Routine histopathological study of cholecystectomy specimens. Useful ? A retrospective study of 1960 cases

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Abstract

Background **: Traditionally, a gallbladder removed for presumed benign disease is sent for histopathological examination, but this practice has been the subject of controversy.**

Aim **: The aim of this study was to assess the usefulness of routine histopathological examination of cholecystectomy specimens and its impact on the management of patients.**

Patients and Methods **: The histopathological reports of 1960 patients who underwent cholecystectomy from January 2011 to November 2016 were retrospectively reviewed. Results : There were 519 men and 1441 women (sex-ratio M/F = 0,36) aged between 8 and 96 years (mean = 51,23 years). All patients underwent cholecystectomy (either open or laparoscopic). Histological examination of the surgical specimens showed chronic cholecystitis (n = 1319) (67,29%), acute cholecystitis (n = 117) (5,96%), cholestrolosis (n = 255) (13%), follicular cholecystitis (n = 230) (11,73%), xanthogranulomatous cholecystitis (n = 6) (0,30%), cholesterol polyps (n = 5) (0,255), tubular adenoma (n = 3) (0,15%), mucocele (n = 2) (0,10%), pancreatic heterotopia (n = 2) (0,10%), hyperplastic Luschka ducts (n = 2) (0,10%), adenomyoma (n = 2) (0,10%), porcelain calcification (n = 2) (0,10%) and biliary-type adenocarcinoma (n = 9) (0,46%). In 9 cases (0,46%), the gallbladder was histologically normal.**

Conclusions **: Our study shows that the incidence of pre-malignant and malignant lesions of the gallbladder is very low. We therefore recommend selective histopathological examination of cholecystectomy specimens with abnormal macroscopic findings.** (Acta gastroenterol. belg., **2017**, 80, **365-370**).

Key words : cholecystectomy, cholecystitis, cholelithiasis, gallbladder neoplasms, histopathology.

Introduction

Cholecystectomy specimens are among the most frequently accessioned specimens in general histopathology departments and account for a significant portion of the workload (1). Histopathological examination of these specimens is primarily intended to rule out significant pathology, such as gallbladder dysplasia or carcinoma, the incidence of which varies greatly worldwide (1). The aim of the present study was to assess the value of routine histological examination of the resected gallbladder.

Patients and methods

We conducted a retrospective analysis of 1960 cholecystectomies performed at our institution (Mongi Slim Hospital, La Marsa) from January 2011 to November 2016. We excluded from this study patients who underwent cholecystectomy for a non-biliary indication. The histopathology reports of all specimens were reviewed. Demographic and clinical data recorded included patients' age and sex, date of surgery and clinical details (where available). Details of macroscopic examination of the specimens included length and integrity of gallbladder, thickness of gallbladder wall, presence or absence of macroscopic lesions and presence of gallstones. In our department, cholecystectomy specimens were routinely sampled for microscopic examination, with representative sections including the fundus, the body and the neck. In cases with any growth, irregular mucosa, thickened wall, calcification or necrosis, complementary sections were taken. Negative cholecystectomy was defined as a specimen that was microscopically normal with no evidence of acute or chronic inflammation, tumours and other pathological abnormalities. Gross and microscopic features of all incidentally detected cases were studied in details. All surgical specimens were fixed in 10% phosphate buffered formaldehyde, embedded in paraffin and sections were prepared for routine light microscopy after staining with haematoxylin and eosin. The American Joint Committee on Cancer (AJCC) Tumour Nodal Metastasis (TNM) system was used to stage gallbladder cancer. Patient confidentiality was maintained.

Results

Over a period of six years (January 2011 - November 2016), 1960 gallbladder specimens were subjected to histopathological examination.

Study population

Among 1960 patients, 519 were males (26,48%) and 1441 were females (73,52%) with a sex ratio M/F = 0,36. The mean age was 51,23 years with a range from 8 to 96 years. Some clinical details beyond the word "gallbladder" or "cholecystectomy" had been provided to the reporting pathologist by the surgeon in 1200 cases (61,22%). The most common clinical presentations

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Submission date : 06/12/2016
Acceptance date : 13/03/2017

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were “cholecystitis”, “stones” and “biliary colic”. In 7 cases (0,35%), there was a radiologic suspicion of a mass, polyp, or cancer. All patients underwent cholecystectomy (either open or laparoscopic).

