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Outcome of routine histopathological examination of gallbladder specimen following elective laparoscopic cholecystectomy

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Abstract:

BACKGROUND: Gallstone disease is one of the commonest surgical ailments encountered in our setup. Its prevalence in India varies from 2% to 29%. Although cholelithiasis accounts for more than 95% of gall bladder related disease, routine histopathological examination (HPE) is vital. It reveals a myriad of benign as well as the malignant surgical pathology of the gallbladder (GB). This part of the world is considered as an endemic region for GB carcinoma as well as gallstone disease. This study intends to evaluate the outcome of the routine HPE of laparoscopic cholecystectomy specimens.

METHODS: This retrospective observational study evaluated the results of the routine HPE of elective laparoscopic cholecystectomy specimens of single tertiary care center. Patients suspected or diagnosed with carcinoma gall bladder were excluded. Demographic data such as age, sex, and pathology results were recorded.

RESULTS: From January 2017 to December 2019, HPEs of 921 patients who had undergone laparoscopic cholecystectomy specimens were analyzed. 97.6% specimens had benign lesion of which chronic calculus cholecystitis was predominantly high (95.01%) followed by cholesterosis (9.9%) and xanthogranulomatous cholecystitis (6.51%). Incidental carcinoma gall bladder was observed in 17 specimens accounting for 1.85%. Mean age of patients who underwent cholecystectomy was 43.10 ± 13.90 with female to male ratio of 3.23:1.

CONCLUSION: Chronic calculus cholecystitis was the most common gall bladder disease with high female preponderance to all GB pathologies. This study affirms the importance of routine HPE after cholecystectomy as early incidental detection of carcinoma gall bladder alters the postoperative management approach and patients are expected to have a better outcome with it.

Keywords:

Cholecystectomy, chronic cholecystitis, gallbladder, gallbladder carcinoma

Introduction

Symptomatic gallstones are a common disease worldwide.^[1] The prevalence of gallbladder (GB) diseases in India is approximately 2%–29%. It is seven times more common in the northern part of India and predominantly affects women.^[2] Among the various diseases affecting the

GB, cholelithiasis is the most common, accounting for over 95% GB related diseases.^[1] Laparoscopic cholecystectomy is a common surgical procedure performed to treat symptomatic gallstone disease. However, before embarking on definitive surgical management, all patients were thoroughly investigated preoperatively. The main purpose of such preoperative work-up is to evaluate the hepatobiliary system and GB, that is, wall thickness,

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any mass lesion of the GB, diameter of the CBD, and intrahepatic biliary dilatation. Despite advancements in imaging techniques, it is almost impossible to differentiate between benign and malignant lesions of the GB without histopathological examination (HPE).^[3,4] In addition to malignancy, histopathological analysis of the GB specimens may reveal myriad disorders such as cholecystitis, cholesterosis, xanthogranulomatous cholecystitis, adenomatous hyperplasia, and metaplasia.

Some studies have advocated for a selective approach for sending cholecystectomy specimens for histopathology.^[5-7] It can be cost-effective but it can result in missing premalignant lesions, carcinoma *in situ*, and early malignancy.^[5,8,9] Carcinoma of the gall bladder is known for its aggressive behavior and missing them, particularly in the early stages, and can have disastrous outcomes for patients.^[10] Moreover, the incidence of incidental carcinoma gall bladder has been reported to be approximately 0.3%–1.5% in various series.^[11,12]

Studies from eastern India recorded GB cancer between 5.8% and 6.0% of all cancers.^[13] Understandably, owing to the large number of gall bladder carcinoma cases in the gangetic belt,^[14] it is prudent to analyze the histopathological spectrum GB specimen following laparoscopic cholecystectomy. In addition, there is a relative paucity of studies on the histopathological data of cholecystectomy specimens from this part of the world.

Methods

This study was done at the Department of General Surgery, AIIMS, Patna. The study proposal was approved by the institute ethics committee. We retrospectively reviewed the data of all patients that underwent elective laparoscopic cholecystectomy between January 2017 and December 2019 for symptomatic cholelithiasis. All of the specimens were sent to the Department of Pathology for routine examination.

Demographic data such as age, sex, operative findings, and histopathology report were recorded. Based on the pathology report; cases were classified as benign, premalignant, and malignant. We examined the distribution of pathological diagnoses, the effect of age and sex on this distribution, and the prevalence of cancer cases. Age and sex distributions were analyzed for each category.

Statistical analyses

Statistical analyses were performed using STATA version. 12. The demographic profile of the cholecystectomy patients and histopathological findings are summarized in proportion (%) and mean (\pm standard deviation). The association between the demographic profile and

histopathological findings was analyzed using the Chi-square test. Bivariate analysis of the association of sociodemographic characteristics, clinical diagnosis, and histopathological findings of excised GB specimens was performed using the Chi-square test. Statistical results were presented at a confidence interval of 95%, and statistical significance was set at $P < 0.05$.

