

Cholecystectomy Specimens: Histopathological Assessment of 923 Cases with Emphasis on Unpredictable Diagnosis

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ABSTRACT

Introduction: Cholecystectomy specimens show wide clinicopathological spectrum varying from common non-neoplastic diseases to rare neoplastic lesions. Often, Gall bladder disease is diagnosed on the basis of clinical and radiological findings, but histopathology remains the gold standard for the final diagnosis. Intraoperative frozen section followed by histopathological examination of the cholecystectomy specimen which aid in the diagnosis of the incidental carcinomas.

Aim: To analyse the histomorphological findings of cholecystectomy specimens with emphasis on unpredictable diagnosis.

Materials and Methods: The retrospective study was conducted from January 2017 to May 2020 in the Department of Pathology at a tertiary care centre in Udaipur. A total of 923 cholecystectomy specimens were evaluated for Histopathological examination. Intraoperative Frozen sections were also studied in clinically suspicious cases. Results were analysed using SPSS version 21. Quantitative variables were expressed as mean±Standard Deviation (SD), whereas qualitative variables were expressed as absolute and relative frequencies.

Results: Cholecystectomy specimens were examined over a wide age range of 22 years to 88 years of age. The male to

female ratio was found to be 1:2.27 in non-neoplastic cases and 1:6.28 in neoplastic cases. On microscopy, the most common histopathological lesion encountered was Chronic cholecystitis (766 cases, 82.99%). Other non-neoplastic pathology included acute cholecystitis (36 cases, 3.9%), cholesterosis (20 cases, 2.16%), gangrenous cholecystitis (15 cases, 1.6%), adenomyomatous hyperplasia (9 cases, 0.97%), Emphyema (6 cases, 0.65%), Mucocele (5 cases, 0.54%), Xanthogranulomatous cholecystitis (3 cases, 0.32%), and others (12 cases, 1.30%). Neoplastic lesions included Carcinoma (41 cases, 4.44%), Biliary Intraepithelial Neoplasia (BillIN- 04 cases, 0.43%) and Intracholecystic papillary neoplasm (ICPN- 06 cases, 0.65%). In eight (0.87%) cases we found unexpected histopathological diagnosis not correlating with the clinical findings and two cases showed the presence of incidental Gall Bladder (GB) carcinoma.

Conclusion: Histopathological examination of cholecystectomy specimens assist in confirming the preoperative diagnosis and proper sampling from any thick wall or suspicious area helps to rule out any incidental findings of dysplasia or malignancy. Frozen sections should be carried out in suspicious cases that further aid in the proper management of the patient.

Keywords: Carcinoma, Histomorphology, Cholecystitis, Intracholecystic papillary neoplasm

INTRODUCTION

Gall bladder is one of the most common surgically resected organs for many pathological lesions, ranging from common benign conditions to relatively rare neoplastic lesions. Non-neoplastic lesions constitute congenital anomalies, cholelithiasis, cholecystitis, adenomyomatous hyperplasia and cholesterosis. Neoplastic category includes adenoma, premalignant lesions and carcinomas [1]. In India and worldwide, chronic cholecystitis (CC) is the most frequently encountered lesion with around 78-90% of them associated with gall stones [2,3]. In India, gallstone disease is seven times more common in the north as compared to the south. Northern and Northeastern states of Uttar Pradesh, Bihar, West Bengal, Orissa, and Assam show the high prevalence of the gall bladder disease. This significant difference was attributed to the environmental factors, diet and lifestyle [4,5].

Risk factors for gall bladder disease include gall stones, fatty diet, obesity, insulin resistance, alcohol consumption, increased triglyceride level, pregnancy and various drugs.

Clinically, most of the gall bladder lesions present vaguely as an abdominal pain and discomfort in the right upper quadrant/right hypochondrium.

Gall Bladder Cancers (GBCs) are rare and account for 0.5% to 1.09% of all gall bladder lesions. It is either clinically suspected

or incidentally diagnosed following cholecystectomy for gall stone disease [1]. The highest incidence of GBC is reported in Chile with an incidence among females of 27.3 cases per 100,000 person years. Higher incidences are also noted in parts of India, Eastern Asia and eastern and central European countries. In India, GBC occurs predominantly in females with cholelithiasis [5]. Cholelithiasis is the most frequently associated finding with GBCs in up to 40%-100% cases [6]. Most of the patients of GBCs are asymptomatic and often diagnosed in the advanced stage or incidentally on histopathological examination accounting for the dismal prognosis [7].

Laparoscopic cholecystectomy is now a gold standard treatment for symptomatic gall stone patients [8]. Histopathological examination of all the surgically resected specimens of the gall bladder is recommended as a routine standard practice postoperatively as many gall bladder lesions present asymptotically and may have a remarkable impact on the management of patients [9]. Incidental malignancies of GBCs are found in around 0.5-1.1% of all cholecystectomies [10].

The purpose of the present study was to analyse the histopathological examination of the resected gallbladder with further classification of gall bladder neoplastic lesions according to the latest WHO Classification of Digestive System tumours, 2019 [6]. Emphasis on the utility of Frozen Section in some cases of unexpected diagnosis is also considered in present study.

MATERIALS AND METHODS

This descriptive cross-sectional included 923 cases of cholecystectomy specimens received at the Pathology Department of a tertiary care centre in Udaipur over three years and five months between January 2017 and May 2020. Study was conducted between May and June 2020.