Macroscopic findings

The specimen was fragmented in 26 cases (1,3%). When intact, the mean gallbladder length was 6,25 cm. In 120 cases (6,12%), the gallbladder wall was described as “thickened,” but a measurement was not provided and in 1823 cases (93%), no comment was made on the thickness of the gallbladder wall. A mural or mucosal lesion was identified macroscopically in 17 cases (0,86%). Gross findings of some gallbladder specimens in our series are illustrated in multipanel Figure 1.

Microscopic findings

The histopathological findings of cholecystectomy specimens in our series are summarized in table 1.

Histological examination of the surgical specimens showed biliary-type adenocarcinoma (n = 9) (0,46%) (Figure.2a), chronic cholecystitis (n = 1319) (67,29%), acute cholecystitis (n = 117) (5,96%), cholesterol polyps (n = 5) (0,25%) (Figures 2b & 2c), xanthogranulomatous cholecystitis (n = 6) (0,30%) (Figure 2d), mucocele (n = 2) (0,10%), tubular adenoma (n = 3) (0,15%), hyperplastic Luschka ducts (n = 2) (0,10%) (Figure 3a), pancreatic heterotopia (n = 2) (0,10%) (Figure 3b), follicular cholecystitis (n = 230) (11,73%) (Figure 3c), cholestrolosis (n = 255) (13%) (Figure 3d) and porcelain calcification (n = 2) (0,10%). Pyloric and intestinal metaplasia were associated with chronic cholecystitis in 80 cases (4,08%) and 10 cases (0,51%) respectively. Some cholecystectomy specimens showed multiple concomitant lesions. In 9 cases (0,46%), the gallbladder was histologically normal. Out of 9 cases diagnosed with incidentally having gallbladder carcinoma (Table 2), 3 were males and 6 were female patients (sex-ratio M/F = 0,5). Mean age of patients was 62,77 years (range 43-78 years). Five patients with gallbladder carcinoma had co-existing cholelithiasis on

