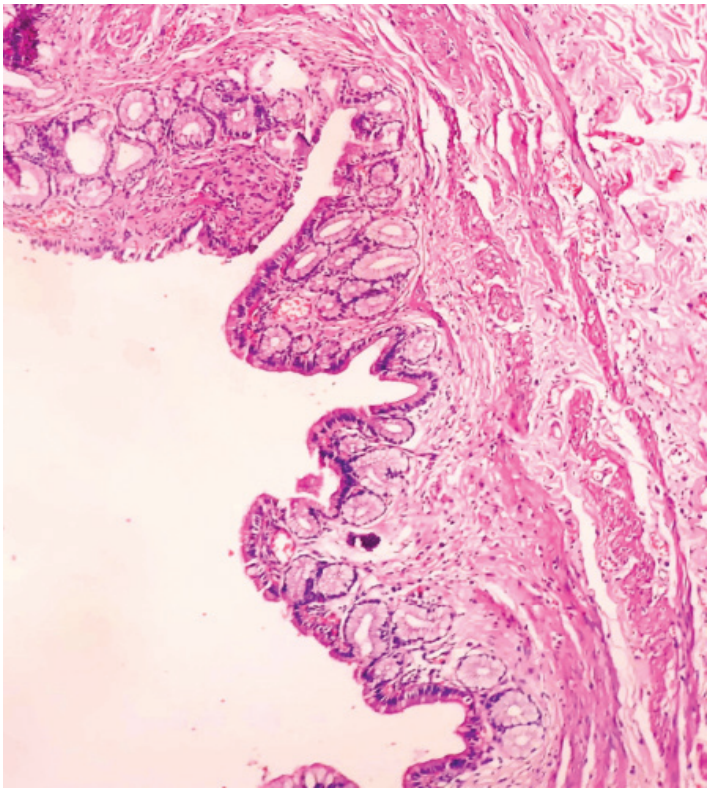

Figure 2. Pyloric metaplasia of the gallbladder (H&E; x200)

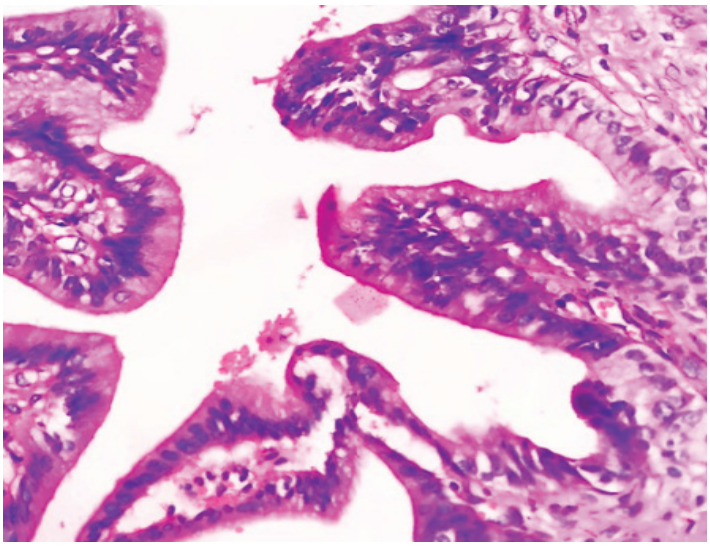

Figure 3. Low-grade dysplasia in gallbladder (H&E; x400)

Chronic cholecystitis in 513 cases (29.9 %), 3 cases (0,12%) follicular cholecystitis, eosinophilic cholecystitis in one patient (0.05%), xanthogranulomatous cholecystitis in 9 cases (0.5%), chronic active cholecystitis in 193 cases (11.2%) and chronic cholecystitis in 981 cases (57.3%). When polypoid lesions were examined, nonneoplastic polyps were found in 78 cases (4.5%) (1 inflammatory polyp, 64 cholesterol polyp, 9 papillary hyperplasia, 4 adenomyomatous hyperplasia), neoplastic polyp were found in 2 cases (0.11%) (1 tubular adenoma, 1 pyloric gland adenoma). Cholelithiasis in 1100 cases (64.2%), reactive / regenerative atypia in 53 cases (3.09%), intestinal metaplasia in 29 cases (1.69%) (Figure 1), pyloric metaplasia in 91 cases (5.3%) (Figure 2), and intestinal + pyloric metaplasia in 30 cases (1,75%) were detected.

