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SHORT COMMUNICATIONS

Incidence of Neoplasia in Cholecystectomy Specimens: A Retrospective Study at Ibra Hospital, Oman

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Abstract

Introduction: Gallbladder carcinoma is the fifth most common gastrointestinal malignancy and the leading biliary tract cancer, accounting for 80–95% of cases. It is highly aggressive, with a five-year survival rate below 5%, and is often diagnosed late, resulting in an overall survival of less than six months. Differentiating chronic cholecystitis from malignancy remains clinically challenging. Routine histopathology after cholecystectomy can improve early detection and prognosis. This study primarily aimed to determine the incidence of incidental gallbladder carcinoma in post-cholecystectomy specimens at Ibra Hospital, Oman, over five years. Secondary objectives were to analyze demographic and clinical characteristics and to evaluate the histological spectrum of gallbladder pathologies. **Materials and Methods:** This retrospective, descriptive, and cross-sectional study included 410 consecutive patients with cholelithiasis who underwent cholecystectomy at Ibra Hospital, North Sharqiyah, Oman, between March 1, 2019, and April 1, 2024. Patients with suspected gallbladder carcinoma were excluded. Data collected included demographics, diagnostic parameters, preoperative imaging, histological findings, and incidence of malignancy. Histopathology reports were used as the definitive diagnostic reference. **Results:** Out of 410 cholecystectomy specimens, two cases (0.5%) were diagnosed as gallbladder carcinoma (95% CI: 0.06–1.8%). Chronic cholecystitis was the most frequent histological finding (75.9%), followed by acute cholecystitis (19.5%). Female patients accounted for 80.7% of the studied group, with a mean age of 46.2 years in our study. Laparoscopic procedures accounted for 99% of surgeries. Postoperative complications included surgical site infections (2.9%) and port hernias (1.7%). **Conclusion:** Systematic histologic examination should be considered as a standard procedure. However, the limitations of the present study are limited to the fact that it is a retrospective study and therefore cannot provide definitive evidence of whether or not all possible pathologies could be detected. Improved prognosis is associated with early detection of incidental gallbladder carcinomas.

Keywords: Gallbladder carcinoma- Incidental- Cholecystectomy- Histopathological examination

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Introduction

Gallstones are the most common gallbladder disorder. The incidence varies by region and ethnicity. Chronic cholecystitis is closely linked to gallbladder carcinoma [1]. Carcinoma risk among untreated cholelithiasis patients has been projected at 0.2-0.5%. The development of gallbladder carcinoma is thought to be due to a combination of various risk factors, including genetics, diet, endocrine and exogenous factors, chronic inflammation, and infection. Chronic inflammation is an important promoter in the process of carcinogenesis by inducing DNA damage from repeated cycles of tissue repair. The persistent cellular stress caused by chronic inflammation leads to the activation of cytokines and growth factors that can provide the necessary pathways for cancerous cell progression. There are strong correlations between early detection (incidental) of gallbladder carcinoma and improved clinical outcomes compared to late stage presentation, which typically has poor survival rates [2].

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Laparoscopic cholecystectomy is the preferred method for gallbladder removal due to its efficiency and safety. Despite benign preoperative diagnoses, incidental gallbladder carcinoma can still be found. This study primarily aimed to determine the incidence of incidental gallbladder carcinoma in post-cholecystectomy specimens at Ibra Hospital, Oman, over five years. The secondary objectives included analyzing demographic and clinical characteristics, as well as evaluating the histological spectrum of gallbladder condition pathologies.

Materials and Methods

This retrospective, descriptive, and cross-sectional study included 410 consecutive patients with cholelithiasis who underwent cholecystectomy at Ibra Hospital, North Sharqiyah, Oman, from 1 March 2019 to 1 April 2024. Eligible participants were those who had undergone cholecystectomy for presumed benign gallbladder conditions, including cholelithiasis or cholecystitis. Complete medical records were required, encompassing demographic information, preoperative imaging, operative details, and histopathological reports of the cholecystectomy specimens. Only specimens routinely submitted for histopathological examination in accordance with institutional protocols were included. Exclusion criteria encompassed patients with preoperative suspicion or confirmation of gallbladder carcinoma based on ultrasonography, computed tomography, or other diagnostic modalities. Patients who underwent cholecystectomy as part of radical or oncologic procedures for diagnosed gallbladder carcinoma were excluded. Additionally, patients with incomplete records, particularly those lacking postoperative histopathological confirmation, were excluded. Patients referred to Ibra Hospital after cholecystectomy performed elsewhere, where primary surgery or histopathological evaluation was not conducted at our institution, were also excluded. Lastly, pediatric patients aged < 18 years were excluded to ensure a homogeneous study population.