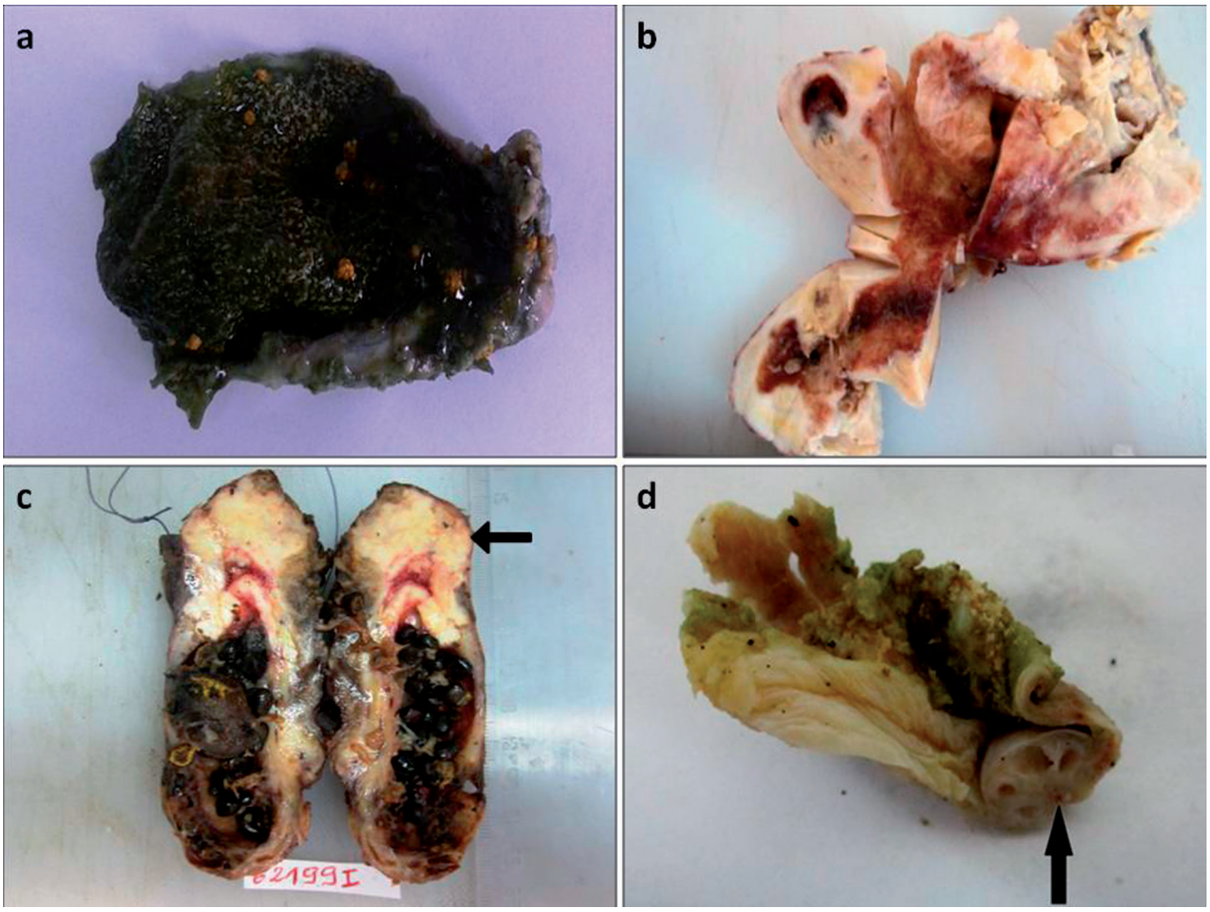

Fig. 1**.** — Macroscopic findings of cholecystectomy specimens. 1a : Macroscopic findings of cholesterolosis. Yellow mucosal flecks and linear streaks are seen with tiny cholesterol gallstones ; 1b : Macroscopic findings of xanthogranulomatous cholecystitis. Gallbladder showing yellow thickening of the gallbladder wall ; 1c : Adenocarcinoma of the gallbladder. The fleshy whitish tumour protrudes into the lumen and invades the wall of the gallbladder. Numerous pigment gallstones were also noted in the lumen ; 1d : Adenomyoma located in the fundus of the gallbladder (black arrow). It has a coarsely trabeculated appearance resulting from cystic dilation of glandular spaces and smooth muscle hyperplasia.