Results

Distribution of cholecystectomy patients on the basis of histopathological findings

A total of 921 patients were examined during the study period. Histopathological lesions seen in gall bladder specimens were categorized as benign, premalignant, and malignant [Table 1]. Most of them were benign lesions (97.6%) followed by incidental carcinoma, the burden of which was 1.8%.

Among the benign lesions and overall, chronic calculus cholecystitis was found to be the most frequent pathology (95.01%). Cholesterosis was reported in one out of ten cholecystectomy specimens (9.9%). The next most common histopathological finding was xanthogranulomatous cholecystitis and metaplasia, accounting for approximately 6.5% and 5.4% of the total cases, respectively. Other findings reported were acute on chronic calculous cholecystitis, chronic follicular cholecystitis, chronic eosinophilic cholecystitis, mucocele, and adenomyomatosis. Two cases of inflammatory fibroblastic tumors have also been reported, which are rare benign findings.

Only five specimens had premalignant lesions dysplasia ($n = 4$) and tubular adenoma ($n = 1$). Incidental

Table 1: Distribution of histopathological findings in gallbladder specimen ($n=921$)

Histopathological findings	n (%)	95% CI
Benign disease	899 (97.61)	0.964-0.985
Chronic calculous cholecystitis	875 (95.01)	93.394-96.320
Cholesterosis	92 (9.99)	8.129-12.109
Xanthogranulomatous cholecystitis	60 (6.51)	5.008-8.306
Metaplasia	50 (5.43)	4.056-7.094
Acute on chronic calculous cholecystitis	5 (0.54)	0.176-1.262
Chronic follicular cholecystitis	3 (0.33)	0.067-0.949
Chronic eosinophilic cholecystitis	2 (0.22)	0.026-0.782
Inflammatory fibroblastic tumour	2 (0.22)	0.026-0.782
Mucocele	1 (0.11)	0.003-0.603
Adenomyomatosis	1 (0.11)	0.003-0.603
Premalignant	5 (0.54)	0.176-1.262
Dysplasia/atypia	4 (0.43)	0.118-1.108
Tubular adenoma	1 (0.11)	0.003-0.603
Malignant	17 (1.85)	1.079-2.939
Adenocarcinoma	17 (1.85)	1.079-2.939

CI: Confidence interval

carcinoma of GB was reported in 17 of 921 specimens, with a prevalence of 1.85%.

Age- and gender-wise distribution of cholecystectomy patients

Of all the patients, 694 were female and 227 were male, with a female/male ratio of 3.06:1 [Table 2]. The mean age of the patients was 43.10 ± 13.90 years, ranging between 15 and 83 years [Table 3]. Benign gall bladder disease was reported in a lower age group than in premalignant and malignant diseases. The mean age for benign disease was 43 years, followed by malignant disease with a mean age of 49 years (median 51 years) and premalignant disease 54 years (median 58 years). This difference in age was statistically significant (F = 3.44, df = 2, 918, P = 0.0326).

Common benign lesions such as cholesterolosis, chronic calculous cholecystitis, metaplasia, and xanthogranulomatous cholecystitis, were present in patients aged < 50 years. Adenocarcinoma was reported in 17 patients, with a mean age of approximately 49 years. Tubular adenoma was reported in a male patient aged 83 years.

Female preponderance in gall bladder disease was observed in all three categories, with a female-to-male ratio of 3.23:1. Among the benign lesions, female predilection was significantly associated with chronic calculous cholecystitis and xanthogranulomatous cholecystitis. Although insignificant, most benign lesions were observed in females, except for chronic follicular cholecystitis. Of the four cases of dysplasia, equal numbers were reported in both men and women. Among 17 incidental carcinoma gall bladder cases, 14 were female, with a female-to-male ratio of 4.67:1.

Incidental carcinoma gall bladder: Demographics and clinic-histopathological findings

The prevalence of incidental carcinoma was compared with that reported in various studies conducted in North India and South India. The burden of incidental carcinoma is reportedly higher in North Indian states (Delhi, Bihar, UP)^[1,15,16] than in the southern states (Tamil Nadu).^[17,18] This ranged from 3% to 1% for the northern states and 0.5% for the southern states^[1,15-21] [Figure 1].

In our study, there were 17 cases of incidental carcinomas. The stages of incidental carcinoma were pT1a (n = 6), pT1b (n = 6), and pT2a (n = 5) respectively, and all were adenocarcinoma. The mean ages were 47, 53, and 49 years for these three stages, respectively. All stages were observed to have a female preponderance [Figure 2].