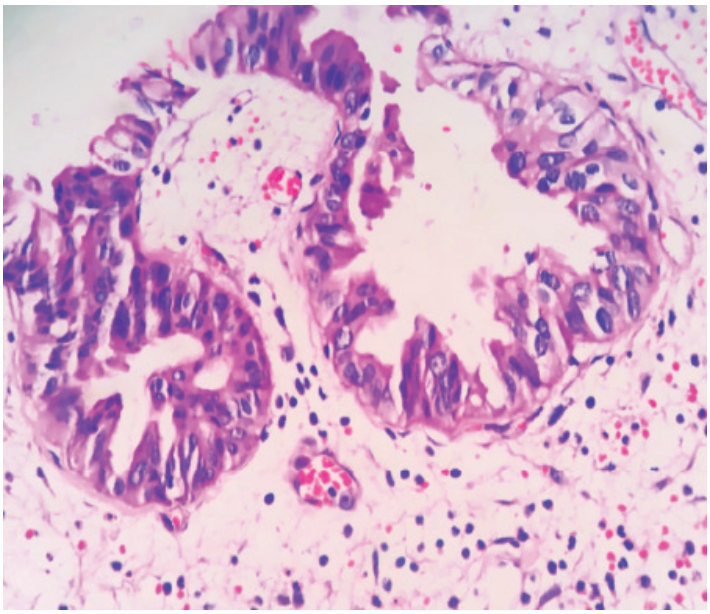

Figure 4. High-grade dysplasia in gallbladder (H&E; x400)

Of the 150 cases with metaplasia, 60 (40%) had gallstones. Gall bladder stones were present in 13 (44.8%) of 29 gallbladder with intestinal metaplasia, 41 (45%) of 91 cases with pyloric metaplasia and 15 (50%) of 30 cases with intestinal + pyloric metaplasia. When the surface epithelium was examined, low grade dysplasia was detected in 57 patients (3.3%) (Figure 3) and high grade dysplasia was detected in 9 patients (0.52%) (Figure 4).

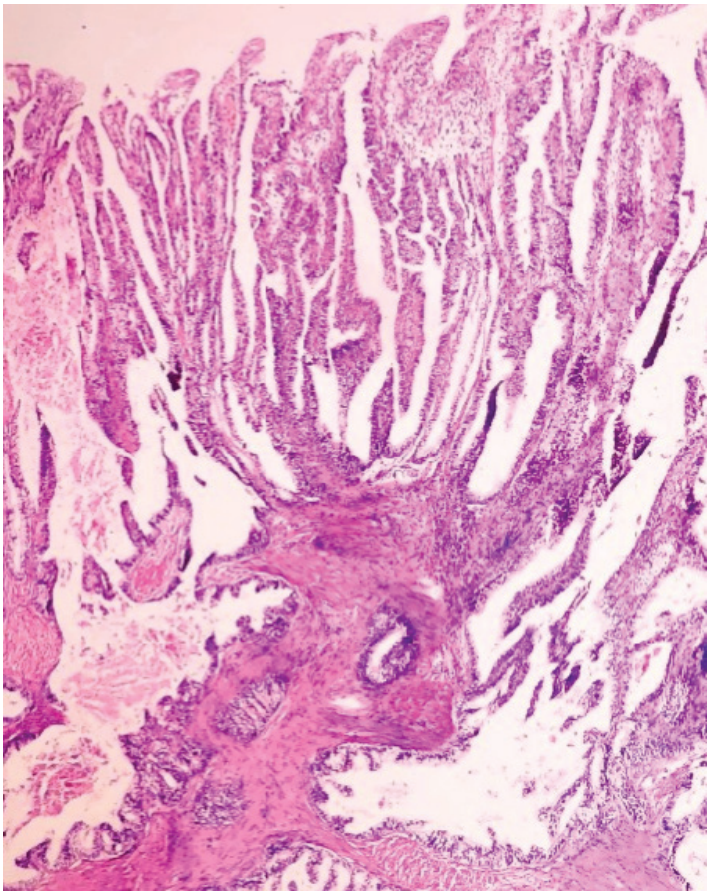

Figure 5. İntracystic papillary neoplasm with invasive carcinoma (H&E; x400).