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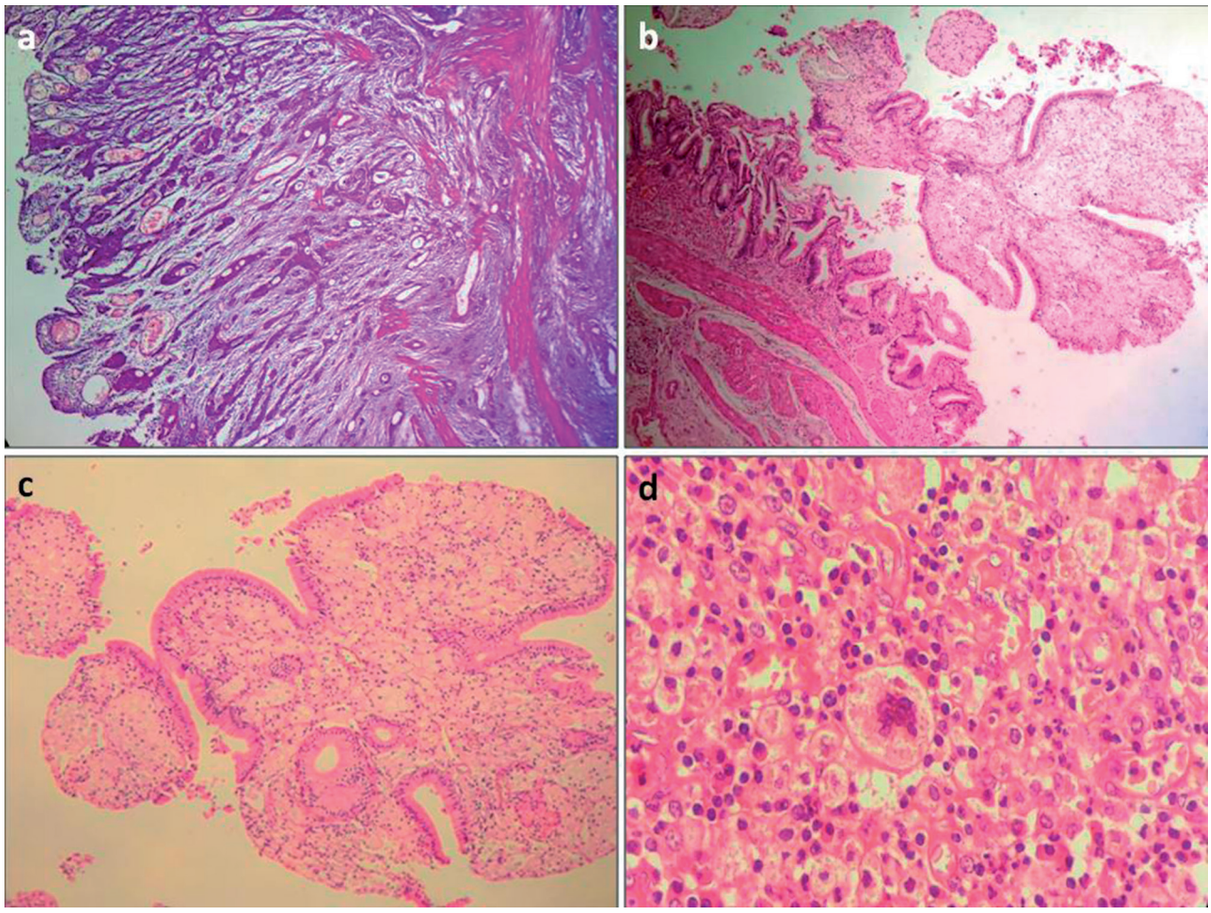

Fig. 2. — Microscopic findings of biliary type adenocarcinoma of the gallbladder, cholesterol polyp and xanthogranulomatous cholecystitis. 2a : Moderately-differentiated biliary-type adenocarcinoma of the gallbladder infiltrating the gallbladder wall, (Haematoxylin and eosin, magnification × 40) ; 2b : Cholesterol polyp. Polypoid lesion with numerous foamy macrophages in the stroma, (Haematoxylin and eosin, magnification × 40) ; 2c : Cholesterol polyp. Foamy macrophages in the axis of the polyp, (Haematoxylin and eosin, magnification × 200) ; 2d : Xanthogranulomatous cholecystitis. Foamy histiocytes and Touton giant cell admixed with polymorphous inflammatory cells. Haematoxylin and eosin, magnification × 400.

pre-operative ultrasonography, while seven patients had ultrasonography evident thickened gallbladder walls. All patients were symptomatic with right upper quadrant pain pre-operatively, however none presented with a palpable mass, clinical jaundice or weight loss. To present date, three patients (cases Nº 2,3 and 6) with gallbladder carcinoma have died from progressive metastatic disease with a postcholecystectomy mean survival time of 20,6 months. The other patients are still being followed-up.

Most gallbladder specimens in our department were processed according to the generally accepted guideline of three pieces (fundus, body, neck) in a single block. Further sampling was undertaken in 15 cases including 9 cases of gallbladder adenocarcinoma, 3 cases of tubular adenoma, two cases of hyperplastic Luschka ducts and two cases of adenomyoma.

