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Indian Journal of Pathology and Oncology

Journal homepage: www.ijpo.co.in

Original Research Article

Spectrum of neoplastic lesions detected incidentally in routine cholecystectomy specimen: A retrospective study

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Abstract

Background: Specimens of cholecystectomy performed for clinically benign diseases, mostly cholecystitis, are usually submitted for routine histopathological examination. Sometimes, the specimen contains neoplastic disease which include intracholecystic papillary neoplasm with dysplasia, low-grade or high grade dysplasia, adenocarcinoma and other entities. It is important to identify these lesions for further patient management and risk assessment.

Aim of the Study: This study was undertaken in a tertiary care hospital in eastern India to determine the spectrum of incidental neoplastic lesion in specimen of routine cholecystectomy performed for clinically benign diseases and the relative incidence of these entities as this influences further patient management and validates the need for careful gross and microscopic examination of these specimens.

Materials and Methods: We identified one thousand seven hundred and ninety-five specimen of cholecystectomy done during the period of January 2023 to July 2024 and these were analysed for age, sex, imaging findings, preoperative clinical findings, intraoperative findings and histopathological findings. Cholecystectomy performed for known malignant diseases were excluded.

Results: Out of the total 1795 cases, 1474 cases were diagnosed as chronic cholecystitis, 264 cases were diagnosed as acute on chronic cholecystitis, 36 cases were diagnosed as xanthogranulomatous cholecystitis, 6 cases were diagnosed as adenocarcinoma, 7 cases were diagnosed as low-grade dysplasia, 5 cases diagnosed as intra cholecystic papillary neoplasm with dysplasia, 2 cases as high grade dysplasia/ intraepithelial carcinoma and one extra-intestinal GIST.

Conclusion: The relative incidence of incidental gallbladder adenocarcinoma was found to be 0.33, low-grade dysplasia was 0.39%, high grade dysplasia/ carcinoma in situ was 0.12%, extra intestinal GIST were found to be 0.06% and intra cholecystic papillary neoplasia with dysplasia was found to be 0.28%. All of these cases were associated with gallstone disease and cholecystitis except one case of intra cholecystic papillary neoplasm.

Keywords: Gall bladder, Intracholecystic Papillary neoplasm, Adenocarcinoma.

Received: 29-12-2024; **Accepted:** 28-01-2025; **Available Online**: 15-03-2025

1. Introduction

Gallbladder carcinoma is a very aggressive cancer with a poor survival rate of < 5%.[1-3] It is the fifth most common cancer of the gastrointestinal tract and the commonest malignancy affecting the biliary tract. The poor survival rate can be partly due to the fact that it is diagnosed late, as the signs and symptoms are vague and non-specific. Therefore, the cancer is at an advanced stage by the time symptoms become apparent. It is, also, due to this reason that many gallbladder carcinomas are detected incidentally. Histopathological examination is routinely performed for cholecystectomy done for clinically benign gallbladder diseases and sometimes we find a spectrum of neoplastic lesions like dysplasia, Intracholecystic papillary neoplasm and malignancy.

Demographically, India is among the regions with a very high incidence of this malignancy.[4,5] The incidence of incidental gallbladder carcinoma is reported to be in the range of 0.3% to 2.9%.[3]

Our study was made to determine the spectrum of neoplastic lesions detected incidentally in routine cholecystectomy specimen and their relative incidence.

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https://doi.org/10.18231/j.ijpo.2025.004

2. Materials and Methods

The study was done in a tertiary care institute in eastern India. It was a retrospective observational study performed in the department of pathology, of all routine cholecystectomy cases performed for clinically benign disease between the time period of January 2023 and July 2024. The patient histories and clinical as well as radiological findings were retrieved from the hospital records and the histopathology slides were retrieved from the archives of the pathology department.

The demographic profile, clinical findings, imaging, intraoperative findings, gross pathological and histopathological findings were analysed. Statistical analysis was performed and the relative incidence determined.

3. Results

1795 cases of cholecystectomy were identified excluding those done for diagnosed case of carcinoma. Demographically, there was an overwhelming majority of female cases, numbering 1171 in comparison to 624 males which gives a M:F ratio of 1:1.8. The age distribution of the patients undergoing cholecystectomy varied from 7 months to 80 years. The 7 month old child had extrahepatic biliary atresia and fibrotic gallbladder, for which tissue from porta hepatis and cholecystectomy was performed and showed mild chronic inflammation in the gallbladder

Aside from cholecystitis, 21 cases with neoplastic aetiology was identified. These varied from intra cholecystic papillary neoplasm to dysplasia, both low-grade and high grade, GIST and adenocarcinoma.