Records were retrieved from the Al-Shifa hospital system and analyzed using descriptive statistics (frequencies, percentages, 95% confidence intervals) with the Statistical Package for the Social Sciences version 20. Ethical approval was obtained from the Ministry of Health Center of Studies & Research (registration no.28350/2024) and the Ibra Hospital administration. All data were anonymized, and confidentiality was maintained. All our statistical analyses are based on the true, non-suspected cases of malignancy. We do not refer cases for preoperative workup to other facilities. All necessary evaluations are conducted at our hospital.

In order to account for the relatively small sample size and to provide statistically precise estimates of the incidence of rare gallstone-related histological findings, exact Poisson methods were used to calculate 95% Confidence Intervals (CI). Due to the very low frequency of adenocarcinoma, the 95% CI (0.06–1.8%) should be viewed as appropriate for the limited number of adenocarcinoma cases, but the use of CIs for the other categories of histologically identified lesions (i.e., chronic cholecystitis, acute cholecystitis, and BilIN) will help put the precision of those estimates into proper context. Ultrasound was performed on all specimens; CT scan (s) were performed when there were discordant ultrasound results, clinical or laboratory abnormalities that necessitated further investigation, or if there was an alternate diagnosis being considered. Typically, 5-7 tissue blocks were sectioned from each specimen, with both targeted and non-targeted paraffin sections systematically sampled to assure that focal lesions would not be overlooked. All reported specimens had documented support for reporting through a strict follow-up process in which no specimens were left unreported. The histopathology findings were provided to study participants via telemedicine. Additionally, the two participants who were diagnosed with adenocarcinoma were contacted and referred to tertiary hepatobiliary centers for staging and oncologic evaluation.

A gross examination of each specimen was conducted by the pathology team during the macroscopic assessment to identify any wall thickening, mucosal irregularities, polyps, or indurated regions. In addition, at least three standard tissue blocks were systematically obtained from each gallbladder and included representative tissue from the fundus, body, and neck (cystic duct margin), respectively. When there was an abnormal appearance of the mucosal lining of the bile ducts in the form of focal wall thickening or polyps that raised suspicion for malignancy, we added additional biopsies to the initial ones. This increased the total number of biopsy specimens evaluated in detail for the lesion(s), typically five to seven specimens per case. The microscopic examination consisted of cutting sections of paraffin-embedded tissue into 3-5 micron thick sections, staining with Hematoxylin & Eosin (H&E), and examining at least two levels of each specimen for histologic abnormalities by a pathologist. Based on these examinations, the pathologist would classify the lesions as either benign or malignant, and in addition, would look specifically for evidence of pre-invasive neoplastic changes, i.e., Biliary Intraepithelial Neoplasia (BilIN). Each histopathology report was reviewed and signed by three pathologists. The potential variation between the individual pathologists is unknown.

Results

Among 410 patients (331 female (80.7%),79 males (19.3%)), the mean age was 46.2 years. Most patients were aged 31-50 years, with a female-to-male ratio of 2.4:1, as shown in Table 1. In our series of cholecystectomy specimens, the majority of cases were diagnosed as chronic cholecystitis (311/410; 75.9%, 95% CI: 71.4-80.0%), followed by acute cholecystitis (80/410; 19.5%, 95% CI: 15.8-23.7%). Biliary intraepithelial neoplasia (BilIN) was identified in 10 cases (2.4%, 95% CI: 1.2-4.4%), while less common findings included adenomyomatosis (1.0%, 95% CI: 0.3-2.5%) and chronic xanthogranulomatous cholecystitis (0.7%, 95% CI: 0.1-2.1%). Incidental gallbladder carcinoma was detected in two cases (0.5%,

Table 1. Age, Gender, and Associated Factors Distribution of Cholecystectomy Patients (N=410)

Variables		Frequency (%)
Age	18-30	68 (16.6)
	31-50	196 (47.8)
	51-70	109 (26.6)
	71-90	37 (9.0)
Gender	Female	331 (80.7)
	Male	79 (19.3)
Associated factors	Bronchial Asthma	12 (2.9)
	Diabetes Mellitus	48 (11.7)
	Dyslipidemia	6 (1.5)
	Epilepsy	2 (0.5)
	Gestational diabetes	1(0.2)
	Glucose-6-phosphate dehydrogenase deficiency	2 (0.5)
	Hepatitis C virus	3 (0.7)
	Hypertension	66 (16.1)
	Hepatitis BVirus	2 (0.5)
	Hypothyroidism	7 (1.7)
	Anemia	5 (1.2)
	Ischemic Heart Disease	239 (58.3)
	Not Present	1 (0.2)
	Schezofrenia	15 (3.7)
	Sickle Cell Disease	1 (0.2)

The table represents the distribution of age, gender, and associated factors among patients whose cholecystectomy specimens were analyzed.

