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Gallbladder Carcinoma: The Value of Histopathological Assessment in Routine Cholecystectomy Samples in a Hospital based study

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ABSTRACT

Introduction: Incidental gall bladder carcinoma is a rare cancer diagnosed during or after cholecystectomy done for benign gall bladder disease. Whether a routine or a selective approach be followed for histopathological evaluation of cholecystectomy specimens is still a matter of debate. **Materials and Methods**: Eight patients diagnosed with Incidental gall bladder carcinoma over a period of 18 months were retrospectively reviewed. Clinical details including clinical presentation and macroscopic features were reviewed retrospectively. Diagnosis of incidental gall bladder carcinoma was made on histopathological examination. **Results:** Of the 946 cholecystectomy specimens examined during this period, diagnosis of incidental gall bladder carcinoma was made in eight cases(0.8%) on histopathological evaluation. **Conclusion:** All gall bladder specimens should be subjected to histopathological evaluation to avoid missing gall bladder carcinoma.

Introduction

The gallbladder, resembling the shape of a pear-like pouch, is intricately interconnected with the biliary system located externally to the right lobe of the liver. In the context of adults, it typically exhibits dimensions measuring approximately 10 centimeters in length and 3 to 4 centimeters in diameter, accompanied by a wall thickness measuring around 1 to 2 millimeters[1]. Notably, the gallbladder's wall is a complex structure comprised of three distinct layers, namely the mucosa, muscular, and perimuscular layers. It is worth highlighting that, in stark contrast to various other components of the digestive system, the gallbladder is distinctive in its lack of a muscularis mucosa and submucosa. Within the lamina propria of the gallbladder, one may observe the presence of a limited number of lymphocytes, plasma cells, and mast cells, whereas neutrophils and eosinophils are typically conspicuous by their absence. This unique anatomical composition underscores the specialized role and function of the gallbladder within the broader digestive processes of the human body[1,2].

Cholecystectomy , the surgical removal of the gallbladder, holds the distinction of being the most frequently performed abdominal procedure in contemporary medical practice. A significant proportion of these surgeries are necessitated by the presence of gallstones and the persistent burden of chronic inflammation[3]. **Figure 1** summarized the factors associated with gallbladder disease. However, within this realm of surgical intervention, there exists a fascinating nuance—the occasional discovery of gallbladder carcinoma as an incidental finding following meticulous histopathological examination.. This intricate facet of diagnosis and surgical management underscores the inherent complexity in distinguishing gallbladder carcinoma from its benign

counterparts, such as cholecystitis and cholelithiasis. The clinical presentations of these conditions bear a remarkable resemblance to each other, often posing a diagnostic challenge that requires careful consideration and expertise[4].

It is pertinent to acknowledge that the landscape of cholecystectomy and gallbladder carcinoma is continually evolving. Recent advancements in medical science and diagnostic techniques have enriched our understanding of these conditions. Therefore, an up-to-date comprehension of the latest developments and trends in the field is essential for medical professionals and researchers alike[5].

Gallbladder carcinoma (GBC) holds a notable position as the most prevalent malignancy within the biliary tract, ranking fifth among gastrointestinal carcinomas. It is of paramount importance to delve into the updated statistics to comprehend its prevalence fully. According to data from the Indian cancer registry, the incidence of GBC is estimated to range between 0.8% and 1%, indicating its significant impact on public health[6].

Delving deeper into regional disparities, we discover intriguing variations in GBC incidence rates. Leading the chart are New Delhi and Bhopal, where the burden of this malignancy is more pronounced. In contrast, Chennai registers the lowest incidence, painting a fascinating geographical pattern in the prevalence of GBC[7].

To gain a comprehensive understanding of the risk factors associated with GBC, one must consider a multifaceted array of factors. These encompass cholelithiasis (the presence of gallstones), a calcified gallbladder wall, adenomatous polyps, obesity, exposure to estrogen, choledochal cysts, and exposure to chemical carcinogens. Notably, gallstones emerge as a well-established risk factor, implicated in 75% to 90% of GBC cases. This underscores the crucial role of gallstone management and prevention in mitigating the risk of GBC[8].