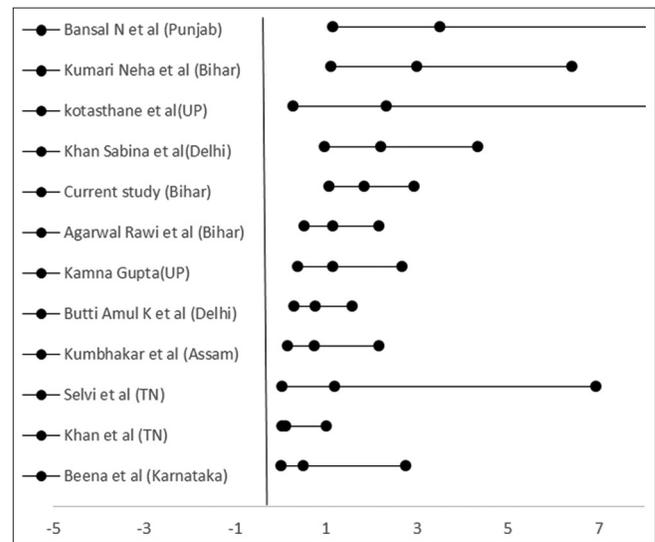


Figure 1: Comparison of prevalence of incidental carcinoma gall bladder as reported across various regions in India

Table 2: Gender wise distribution of histopathological findings in gallbladder specimen (n=921)

Histopathological findings	Female (n=694), n (%)	Male (n=227), n (%)	P
Benign disease	678 (75.42)	221 (24.58)	0.772
Chronic calculous cholecystitis	668 (76.34)	207 (23.66)	0.003
Cholesterosis	75 (81.52)	17 (18.48)	0.148
Metaplasia	36 (72.0)	14 (28.0)	0.572
Xanthogranulomatous cholecystitis	36 (60.0)	24 (40.0)	0.004
Acute on chronic calculous cholecystitis	4 (66.67)	2 (33.33)	0.64*
Inflammatory fibroblastic tumour	2 (100)	0	1*
Chronic eosinophilic cholecystitis	2 (100.0)	0	1*
Chronic follicular cholecystitis	1 (33.33)	2 (66.67)	0.152*
Mucocele	1 (100.00)	0	1*
Adenomyomatosis	0	1 (100)	0.246*
Premalignant	2 (40.0)	3 (60.00)	0.099*
Dysplasia/atypia	2 (50.00)	2 (50.00)	0.256*
Tubular adenoma	0	1 (100)	0.246*
Malignant	14 (82.35)	3 (17.65)	0.776*
Adenocarcinoma	14 (82.35)	3 (17.65)	0.776*

*Fisher exact test

Table 3: Age-wise distribution of histopathological findings in gallbladder specimen (n=921)

Histopathological findings	Mean age (95% CI)
Overall mean age±SD	43.10±13.90 (42.21-44.00)
Benign disease	42.92±13.89
Acute on chronic calculous cholecystitis	55.83±16.34 (38.69-72.98)
Cholesterosis	43.82±13.64 (40.99-46.64)
Chronic calculous cholecystitis	42.90±13.92 (41.97-43.82)
Metaplasia	48.42±14.57 (44.28-52.47)
Chronic follicular cholecystitis	54±6.24 (46.92-61.08)
Mucocele	47
Xanthogranulomatous cholecystitis	46.52±12.32 (43.33-49.70)
Chronic eosinophilic cholecystitis	48±9.90 (40.94-136.94)
Adenomyomatosis	39
Inflammatory fibroblastic tumour	30±7.07 (20.19-39.81)
Premalignant	54.2±20.04
Tubular adenoma	83
Dysplasia/atypia	47±13.78 (25.07-68.93)
Malignant	49.41±10.47
Adenocarcinoma	49.41±10.47 (44.43-54.39)

SD: Standard deviation

Patients with T1a tumors did not undergo any further procedure, whereas for T1b and T2 lesions, we could perform curative radical cholecystectomy.

Discussion

Gallstone disease is fairly common and requires elective laparoscopic cholecystectomy. These diseases are more common in women. In our study, females were predominantly affected (75.35%) in overall gall bladder diseases, with a male/female ratio of 1:3.06. This was in accordance with other studies by Kotasthane *et al.* (UP)^[1] 70.93%.

The incidence of incidental carcinoma GB in women in our study was higher, with a female/male ratio of 4.67:1, which is comparable with the findings of Kotasthane *et al.*^[1] and Khan *et al.*^[15]

In India, there is regional variation in gender involvement in both neoplastic and nonneoplastic groups. Females are more commonly involved in northern India than in southern India, where males are predominantly involved.^[21] Many studies suggest that GB diseases are common in the age group between 3rd and 5th decades.^[1,15,22] The overall mean age in our study was 43 years, with nonneoplastic lesions mainly in the age range of 40–50 years. The mean age of the neoplastic group was 49 years, with more than half of the patients in the 6th decade.