Table 1: Break of diagnosis

S. No.	Diagnosis	Total Cases
1.	Chronic Cholecystitis	1474
2.	Acute cholecystitis	264
3.	Xanthogranulomatous cholecystitis	36
4.	Low grade dysplasia	7
5.	High grade dysplasia	1
6.	High grade intraepithelial neoplasm	1
7.	Intracholecystic papillary neoplasm	5
8.	Extra gastrointestinal GIST	1
9.	Adenocarcinoma	6
Sum Total		1795

On an average, the age profile of those with neoplastic lesions were higher, most of them were above 50 yrs., a few were above 30 years of age and one case of ICPN, which was of 25 years age.

Table 2: Findings in the neoplastic cases

S. No	Age	Sex	Pre-operative findings	Imaging findings	Intraoperative findings	Gross pathological findings	Microscopy and diagnosis
1	66	M	Upper abdominal pain	Calculous cholecystitis and adenomyosis	Stone at neck, acute on chronic inflammation	Maximum wall thickness of 0.8 cm; ulcerated mucosa	Biliary type adenocarcinoma; pt2bn1; lvi & pni present
2	77	M	Upper abdominal pain, vomiting, fever with chills, jaundice	Calculous cholecystitis, adenomyosis, hepatosplenomegali	Thickened gallbladder wall; calculi; omental adhesion	Maximum wall thickness of 1.0 cm; ulcerated mucosa	Biliary type adenocarcinoma; Pt2bn1; lvi present; pni not identified
3	62	F	Right upper abdominal and epigastric pain	Collapsed gallbladder with few stones; irregular thickening of gallbladder wall and pericholecystic collection	Thickened gallbladder wall with multiple stones; frozen calot's triangle; liver abscess and dense adhesion with omentum, colon and duodenum	Fragmented gallbladder with maximum wall thickness of 0.3 cm; congested serosa and yellowish ulcerated mucosa	Biliary type adenocarcinoma; pt2 m not assigned m not applicable; lvi present, pni not identified with background xanthogranulomatous cholecystitis

Table 2 continued

4	59	F	Pain abdomen	Mirizzi syndrome, gallbladder stone, thickened gallbladder wall	Thick walled gallbladder with stones; friable calot's triangle with omental and common bile duct adhesions	Localised thickening of the gallbladder wall with a well circumscribed tumour	extra gastrointestinal stromal tumour (egist); 2.3 cm
5	57	F	Upper abdominal pain, vomiting	Multiple calculi, dilated proximal common bile duct	Multiple gallbladder stones, dense adhesion with plastered adhesion near cystic duct	Maximum wall thickness of 0.6 cm, calculi and ulcerated mucosa	Biliary type adenocarcinoma, pt2bn1;. Lvi not identified; pni present
6	47	F	Epigastric pain	Multiple gallstone; thickened gallbladder wall Gallbladder polyp	Extensive omental band adhesion to gallbladder and inferior surface of liver	Maximum wall thickness of 1.4 cm; mucosal polyp measuring 2.5 x 1 x 1 cm	Biliary type adenocarcinoma in a background of highgrade dysplasia and infracolic cystic papillary neoplasm; pt2n not assigned; lpi and pni not identified
7	73	F	Pain abdomen	Irregular thick walled gallbladder	Omental adhesions;	Fragmented gallbladder wall with maximum thickness of 0.4 cm	Moderately differentiated adenocarcinoma; pathological staging could not be assigned; lvi and pni not identified
8	38	F	Upper abdominal pain	Gallbladder stone	Inflamed gallbladder	Wall thickness 0.2-0.3 cm	Chronic cholecystitis with low-grade dysplasia
9	75	F	Pain abdomen	Gallstone, normal wall thickness	Unremarkable	Wall thickness 0.2-0.4 cm	Chronic cholecystitis with moderate dysplasia
10	31	F	Intermittent abdominal pain vomiting	Gallstone	Unremarkable	Wall thickness 0.2-0.4 cm	Chronic cholecystitis with low-grade dysplasia
11	37	F	Pain abdomen and dyspepsia	Gallstone, normal wall thickness	Unremarkable	Wall thickness 0.2-0.4 cm	Chronic cholecystitis with focal low-grade dysplasia
12	55	M	Upper abdominal pain nausea, vomiting	Gallbladder sludge ball, dilated CBD	Contracted, thickwalled gallbladder, frozen and obliterated calot's triangle, adherent to liver	Wall thickness 0.2-0.4 cm	Chronic cholecystitis with low-grade dysplasia and intestinal metaplasia
13	64	F	Upper abdominal pain			Wall thickness 0.2-0.4 cm	Chronic cholecystitis with focal low-grade dysplasia
14	32	M	Abdominal pain, vomiting	Cholecystitis, cholelithiasis	Distended gallbladder with edematous thickened wall, impacted gallstone	Wall thickness 0.2-0.5 cm, mucosa show whitish areas	Chronic cholecystitis with focal low-grade dysplasia

