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Original Research Article

HISTOPATHOLOGICAL DETECTION OF INCIDENTAL GALLBLADDER NEOPLASIA IN ROUTINE CHOLECYSTECTOMY SPECIMENS

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ABSTRACT

Background: Gallbladder neoplasms may remain clinically and radiologically occult because their manifestations frequently overlap with benign gallstone-related disease. Routine histopathological examination of cholecystectomy specimens may identify biliary intraepithelial neoplasia (BilIN), other preinvasive neoplasms and early invasive carcinoma that would otherwise remain undetected. This study evaluated the frequency, histopathological spectrum and associated factors of neoplastic lesions incidentally identified in routine cholecystectomy specimens.

Materials and Methods: This five-year retrospective observational study included 2,108 consecutive cholecystectomy specimens removed for clinically and radiologically presumed benign gallbladder disease at a tertiary-care hospital. Demographic, clinical, radiological, operative, gross and microscopic findings were retrieved from institutional records. Neoplastic lesions were classified according to the World Health Organization Classification of Tumours, fifth edition, and invasive carcinomas were staged using the eighth edition of the American Joint Committee on Cancer TNM system. Eight prespecified variables were entered simultaneously into an exploratory multivariable logistic regression model.

Results: Of 2,108 specimens, 2,047 (97.1%) showed non-neoplastic pathology and 61 (2.9%) contained incidental neoplastic lesions. Chronic calculous cholecystitis was the predominant diagnosis (1,584/2,108; 75.1%). Among the 61 neoplastic lesions, there were 22 (36.1%) low-grade BilINs, 11 (18.0%) high-grade BilINs, five (8.2%) adenomas, three (4.9%) intracholecystic papillary neoplasms and 20 (32.8%) invasive carcinomas. Incidental invasive carcinoma occurred in 20/2,108 specimens (0.95%); conventional biliary-type adenocarcinoma comprised 17/20 invasive carcinomas (85.0%). Patients with neoplasia were older than those with non-neoplastic disease (57.2±11.2 versus 43.8±13.5 years; $p<0.001$). Age >50 years, gallstone size ≥3 cm, wall thickness >3 mm and an ultrasonographically detected polypoid lesion retained statistical associations with neoplasia after adjustment. No gross abnormality was identified in 26/41 preinvasive lesions (63.4%) and 5/20 invasive carcinomas (25.0%).

Conclusion: A small but clinically important proportion of cholecystectomy specimens contained unsuspected BilIN or invasive carcinoma. Because several lesions were macroscopically inapparent, the findings suggest potential value in routine microscopic assessment within the study setting. However, this retrospective study did not directly compare routine with selective examination or evaluate patient outcomes; larger multicentre comparative studies are needed before recommending a universal policy.

Keywords: Cholecystectomy; gallbladder neoplasms; incidental gallbladder carcinoma; biliary dysplasia; cholelithiasis.

INTRODUCTION

Cholecystectomy is one of the most frequently performed abdominal operations, predominantly undertaken for symptomatic cholelithiasis and chronic cholecystitis. Although most resected gallbladders demonstrate inflammatory or degenerative changes, histopathological examination occasionally reveals unsuspected neoplastic lesions ranging from biliary intraepithelial neoplasia (BilIN) and intracholecystic papillary neoplasm (ICPN) to invasive carcinoma. These lesions may be clinically silent and can closely mimic benign gallstone-related disease on imaging and gross examination.[1–3]

Gallbladder carcinoma is the most common malignancy of the biliary tract and demonstrates marked geographical and ethnic variation. An Indian epidemiological review estimated that India contributes approximately 10% of the global gallbladder-cancer burden and identified northern, north-eastern, eastern and central India as higher-incidence regions; the same review reported age-standardised incidence rates of approximately 11.8 and 17.1 per 100,000 among women in northern and north-eastern India, respectively.[1] Gallstones were reported in approximately 80% of Indian patients with gallbladder carcinoma.[1] while another Indian series reported gallstones in 70–80% of gallbladder malignancies.[3] Repeated gallstone-related mucosal injury may sustain inflammation and regenerative proliferation, providing a biological context for progression through metaplastic change, low-grade BilIN, high-grade BilIN and invasive carcinoma.[1–3]