The specimens which fulfilled the inclusion criteria were included in the study and rest were excluded.

Inclusion criteria:

- Formalin fixed cholecystectomy specimens excised for clinically diagnosed gall bladder diseases and received in pathology department.
- Cholecystectomy specimens received for intraoperative frozen section.

Exclusion criteria:

- Small biopsies of gall bladder
- Cholecystectomy associated with other surgeries, e.g., Whipple's procedure.

The study was conducted after getting permitted by the Institutional Ethical Committee under the IEC no. 1817. All the relevant clinical findings were noted and properly formalin fixed specimens were grossed with three sections each from fundus, body and neck region of the gall bladder. Extra sections were also taken from the tumour or any thickened area of wall in clinically suspicious cases of GBCs.

Sections were processed and were further subjected to Haematoxylin and Eosin (H&E) stain. H&E stain was done using Harris haematoxyline with a regressive staining method. After dewaxing, sections were rehydrated through graded alcohol followed by staining with haematoxylin, then bluing, and differentiation further followed by staining with eosin. Sections were dehydrated through graded alcohol followed by clearing in Xylene and mounting with DPX.

In eight clinically suspicious cases, intraoperative frozen sections were taken on Cryostat (Leica CM 1860 UV) followed by rapid H&E staining.

Sections were examined microscopically and histomorphological evaluation for a wide spectrum of gall bladder lesions was done. The neoplastic lesions were further classified according to the latest 2019 WHO Classification of Digestive System Tumours that includes BillIN, ICPN and Carcinoma [6].

STATISTICAL ANALYSIS

Data was analysed using SPSS version 21. Quantitative variables were expressed as mean±SD, whereas qualitative variables were expressed as absolute and relative frequencies. Chi-square test (χ^2) and z-test were used as tests of significance for univariate analyses of categorical variables and quantitative data respectively. A p-value of less than 0.05 was considered significant.

RESULTS

Detailed analysis of 923 patients of cholecystectomy was performed under parameters including age, gender and histopathological findings.

In present study, cholecystectomies were performed in the patients of age ranged from 22 to 88 years with mean age of 46.28±17.07 years. For various non-neoplastic lesions, patient's age ranged from 22 to 76 years (mean: 52 years). Median patient age for neoplastic lesions was 58 years with age ranged from 41 to 88 years.

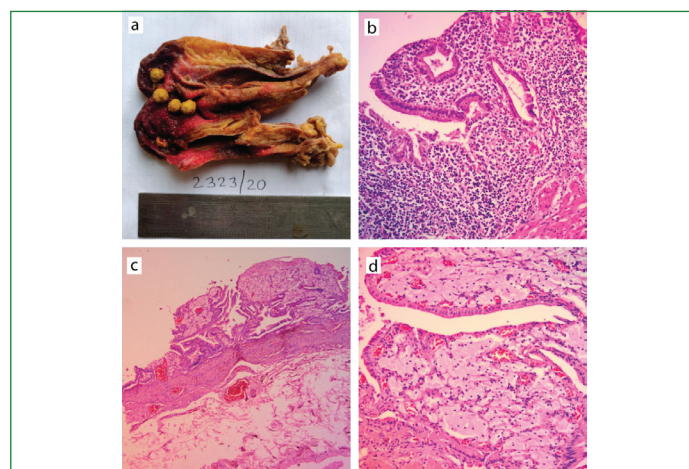
Gender distribution of 923 cases with male to female ratio was found to be 1:2.38 (273/650). Male to female ratio in non-neoplastic cases was 1: 2.27 (266/606) and in neoplastic cases was 1:6.28 (07/44). Study showed the mean age distribution

among males and females as 58.2±7.3 and 54.6±10.8, respectively. The gender wise analysis of the mean age of patients of cholecystectomy using z test was done to find out any significant difference between the mean age of male and female gender. The z test indicated that there is no significant difference between the mean age group of patients undergoing cholecystectomy and gender distribution of males and females (z= 0.47, p-value= 0.3).

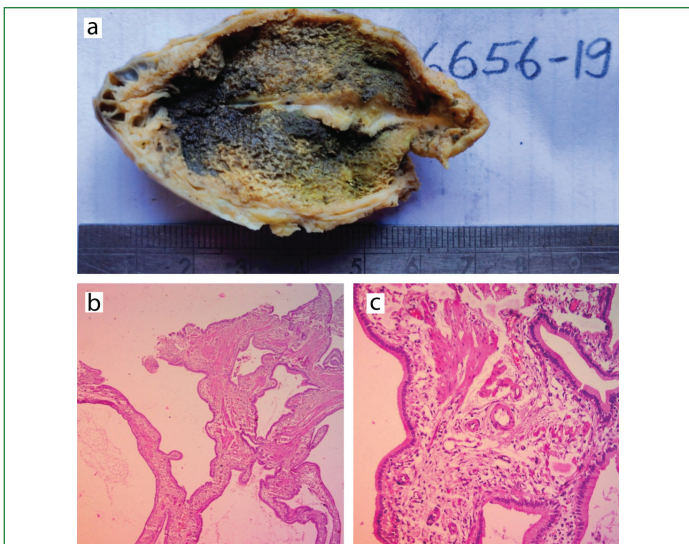
On histopathology examination, the most common histopathological lesion encountered was chronic cholecystitis (766 cases, 82.99%). Other non-neoplastic lesions included acute cholecystitis (36 cases, 3.9%), cholesterosis (20 cases, 2.16%), gangrenous cholecystitis (15 cases, 1.6%), Adenomyomatous hyperplasia (9 cases, 0.97%), Empyema (6 cases, 0.65%), Mucocele (5 cases, 0.54%), Xanthogranulomatous cholecystitis (3 cases, 0.32%), and others (12 cases, 1.30%). Neoplastic lesions were carcinoma (41 cases, 4.44%), BillIN (04 cases, 0.43%) and ICPN (06 cases, 0.65%). Out of 41 cases of carcinomas, the most common subtype was biliary-type adenocarcinoma including one case of carcinoma arising from ICPN (37 cases 90.24%), followed by poorly cohesive carcinoma with signet ring cells (2 cases, 4.87%), intestinal-type adenocarcinoma (1 case, 2.43%) and sarcomatoid carcinoma (1 case, 2.43%). Out of total 923 cases only 02 (0.21%) cases were diagnosed as incidental carcinoma [Table/Fig-1-9].