Table 2 continued

15	57	F	Abdominal pain	Cholelithiasis	Thinwalled gallbladder with calculus	Wall thickness 0.2-0.4 cm, irregular mucosa in body of gallbladder	Chronic cholecystitis with high grade dysplasia
16	60	M	Asymptomatic Incidental detection of gallstone during health checkup	Gallstone	Impacted stone, distended gallbladder, thickened wall, normal callot's triangle	Wall thickness 0.2-0.6 cm. Mucosal denudation with irregular white plaque	High grade biliary intraepithelial neoplasm, ptis
17	69	F	Abdominal pain, vomiting	Gallstone	Thickened fundal wall	Papillaroid lesion at fundus measuring 1.1x1x0.3 cm.	ICPN, biliary type with low grade dysplasia
18	61	M	Pain abdomen	Calculi and diffuse wall thickening on MRCP	Wall thickening	Papillaroid lesion at neck and body measuring 1.5x1.5x0.3 cm	ICPN, biliary type with low grade dysplasia
19	66	M	Pain abdomen	Gallbladder polyp	Gallbladder polyp	Polypoidal lesion in body measuring 1.8 cm	ICPN, biliary type with low grade dysplasia and focal highgrade dysplasia
20	25	M	Pain abdomen	Gallstone, smooth tappering of gallbladder ?benign lesion	Moderately distended gallbladder, fat wrapped calot's triangle	Polyp in body measuting 1.5x0.7x0.5 cm	Icpn, biliary type with moderate dysplasia
21	38	F	Dyspepsis, upper badominal discomfort	Gallstone	Omental and duodenal adhesion, multiple calculi	Polypoidal mucosa all over the gallbladder	ICPN, biliary type with low grade dysplasia

In the group of neoplastic lesions, there were 13 females and 8 males. The group with adenocarcinoma had a male to female ratio of 1:2, the group with low-grade dysplasia had a male to female ratio of 1:2.5, the group with high grade dysplasia/intraepithelial neoplasm was 1:1, ICPN was 1.5:1 male to female ratio. A single case of GIST, suspected of arising from the Gallbladder, was also diagnosed in a female patient.

All of the cases were associated with gallstones and symptoms of upper abdominal pain except for 1 case of intra cholecystic papillary neoplasm which showed a polyp and no gallstone.

Radiologically, most were associated with gallstones except 1 case, thickened gallbladder wall in the 5 cases of adenocarcinoma with 2 of them showing foci suggestive of adenomyosis.

Those with dysplasia had no evidence of wall thickening on imaging except one case of high-grade dysplasia. In the cases with intra cholecystic papillary neoplasm, thickened walls were noted in one of the cases, 1 showed a gallbladder polyp and another showed smooth tapering of the gallbladder wall suggestive of a benign lesion.

Intraoperative findings in the adenocarcinoma group where a thickened gallbladder wall, adhesions and a frozen Calot's triangle. In the group with dysplasia, the findings were mostly non-specific except for 1 case in the low-grade dysplasia group which showed a thickened gallbladder wall and frozen and obliterated Calot's triangle with adhesions and one in the high grade dysplasia group.

In the cases with adenocarcinoma, the gross histopathological findings were thickened gallbladder wall, ulcerated mucosa and 1 case with a mucosal polyp. Those in the dysplasia group showed non-specific gross histological findings and those in the ICPN group had papillary

gallbladder mucosa. No association was found between adenomyosis and gallbladder adenocarcinoma in our study, though the imaging were suggestive of adenomyosis in some of the patients with adenocarcinoma.