Incidental gallbladder carcinoma refers to malignancy detected during or, more commonly, after cholecystectomy performed for a presumed benign disorder. A meta-analysis of 51 studies involving 436,636 cholecystectomies estimated its pooled incidence at 0.6%.[4] while another systematic review reported a frequency of 0.25–0.89%.[5] Indian studies have documented rates ranging from approximately 0.4% to 1.0%.[6,7] Importantly, some affected specimens show neither radiological suspicion nor obvious macroscopic abnormality.[6] Besides conventional adenocarcinoma, routine histopathology may identify BilIN, pyloric gland adenoma of the gallbladder, intracholecystic papillary neoplasm and uncommon malignant variants.[2,3,8]

The selective versus routine submission of cholecystectomy specimens for microscopy remains debated, particularly in resource-constrained settings.[8,9] Nevertheless, detecting an occult neoplasm and accurately determining its depth of invasion directly influence staging, re-resection and prognosis. Therefore, evaluating the spectrum and frequency of incidentally detected neoplastic lesions is essential for guiding institutional histopathological protocols and avoiding missed, potentially curable malignancies.

MATERIALS AND METHODS

Study design and setting: This retrospective, descriptive observational study was conducted in the Department of Pathology in collaboration with the Department of General Surgery at a tertiary-care teaching hospital in India. Histopathology records of routine cholecystectomy specimens received over a period of five years, from June 2020 to May 2025 were reviewed. The study was designed to determine the frequency, demographic distribution and histomorphological spectrum of neoplastic lesions detected incidentally in gallbladders removed for clinically and radiologically presumed benign disease.

Study population and sample size: All consecutive cholecystectomy specimens submitted for histopathological examination during the study period constituted the study population. Because the investigation was retrospective and intended to include the complete spectrum of eligible cases, a census sampling method was used; therefore, no separate sample-size calculation was performed. The total number of eligible cholecystectomy specimens received during the defined period formed the denominator for calculating the frequency of incidental neoplastic lesions.

Eligibility criteria: The study included cholecystectomy specimens removed for presumed benign indications, including symptomatic cholelithiasis, acute or chronic cholecystitis, mucocele, empyema, gallbladder polyps and biliary pancreatitis, provided that adequate clinical, radiological and histopathological records were available. Both laparoscopic and open cholecystectomy specimens were eligible. Specimens from patients with a preoperative radiological diagnosis or strong clinical suspicion of gallbladder malignancy, cholecystectomies performed as part of another oncological procedure, repeat specimens, fragmented or autolysed specimens unsuitable for evaluation, and cases with incomplete histopathological records were excluded. Neoplastic lesions were considered incidental when they were not suspected clinically, radiologically or intraoperatively and were first identified during histopathological examination.

Data collection: Eligible cases were identified from the histopathology accession registers and laboratory information system. Demographic and clinical information, including age, sex, presenting symptoms, preoperative diagnosis, ultrasonographic findings, presence and number of gallstones, gallbladder wall thickness, polypoid lesions and operative observations, was retrieved from histopathology requisition forms and available medical records. Gross and microscopic findings were recorded using a structured data-extraction form. The primary outcome was the proportion of routine cholecystectomy specimens containing an incidental neoplastic lesion. Secondary outcomes

included the histological spectrum, anatomical location, grade, depth of invasion, margin status and association with age, sex, gallstones and wall thickening.