Histopathological diagnosis	N (%)	Age (mean±SD)	M/F
Acute cholecystitis	36 (3.9)	43.4±15.7	11/25
Gangrenous cholecystitis	15(1.6)	41.4±17.5	4/11
Chronic cholecystitis	766 (82.99)	44.2±20.2	241/525
Empyema	06 (0.65)	41.3±14.8	01/05
Cholesterosis/Cholesterol polyp	20 (2.16)	38.9±16.3	03/17
Mucocele	05 (0.54)	36.6±13.8	00/05
Xanthogranulomatous cholecystitis	03 (0.32)	45.3±17.8	00/03
Adenomyomatous hyperplasia	09 (0.97)	51.4±15.5	02/07
Biliary intraepithelial neoplasia (BillIN)	04 (0.43)	56±16.6	00/04
Intracholecystic papillary neoplasm (ICPN)	06 (0.65)	58.1±18.3	01/05
Carcinoma	41 (4.44)	68.3±20.4	06/35
Others	12 (1.30)	40.2±17.5	04/08
Total	923 (100%)	-	273/650 (0.42:1)

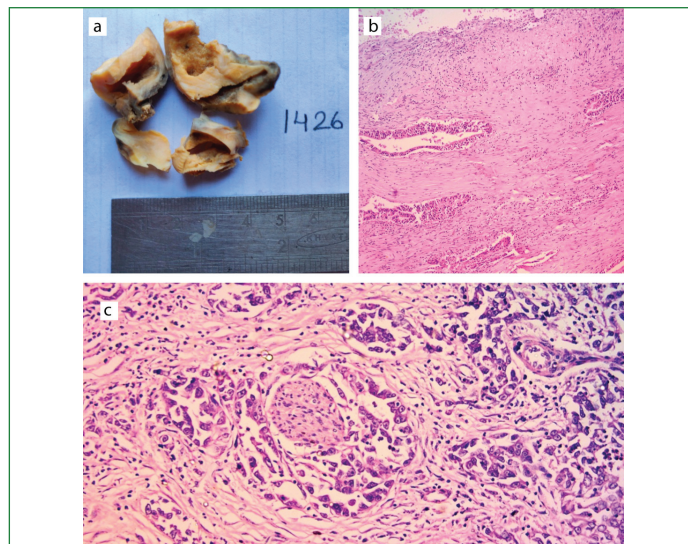
[Table/Fig-1]: Histopathological diagnosis and demographic details.



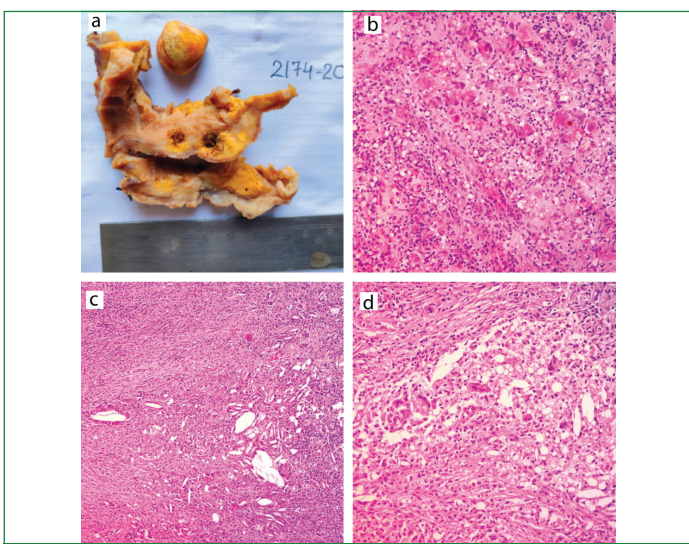
[Table/Fig-2]: a) Macroscopic finding of chronic cholecystitis in cholecystectomy specimen showing dark brown mucosa with multiple yellow coloured stones; b) Microscopic examination of chronic cholecystitis showing surface mucosal ulceration and chronic inflammatory cells in the lamina propria, Haematoxylin and Eosin (H&E) stain, x100 magnification; c) H&E section of Cholesterol Polyp showing polypoidal lesion with collection of foamy macrophages in the subepithelium.(magnification x40); d) Microscopy of Cholesterosis showing collection of foamy macrophages and congested blood vessels in the lamina propria. (H&E stain, magnification x200)