Our study showed the predominance of nonneoplastic lesions accounting for 97.61%, which was comparable to the results of different studies conducted in other

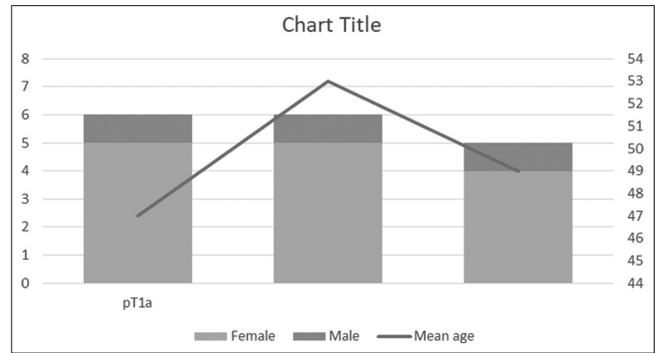


Figure 2: Age and gender wise distribution of different stages of incidental carcinoma gall bladder

parts of India, Kotasthane *et al.* (UP)^[1] 95.34%, 93.6%, Beena and Jayaprakash Shetty (Karnataka).^[21] Among the nonneoplastic lesions, chronic cholecystitis (95.01%) was the most common histopathological lesion in our study, similar to studies of 93.1%, Kotasthane *et al.* (UP)^[1] 95.34%, Beena and Jayaprakash Shetty (Karnataka)^[21] 82%. The percentage of xanthogranulomatous cholecystitis in our study was 6.51%, which is higher than that reported in other studies from different parts of India (Kotasthane *et al.*, 1;2.33%). Xanthogranulomatous cholecystitis is a rare form of chronic cholecystitis that can mimics as GB cancer.

Heterogeneity in the incidence of GB cancer and incidental GB carcinoma, based on various patient demographic factors, including worldwide location, ethnicity, and age, is a well-documented fact.^[8,22] Even in India, the incidence varies widely across countries.^[21] In North India, the frequency of Ca GB is 9.6%, followed by eastern India (6%).^[13] Similarly, incidental carcinoma GB is more common in northern and eastern India along the Gangetic region (1.33%).^[1,16]

In our study, incidental carcinoma of the GB was observed in 17 patients (1.85%). The incidence of incidental carcinoma of the GB was comparable to that in other studies performed in the Gangetic region.^[1,16] Although ultrasound is considered useful first-line investigation to raise the concern of GB cancer,^[23] none of the 17 carcinomas in this series could be picked up on preoperative ultrasonography. In addition, all 17 GB specimens showed no macroscopic evidence of malignancy when they were opened during surgery.

Various putative factors have been proposed to partly explain the differences in the incidence across the country and the high incidence in this region.^[24] As the Ganges arise from the glaciers in the Himalayas and flow towards the east, the industrial pollutant concentration and bacterial contamination by human waste have been found to steadily rise. High levels of pesticides, heavy metals, and nitrates, both of which are carcinogenic, have

been identified as pollutants in the Ganges.^[25] Untreated sewage, industrial waste, and agricultural effluents have been added to water throughout the course of the process.^[26] The fecal coliform count steadily rises as the river flows toward the east.^[27] *Salmonella typhi* and *Helicobacter pylori* are feco-orally transmitted organisms that are associated with the pathogenesis of GB carcinoma and are likely to increase as the river flows downstream.^[27,28]

Another factor may be the usage of mustard oil. In Bihar, mustard oil is the staple cooking oil in contrast to coconut oil, sesame oil, and groundnut oil in southern and western India. Mustard oil has irritant properties in the gut and is often adulterated. Higher levels of sanguinarine and diethylnitrosamine, which are carcinogenic adulterants in mustard oil, have been found in the blood and tissues of patients with GB carcinoma than in patients with cholelithiasis. Diethyl nitrosamine has been reported to induce hepatic carcinogenesis. Mustard oil has pro-inflammatory properties and can induce tumors.^[28]

Conclusion

The present study revealed that a different type of histopathological lesions following elective laparoscopic cholecystectomy specimens. Chronic cholecystitis was the most common GB disease in the present study. Females have increased preponderance for the development of all GB diseases, including malignancy. Nonneoplastic lesions were more common below 5th decade and neoplastic lesions thereafter.

In our opinion, routine HPE for all laparoscopic cholecystectomy specimens should be done; particularly to detect incidental GB malignancy and to ensure favorable patient's outcome.

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Conflicts of interest

There are no conflicts of interest.

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