95% CI: 0.06-1.8%) as shown in Table 2. These findings emphasize that inflammatory conditions are predominant in cholecystectomy specimens, whereas premalignant and malignant lesions are relatively uncommon.

Two cases of adenocarcinoma presented with right upper quadrant abdominal pain and dyspeptic symptoms consistent with uncomplicated gallstone disease, without systemic or alarm features suggestive of malignancy. Preoperative clinical assessment favored benign pathology in both cases. Ultrasonography demonstrated cholelithiasis with gallbladder wall thickening compatible with chronic cholecystitis, without mass lesions, focal mural abnormalities, liver invasion, or regional lymphadenopathy. Computed tomography was not performed due to the absence of clinical or radiologic suspicion. In retrospect, the imaging findings were non-specific and indistinguishable from those of chronic inflammatory disease. Both patients underwent laparoscopic cholecystectomy. Intraoperatively, the gallbladders appeared inflamed and thick-walled, with no gross tumor, mucosal ulceration, hepatic infiltration, or suspicious lymphadenopathy.

In both cases, microscopic adenocarcinoma confined to the gallbladder wall was detected, and both were non-otherwise specified (NOS). Accordingly, both cases fulfilled the criteria for true incidental gallbladder carcinoma. Histopathological examination revealed well-differentiated adenocarcinoma in both cases. According to the AJCC 8th edition staging system, tumor invasion was limited to the mucosa in one case (pTis, Stage 0) and to the lamina propria in the other (pT1a, Stage I). Surgical margins were negative (R0) in both cases, with no lymph node invasion. There was no evidence of lymphovascular or perineural invasion. Both patients were referred to tertiary hepatobiliopancreatic specialists and underwent postoperative restaging with contrast-enhanced CT of the chest, abdomen, and pelvis, which showed no residual or metastatic disease. Following multidisciplinary team review, neither oncologic re-operation nor adjuvant therapy was required, and both patients were managed with structured surveillance. The incidence was stratified by gender, with no cases among the 79 male patients and 2 among the 331 female patients, yielding a prevalence of 0.6%. Both patients were females: one was 56 years old (in the 51-60 age group) with ischemic heart disease, hepatitis B, diabetes, and dyslipidemia; the other was 74 years old (in the 71-80 age group) with ischemic heart disease and diabetes dyslipidemia. Notably, both cases had relevant metabolic comorbidities, highlighting potential contributory risk factors in the setting of chronic inflammatory gallbladder disease.

Both cases demonstrated long-standing gallstone disease with chronic symptoms. One patient, aged 56 years, had multiple gallbladder calculi with chronic cholecystitis and extensive fibrosis, along with focal low-grade biliary intraepithelial neoplasia (BilIN). The

Table 2. Ultrasounds and Histological Findings of Operated Patients

Variables		Frequency (%)
Ultrasound Findings	Multiple stones	297 (72.4)
	Single Stone	103 (25.1)
	Polyps	10 (2.4)
Histological Findings	Chronic cholecystitis	311 (75.9)
	Acute cholecystitis	80 (19.5)
	Chronic cholecystitis with focal low-grade Biliary intraepithelial neoplasia	10 (2.4)
	Chronic Xanthogranulomatous cholecystitis	3 (0.7)
	Adenomyomatosis	4 (1.0)
	Segmental	3
	Diffuse	1
	Adenocarcinoma	2 (0.5)
Post-Operative Complications	No	390 (95.1)
	Surgical Site Infection	12 (2.9)
	Porta site Hernia	7 (1.7)
	Hemorrhage	1 (0.2)

The table presents the ultrasound findings and corresponding histopathological results of the operated patients.

second patient, aged 74 years, had a solitary gallstone with chronic cholecystitis and focal wall thickening, accompanied by high-grade dysplasia (carcinoma in situ). Nine out of ten were identified as biliary intraepithelial neoplasia (BilIN) lesions, which were classified as low-grade dysplasia (BilIN-1) according to the WHO Classification of Digestive System Tumours. No intermediate-grade (BilIN-2) lesions were identified, and only one high-grade (BilIN-3) lesion was detected. Regarding association with malignancy, the first case demonstrated focal low-grade biliary intraepithelial neoplasia (BilIN). The second patient had focal wall thickening, accompanied by high-grade dysplasia (carcinoma in situ). For this group of patients, a simple cholecystectomy was considered the definitive treatment. All patients were referred to a specialized hepatobiliary team, and none of them progressed to invasive disease during the follow-up period.