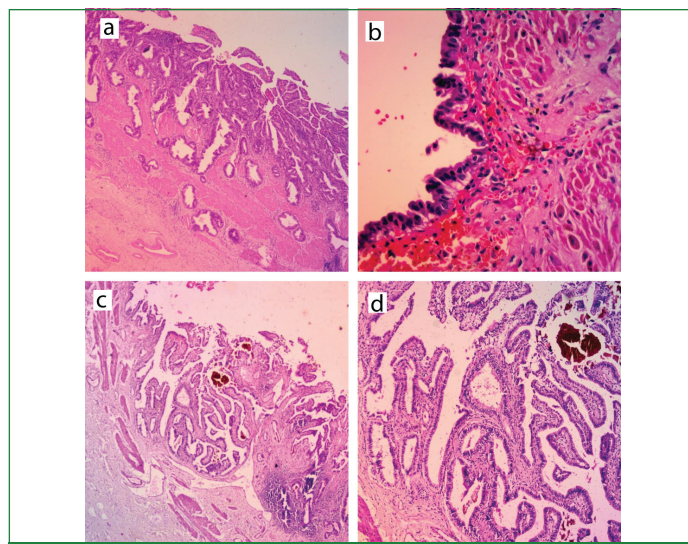
[Table/Fig-3]: Adenomyomatous hyperplasia/Cholecystitis glandularis proliferans: a) Gross findings of Cholecystitis glandularis proliferans showing cystic spaces in the fundic wall of the gall bladder; b,c) Microscopy findings show cystic dilation and proliferation of glands with chronic inflammation in the muscle layer (H&E stain, x40 magnification and x100, respectively)



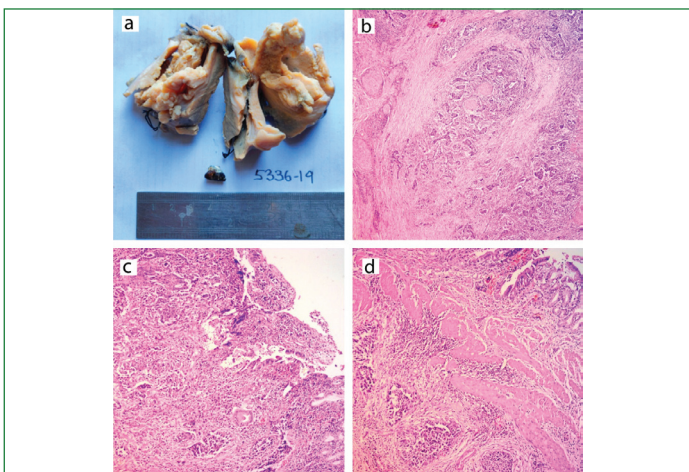
[Table/Fig-6]: Gall bladder Adenocarcinoma, biliary type. a) Macroscopic findings showing thickened gall bladder wall; b) Microscopic findings showing infiltration of glands lined by malignant cells in the stroma. (H&E stain, magnification x40); c) Low power view showing perineural invasion by tumour cells. (H&E stain, magnification x100).



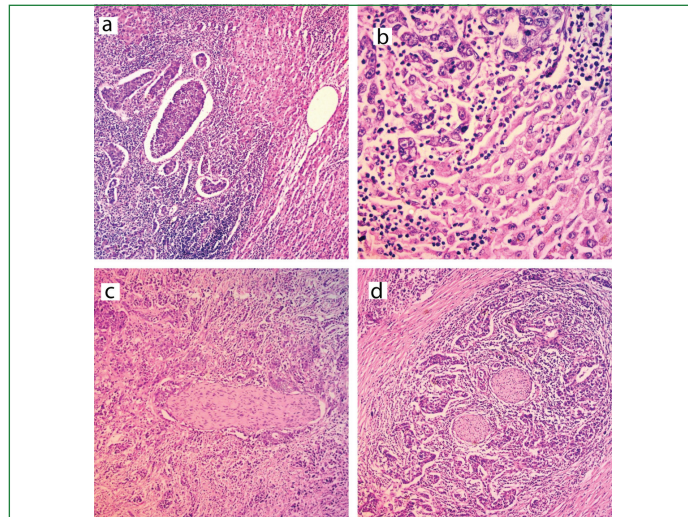
[Table/Fig-4]: Xanthogranulomatous Cholecystitis: a) Gross findings showing yellowish thickening of the gall bladder wall with multiple impacted stones in the wall and single large yellow coloured stone in the lumen; b) Low power frozen section showing collection of foamy histiocytes, mononuclear inflammatory cells and giant cells in the stroma. (Frozen H&E stain, magnification x100); c) Scanner microscopic view showing cholesterol clefts (H&E stain, magnification x40); d) Low power view showing granuloma formation with cholesterol clefts and giant cells. (H&E stain, magnification x200).