Diagnosis of GBC is made through histopathological examination subsequent to cholecystectomy, initially performed to address benign gallbladder disease. GBC is often characterized by its stealthy nature, with most patients lacking any preoperative radiological or intraoperative suspicion for malignancy. This distinctive profile adds a layer of complexity to the clinical landscape, necessitating a keen eye and a high index of suspicion during the diagnostic and therapeutic journey[9].

The question of whether a routine histopathological examination should be conducted on all cholecystectomy specimens performed for benign gallbladder diseases remains a topic of ongoing debate and discussion within the medical community. To shed light on this matter, it is essential to consider the latest guidance provided by authoritative bodies. For instance, the Royal College of Pathologists advocates for the histopathological examination of all cholecystectomy specimens, emphasizing the potential for Carcinoma (GBC) to elude detection if such examinations are not routinely carried out[10].

However, it is imperative to note that there exist contrasting vi-ewpoints among experts in the field. Some authors argue that histopathological analysis may not be warranted for all surgically resected benign gallbladders. Their perspective hinges on the belief that the incidence of GBC is relatively low, and a substantial number of cases are diagnosed at an early stage, where simple cholecystectomy serves as the optimal treatment modality. This viewpoint underscores the importance of carefully assessing the risk factors and clinical presentations of individual cases[11].

The present study contributes significantly to this ongoing discourse by delving into various aspects of GBC. Specifically, it highlights the clinicopathological features, encompassing not only clinical manifestations but also preoperative imaging and postoperative gross examination findings in patients with GBC. Through a comprehensive analysis, we aim to discern the nuanced factors that may guide the decision-making process regarding the necessity of histopathological evaluation in surgically resected gallbladders. This multifaceted approach seeks to provide a more holistic understanding of the diagnostic and therapeutic considerations surrounding this complex medical scenario[12].

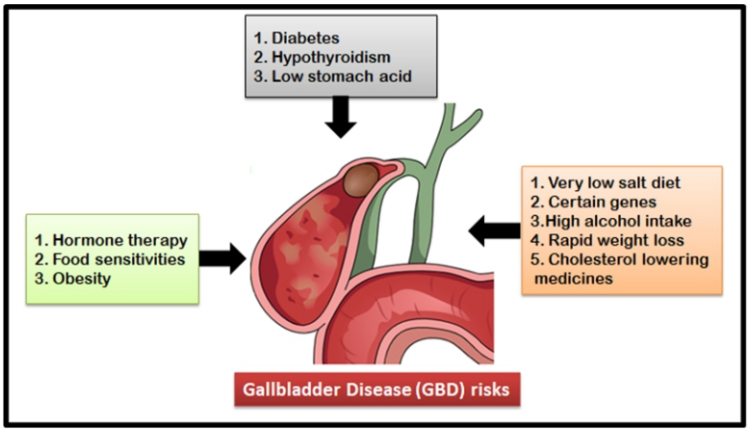

Figure 1: Various factors responsible for gallbladder disease

Materials and Methods

An extensive retrospective research study was conducted in the Department of Pathology at Ganesh Shankar Vidyarthi Memorial Medical College, Kanpur, Uttar Pradesh, India. This meticulous investigation took place over a specific period, starting in March 2022 and concluding in July 2023. Our primary focus was on carefully examining the records stored in the Department of Histopathology, which consisted of an impressive collection of 10,000 cases. From this extensive dataset, we specifically selected cholecystectomy specimens that exhibited clinical diagnoses indicating benign gall bladder diseases. It is important to note that our research encompassed a wide range of cholecystectomy specimens, including both laparoscopic and open procedures. In order to gain comprehensive insights, we gathered a comprehensive set of patient details, such as names, ages, genders, chief complaints, specific surgical procedures performed, and the outcomes of relevant diagnostic measures. These intricate specifics were meticulously recorded on pathology requisition forms, providing our study with a wealth of patient-related information.