The case of gallbladder adenocarcinoma with gross finding of a polyp was associated with intra cholecystic papillary neoplasm with high grade dysplasia. All cases of adenocarcinoma were of biliary type and were stage as pT2, 2 cases had lymph node involvement, 3 cases showed lymphovascular invasion and 2 cases showed perineural invasion.

The patients with gallbladder adenocarcinoma were subjected to staging Positron emission tomography and completion radical cholecystectomy with segmental liver resection at a later date, and are undergoing chemotherapy at present, except in two, who were lost to follow-up. MSI immunohistochemistry was performed in one patient which was MSI-stable.

Gross images were unfortunately unavailable as this is an observational retrospective study on incidental neoplastic lesions.

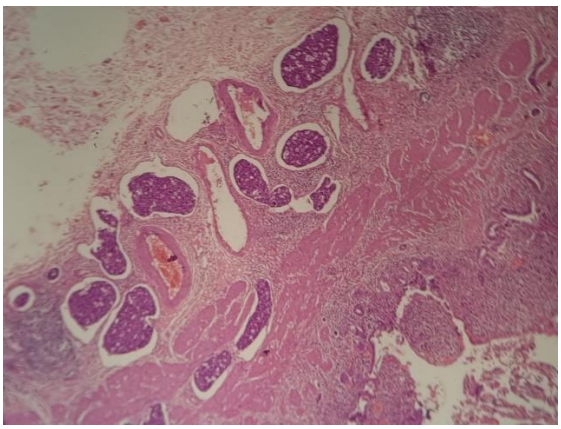

Figure 1: Adenocarcinoma with lymphovascular invasion (x 100)

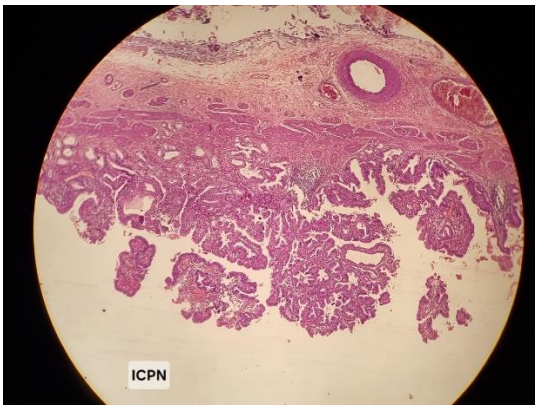

Figure 2: Intracholecystic papillary neoplasm with lowgrade dysplasia (x 100)

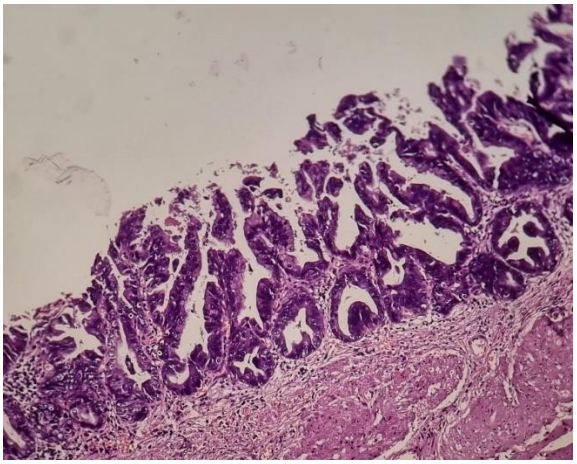

Figure 3: High grade dysplasia (x 400)

4. Discussion

Gallbladder specimens are among the commonest resection specimen submitted for routine histopathology. The commonest indication for resection is cholecystitis associated with gallstone. During the routine histopathological examination, neoplastic lesions are sometimes encountered in the specimen, which were resected due to clinically benign diagnosis, and these includes incidental gallbladder carcinoma.

Gallbladder carcinoma is the most common carcinoma of the biliary tract and the fifth most common malignancy of the gastrointestinal tract.[1,3] The incidence of gallbladder carcinoma varies from place to place with low incidence in western countries and higher incidence in Asian countries like Japan and India. The role of diet, habitat, pollutants, atmospheric/environmental factors have been implicated but is not gone into in detail here since these do not come under the preview of this present study. The prognosis of this cancer depends on the staged at which the cancer is detected. Since the symptoms and clinical signs are non-specific, they can often be misinterpreted as suffering from cholecystitis. The signs and symptoms of cancer become apparent only at late stage and due to this, the prognosis is bad. The reported 5 years survival is around 0.5%.[1]