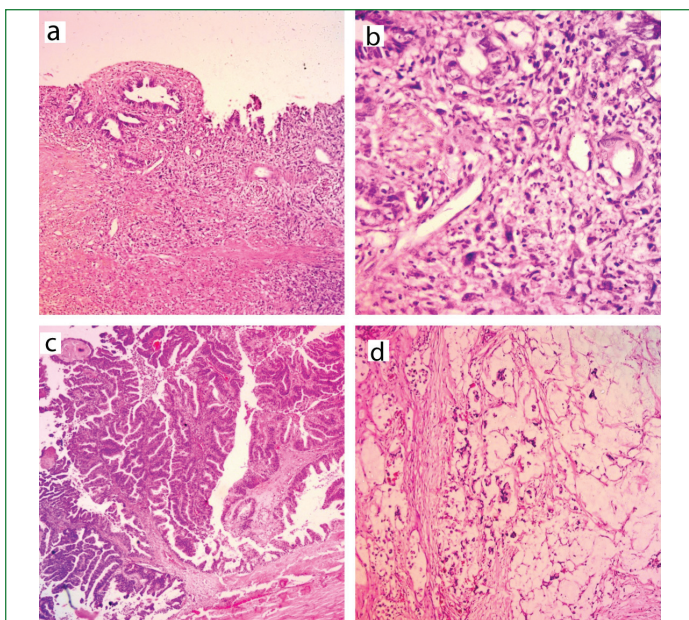
[Table/Fig-7]: a) Microscopic findings of Adenomyomatous Hyperplasia showing proliferation of benign glands infiltrating the muscularis propria. (H&E stain, magnification x40); b) High power view of low-grade Biliary Intraepithelial Lesion (BILLN) showing pseudostratification of nuclei with hyperchromasia and increased N/C ratio. (H&E stain, magnification x400); c) Scanner view of Intracholelithic Papillary Neoplasm (ICPN) showing tubulopapillary intraluminal proliferation of back to back glands (H&E stain, magnification x40); d) Low power view of ICPN showing biliary morphology and dysplasia in the epithelium. (H&E stain, magnification x100).



[Table/Fig-5]: Gall Bladder Adenocarcinoma: a) Macroscopic findings of a specimen of gall bladder adherent to a part of the liver showing a grey-white exophytic growth in the lumen along with single gall stone; b) Microscopic image showing infiltration of the tumour cells in the gallbladder wall (H&E stain, magnification x40); c) Low power view showing proliferation of malignant glands in the stroma with surface ulceration. (H&E stain, magnification x100); d) Scanner view showing the presence of tumour cells infiltrating the muscle layer and invading the subserosa. (H&E stain, magnification x40).



[Table/Fig-8]: a) Low power view showing infiltration of Gall bladder Adenocarcinoma into the adjacent liver parenchyma. (H&E stain, magnification x100); b) High power view showing the presence of tumour cells with large, hyperchromatic and pleomorphic nuclei infiltrating the liver parenchyma. (H&E stain, magnification x400); c,d) Foci of perineural invasion by the malignant cells seen. (H&E stain, magnification x200).



[Table/Fig-9]: a) Scanner view of Sarcomatoid Carcinoma of Gall Bladder showing spindle cell proliferation with invasion into the muscle fibres. (H&E stain, magnification x40); b) Sarcomatoid Carcinoma showing diffuse infiltration of the stroma by spindle cells having pleomorphic, hyperchromatic and bizarre nuclei. (H&E stain, magnification x200); c) ICPN with associated invasive adenocarcinoma showing papillary growth pattern (H&E stain, magnification x200); d) low power view of Poorly cohesive carcinoma with Signet ring cells showing pools of extracellular mucin and scattered signet ring cells. (H&E stain, magnification x100).

Study showed that about 535 (57.96%) patients presented with gall stones. 31 cases (60.78%) of neoplastic lesions and 504 cases (57.8%) of non-neoplastic lesions were associated with the gall stones. Chi-square test showed a non-significant association between cholelithiasis and neoplastic lesions. (chi-square score= 0.17, p-value= 0.6) [Table/Fig-10].

Characteristics	Neoplastic	Non-neoplastic	p-value
GB with stone	31 (60.78%)	504 (57.8%)	0.6
GB without stone	20 (39.21%)	368 (42.2%)	
Total	51 (100%)	872 (100%)	

[Table/Fig-10]: Correlation of gall stones with neoplastic and non-neoplastic lesions. (chi-square test; score= 0.17; p-value= 0.6).

In this study, Carcinoma was found more commonly in females as compared to males, 35 females (5.4%) while only 6 males (2.2%) showed features of carcinoma. The difference was found to be significant. (chi-square score= 4.6, p-value= 0.03) [Table/Fig-11].

Gender	Carcinoma		Total	p-value
	Yes	No		
Female	35 (5.4%)	615 (94.6%)	650	0.03
Male	6 (2.2%)	267 (97.8%)	273	

[Table/Fig-11]: Distribution of carcinoma cases according to gender. (chi-square test; score= 4.6; p-value= 0.03; significant).

Following table represents an overview of comparison between neoplastic and non-neoplastic lesions of gall bladder [Table/Fig-12].

Characteristics	Non-neoplastic	Neoplastic		
		BillIN	ICPN	Carcinoma
Age (yrs)	22-76	38-70	40-76	48-88
Gender (M/F)	266/606	00/04	01/05	06/35
No. of cases	872 (94.47%)	04 (0.43%)	06 (0.65%)	41 (4.44%)
GB with stone	504	03	04	24
GB without stone	368	01	02	17

[Table/Fig-12]: Comparison of Non-neoplastic and Neoplastic lesions.