Metaplasia adjacent to or accompanied by dysplastic epithelium was detected in 35 (53%) of 66 cases with dysplasia. Metaplasia rates were intestinal in 37.2% (13 cases), intestinal + pyloric in 40% (14 cases), intestinal metaplasia in 22.8% (8 cases). Of the cases with dysplasia, 26 (39.3%) were male and 40 (60.7%) were female. The age range was 25-81 years and the mean age was 57 years. The mean age of the patients with chronic cholecystitis with stone was 47.9 years (range 18-84 years). Cholesterolosis was detected in 190 cases (1.1%) and 77 (40.5%) of these had chronic cholecystitis, 97 (51%) had chronic cholecystitis with stone and 13 (8.5%) had chronic active cholecystitis. The mean age of the patients with cholesterolosis was 48.2 years and the age range was 22-77 years. In the study cases, 12 cases (0.7%) had primary gallbladder carcinoma, 2 of them had intracystic papillary neoplasia (Figure 5) accompanied by invasive carcinoma and 10 of them had adenocarcinoma (2 of them containing signet ring cell components) (Figure 6).

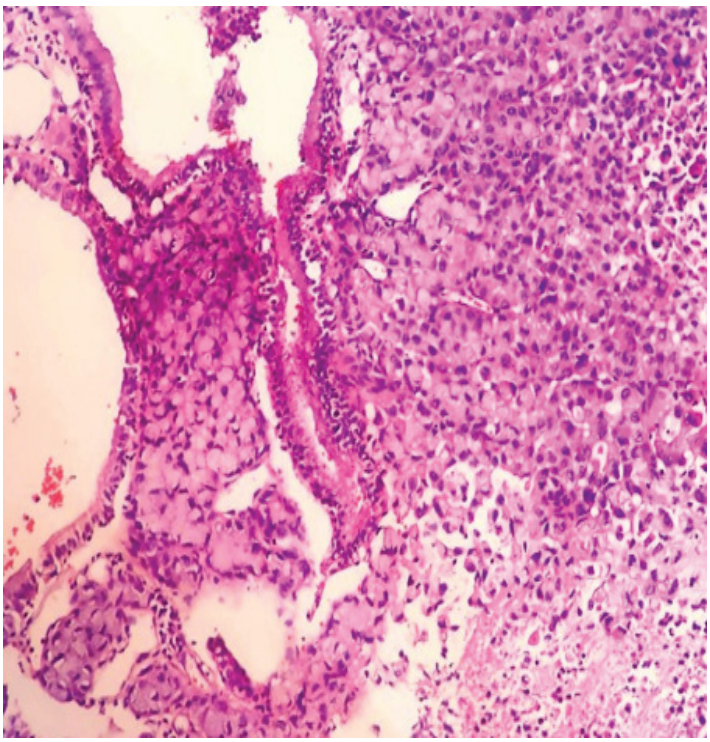

Figure 6. Adenocarcinoma (including) signet ring cell component of the gallbladder (H&E; x400)

Of these carcinoma cases, 5 were pT2 (41.6%) and 7 (58.4%) were pT3. Among carcinoma cases, 5 (41.6%) and 7 (58.3%) of the metaplastic and dysplastic changes in malignant tissue or concomitant were detected. The average age of 12 patients with malignant tumors was 66 (53-79). Eight of the 12 cases (66.6%) were female and 4 (33.4%) were male. Although 8 (66.6%) of the cases were detected by preoperative imaging techniques, 4 (33.4%) had no suspicious symptoms and the tumor was found incidentally on postoperative histopathological evaluation. The histopathological distribution of the cases is shown in Table 1. Our incidentally detected gallbladder carcinoma rate is 0.23%. The macroscopic and histopathological findings and survival times of gallbladder carcinoma for each case are summarized in Table 2. The longest follow-up period was 36 months and follow-up results were not achieved in 4 cases.