Discussion

In our institution, all gallbladder samples collected after cholecystectomy are sent for histopathological examination. This is currently a routine practice for most of the centers in Tunisia. The main reason of routine pathological examination of cholecystectomy specimens is the exclusion of malignancy from the gallbladder as early diagnosis of gallbladder carcinoma is rarely achieved due to lack of specific signs and symptoms (2). Histopathological examination is an important tool of prognostic and diagnostic value helping in further patient management (3). Incidental gallbladder carcinoma is found in about 0,5-1,1% of cholecystectomies for gallstone disease (4-6). In our series, gallbladder carcinoma accounted for 0,46% of all cholecystectomy specimens. Gallbladder carcinoma is an aggressive malignancy with a female predominance (7). In our series, there was a female predominance with a sex-ratio (M/F) = 0,5. Signs and symptoms are often non-specific and disease often presents late with a fatal outcome (7). Delay in diagnosis and aggressive nature of disease leads to a median survival of less than six months while 5 years survival is less than 5% (7). The majority (85%) of the malignant cases of gallbladder are associated with gallstones while porcelain gallbladder

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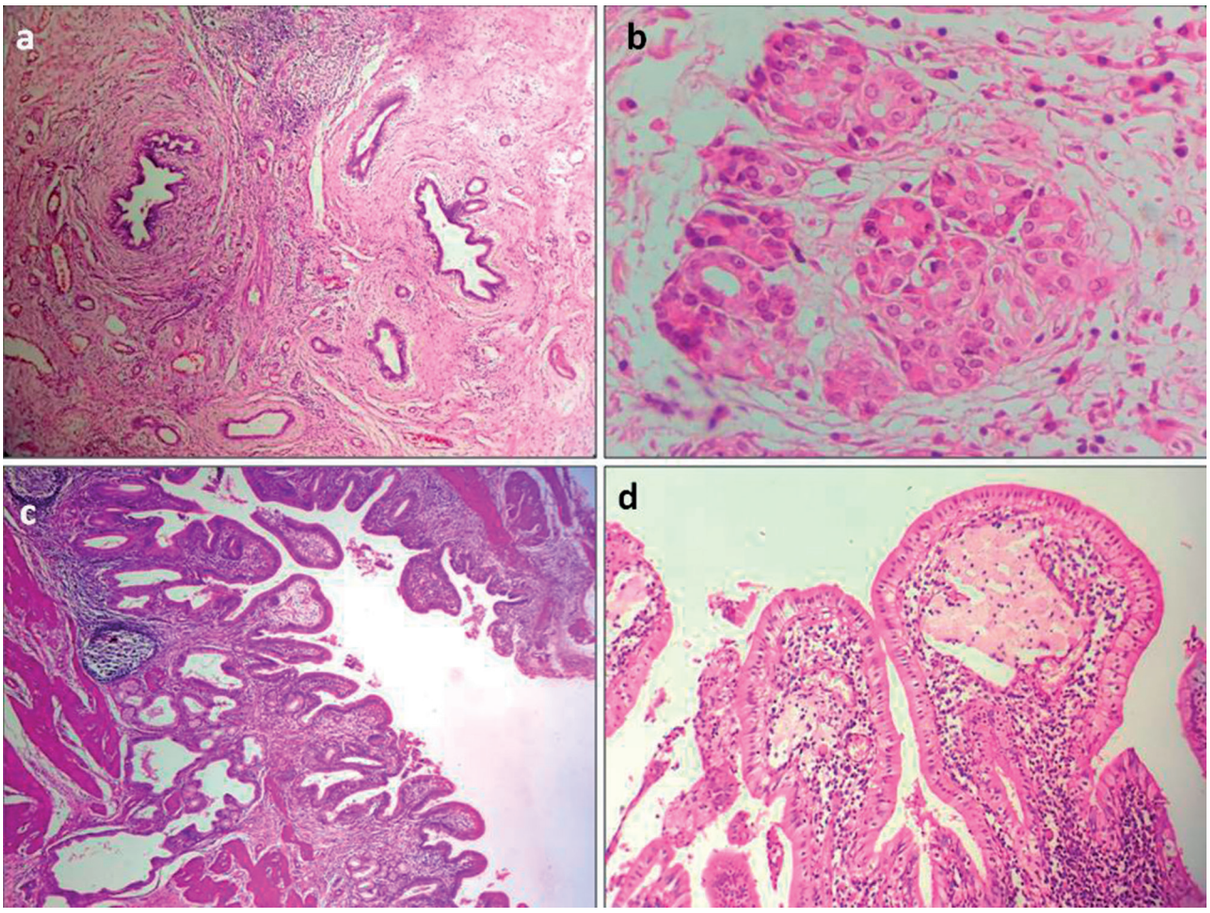