Specimen processing and histopathological evaluation: All gallbladder specimens had been fixed in 10% neutral-buffered formalin. During gross examination, the specimen dimensions, external surface, mucosal appearance, wall thickness, gallstones and any focal thickening, ulceration, induration, nodularity or polypoid growth were documented. Routine representative sections were taken from the fundus, body, neck and cystic-duct margin. Additional sections were obtained from all grossly abnormal areas. When dysplasia or malignancy was identified microscopically, the remaining gallbladder was extensively sampled to determine the extent of the lesion and exclude occult invasion.

Tissue sections of approximately 3–5 µm thickness were prepared from paraffin-embedded blocks and stained with haematoxylin and eosin. All neoplastic cases were independently reviewed by two pathologists; disagreements were resolved by joint microscopic examination and consensus. Immunohistochemistry was employed only where required for histological classification or confirmation of uncommon tumours.

Classification of lesions: Neoplastic lesions were classified according to the fifth edition of the World Health Organization Classification of Tumours: Digestive System Tumours. Flat microscopic precursor lesions were reported using the preferred two-tier terminology low-grade biliary intraepithelial neoplasia (BilIN) and high-grade BilIN; the term carcinoma in situ was not used as a separate diagnostic category. Mass-forming preinvasive lesions were classified as pyloric gland adenoma of the gallbladder or intracholecystic papillary neoplasm (ICPN), as appropriate. One archived lesion that could not be reassigned confidently to either entity was retained as adenoma, not otherwise specified (NOS), with biliary phenotype. Invasive carcinomas were classified by histological type and graded as well, moderately or poorly differentiated where applicable. Pathological tumour stage was assigned according to the eighth edition of the American Joint Committee on Cancer tumour–node–metastasis classification. The cystic-duct margin, lymphovascular invasion and perineural invasion were documented whenever assessable.

Statistical analysis: Data were entered into Microsoft Excel and analysed using IBM SPSS Statistics version 20.0. Categorical variables were summarised as frequencies and percentages, and continuous variables as mean±standard deviation or median with interquartile range, according to distribution. Group comparisons used the chi-square test or Fisher's exact test for categorical variables and the independent-samples t-test or Mann–Whitney U test for continuous variables, as appropriate. For exploratory multivariable binary logistic regression, eight candidate variables were prespecified from clinical relevance and published literature rather than selected by automated stepwise procedures: age >50 years, female sex, gallstones present, multiple gallstones, largest gallstone ≥3 cm, ultrasonographic wall thickness >3 mm, ultrasonographic polypoid lesion and open cholecystectomy. All eight variables were entered simultaneously. Reference categories were age ≤50 years, male sex, no gallstones, single or no gallstones, largest stone <3 cm or no stone, wall thickness ≤3 mm, no polypoid lesion and laparoscopic cholecystectomy, respectively. With 61 neoplastic events and eight regression coefficients, the model had 7.6 events per variable; therefore, adjusted estimates were considered exploratory and potentially susceptible to overfitting. Adjusted odds ratios (ORs) with 95% confidence intervals (CIs) were reported. Calibration was assessed using the Hosmer–Lemeshow test, and model explanatory performance was summarised using Nagelkerke R^2. A two-sided p value <0.05 was considered statistically significant.

Ethical considerations: The study was initiated after approval from the Institutional Ethics Committee. As it involved retrospective review of archived specimens and records without direct patient contact, waiver of individual informed consent was obtained. Patient identifiers were removed, and confidentiality was maintained throughout data collection and analysis.

RESULTS

Among 2,108 patients, 61 (2.9%) had incidental neoplastic lesions and 2,047 (97.1%) had non-neoplastic lesions. Patients with neoplastic lesions were significantly older than those with non-neoplastic pathology (57.2±11.2 versus 43.8±13.5 years; p<0.001), and the proportion of neoplasia increased progressively across age groups, reaching 8.1% among patients older than 60 years. Although females predominated overall (72.1%), sex distribution did not differ significantly between groups (p=0.239). Neoplastic lesions were significantly associated with gallstones ≥3 cm (23.0% versus 9.7%; p=0.001), ultrasonographic wall thickness >3 mm (49.2% versus 23.2%; p<0.001), polypoid lesions (13.1% versus 1.9%; p<0.001), and open cholecystectomy (13.1% versus 5.3%; p=0.012). The presence and multiplicity of gallstones were not significantly associated with neoplasia [Table 1].