Inclusion Criteria: We defined specific criteria for the inclusion of ca-

cases in our study. We included all cases that had undergone cholecystectomy and had been clinically diagnosed with a range of gallbladder conditions, encompassing cholecystitis, empyema, gallbladder polyps, as well as premalignant and malignant gall bladder diseases.

Exclusion Criteria: To ensure the integrity and relevance of our research, we also established a set of exclusion criteria. These encompassed instances of secondary gall bladder carcinoma stemming from metastatic sources, as well as cases involving gall bladder malignancies in individuals who had previously undergone chemotherapy or radiotherapy treatment. This meticulous delineation of inclusion and exclusion criteria served as a crucial framework for the selection of cases in our study, enhancing its precision and validity.

Histopathological Examinations

A thorough histopathological analysis was conducted on the specimens to reveal underlying conditions of the gall bladder. The approach involved precise sectioning of segments from different anatomical regions, focusing on mucosal areas with anomalies. Hematoxylin and Eosin staining was then performed to unveil cellular structures and anomalies **(figure 2).** The Pathology Department ensured precise diagnoses, while categorizing premalignant and malignant cases under the term 'PM-M conditions', contributing to a comprehensive understanding of gall bladder pathology[13].

Statistical Analysis

For the statistical component of this investigation, we utilized the Microsoft Excel, a widely recognized and versatile software tool for conducting calculations and data analysis[14].

RESULTS

The present study involved an examination of 946 cases, comprising 548 female patients and 398 male patients. The analysis revealed that 42.07% of the cases were male, while 57.93% were female, as depicted in **Table 1.** It is noteworthy that Table 1 illustrates that there is a higher percentage of male patients compared to female patients.

Furthermore, **Table 2** provides a breakdown of the patient population according to age groups. It is evident that the largest proportion of patients (48.42%) fell within the 21-40 age range, followed closely by the 41-60 age group, which accounted for 36.91% of the total cases

The investigation unveiled that chronic cholecystitis emerged as the predominant histopathological finding, encompassing a substantial 72.516% of the entire patient cohort. Our study cohort also exhibited a noteworthy prevalence of cholesterolosis and acute-on-chronic cholecystitis. Remarkably, a mere four cases of gallbladder adenocarcinoma were detected. The investigation unveiled that chronic cholecystitis emerged as the predominant histopathological finding, encompassing a substantial 72.516% of the entire patient cohort. Our study cohort also exhibited a noteworthy prevalence of cholesterolosis and acute-on-chronic cholecystitis. Remarkably, a mere four cases of gallbladder adenocarcinoma were detected. **Table 3** provides a comprehensive breakdown of the frequencies of these diverse histopathological features, along with their distribution stratified by gender.

It is important to highlight that the results of our study align with prior research, emphasizing the prevalent occurrence of chronic cholecystitis among individuals with gallbladder ailments. Furthermore, the elevated frequency of cholesterolosis observed within our study cohort mirrors the findings from earlier investigations that have underscored a robust link between gallbladder disorders and cholesterol metabolism.. Additionally, the limited occurrence of gallbladder adenocarcinoma is in harmony with the relatively rare prevalence of this condition within the general population[15].

The outcomes of this research carry significant implications for the diagnosis and treatment of gallbladder disease. The substantial prevalence of chronic cholecystitis underscores the critical importance of precise and prompt diagnosis, as well as the development of effective treatment approaches. Additionally, the correlation between cholesterolosis and gallbladder disease underscores the significance of dietary interventions as a preventive and management strategy for this condition. Moreover, the limited occurrence of gallbladder adenocarcinoma suggests that routine screening may not be warranted in the absence of other risk factors[16].