Fig. 3. — Microscopic findings of non neoplastic lesions of the gallbladder. 3a : Hyperplastic Luschka ducts of the gallbladder. (Haematoxylin and eosin, magnification × 40) ; 3b : Pancreatic heteroptopia of the gallbladder. (Haematoxylin and eosin, magnification × 400) ; 3c : Chronic follicular cholecystitis, (Haematoxylin and eosin, magnification × 40) ; 3d: Cholesterolosis. Accumulation of foamy macrophages in the lamina propria of the gallbladder, (Haematoxylin and eosin, magnification × 100).

is the only recognized pre-malignant lesion (7). In our series, there were two cases of porcelain gallbladder but were not associated with carcinoma.

Other unexpected pathologic gallbladder findings found in our series included : mucocele (n = 2), cholesterol polyps (n = 5), tubular adenoma (n = 3), pancreatic heterotopia (n = 2), hyperplastic Luschka ducts (n = 2), and adenomyoma (n = 2). Among all fortuitously discovered lesions in our series, only tubular adenoma, porcelain gallbladder and biliary-type adenocarcinoma have clinical significance. Importance of routine histopathologic examination of the surgical specimens is now being debated because many incidental findings have little clinical significance. Specimens of gallbladder are regularly seen in daily routine histopathological work of the pathology department. They do not only consume time but also increase the workload (3). The question remains as to whether there is a need to send all gallbladder specimens for analysis after surgery since it does not necessarily alter the management or provide an absolute advantage to the patient, surgeon or pathologist (3). Macroscopic examination plays an important role in gallbladder analysis and can be conducted by pathologists as well as trained surgeons. During the first step of the macroscopic gallbladder analysis, the serosa of the gallbladder is observed and palpated on its entire surface. In the second step, the gallbladder is incised longitudinally and the mucosa is irrigated, observed and palpated. During the serosa and mucosa exploration, the pathologist or the surgeon looks for abnormalities that includes masses, indurations, calcifications and/or ulcers. A study by *Darmas et al.* concluded that a selective approach to histopathological examination is better in terms of reducing the demands on the hospital without compromising patient safety (8). Bazoua *et al*. reported an analysis of histopathological examination reports for 2890 cholecystectomy specimens which showed malignancy in 10 cases, all of which had demonstrated thick-walled gallbladders on gross examination and in two of which suspicious mass had been apparent (9). Recently, a centre in the south of India reported its experience with 1312 cholecystectomy cases over a 10-year period. Of these, 610 (46,5%) cholecystectomy specimens showed macroscopic abnormalities in the

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Table 1. — **Histopathological Findings in cholecystectomy specimens**

	Number of cases	%
Non Neoplastic lesions		
Acute cholecystitis	117	6
Chronic cholecystitis	1319	67
Follicular cholecystitis	230	12
Xanthogranulomatous cholecystitis	6	0,30
Cholesterolosis	255	13
Cholesterol polyps	5	0,25
Adenomyoma	2	0,10
Mucocele	2	0,10
Hyperplastic Luschka ducts	2	0,10
Pancreatic heterotopia	2	0,10
Porcelain calcification	2	0,10
Intestinal Metaplasia	10	0,51
Pyloric Metaplasia	80	4
Neoplastic lesions		
Adenocarcinoma, biliary type	9	0,46
Tubular adenoma	3	0,15
Histologically normal gallbladder	9	0,46
Total	**1960**	**100**