Table 1: Demographic, clinical and radiological characteristics of patients according to the presence of incidentally detected neoplastic lesions in routine cholecystectomy specimens.

Characteristic	Total (N=2,108)	Non-neoplastic lesions (n=2,047)	Neoplastic lesions (n=61)	p value
	Frequency (%)/mean ± SD			
Age, years	44.2 ± 13.7	43.8 ± 13.5	57.2 ± 11.2	<0.001
Age group				
≤30 years	310 (14.7)	309 (15.1)	1 (1.6)	<0.001
31–40 years	521 (24.7)	516 (25.2)	5 (8.2)	
41–50 years	585 (27.8)	572 (27.9)	13 (21.3)	
51–60 years	407 (19.3)	388 (19.0)	19 (31.1)	
>60 years	285 (13.5)	262 (12.8)	23 (37.7)	
Gender				
Female	1,519 (72.1)	1,471 (71.9)	48 (78.7)	0.239
Male	589 (27.9)	576 (28.1)	13 (21.3)	
Gallstones present	1,903 (90.3)	1,847 (90.2)	56 (91.8)	0.684
Multiple gallstones	1,231 (58.4)	1,196 (58.4)	35 (57.4)	0.87
Largest stone ≥3 cm	212 (10.1)	198 (9.7)	14 (23.0)	0.001
Gallbladder wall thickness >3 mm on ultrasonography	505 (24.0)	475 (23.2)	30 (49.2)	<0.001
Polypoid lesion on ultrasonography	47 (2.2)	39 (1.9)	8 (13.1)	<0.001
Laparoscopic cholecystectomy	1,992 (94.5)	1,939 (94.7)	53 (86.9)	0.012
Open cholecystectomy	116 (5.5)	108 (5.3)	8 (13.1)	

Percentages in the two diagnostic columns use n=2,047 and n=61 as their respective denominators.

Non-neoplastic lesions accounted for 2,047 (97.1%) of the 2,108 specimens, while 61 (2.9%) contained neoplastic pathology. Chronic calculous cholecystitis was the predominant diagnosis, occurring in 1,584 (75.1%) specimens, followed by acute-on-chronic cholecystitis in 211 (10.0%) and cholesterolosis in 75 (3.6%). Less frequent non-neoplastic conditions included chronic acalculous cholecystitis (2.3%), adenomyomatous hyperplasia or adenomyomatosis (2.0%), xanthogranulomatous cholecystitis (1.9%), mucocele (1.1%) and empyema (0.7%). Porcelain, eosinophilic and granulomatous cholecystitis were uncommon, together representing fewer than 0.5% of specimens [Table 2].

Table 2: Overall histopathological spectrum of routine cholecystectomy specimens during the five-year study period.

Histopathological diagnosis	Number	Percentage of total specimens
Non-neoplastic lesions	2,047	97.1
Chronic calculous cholecystitis	1,584	75.1
Acute-on-chronic cholecystitis	211	10
Chronic acalculous cholecystitis	48	2.3
Cholesterolosis	75	3.6
Adenomyomatous hyperplasia/adenomyomatosis	42	2
Xanthogranulomatous cholecystitis	39	1.9
Mucocele of the gallbladder	24	1.1
Empyema of the gallbladder	15	0.7
Porcelain gallbladder	4	0.2
Eosinophilic cholecystitis	3	0.1
Granulomatous cholecystitis	2	0.1
Neoplastic lesions	61	2.9
Total	2,108	100

Percentages use the full cohort (N=2,108) as the denominator. The principal histopathological diagnosis was used for classification; associated findings were not counted separately when neoplasia was present.