The findings of this study offer valuable insights into the prevalence and distribution of histopathological characteristics among individuals with gallbladder disease. The notable occurrence of chronic cholecystitis and cholesterolosis underscores the imperative for well-considered management approaches, encompassing precise diagnostic methods and dietary interventions to effectively address these conditions. Additionally, the relatively infrequent cases of gallbladder adenocarcinoma imply that regular screening may not be warranted unless other risk factors are present. Further research is essential to delve into the underlying mechanisms of gallbladder disease, fostering the development of more efficacious prevention and treatment strategies[17].

Table 1: Distribution of study participants based on their gender

Gender	Number of Patients	Percentage
Male	389	42.07 %
Female	548	57.93 %

Table 2: Distribution of study participants on the basis of

Age	Percentage of patients
5-20 Years	6.66 %
21- 40 Years	48.42 %
41-60 Years	36.91 %
61-70 Years	5.60 %
> 70 Years	1.41 %

Table 3: The histopathological findings observed in the study population in relation to gender

Histo-pathological features	Males	Females	Total
Chronic cholecystitis	301	385	686 (72.516%)
Acute cholecystitis	7	11	18 (1.902%)
Acute on chronic cholecystitis	12	26	38 (4.017%)
Chronic cholecystitis with pyloric metaplasia	22	39	61 (6.448%)
Xanthogranulomatous cholecystitis	9	21	30 (3.171%)
Cholecytitis with cholesterolosis	36	58	94 (9.937%)
Gall bladder polyp	3	3	6 (0.634%)
Empyema	3	2	5 (0.529%)
Gall badder adenocarcinoma	5	3	8 (0.846%)
Total	**398**	**548**	**946**

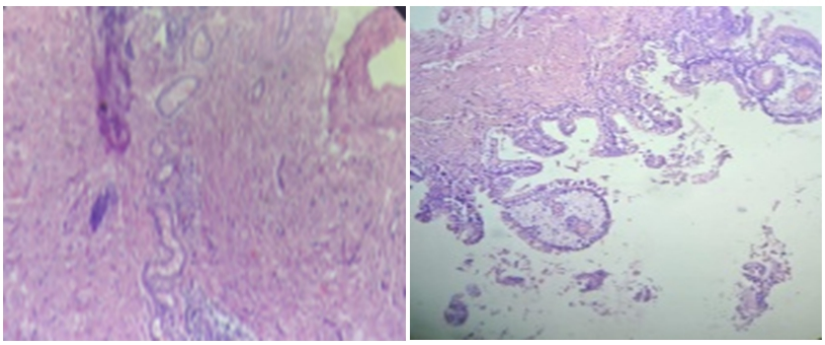

Figure 2: Gall bladder adenocarcinoma (H & E , 10 X)

Discussion:

Cholecystectomy stands as a frequently performed surgical procedure employed to manage a range of pathologies, encompassing cholelithiasis, cholecystitis, gallbladder (GB) polyps, and gallbladder cancer (GBC). Globally, cholelithiasis emerges as the most prevalent disorder of the biliary tract, with an estimated prevalence rate of approximately 10% to 15%. While gallstones themselves are typically benign, they carry an elevated risk of hepatobiliary issues and the development of gallbladder cancer (GBC). Notably, despite the relatively low incidence of GBC in the general population, it accounts for a striking 80% of all biliary tract cancers. The challenge in managing GBC lies in its tendency to be diagnosed at an advanced stage, contributing to a grim prognosis and notably low five-year survival rates[18].

This study involved the examination of a patient cohort, and intriguingly, it revealed a predominance of female patients. This aligns with a study conducted in India, an adjacent country, which underscores the significance of the female gender as a risk factor for gallstone development. Notably, the majority of patients in our study presented with cholelithiasis, a condition associated with various potential pathologies, including acute cholecystitis, chronic cholecystitis, follicular cholecystitis, and cholesterolosis[19].