without macroscopic abnormalities were found to have gallbladder cancer (9). Several studies have considered whether histological evaluation of some cholecystectomy specimens may be safely omitted, for example, when the specimen appears macroscopically normal. A thickened gallbladder wall has been commonly described in cases of unsuspected gallbladder cancer (9,11). However, a thickened wall is not specific to malignant transformation as it is also seen in an acutely inflamed gallbladder or chronic cholecystitis. The Royal College of Pathologists in their report titled "Histopathology and cytopathology of limited or no clinical value" recommended that all gallbladder specimens should be examined, as significant pathology may be present with normal gross morphology (11). Gallbladder cancer has a very poor prognosis, even when of early stage and potentially not macroscopically evident. For this reason, according to some authors a selective approach to gallbladder histology should only be considered in regions of very low incidence, if at all (3).

In a prospective comparative study by *Romero-González* et *al.,* it was concluded that it was safe not to send almost half (46%) of cases for histopathology by considering pre-operative, intra-operative and post-operative evidence pointing towards malignancy (12). In our series, 1960 gallbladder specimens were sent

Table 2. — **Characteristics of the patients with gallbladder malignancy**

Case	Age	Sex	Preoperative	Histological type	Tumour	pTNM
N			**US findings**		**size (cm)**	**stage**
1	74	F	Stones, thickened gallbladder	Poorly differentiated	2,5	pT2N0
			wall	adenocarcinoma biliary type		
2	60	M	thickened gallbladder	Poorly differentiated	4	pT2N0
			wall	adenocarcinoma biliary type		
3	72	F	thickened gallbladder	Well differentiated	3	pT2N0
			wall	adenocarcinoma biliary type		
4	57	M	Multiple small gallstones	Moderately differentiated	1	pT3N0
				adenocarcinoma biliary type		
5	65	F	Stones, thickened	Well differentiated	2,3	pT2N0
			gallbladder wall	adenocarcinoma biliary type		
6	54	M	Stones, thickened	Well differentiated	3	pT3N0
			gallbladder wall	adenocarcinoma biliary type		
7	78	F	thickened gallbladder wall	Moderately differentiated	2	pT2N0
				adenocarcinoma biliary type		
8	62	F	thickened gallbladder wall	Well differentiated	2	pT2N0
				adenocarcinoma biliary type		
9	43	F	Multiple small gallstones	Moderately differentiated	1	pT2N0
				adenocarcinoma biliary type		

form of thickening, mucosal ulcerations or polypoidal lesions (10). Malignancy was found in 13 of these 610 cholecystectomy specimens with macroscopic abnormalities. None of the cholecystectomy specimens to our department but only 137 out of 1960 cases showed macroscopic abnormalities. By sending each resected gallbladder to the pathologist, costs generated for the health system are very high. We therefore

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suggest that before sending gallbladder specimens to the pathology department, trained surgeons should first identify risk factors and, second carry out a careful macroscopic analysis of the extracted gallbladder. We propose that only macroscopically abnormal gallbladder specimens should be sent to the pathology department. Our study has several weaknesses. Owing to the large number of cases, the results are based on review of histopathological reports rather than detailed review by a pathologist of every glass slide. This means that some of the data are incomplete and the effect is to bias some of the results relating histological abnormalities considered unimportant by the reporting pathologist. Other limitations of this study include the patient population associated with the single-center study, which may not reflect the demographics of other regions, nations, and medical centers. Thus, the results may not be applicable to patient populations dissimilar to our study.

Conclusions

In summary, the histopathological spectrum of gallbladder after cholecystectomy is extremely variable. Despite all the advancements in the imaging techniques, the suspicion of gallbladder cancer is usually intra-operative and the confirmation of malignancy can only be done by histological assessment. Selective approach for sending cholecystectomy specimens for histopathology can result in missing premalignant lesions such as adenomas, porcelain gallbladder, carcinoma-in-situ, and early carcinomas (13-15). However, the incidence of premalignant and malignant lesions of the gallbladder is very low as demonstrated in our study. We therefore recommend selective histopathological examination of cholecystectomy specimens with abnormal macroscopic findings.

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