Table 1. Histopathological distribution of cases

	Female n=1252(%)	Male n=460 (%)	Total n=1712 (%)
Type of Inflammation			
Chronic cholecystitis	362(70.5)	151(29.5)	513(29.9)
Chronic active cholecystitis	112(58.1)	81(41.9)	193(11.2)
Chronic calculous cholecystitis	743(75.8)	238(24.2)	981 (57.3)
Eosinophilic cholecystitis	1(100)	-	1(0.05)
Xanthogranulomatous cholecystitis	5(55.6)	4(44.4)	9(0.12)
Follicular cholecystitis	2(66.7)	1(33.3)	3(0.12)
Cholesterolosis			
Metaplasia			
pyloric type	66(72.5)	25(27.5)	91(5.3)
intestinal type	17(58.6)	12(41.4)	29 (1.69)
P + I type	18(70)	12(30)	30 (1.75)
Polyp, hyperplasia			
Cholesterol polyp	42(65.6)	22(34.4)	64(3.7)
adenomyomatous hyperplasia	3(75)	1(25)	4(0.23)
papillary hyperplasia	6(66.6)	3(33.4)	9(0.52)
Adenoma			
Tubular adenoma	-	1(100)	1(0.05)
pyloric gland adenoma	1(100)	-	1(0.05)
Dysplasia			
Low grade	32(56.2)	25(43.8)	57(3.3)
High grade / Carcinoma in situ	7(77.8)	2(22.2)	9(0.52)
Carcinoma	8(%66.6)	4(%33.4)	12(0.7)
Total	1252(73.1)	460(26.9)	1712(100)

P: Pyloric, **I:** Intestinal

Table 2. Comparison of macroscopic-histopathological findings and survival

Case No	Macroscopic tumor structuring	Pathological Diagnosis	Grade	pT	PI	LVI	Survival (months)	Age
1	Polypoid	İntracystic papillary neoplasm with invasive carcinoma	Moderately differentiated	pT2	present	present	36	79
2	Diffuse	Adenocarcinoma (ıncludıng) signet ring cell component)	Moderately differentiated	pT2	present	present	could not be reached	64
3	Polypoid	intracystic papillary neoplasm with invasive carcinoma	Poorly differentiated	pT2	present	present	7	62
4	Diffuse	Adenocarcinoma (ıncludıng) signet ring cell component)	Moderately differentiated	pT2	absent	absent	could not be reached	72
5	Diffuse	Adenocarcinoma	Well differentiated	pT2	present	present	could not be reached	58
6	Diffuse	Adenocarcinoma	Moderately differentiated	pT3	present	present	18	60
7	Diffuse	Adenocarcinoma	Poorly differentiated	pT3	present	present	12	53
8	Diffuse	Adenocarcinoma	Moderately differentiated	pT3	present	present	14	79
9	Diffuse	Adenocarcinoma	Moderately differentiated	pT3	present	present	6	79
10	Diffuse	Adenocarcinoma	Well differentiated	pT3	present	present	could not be reached	63
11	Diffuse	Adenocarcinoma	Well differentiated	pT3	present	present	2	56
12	Diffuse	Adenocarcinoma	Poorly differentiated	pT3	present	present	6	63

Grade: Tumor differentiated, **pT:** Pathological Stage, **PI:** Perineural invasion, **LVI:** Lymphovascular invasion