Out of eight cases of unexpected diagnosis, two cases were operated for chronic cholecystitis but turned out to Carcinoma

on histopathological examination. Two cases with wall thickening and malignant suspicion were diagnosed as adenomyomatous hyperplasia on microscopy. One case with Strong suspicion of malignancy due to serosal adhesions was diagnosed as Xanthogranulomatous cholecystitis on frozen section and routine HE examination. Other unexpected diagnosis includes one case of BillIN and two cases of ICPN [Table/Fig-13].

DISCUSSION

Cholecystectomies are frequently done for gall bladder diseases, which is a major health problem and its incidence show significant variation worldwide [5].

Gall stones cause obstruction that leads to development of chronic cholecystitis which, in turn, chronically predisposes to carcinoma of the gallbladder. Around 85% cases of gallbladder carcinoma are associated with gall stones. This association of gallbladder carcinoma with gall stones in some case control studies ranges from 2.3 to 34.4 [11]. Risk factors associated with carcinoma are GB stones, chronic sclerosing cholangitis, aflatoxin B1 & salmonella typhi infection [6].

Gallbladder Cancer (GBC) ranks fifth among the gastrointestinal carcinomas and is the most common cancer of the biliary tract [12]. The frequency among all cholecystectomy cases has been reported between 0.23 and 3.30% [13]. Histopathological assessment of the resected gall bladder is recommended as a routine practice to rule out any possibility of incidental neoplastic pathology.

In the present study, mean age for non-neoplastic lesions was 52 years and for neoplastic lesions was 58 years. Non-neoplastic lesions occurred at an early age whereas neoplastic lesions were presented relatively at an advanced age. Similar findings were present in the study by Dowerah S et al., [14].

For all non-neoplastic gall bladder lesions M:F ratio was 1:2.27 (266/606), whereas for neoplastic lesions, M:F ratio was 1:6.28 (07/44). Overall male to female ratio was 1:2.38 (273/650). In a study by Selvi TR et al., gall stone disease was predominantly seen in females (61.5%) as compared to males (38.4%) [15]. Several other studies have also reported the preponderance of female in gall bladder disease but the ratio was slightly higher [16-18]. Thus, it appears that gall bladder disease is more common in females attributable to female sex hormones and sedentary lifestyle as the risk factors.

The study also showed that 535 cholecystectomy specimen (57.96%) was associated with gall stones. More number of neoplastic lesions, 60.78% (31/51) cases were associated with cholelithiasis in comparison to 39.21% (20/51) cases being without gall stones as seen in the study by Dinesh S et al., and Khoo JJ et al., [19,20]. However, Chi-square test showed a non-significant association between cholelithiasis and neoplastic lesions (chi-square score=0.17, p-value=0.6). This is in sharp contrast to other studies in which significant association was noted between cholelithiasis and neoplastic lesions [5,21,22].

Distribution of carcinoma cases among male and female gender shows that 85.36% of total carcinoma cases (35/41) were women, and 14.64% (6/41) were male patients, correlating with the results done by Gupta V et al., [23]. The association of carcinoma with the female patients was found to be significant in present study (z score=4.6, p-value= 0.03).

On histopathological examination, non-neoplastic cases (872 cases, 94.47%) outnumbered the neoplastic lesions (51 cases, 5.53%). The most common non-neoplastic lesion was found to be chronic cholecystitis in 766 (82.99%) cases, that corroborates with the results of Srivastav AC et al., and several other studies [5,24].

A wide spectrum of non-neoplastic morphological lesions of the gall bladder is commonly seen on microscopy. Chronic

S. No	Age (in years)	Gender	Preoperative diagnosis	Surgery	Frozen diagnosis	Histopathological diagnosis
1	56	F	Chronic cholecystitis with cholelithiasis	Cholecystectomy	-	Biliary Intraepithelial Neoplasm (BillIN)
2	60	F	Malignancy	Cholecystectomy	Xanthogranulomatous cholecystitis	Xanthogranulomatous cholecystitis
3	62	F	Cholecystitis	Cholecystectomy	-	Adenocarcinoma
4	54	M	Wall thickening suspicious for malignancy	Cholecystectomy	Benign hyperplasia of glands	Adenomyomatous hyperplasia
5	58	F	Cholelithiasis	Cholecystectomy	-	Intra Cholecystic Papillary Neoplasm (ICPN)
6	55	F	Malignancy	Cholecystectomy+LND	-	Intra Cholecystic Papillary Neoplasm (ICPN)
7	68	F	Chronic cholecystitis	Cholecystectomy	-	Sarcomatoid carcinoma
8	64	F	Diffuse wall thickening	Cholecystectomy	Adenomatous hyperplasia	Adenomyomatous hyperplasia

[Table/Fig-13]: Cases with unexpected diagnosis.

cholecystitis show chronic inflammation in lamina propria with variable surface ulceration. It may be associated with cholelithiasis. In contrast, acute cholecystitis shows mainly acute inflammatory cells in lamina propria, presented with sudden onset of pain. Gangrenous cholecystitis shows mainly acute inflammatory exudates with necrotic mucosa. Empyema shows dilated cavity filled with pus along with atrophied lining. Cholesterolosis and cholesterol polyp show sheets of foamy macrophages in lamina propria. Mucocele consists of benign mucinous cyst lined by single layer of epithelium. Adenomyomatous hyperplasia also known as cholecystitis glandularis proliferans or gall bladder diverticula shows presence of cystically dilated glands invading the hypertrophic muscle layer [25].