Among the 61 incidentally detected neoplastic lesions, low-grade BilIN was the most frequent, accounting for 22 (36.1%) cases, followed by conventional biliary-type adenocarcinoma in 17 (27.9%) and high-grade BilIN in 11 (18.0%). Pyloric gland adenoma of the gallbladder was identified in four (6.6%) specimens, intracholecystic papillary neoplasm in three (4.9%) and adenoma NOS with biliary phenotype in one (1.6%). The uncommon malignant lesions comprised one case each of papillary adenocarcinoma, adenosquamous carcinoma and neuroendocrine carcinoma. Overall, preinvasive neoplasms were detected in 41/2,108 specimens (1.95%), while incidental invasive carcinoma was identified in 20/2,108 (0.95%) [Table 3].

Table 3: Histopathological spectrum and frequency of incidentally detected neoplastic gallbladder lesions.

Neoplastic lesion	Number (n=61)	Percentage among neoplastic lesions	Percentage among all specimens (N=2,108)
Biliary intraepithelial neoplasia, low grade (low-grade BilIN)	22	36.1	1.04
Biliary intraepithelial neoplasia, high grade (high-grade BilIN)	11	18	0.52
Pyloric gland adenoma of the gallbladder	4	6.6	0.19
Adenoma, NOS (biliary phenotype)	1	1.6	0.05

Intracholecystic papillary neoplasm (ICPN)	3	4.9	0.14
Conventional adenocarcinoma, biliary type	17	27.9	0.81
Papillary adenocarcinoma	1	1.6	0.05
Adenosquamous carcinoma	1	1.6	0.05
Neuroendocrine carcinoma	1	1.6	0.05
Total	61	100	2.89

BilIN, biliary intraepithelial neoplasia; ICPN, intracholecystic papillary neoplasm; NOS, not otherwise specified. Percentages in the third column use the 61 neoplastic lesions as denominator; percentages in the fourth column use all 2,108 specimens. Values may not total exactly 100% because of rounding. Preinvasive lesions totalled 41 (33 BilIN, five adenomas and three ICPNs); invasive carcinomas totalled 20.

Conventional biliary-type adenocarcinoma was the predominant histological subtype, comprising 17/20 (85.0%) invasive carcinomas. Papillary adenocarcinoma, adenosquamous carcinoma and neuroendocrine carcinoma accounted for one case each (1/20; 5.0%). Nine of 20 carcinomas (45.0%) were pT1a–pT1b, nine (45.0%) were pT2a–pT2b and two (10.0%) were pT3. Histological differentiation was evaluated in the 19 epithelial carcinomas, excluding the neuroendocrine carcinoma: nine (47.4%) were moderately differentiated, six (31.6%) were well differentiated and four (21.1%) were poorly differentiated. Using all 20 invasive carcinomas as the denominator, lymphovascular invasion was present in five (25.0%), perineural invasion in four (20.0%), adjacent high-grade BilIN in 11 (55.0%), and cystic-duct margin involvement and liver infiltration in two (10.0%) cases each [Table 4].

Table 4: Histological type, pathological tumour category and adverse pathological characteristics of incidental invasive gallbladder carcinomas.

Histopathological characteristic	Number (n=20)	Percentage
Histological type (n=20)		
Conventional adenocarcinoma, biliary type	17	85
Papillary adenocarcinoma	1	5
Adenosquamous carcinoma	1	5
Neuroendocrine carcinoma	1	5
Pathological tumour category (n=20)		
pT1a: invasion of lamina propria	4	20
pT1b: invasion of muscular layer	5	25
pT2a: perimuscular connective tissue invasion, peritoneal side	5	25
pT2b: perimuscular connective tissue invasion, hepatic side	4	20
pT3: serosal perforation and/or liver invasion	2	10
Histological grade of epithelial carcinomas (n=19)		
Well differentiated	6	31.6
Moderately differentiated	9	47.4
Poorly differentiated	4	21.1
Lymphovascular invasion present	5	25
Perineural invasion present	4	20
High-grade BilIN adjacent to invasive carcinoma	11	55
Positive cystic-duct margin	2	10
Liver parenchymal involvement	2	10