Discussion

Chronic cholecystitis is the most common pathology in the gallbladder, and most of the cholecystectomy operations are due to chronic cholecystitis [2,5]. In many studies, chronic cholecystitis has been associated with cholelithiasis (85-95%). Gallbladder diseases are more common in women [1-5]. In the present study, the most common diagnosis was chronic cholecystitis with stone (57.3%) and the female / male ratio was 2.8. According to histopathological features, chronic cholecystitis are divided into sub-types such as follicular, eosinophilic, granulomatous, xanthogranulomatous, lymphoplasmacytic and AIDS-related [2,5]. Lymphoplasmacytic variant usually develops as cholecystitis with no stone associated with autoimmune diseases [5]. Cholecystitis presenting with germinal centers in the lamina propria are follicular cholecystitis and are seen in 0.1% of cases. Cases with more than 90% eosinophilic infiltration with other inflammatory cells in the gallbladder mucosa are defined as eosinophilic cholecystitis and constitutes 20% of cholecystectomy materials. Hypereosinophilic syndrome, eosinophilimialgia syndrome, parasitic infections, some herbal and drugs are responsible from etiology of eosinophilic cholecystitis [2,5]. Factors that are characteristic for particularly immunosuppressive patients such as cytomegalovirus, candida, mycobacterium and microsporidia have an important role in the formation of AIDS-related cholecystitis [5]. Another type is xanthogranulomatous cholecystitis. Histopathological examination is important in the final diagnosis, because it can be confused with malignancy clinically, macroscopically and radiologically [2]. Microscopically, mixed inflammatory cell infiltration of the gallbladder wall with numerous foamy macrophage - histiocyte groups and occasional granuloma structures is characteristic [2,5]. In our study, 57.3% of cases had chronic cholecystitis with stone, 29.9% had chronic cholecystitis, and 11.2% had chronic active cholecystitis without specific subtypes. In addition, specific chronic cholecystitis types such as xanthogranulomatous cholecystitis (0.5%), follicular cholecystitis (0.12%) and eosinophilic cholecystitis (0.05%) were found. The accumulation of cholesterol esters and triglycerides in the cytoplasm of macrophages in the gallbladder wall results in a pathology called as cholesterolosis and it is found in 20% of cholecystectomy materials [2,3,6]. Macroscopically, there are yellow streaks on the mucosal surface, and microscopically, macrophages in villous mucosal hyperplasia are seen [2,3]. Occasionally, they are seen as 1-5 mm polypoid lesions in the mucosa, which are then called cholesterol polyps and in diffuse involvement they are called “strawberry sacs” [6]. It is the most common type of polyp in the gallbladder. Various inflammatory, reactive and neoplastic polyps can also be found in the gallbladder mucosa [2,3,6]. In our study, the most common polyp type was cholesterol polyp (3.7%), followed by inflammatory polyp (0.05%), tubular adenoma (0.05%), and pyloric gland adenoma (0.05%). Pyloric gland metaplasia (particularly in atrophic epithelium, in 66-84% of cholecystectomy materials) is the most common metaplasia type, and intestinal metaplasia (in 10-30% of cholecystectomy specimens) is the second common metaplasia type in the gallbladder [2,3,7]. In a study by Sharma et al. [8], pyloric metaplasia was observed in 30.2% of cases. Meirelles-Costa et al. [9] reported that pyloric metaplasia was found in 4.3% of 1091 cases. In these studies, intestinal metaplasia rates were found as 3.36 and 1.1%, respectively. In a study by Akay et al. (10), 18 (64.3%) of 28 metaplasia cases had pyloric metaplasia and 10 (35.7%) had intestinal metaplasia. In addition, they reported that the rate of intestinal metaplasia was found to be more frequent in metaplasia in mucosa adjacent to cancer compared to intestinal metaplasia in mucosa no adjacent to cancer. In the series of 351 cases of Bahadir et al. [11], 81 had pyloric type metaplasia and 18 had intestinal metaplasia. Additionally, in their study, 8 cases had simultaneous pyloric and intestinal metaplasia. In our study, we detected intestinal metaplasia in 29 cases (1.69%), pyloric metaplasia in 91 cases (5.3%), and intestinal + pyloric metaplasia in 30 cases (1.75%). Although the high incidence of pyloric gland metaplasia compared to intestinal metaplasia has been in parallel with the literature, our rates have been below the reported rates. We think that this is due to differences in macroscopic sampling. Pyloric gland metaplasia and intestinal metaplasia occur as a result of prolonged inflammation and the presence of stones in the gallbladder [3].