Within our patient population, chronic cholecystitis emerged as the most prevalent pathology, affecting a substantial 72.516% of cases. It is worth noting that a separate study conducted elsewhere reported a similar prevalence rate of 79.8% for chronic cholecystitis, further substantiating the consistency of our findings. Chronic cholecystitis is characterized by the thickening of the gallbladder wall and the presence of calcifications, which, over time, can progress to a condition known as a porcelain gallbladder[20].

Conversely, cholesterolosis arises from the hypertrophy of mucosal villi and the accumulation of cholesterol esters and triglycerides, either in a diffuse or polypoid form within the macrophages situated within the gallbladder wall. In our investigation, we found that cholesterolosis manifested in 9.937% of the cases under scrutiny. Interestingly, a study conducted by Mondal et al. reported a notably lower prevalence of just 2.9% among their patient cohort, while Sangwan et al. documented a prevalence rate of 9.43%. It's worth noting that the prevalence of cholesterolosis observed in our study stands significantly higher than that reported by Mondal et al., but it closely aligns with the findings of Sangwan et al[21].

It is crucial to emphasize that the female gender has been consistently identified as a risk factor for gallstone development, a finding corroborated by our study and numerous others. Cholelithiasis, a prevalent condition in nearly all patients within our study, has the potential to give rise to various pathologies, including chronic cholecystitis, follicular cholecystitis, and cholesterolosis. Among these pathologies, chronic cholecystitis emerged as the predominant condition within our patient population. It is distinguished by the thickening of the gallbladder wall and the presence of calcifications. Importantly, the prevalence of chronic cholecystitis observed in our study aligns with figures reported in prior research[22].

This study offers valuable insights into the prevalence of different pathologies linked to cholelithiasis, notably chronic cholecystitis and cholesterolosis. The noteworthy observations of a female predominance and a substantial prevalence of cholesterolosis deserve additional scrutiny and exploration. In sum, this study enhances our comprehension of the risk factors and pathologies linked to gallstones, which has significant implications for their management. Moreover, this research underscores the importance of further investigation to build upon these findings and formulate more efficacious treatments for individuals affected by cholelithiasis and its associated pathologies[23].

Xanthogranulomatous cholecystitis (XGC), a persistent and often extensive fibro-inflammatory process triggered by the intramural accumulation of foamy histiocytes, was identified in 3.17% of the cases. The clinical and surgical observations of XGC closely resemble those of gallbladder cancer (GBC). XGC is characterized by pericholecystic infiltration, involvement of the liver, and the presence of enlarged lymph nodes, which collectively pose diagnostic challenges.. The timely detection of XGC is crucial since it often necessitates a more radical surgical approach compared to the standard cholecystectomy. Additionally, its well-established association with GBC underscores the importance of early identification and intervention[24].

Empyema of the gallbladder is a complication that arises from acute cholecystitis and has been documented to occur in approximately 5% to 15% of cases. Clinically, this condition manifests as a distended gallbladder filled with pus, and histopathological examination reveals significant edema, inflammation, and the presence of fibrinous exudate

encircling the gallbladder wall[25].

In our study, we observed empyema of the gallbladder in 0.529% of the cases, which aligns with the prevalence rate reported in a separate investigation. The presence of empyema in the gallbladder necessitates immediate medical intervention due to the potential for severe complications such as sepsis and perforation. Distinguishing between simple and complicated cases of cholecystitis through radiological and laboratory assessments is critical, as it influences the approach to management. Timely recognition and treatment of these conditions are paramount for reducing morbidity and mortality rates. There is a compelling need for further research to investigate the incidence of these diseases in the population, identify associated risk factors, and formulate preventive measures. It's crucial to underscore the significance of public education on the symptoms and signs of gallbladder diseases as a means of facilitating early detection and management[26].