pT, pathological primary tumour category; BilIN, biliary intraepithelial neoplasia. Histological type, pT category, lymphovascular invasion, perineural invasion, adjacent high-grade BilIN, margin status and liver involvement use all 20 invasive carcinomas as denominator. Histological differentiation uses 19 epithelial carcinomas as denominator because the neuroendocrine carcinoma was excluded from conventional epithelial grading. Staging followed the AJCC TNM classification, eighth edition.

Table 5: Clinicopathological comparison between incidentally detected preinvasive neoplasms and invasive gallbladder carcinomas.

Characteristic	Preinvasive neoplasms (n=41)	Invasive carcinomas (n=20)	p value
	Frequency (%)/mean ± SD		
Age, years	54.4 ± 10.5	63.0 ± 10.1	0.004
Age >50 years	24 (58.5)	18 (90.0)	0.013
Female gender	31 (75.6)	17 (85.0)	0.514
Gallstones present	37 (90.2)	19 (95.0)	0.662
Largest gallstone ≥3 cm	7 (17.1)	7 (35.0)	0.119
Wall thickness >3 mm on ultrasonography	17 (41.5)	13 (65.0)	0.085
Polypoid lesion on ultrasonography	7 (17.1)	1 (5.0)	0.255
No grossly identifiable abnormality	26 (63.4)	5 (25.0)	0.005
Diffuse or focal wall thickening on gross examination	10 (24.4)	12 (60.0)	0.006
Gross polypoid growth	5 (12.2)	2 (10.0)	1
Mucosal ulceration or infiltrative nodule	0	1 (5.0)	0.328
Lesion located in fundus/body	29 (70.7)	12 (60.0)	0.399
Lesion located in neck/cystic-duct region	12 (29.3)	8 (40.0)	

BilIN, biliary intraepithelial neoplasia; The preinvasive group (n=41) comprised 33 BilINs, five adenomas and three ICPNs.

Patients with invasive carcinoma were significantly older than those with preinvasive lesions (63.0±10.1 versus 54.4±10.5 years; p=0.004), and 90.0% of patients with invasive carcinoma were older than 50 years compared with 58.5% of those with preinvasive neoplasms (p=0.013). Sex, gallstone status, gallstone size, ultrasonographic wall thickening, polypoid lesions and lesion location did not differ significantly between groups. Nevertheless, gross abnormalities were more frequent in invasive carcinoma: focal or diffuse wall thickening was present in 60.0% of invasive cancers compared with 24.4% of preinvasive lesions (p=0.006). Conversely, no grossly identifiable abnormality was observed in 63.4% of preinvasive lesions and 25.0% of invasive carcinomas (p=0.005) [Table 5].

In the exploratory adjusted model, age >50 years was associated with higher odds of incidental neoplasia (adjusted OR=3.76; 95% CI: 2.09–6.77; p<0.001). An ultrasonographically detected polypoid lesion showed the largest adjusted association (adjusted OR=5.92; 95% CI: 2.48–14.13; p<0.001). Gallbladder wall thickness >3 mm (adjusted OR=2.48; 95% CI: 1.45–4.25; p=0.001) and a gallstone measuring ≥3 cm (adjusted OR=2.03; 95% CI: 1.05–3.93; p=0.035) also retained statistical associations. Female sex, gallstone presence or multiplicity, and open surgery were not statistically associated after adjustment. The model demonstrated acceptable calibration by the Hosmer–Lemeshow test (p=0.624), with a Nagelkerke R^2 of 0.18. Given 61 events and eight fitted coefficients (7.6 events per variable), these estimates should be interpreted as exploratory [Table 6].