In our study, we detected gallbladder stones and chronic inflammation in 44.8% of patients with intestinal metaplasia, 45% of patients with pyloric metaplasia, and 50% of patients with intestinal + pyloric metaplasia. Papillary epithelial hyperplasia and adenomyomatosis in the gallbladder are rarely seen and are usually associated with pyloric gland and intestinal metaplasia. Kılınc et al.[12] found adenomyoma / adenomyomatosis in 0.4%, Bolat et al. [3] found epithelial hyperplasia in 37.3% of the cases. Epithelial dysplasia or carcinoma in situ are the most important lesions in the development of carcinoma [2]. In our study, we detected papillary hyperplasia in 9 cases (0.52%) and adenomyomatous hyperplasia in 4 cases (0.23%). Pyloric metaplasia was found in 4 cases, intestinal + pyloric metaplasia in 1 case and intestinal metaplasia in 1 case of papillary hyperplasia [3]. It has been suggested that the gastric metaplasia-dysplasia cycle may be the onset of gallbladder cancer, so the detection of these lesions are important. Although the molecular changes seen in dysplasia are similar to those seen in carcinoma, there are no such molecular changes in adenomas. In dysplasia-carcinoma sequence and early stage carcinogenesis, p53 gene inactivation, K-ras oncogen activation, and cyclin D1 overexpression are characteristic. In contrast, p27Kip1 secretion has been shown to decrease in advanced gallbladder carcinogenesis such as tumor progression and metastasis [3]. Dysplasia may be present in the gallbladder alone or in combination with adenoma or carcinoma. The rate of dysplasia in cholecystectomy materials varies between 0.7% and 34% in various series. [3,7]. The rate of dysplasia was found to be 0.25% in the study of Esendağlı et al. [7]. In the evaluation of gallbladder pathologies, it is recommended to interpret the changes as reactive if there is ulceration and intense inflammation in cases which reactive atypia and low-grade dysplasia can be mimicked. Dysplasias are usually associated with stones and inflammation. Dysplasia is characterized by varying degrees of pseudostratification in the epithelium, nuclear atypia, loss of polarity and mitotic figures. Dysplasia is classified into two as mild and / or severe (low / high grade), or three as mild-moderate-severe (Biliary intraepithelial neoplasia, BilIN 1,2) according to cellular and structural atypia. [3,12]. Carcinoma and dysplasia are often accompanied by metaplastic lesions. It has been shown in several publications that intestinal metaplasia has an important role in the development of carcinoma and intestinal metaplasia - dysplasia relationship is more significant when compared with antral type metaplasia. [4]. However, there

are studies advocating that gastric metaplasia-dysplasia cycle may also be the onset of gallbladder cancer. In many studies increased incidence of precancerous lesions such as dysplasia and metaplasia was seen by increasing the number of samples taken for microscopic examination. [3,4]. Mazlum et al.[13], Argon et al. [14] recommends taking a full slice of the gallbladder to detect the presence of more pyloric metaplasia, intestinal metaplasia, low-grade dysplasia, and invasive carcinoma. Seçinti et al. [4)] detected dysplasia in 85.7%, intestinal metaplasia in 100%, and gastric metaplasia in 28.5% of seven cases of gallbladder cancer. They found that all foci of intestinal metaplasia were intratumoral and detected that in six cases (85.7%) of all gallbladder cancer cases, 83.3% of incidental gallbladder cancer cases) dysplasia was accompanied by intestinal metaplasia, only in two cases (28.5% of all gallbladder cancer cases, 16.6% of incidental gallbladder cancer cases) dysplasia is associated with gastric metaplasia. In our study, dysplasia and in situ areas were detected in all patients with cancer, intestinal metaplasia in 6 (58.3%), intestinal + pyloric metaplasia in 3 (25%), and pyloric metaplasia in 2 (16.7%). The fact that some of the detected rates are below of the rates reported in the literature suggests that these epithelial lesions can not be sampled, are not sufficiently recognized or misinterpreted as regenerative atypia instead of low grade dysplasia.