Xanthogranulomatous cholecystitis shows nodular collection of lipid laden foamy histiocytes and cholesterol crystals with foreign body giant cell reaction that may mimic carcinoma [26].

Total number of carcinomas in the present study, 41 cases (4.44%) were found to be consistent with the study of Yadav A et al., with 4.7% of carcinomas [27]. However, total neoplastic lesions were found to be greater in number as compared to study done by Siddiqui FG et al., with gallbladder carcinoma in 2.7% of cases and 3% in the study by Jokhi D et al., [17,28]

BillIN, a new terminology for dysplasia in gall bladder shows focal pseudostratification of nuclei with hyperchromasia and increased N/C ratio. A small proportion of patients of BillIN show recurrences and metastasis. ICPN shows macroscopically mass in gall bladder with microscopic features of tubulopapillary intraluminal proliferation of back to back glands. ICPNs can also be associated with invasive carcinoma, but the overall outcome is better. ICPNs are found in 0.4% of cholecystectomies and about 6% of GBC arise from it [29,30].

The most common type of GBC is Adenocarcinoma, with biliary subtype the commonest, followed by intestinal type, mucinous, clear cell carcinoma, poorly cohesive carcinoma with or without signet ring cells, adenosquamous cell carcinoma and squamous cell carcinoma [6]. In the present study, the most common carcinoma was found to be Adenocarcinoma – Biliary type, 37 cases (90.24%), similar to study done by Jokhi D et al., [28].

The study also found eight cases of unexpected Histopathological diagnosis [Table/Fig-13]. One case was diagnosed as BillIN on histopathological examination which was resected for chronic cholecystitis. Two cases were operated for chronic cholecystitis, which turned out to be gall bladder carcinoma, one case each of poorly cohesive Adenocarcinoma with signet ring cells and Sarcomatoid Carcinoma. Signet ring Adenocarcinoma was diffusely infiltrating the stroma without any grossly visible tumour mass. Sarcomatoid Carcinoma was showing intact mucosa with

subepithelial proliferation of atypical spindle cells mixed with occasional dysplastic glands [Table/Fig-9].

One case was removed with a preoperative diagnosis of malignancy because of serosal adhesions. Intraoperative frozen sections were carried out that showed the features of Xanthogranulomatous Cholecystitis, which was further, confirmed on H&E sections. It consisted of submucosal collection of foamy macrophages, histiocytes, giant cells, chronic inflammatory cells and cholesterol clefts extending up to serosa. These foamy macrophages were mimickers of signet ring cell type carcinoma cells, so this case was both clinically and histomorphologically close mimicker of malignancy that justified the role of intraoperative frozen section [Table/Fig-4].

Two cases of diffuse GB wall thickening with suspicion of malignancy were subjected to an intraoperative frozen section on which they were diagnosed as Benign hyperplasia and adenomatous hyperplasia respectively. Both were confirmed as Adenomyomatous hyperplasia on routine H&E [Table/Fig-3].

Two cases on Histopathological examination were turned out to be ICPN with preoperative diagnosis of cholelithiasis in one case and suspected malignancy in other [Table/Fig-7].

Very few literature is available on the Histopathological spectrum of the neoplastic gall bladder lesions according to latest 2019 WHO Classification, so further studies are needed to be carried out to know the incidence of carcinoma arising from premalignant lesions [6].

Limitation(s)

As the present study is retrospective, it has limited the ability to conduct follow up of patients and to study disease free survival rate in malignant and premalignant conditions. So, further studies need to be carried out regarding the role of early diagnosis of neoplastic gall bladder lesions in the patient management.

CONCLUSION(S)

Although the most common gall bladder histopathology is chronic cholecystitis, the possibility of any incidental malignancy needs to be ruled out. Extra sections need to be submitted from any suspicious area or thickened wall. Frozen section study is useful to differentiate clinical and radiological mimickers of malignancy from true invasive malignancy, which can further obviate the need for extensive surgical resection.

REFERENCES

- [1] Kumari NS, Sireesha A, Srujana S, Kumar OS. Cholecystectomies – A 1.5 year histopathological study. IAIM. 2016;3(9):134-39.
- [2] Nordenstedt H, Mattsson F, El-Serag H, Lagergren JJ. Gallstones and cholecystectomy in relation to risk of intra and extra hepatic cholangiocarcinoma. Br J Cancer. 2012;106(5):1011-15.
- [3] Lazcano-Ponce EC, Miquel JF, Muñoz N, Herrero R, Ferrecio C, Wistuba II, et al. Epidemiology and molecular pathology of gallbladder cancer. CA Cancer J Clin. 2001;51:349-64.