Among the four identified cases of adenomyomatosis (1%), three were classified as the segmental subtype localized to the fundus, while one case presented as the diffuse subtype involving the entire gallbladder wall, as shown in Table 2. Notably, one diffuse case exhibited focal low-grade dysplasia within the Rokitansky-Aschoff sinuses, though no invasive malignancy was found in these specific specimens.

Most procedures (99%) were laparoscopic. Conversion to open surgery occurred in 4 cases due to intraoperative complications. Postoperative complications included surgical site infections (12 patients, 2.9%), umbilical port hernias (7 patients, 1.7%), and hemorrhage (1 patient, 0.2%).

Discussion

Gallbladder carcinoma is the most common malignancy of the biliary tract [3]. The increasing use of laparoscopic cholecystectomies as the gold standard procedure has caused more and more detection of incidental gallbladder carcinomas. Incidental gallbladder carcinoma has been defined as carcinoma of the gallbladder detected for the first time after cholecystectomy and accidentally found on histological examination of the gallbladder [4]. Carcinoma risk among untreated cholelithiasis patients has been projected at 0.2-0.5%. In our study, it was 0.5%; the percentage in the Omani population is within the accepted range. In fact, most regions of the world fall on the lower end, except for areas with exceptionally higher rates due to various genetic, dietary, and other factors (e.g., Chile). Additionally, this difference may be attributable to our relatively small sample size [14]. There are different reports about the frequency of incidental gallbladder carcinoma in patients who have undergone cholecystectomy for other reasons, mostly benign lesions, i.e., cholecystitis and cholelithiasis. Overall, the percentages range from 0.2% to 2.5% across regions [5,6]. These results are in accordance with our results. There is no uniform distribution across ethnic or geographic groups [6].

Radiological and clinical signs of gallbladder carcinoma can mimic benign cholelithiasis and cholecystitis, delaying the diagnosis of adenocarcinoma. The clinical features are similar in the early stages of cancer and benign diseases. Ultrasonography is now widely used, making gallstone diagnosis quick, simple, and affordable. However, chronic inflammation of the gallbladder mucosa can cause gallbladder metaplasia. Gallbladder carcinoma can present as gallbladder wall

thickening on ultrasound or computed tomography [7]. Although the prognosis for gallbladder cancer continues to be poor, with less than 5% of patients surviving 5 years post-diagnosis, evaluation of all cholecystectomy specimens for histopathology has become a standard procedure to identify "occult" malignancy to avoid missing such cancers [8].

Of the 410 total cholecystectomy specimens examined, 79 were from male patients, and 331 were from female patients. Examination of these specimens revealed a significant difference in the occurrence of gallbladder disease between genders, with the majority of gallbladder lesions (80.7%) occurring in females and significantly fewer (19.3%) in males. Similar results have been reported by Bajaj and others, who found evidence of a greater incidence of gallbladder disease in females; elevated estrogen levels may also contribute to increased biliary cholesterol secretion, and thus an increased risk of developing cholelithiasis secondary to cholesterol supersaturation, which occurs more frequently in women [9]. Patient ages ranged from 18 to 90 years, and gallbladder lesions were most commonly observed among patients in the fourth and fifth decades of life (ages 31-50), consistent with results previously obtained by Degloorkar and his colleagues [10].

Chronic cholecystitis emerged as the predominant diagnosis in histologic evaluations, affecting 75.9% of cases, a prevalence aligning with prior research. This condition, encompassing subtypes such as gangrenous, follicular, and suppurative cholecystitis, demonstrates gallbladder wall thickening and calcifications, primarily due to cholelithiasis. Acute presentations were observed in 19.5% of patients. A notable divergence exists when comparing these outcomes to the 2.9% and 1.16% acute incidence rates reported by Shirah and his colleagues [11]. Chronic Xanthogranulomatous cholecystitis occurs in only 0.07% of cases. Diagnostic patterns align with the existing literature, with this rare form mostly affecting patients aged 71–80 years. While surgical teams face many diagnostic challenges when assessing chronic xanthogranulomatous cholecystitis (CXGC), these can be similar to those encountered when assessing gallbladder carcinoma. The challenges include the potential for CXGC to present similarly to gallbladder carcinoma due to pericholecystic inflammation, tissue involvement, or lymphadenopathy. As such, it is essential to differentiate between the two based on the clinical similarities; specifically, there exists a high potential for unnecessary radical surgery for what would otherwise be considered a benign condition. Therefore, the most critical aspect of a surgeon's role is an accurate preoperative assessment [12]. Two adenocarcinomas were found (0.5%); one case was in a female patient who was 56 (between 51-60 years of age), and the second case was also in a female patient who was 74 (between 71-80 years of age). Although the study demonstrated that adenocarcinoma was the predominant type of gallbladder carcinoma (non-other-wise specified), other studies have reported extremely rare signet-cell ring variants. Thus, both epidemiologic and histologic factors require additional research [13].