Table 6: Multivariable logistic regression analysis of factors associated with incidental neoplastic lesions in routine cholecystectomy specimens.

Factor	Neoplastic lesions (n=61)	Non-neoplastic lesions (n=2,047)	Adjusted odds ratio (95% CI)	p value
Age >50 years	42 (68.9)	650 (31.8)	3.76 (2.09–6.77)	<0.001
Female gender	48 (78.7)	1,471 (71.9)	1.31 (0.68–2.51)	0.415
Gallstones present	56 (91.8)	1,847 (90.2)	1.08 (0.40–2.88)	0.879
Multiple gallstones	35 (57.4)	1,196 (58.4)	0.87 (0.50–1.51)	0.617
Largest gallstone ≥3 cm	14 (23.0)	198 (9.7)	2.03 (1.05–3.93)	0.035
Wall thickness >3 mm on ultrasonography	30 (49.2)	475 (23.2)	2.48 (1.45–4.25)	0.001
Polypoid lesion on ultrasonography	8 (13.1)	39 (1.9)	5.92 (2.48–14.13)	<0.001
Open cholecystectomy	8 (13.1)	108 (5.3)	1.46 (0.63–3.39)	0.378

OR, odds ratio; CI, confidence interval. Outcome: incidental neoplastic lesion (yes/no). Eight prespecified binary variables were entered simultaneously. Reference categories were age ≤50 years, male gender, no gallstones, single or no gallstones, largest stone <3 cm or no stone, wall thickness ≤3 mm, no polypoid lesion and laparoscopic cholecystectomy. Model fit: Hosmer–Lemeshow p=0.624; Nagelkerke R^2=0.18. With 61 events and eight fitted coefficients, there were 7.6 events per variable; adjusted estimates are exploratory and potentially susceptible to overfitting.

DISCUSSION

The present study demonstrated that most routine cholecystectomy specimens showed benign inflammatory pathology; however, 61 of 2,108 specimens (2.9%) harboured an unsuspected neoplastic lesion. Chronic calculous cholecystitis was the predominant diagnosis (75.1%), reflecting the high burden of symptomatic cholelithiasis in the study population. The observed neoplastic frequency was comparable to the approximately 3% prevalence of incidental dysplasia and carcinoma reported by Solaini et al,.[10] Almas et al. similarly found chronic cholecystitis in 78.6% of specimens, although adenocarcinoma occurred in only 0.2%, illustrating geographical variability.[11] Differences in age distribution, gallstone prevalence, pathological sampling and background population risk may explain the variation.

Incidental invasive carcinoma was detected in 0.95% of specimens. This frequency was higher than the 0.44% reported by Kalita et al., in 4,115 Indian cholecystectomies.[12] and the 0.23% observed by Basak et al., among 1,747 laparoscopic cholecystectomies.[13] but lower than the 1.75% reported by Mistry et al,.[14] Yadav et al., also documented a meaningful burden of incidental carcinoma in a North Indian population and recommended routine histopathological examination.[15] In contrast, Di Mauro et al., identified incidental cancer in only 0.1% of 5,779 specimens in a lower-incidence Western population.[16] The relatively higher frequency in the present series may reflect the greater background risk of gallbladder cancer in India and the inclusion of patients from areas with a high prevalence of longstanding gallstone disease.

Preinvasive neoplasms constituted 41/2,108 specimens (1.95%) and 41/61 neoplastic lesions (67.2%). Low-grade BilIN was the commonest lesion, followed by high-grade BilIN, pyloric gland adenoma of the gallbladder, adenoma NOS and intracholecystic papillary neoplasm. Koshiol et al.

detected dysplasia or carcinoma in 12% of extensively sampled gallbladders from a high-risk Chilean population, demonstrating that small or geographically discontinuous precursor foci may be underestimated by limited sampling.[17] Chronic mechanical irritation by calculi may promote epithelial injury, oxidative stress, inflammatory signalling and repeated regeneration, facilitating progression through metaplasia, BilIN and carcinoma. Seretis et al. found metaplasia in 25.6% of chronic cholecystitis specimens and reported more frequent dysplasia in gallbladders showing metaplasia.[18] Bangash et al. likewise associated longstanding calculous inflammation with premalignant epithelial alterations.[19]