- [4] Mohan H, Punia RP, Dhawan SB, Ahal S, Sekhon MS. Morphological spectrum of gallstone disease in 1100 cholecystectomies in North India. *Indian J Surg.* 2005;67:140-42.
- [5] Srivastav AC, Srivastava M, Paswan R. Spectrum of clinicopathological presentations of gall bladder diseases in eastern UP. *International Journal of Contemporary Medicine Surgery and Radiology.* 2019;4(1):A18-A23.
- [6] Rao JC, Adsay NV, Arola J, Tsui WM, Zen Y. Carcinoma of gall bladder. In: Cree IA, editor. *WHO classification of Tumours of the digestive system 5th ed.* Lyon: IARC; 2019. Pp.283-88.
- [7] Kafle SU, Sinha AK, Pandey SR. Histomorphology spectrum of gall bladder pathology in cholecystectomy specimens with clinical diagnosis of chronic cholecystitis. *J Nepal Med Assoc.* 2014;52(192):600-07.
- [8] Halldestam I, Enell EL, Kullman E, Borch K. Development of symptoms and complications in individuals with asymptomatic gallstones *Br J Surg.* 2004;91(6):734-38.
- [9] Royal College of Pathologists, "Histopathology and cytopathology of limited or no clinical value," in Report of Working Group of The Royal College of Pathologists, Royal College of Pathologists, London, UK, 2nd edition, 2005.
- [10] Tantia O, Jain M, Khanna S, Sen B. Incidental carcinoma gall bladder during laparoscopic cholecystectomy for symptomatic gall stone disease *Surg Endosc.* 2009;23(9):2041-46.
- [11] Navyashree N, Giriyan SS. Can gallbladder wall thickness by gross examination predicts its carcinoma before histopathological study? *Trop J Path Micro.* 2019;5(12):1039-45.
- [12] Goyal S, Singla S, Duhan A. Correlation between gallstones characteristics and gallbladder mucosal changes: A retrospective study of 313 patients. *Clin Cancer Investig J.* 2014;3(2):157-61.
- [13] Dincel O, Goksu M, Hatipoglu HS. Importance of routine histopathological examination of a gallbladder surgical specimen: Unexpected gallbladder cancer. *J Can Res Ther.* 2018;14:1325-29.
- [14] Dowerah S, Deori R. A study of benign histopathological changes in cholecystectomy specimen: experience at a referral hospital. *International Journal of Contemporary Medical Research.* 2016;3(8):2392-94.
- [15] Selvi TR, Sinha P, Subramaniam PM, Konapur PG, Prabha CV. A clinicopathological study of cholecystitis with special reference to analysis of cholelithiasis. *Int J Basic Med Sci.* 2011;2(2):68-72.
- [16] Butti AK, Yadav SK, Verma A, Das A, Naeem R, Chopra R, et al. Chronic calculus cholecystitis: Is histopathology essential post-cholecystectomy? *Indian J Cancer.* 2020;57:89-92.
- [17] Siddiqui FG, Memon AA, Abro AH, Sasoli NA, Ahmad L. Routine histopathology of gallbladder after elective cholecystectomy for gallstones: Waste of resources or a justified act? *BMC Surg.* 2013;13:26.
- [18] Awasthi N. A retrospective histopathological study of cholecystectomies. *Int J Health Allied Sci.* 2015;4:203-06.
- [19] Singh D, Poojary S, Bhunia S, Ahmad M, Gupta S, Shrivastav R. Epigenetic mutation of APC in molecular pathogenesis of gallbladder cancer. *Indian J of Med Res.* 2016;143:82-90.
- [20] Khoo JJ, Nurul AM. A clinicopathological study of nine cases of gallbladder carcinoma in 1122 cholecystectomies in Johor, Malaysia. *Malaysian J Pathol.* 2008;30(1):21-26.
- [21] Ahrendt SA, Pitt HA. Biliary tract. In: Townsend CM, Beauchamp RD, Evers BM, Mattox KL (eds), *Sabiston Textbook of Surgery*, 17th edition; New Delhi: Elsevier, 2004; Pp. 1597-1641.
- [22] Agarwal S, Pandey P, Ralli Male, Agarwal R, Saxena P. Morphologic characterisation of 1693 cholecystectomy specimens- a study from tertiary care center in northern India *J Clin Diagn Res.* 2018;12(1):5-9.
- [23] Gupta V, Goel MM, Chandra A, Gupta P, Kumar S, Nigam J. Expression and clinicopathological significance of antiapoptosis protein survivin in gallbladder cancer. *Indian J Pathol Microbiol.* 2016;59:143-47
- [24] Khan S, Jetley S, Husain M. Spectrum of histopathological lesions in cholecystectomy specimens: A study of 360 cases at a teaching hospital in South Delhi. *Arch Int Surg.* 2013;3:102-05.
- [25] Srinivasan G, Sekar ASI. Study of histopathological spectrum of gallbladder in cholecystectomy specimens. *Int J Res Med Sci.* 2019;7:596-602.
- [26] Makino I, Yamaguchi T, Sato N, Yasui T, Kita I. Xanthogranulomatous cholecystitis mimicking gallbladder carcinoma with a false-positive result on fluorodeoxyglucose PET. *World J Gastroenterol* 2009;15(29):3691-93.
- [27] Yadav A, Singh V, Chauhan K, Sharma SP, Verma N, Yadav A. Prevalence of gallstone in western Uttar Pradesh population. *J Anat Sciences.* 2016;24(1):38-42.
- [28] Jokhi CD, Kanetkar SR, Vohra, NV. Study of histopathological findings in gallbladder diseases. *Indian J Pathol Oncol.* 2019;6(4):627-35.
- [29] Basturk O, Aishima S, Esposito I. Biliary intraepithelial neoplasia. In: Cree IA, editor. *WHO classification of Tumours of the digestive system 5th ed.* Lyon: IARC; 2019. Pp.273-75.
- [30] Basturk O, Aishima S, Esposito I. Intracholecystic papillary neoplasm. In: Cree IA, editor. *WHO classification of Tumours of the digestive system 5th ed.* Lyon: IARC; 2019. Pp.276-78.

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