Adenoma - carcinoma sequence has also been extensively discussed recently. [2] Some authors have argued that adenoma-carcinoma sequence is a natural process in the development of adenocarcinoma, while others claim that adenomatous residues are present in areas where invasive carcinoma develops. There are also other case series where early microcarcinoma development has been reported in the field of adenoma. [7]. Although malignant tumors of the gallbladder are rare, 80-95% of the malignant tumors in the hepatobiliary system comprise gallbladder origin. [4]. Gallbladder cancer is seen in 0.3 - 0.7% of all cancers and 0.19 - 3.3% of cases after cholecystectomy. [4]. The global incidence, mortality and prevalence rates for the 5-year gallbladder cancer that have identified current estimates in the GLOBOCAN Project have been reported to be 1.3%, 1.7% and 6%, respectively. [7]. 5-year prevalence rate of gallbladder cancer, in a multicenter study of Esendagli et al. in Turkey, were found to be 0.5% in 89.324 cholecystectomy materials. [7] . Incidental gallbladder cancer rate was found as 0.11% in the study of Keskin et al. [15], as 2.3% in the study of Utsumi et al. [1], and as 0.87% in the study of Dorobisz et al. [17] . This rate was 33.4% in our study. Gallbladder carcinoma affects the population 15-20 years older than those with gallbladder stones and peaks in the 7th decade. [15]. The mean age at presentation is 72 years, and 2/3 of the cases are over 65 years. [12]. The mean age of our patients was 66 years. Gallbladder cancer female / male ratio varies between 1 / 1-5 / 1 in different parts of the world and the average is 3/1. Hormonal changes such as multiparity and high pregnancy rate are blamed for the high incidence of gallbladder cancers in women. [4]. In our study, the female / male ratio was 2/1, which was consistent with the literature. Other risk factors include genetic factors, gallbladder stones, obesity, porcelain gallbladder and single sessile (> 10 mm) polyps. [4,15]. Gallbladder stones are found in > 80% of gallbladder with carcinoma. There was a positive correlation between the diameter, volume, weight and number of the stones and the risk of cancer. However, the effect of the constituents of the stone is not fully known. [4,15]. In our study, gallbladder stones were found in 5 (41.6%) of 12 cancer cases. Because of the presence of nonspecific symptoms such as nausea and vomiting in early stage tumors, like as in chronic cholecystitis and cholelithiasis, and lack of specific serological markers and physical examination findings, patients who can be diagnosed preoperatively are usually in advanced stage. [4]. Approximately 50% of gallbladder carcinomas are diagnosed incidentally and therefore have a poor prognosis. Worldwide incidence is 1-2% and five-year survival rates are reported to be less than 5% for advanced stages. [15]. In our study, only 4 (33.3%) of 12 cases were found to be incidental and two of them were pT2 and two were pT3. Of the remaining 8 (66.7%) cases, 3 were pT2 and 5 were pT3. In other words, most of our cases (58.3%) were detected in advanced stage (pT3).

Esendağlı et al. [7] reported that most of these tumors were diagnosed in advanced stages and the tumor muscle layer exceeded the tumor layer at the time of diagnosis [2]. In our study, 58.3% of the cancer cases were in advanced stage for the patients who passed the muscle layer. All of the cancer cases in our series are consisted of epithelial origin and 83.3% of them were diagnosed as adenocarcinoma. Histological grading of adenocarcinomas is done according to tubule formation. If the tubule formation is above the 95%, it is well differentiated; It is defined as when 40% to 95% moderately differentiated, 5% to 39% less poorly differentiated. In the literature, the differentiation of these tumors has been described as poor, and moderate or low differentiation was observed in 2/3 of the cases. Macroscopically diffuse enlargement (70%) or polypoid mass (30%) can be seen as the most common histopathological examination [2,4]. In our study, 6 (50%) of 12 cases were moderately differentiated, 3 (25%) were good and slightly differentiated. İn terms of growth patterns, we found that 10 of them showed diffuse (wall thickening) and 2 of them showed polypoid growth. Other epithelial tumors include papillary, mucinous, squamous, and adenosquamous carcinomas. Less frequently, small cell carcinoma, undifferentiated carcinoma and other tumors are seen [2,4].

One of the important limitations of the present study is that the low- and high-grade dysplasia rates, which might accompany the findings such as chronic cholecystitis, choleithiasis, ulcer- erosion, and reactive-reparative changes – atypia, were detected to be lower than they should be because no common sampling protocol other than the routine protocol, in which three specimens (one from each of neck, corpus, and fundus) were obtained, due to retrospective nature of the present study

Conclusion

As a result, we conducted a local retrospective study covering the province of Usak and its environs and detected epithelial changes in the general population at a considerable rate. Considering that most premalignant lesions and even malignancy do not give macroscopic and clinically specific findings, it is a fact that increasing the number of samples in cases with metaplasia and dysplasia detected during microscopic examination will increase the chance of catching a further lesion. For this reason, we believe that it is necessary to carry out further studies multicentric and prospectively in the way involving different geographical regions and according to the results to be obtained from those studies, the accurate incidence values should be determined and a standard should be set for macroscopic sampling, pathological diagnosis criteria, and reporting template.

Informed Consent
Informed consent was obtained from all individual participants included in the study.

Competing interests
The authors declare that they have no competing interest.

Financial Disclosure
There are no financial supports

Ethical approval
The study was in accordance with the principles outlined in the Declaration of Helsinki. Ethical approval was received from the local Human Non-invasive Clinical Research Ethics Committee. The informed consent was not requested, since the study was retrospective and the data were analyzed anonymously.

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