Patients with neoplasia were significantly older than those with non-neoplastic disease (57.2 versus 43.8 years), and age >50 years was associated with higher adjusted odds of neoplasia. Patients with invasive carcinoma were older than those with preinvasive lesions (63.0 versus 54.4 years), consistent with age-dependent accumulation of molecular alterations. Female predominance was observed, but female sex did not retain a statistical association after adjustment. This may partly reflect the higher prevalence of gallstones and cholecystectomy among women rather than an independent neoplastic effect. Solaini et al. similarly identified increasing age and abnormal gallbladder morphology as markers of incidental dysplasia or carcinoma.[10] These adjusted findings remain exploratory because the model contained eight coefficients for 61 events.

Large gallstones, wall thickening and polypoid lesions retained statistical associations in the exploratory model. Stones ≥3 cm were associated with approximately twofold higher adjusted odds of neoplasia, while wall thickness >3 mm was associated with approximately 2.5-fold higher odds. Large calculi may produce sustained mucosal trauma, whereas wall thickening may reflect chronic inflammation, fibrosis or tumour infiltration. Ultrasonographically detected polypoid lesions showed the largest adjusted association (OR=5.92), consistent with their potential to represent epithelial neoplasms. Nevertheless, gallstone presence alone was not statistically associated because stones were common in both groups. The 91.8% prevalence of cholelithiasis among neoplastic cases therefore indicates frequent coexistence but limited discriminatory value.

Conventional biliary-type adenocarcinoma constituted 17/20 (85.0%) invasive tumours, with 9/20 (45.0%) classified as pT1 and 9/20 (45.0%) as pT2. Mistry et al. similarly found pancreaticobiliary-type adenocarcinoma predominance, with most incidental tumours staged as pT1b or pT2.[14] These stages are clinically important because pT1a disease may be adequately treated by simple cholecystectomy, whereas pT1b and pT2 tumours generally require assessment for completion radical resection.[20,21] Although gross abnormalities were more frequent in invasive carcinoma, 5/20 cancers (25.0%) and 26/41 preinvasive lesions (63.4%) had no visible abnormality. Koppatz et al. and Mittal et al. suggested that careful macroscopic selection could reduce unnecessary microscopy.[22,23] whereas the occult lesions in the present cohort illustrate what a selective approach might miss. Because this study did not directly compare routine with selective examination, evaluate costs or measure patient outcomes, it cannot establish the superiority of either policy. The findings instead suggest potential value in routine examination within comparable settings and warrant confirmation in larger multicentre comparative studies.

Limitations: Its retrospective, single-centre design limits generalisability and depended on the completeness of archived records. Histological sampling may have underestimated small or multifocal BilIN. The logistic model included eight coefficients for 61 events (7.6 events per variable), creating potential overfitting and limiting precision. Moreover, the study neither directly compared routine with selective histopathology nor assessed costs, treatment changes or patient outcomes; therefore, policy and clinical-benefit inferences should remain cautious.

CONCLUSION

Incidental neoplastic lesions were identified in 61/2,108 (2.9%) routine cholecystectomy specimens, while invasive carcinoma was present in 20/2,108 (0.95%). Low-grade BilIN was the most frequent precursor lesion, and conventional biliary-type adenocarcinoma predominated among invasive malignancies. Older age, large gallstones, wall thickening and ultrasonographically detected polypoid lesions retained associations with neoplasia in an exploratory adjusted model. A substantial proportion of preinvasive lesions and one-quarter of invasive cancers lacked a grossly identifiable abnormality. These findings suggest potential value in careful routine histopathological assessment within the study setting, but do not establish superiority over selective examination.

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