Most cases of gallbladder carcinoma are associated with calculi and chronic cholecystitis.[1-8] An important aspect of cancer development is related to the constant irritation of the gallbladder mucosa by calculi which causes the sequence of metaplasia to dysplasia to the development of carcinoma.[1,3-5] In their study about risk factors for gallbladder cancer development in north India, Kumudesh Mishra et al, found that the development of gallbladder cancer is a multifactorial process starting from the presence of gallstones. They also found that advanced age, lower bowel movements of once per day or less and multiple pregnancy were associated with an increased risk.[8]

The incidence of primary gallbladder carcinoma is reported to be 1.2%-10.6% depending on the geographical

location.[2] The incidence of incidental gallbladder carcinoma was found to be about 0.1%- 2.9% by various studies.[1-6,9] Di Mouro et al, found the incidence to be 0.1% in their study conducted in the UK,[1] Neha Singh et al found the incidence to be 0.87% in India,[4] Bhanu Pratap et al, found an incidence of 0.5% in India[3] and R Shrestha et al, found an incidence of 1.4% in their study conducted in Nepal.[9] In our study the incidence of gallbladder adenocarcinoma was 0.33% which is within the range, although compared to the incidence recorded in other studies done in India and Nepal, it is lower whereas, it is higher than that reported in the UK. This affirms the difference in incidence rate in different part of the world.

Most studies showed the occurrence of incidental gallbladder carcinoma to be more in females.[1-6] So, also, in our case we found the incidence of incidental gallbladder adenocarcinoma to be more in female with male to female ratio of 1:2. The overall incidence of neoplastic lesions showed a male to female ratio of 1:1.5. The male to female ratio in the group with intra cholecystic papillary neoplasm was altered with the higher male occurrence, with a male to female ratio of 1.5:1. These findings could be skewed because of the low number of cases.

Studies also had been conducted about the selective histological examination and gross procedures.[9,10] Emmett et al, concluded that microscopically abnormal gallbladder specimen, emergency surgery specimen, all open/subtotal procedure should be subjected to histopathological examination especially in patients over 50 years of age, and macroscopically normal gallbladder in younger patient may not be subjected to histopathological examination. This will ensure economic benefits.[9] In our study we found that the cases with incidental gallbladder carcinoma were mostly in the late 50s and above with only one being 47 years of age. But patients with intra cholecystectomy biliary neoplasm with dysplasia and dysplasia, the age group was lower and 1 was as young as 25 years of age. Most case with dysplasia had no macroscopic abnormalities. Though cholecystectomy is curative in these patients, there can be chances that the resection margin was involved by the dysplasia, in which case the patient management with be affected. Therefore, it would be prudent to send all routine cholecystectomy cases for histopathological examination.

Ezgi et al, in their study, showed that the full thickness slice sampling method was superior in detecting incidental gallbladder carcinoma rather than random sampling.[10] At our hospital, we have a protocol of sampling full thickness wall of the gallbladder from the neck, body and fundus. In addition, we sample areas that may be grossly suspicious.

We could not correlate imaging finding or of macroscopical wall thickening with certainty of diagnosing gallbladder carcinoma, even though most of the gallbladder carcinoma cases had wall thickening. This was due to the fact that the imaging often missed wall thickening and showed only evidence of gallstone. The fact that many benign lesions also had wall thickening, especially those with adenomyosis and xanthogranulomatous inflammation also were a hindrance to successfully correlate wall thickening with the certainty of diagnosing gallbladder carcinoma. Intraoperative findings like omental adhesion and frozen Calot's triangle were consistent finding in favour of gallbladder carcinoma but were not 100% specificity either. It can be suggested that if they are found intraoperatively, either a frozen section study may be conducted or the patient counselled regarding the probable nature of the pathology and possible need for repeat surgery.

5. Conclusion

It is not uncommon to find incidental gallbladder carcinoma in specimen resected for clinically benign disease. The fact that clinical symptoms are non-specific is also a difference to the diagnosis of gallbladder carcinoma. A thorough and careful imaging including CT scan and MRI, careful examination intraoperatively and careful gross and histopathological can help in diagnosing gallbladder carcinoma and the further patient management.

6. Source of Funding

None.

7. Conflict of Interest

None.

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Cite this article: Sinha B, Sutradhar A, Sinha V. Spectrum of neoplastic lesions detected incidentally in routine cholecystectomy specimen: A retrospective study. *Indian J Pathol Oncol*. 2025;12(1):15–21.