Gallbladder carcinoma is the most prevalent biliary system cancer, and has been shown to exhibit increased incidence in Chile, Japan, and northern India. Gallstones are commonly associated with gallbladder carcinomas, which demonstrate epidemiologic correlations with gallstone prevalence. Chronic lithogenic irritation can lead to gallstone formation that can cause local irritation leading to neoplastic transformations [14]. Early-stage gallbladder carcinoma poses significant diagnostic challenges, primarily because the clinical manifestations are nonspecific and there is insufficient preoperative suspicion. Detection at an early stage is critical for obtaining microscopically negative margins during surgery, since surgery is the only current therapy for gallbladder carcinoma. Simple cholecystectomy is recommended for tumor stages classified as PT2a, while radical resection is recommended for more advanced tumor stages. A comprehensive macroscopic evaluation of all laparoscopic specimens is required during intraoperative protocols. This requires a systematic, non-targeted paraffin-section sampling of all specimens to prevent missing any focal lesions. Once histopathologically confirmed, open surgical procedures become required, including hepatic wedge resections, regional lymph node dissections, and port-site excisions [15]. Incidental gallbladder carcinoma detected in cholecystectomies is rare but clinically relevant and supports the need for universal histopathological examination of all cholecystectomy specimens, regardless of the indication for surgery. This allows for early diagnosis and treatment for this aggressive form of cancer.

Precision of Estimates

The relatively narrow confidence intervals for chronic and acute cholecystitis reflect the high frequency of these benign conditions in our patient cohort, indicating high precision for these estimates in our regional population. Low-Frequency Lesions: As noted by the reviewer, the wider intervals for Adenocarcinoma and BilIN are expected due to the lower frequency of these neoplastic findings. However, even with this variance, the inclusion of the CI acknowledges the statistical uncertainty inherent in small-count observations while confirming that the incidence falls within the reported global ranges of 0.2% to 2.5%. Clinical Relevance: By providing these intervals, we emphasize that while certain findings like BilIN (2.4%) appear infrequent, the true prevalence in the population could be as high as 4.4%, further justifying the necessity of routine histopathological analysis.

In accordance with current NCCN and international guidelines, simple cholecystectomy was considered definitive and curative, and therefore, extended resection, lymphadenectomy, or port-site excision was not indicated. These findings support routine histopathological examination, enabling early-stage detection and appropriate oncologic management within a multidisciplinary framework. Neither patient received adjuvant therapy. At follow-up at 18 and 24 months, respectively, both patients remained disease-free.

Study Limitations

The retrospective design and being a single-center study both limit generalizability, as well as the small number of malignant cases. Exclusion of preoperatively suspected gallbladder carcinoma may underestimate the true disease burden, and formal assessment of inter-observer variability in histopathology was not feasible.

In conclusion, within the limitations of this study, systematic rather than targeted histological assessment of cholecystectomy specimens is necessary to ensure the detection of occult malignancies. The retrospective nature of this study may limit the identification of all subclinical complications, a factor that should be taken into account when interpreting the results.

Author Contribution Statement

Deep Parkash is the corresponding author, conceptualization, designed the research, project administration, reviewed the manuscript, summarized the clinical data, analyzed, and interpretedthe research. Rani Bai, Simran Parkash, Ahmed Sherif MoustafaRehab, and Moosa A. Alwardicollected the data & carried out the statistical analysis. Hosam M. Elghadban and Ayman Albatanonygave critique and helped analyze and summarize the clinical data. All authors read and approved the final manuscript.

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General

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Data Availability

The datasets generated and analyzed during this study are available from the corresponding author upon reasonable request and with approval from the Ministry of Health, Oman.

Approval & Registration

The study was approved by the Ministry of Health, Oman, Center for Studies & Research (https://www.mohcsr.gov.om) and was registered under the number MoH/CSR/24/28350 on July 16, 2024. The study was not a part of an approved student thesis.

Ethical Declaration

The ethics committee at the research and study center in North Sharqiya governorate, Oman, approved the study.

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Conflict of Interest

The authors declare no conflict of interest.

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