Chronic cholecystitis accompanied by pyloric metaplasia was a relatively rare finding in our current study, accounting for just 6.448% of the cases. However, despite their low prevalence, it is imperative to recognize the potential for malignancy associated with these premalignant conditions. Both intestinal metaplasia and pyloric metaplasia have the potential to progress to carcinoma, underscoring the critical importance of early detection. Notably, a significant number of patients presenting with these premalignant conditions were in older age groups, suggesting that an advanced age at presentation increases the risk of malignant transformation. Failure to identify these lesions in their early stages can contribute to the pathogenesis leading to gallbladder cancer (GBC)[27].

Therefore, it is essential to thoroughly assess the histopathology of each gallbladder specimen, regardless of its macroscopic appearance during surgery. This approach aids in the early detection of carcinoma in high-risk patients, potentially preventing the progression to advanced disease. It's noteworthy that gallbladder adenocarcinoma was observed in only 0.847% of cases in our study, which is lower than the prevalence rates reported in various other studies, ranging from 0.5% to 1.05% of the total cases[10,28].

Despite the advancements in modern diagnostic methods, gallbladder cancer (GBC) continues to be frequently diagnosed at an advanced stage, leading to a grim prognosis. The insidious nature of GBC, often remaining asymptomatic in its early phases, poses a challenge for timely detection[29]. Nonetheless, the integration of histopathological examination, enhanced imaging technologies, and specific diagnostic markers can play a pivotal role in achieving an early diagnosis, thereby offering improved prospects for managing the disease[30].

Detecting GBC in its nascent stages is of paramount importance to avert unfavorable outcomes. Consequently, it is essential to underscore the significance of screening initiatives, especially among high-risk groups. This includes individuals residing in regions with a high incidence rate of GBC, women, and those with a history of gallstones or biliary tract disorders. Screening modalities may encompass a range of imaging techniques such as ultrasonography, computed tomography, magnetic resonance imaging, and endoscopic retrograde cholangiopancreatography to facilitate early identification and intervention[31].

Conclusion:

In summary, gallbladder cancers represent a prevalent malignancy within the gastrointestinal tract and are notorious for their dismal prognosis. Gallbladder Cancer (GBC) is relatively rare and typically presents as early-stage cancer, offering a more favorable 5-year survival rate when compared to typical Gallbladder Cancer (GBC). Notably, radiological and macroscopic evaluations often do not raise suspicions of malignancy, especially in the case of GBC. Hence, histopathological analysis of cholecystectomy specimens remains the gold standard for identifying hidden malignancies. In resource-constrained environments, selectively sampling resected gallbladders can be cost-effective. However, given the aggressive nature and poor prognosis associated with GBC, opting for selective sampling is not a justifiable approach for cholecystectomy specimens. Consequently, we strongly advocate for the comprehensive histological assessment of all cholecystectomy specimens, irrespective of their radiological or macroscopic characteristics. This approach is vital in ensuring the early detection of potential malignancies and subsequent appropriate management.

Conflict of Interest- "All the authors declare that they have no conflict of interest."

References:

1. Lung, K. and F. Lui, *Anatomy, Abdomen and Pelvis: Arteries*, in *StatPearls*. 2023, StatPearls Publishing Copyright © 2023, StatPearls Publishing LLC.: Treasure Island (FL) ineligible companies. Disclosure: Forshing Lui declares no relevant financial relationships with ineligible companies.
2. Hundt, M., C.Y. Wu, and M. Young, *Anatomy, Abdomen and Pelvis: Biliary Ducts*, in *StatPearls*. 2023, StatPearls Publishing Copyright © 2023, StatPearls Publishing LLC.: Treasure Island (FL) ineligible companies. Disclosure: Cheng Ying Wu declares no relevant financial relationships with ineligible companies. Disclosure: Michael Young declares no relevant financial relationships with ineligible companies.
3. Stinton, L.M. and E.A. Shaffer, *Epidemiology of gallbladder disease: cholelithiasis and cancer.* Gut Liver, 2012. **6**(2): p. 172-87.
4. Alabi, A. and A.D. Arvind, *Incidental Gallbladder Cancer: Routine versus Selective Histological Examination After Cholecystectomy.* 2021. **7**(1): p. e22-e25.
5. Dwivedi, A.N., S. Jain, and R. Dixit, *Gall bladder carcinoma: Aggressive malignancy with protean loco-regional and distant spread.* World J Clin Cases, 2015. **3**(3): p. 231-44.
6. Hundal, R. and E.A. Shaffer, *Gallbladder cancer: epidemiology and outcome.* Clin Epidemiol, 2014. **6**: p. 99-109.
7. Malhotra, R.K., et al., *Gallbladder cancer incidence in Delhi urban: A 25-year trend analysis.* Indian J Cancer, 2017. **54**(4): p. 673-677.
8. Rustagi, T. and C.A. Dasanu, *Risk factors for gallbladder cancer and cholangiocarcinoma: similarities, differences and updates.* J Gastrointest Cancer, 2012. **43**(2): p. 137-47.
9. Andrén-Sandberg, A., *Diagnosis and management of gallbladder cancer.* N Am J Med Sci, 2012. **4**(7): p. 293-9.
10. Benkhadoura, M., et al., *Routine histopathological examination of gallbladder specimens after cholecystectomy: Is it time to change the current practice?* Turk J Surg, 2019. **35**(2): p. 86-90.
11. Patel, K., et al., *Incidental non-benign gallbladder histopathology after cholecystectomy in an United Kingdom population: Need for routine histological analysis?* World J Gastrointest Surg, 2016.

8(10): p. 685-692.
12. Rammohan, A., et al., *Incidental gall bladder cancers: Are they truly incidental?* World J Gastrointest Oncol, 2014. **6**(12): p. 441-3.13. Singh, A., et al., *Histopathological Changes in Gallbladder Mucosa Associated with Cholelithiasis: A Prospective Study.* Niger J Surg, 2019. **25**(1): p. 21-25.
14. Elliott, A.C., et al., *Preparing data for analysis using microsoft Excel.* J Investig Med, 2006. **54**(6): p. 334-41.
15. Ajani, J.A., et al., *Gastric adenocarcinoma.* Nat Rev Dis Primers, 2017. **3**: p. 17036.
16. Pisano, M., et al., *2020 World Society of Emergency Surgery updated guidelines for the diagnosis and treatment of acute calculus cholecystitis*. World Journal of Emergency Surgery, 2020. **15**(1): p. 61.
17. Almas, T., et al., *The Spectrum of Gallbladder Histopathology at a Tertiary Hospital in a Developing Country: A Retrospective Study.* Cureus, 2020. **12**(8): p. e9627.
18. Andrén-Sandberg, A., *Diagnosis and management of gallbladder polyps.* N Am J Med Sci, 2012. **4**(5): p. 203-11.
19. Unisa, S., et al., *Population-based study to estimate prevalence and determine risk factors of gallbladder diseases in the rural Gangetic basin of North India.* HPB (Oxford), 2011. **13**(2): p. 117-25.
20. Jones-Monahan, K. and J.C. Gruenberg, *Chronic acalculous cholecystitis: changes in patient demographics and evaluation since the advent of laparoscopy.* Jsls, 1999. **3**(3): p. 221-4.
21. Strömsten, A., et al., *Studies on the mechanism of accumulation of cholesterol in the gallbladder mucosa. Evidence that sterol 27-hydroxylase is not a pathogenetic factor.* J Hepatol, 2004. **40**(1): p. 8-13.
22. Novacek, G., *Gender and gallstone disease.* Wien Med Wochenschr, 2006. **156**(19-20): p. 527-33.
23. Schirmer, B.D., K.L. Winters, and R.F. Edlich, *Cholelithiasis and cholecystitis.* J Long Term Eff Med Implants, 2005. **15**(3): p. 329-38.
24. Singh, V.P., et al., *Xanthogranulomatous cholecystitis: What every radiologist should know.* World J Radiol, 2016. **8**(2): p. 183-91.25. Elkbuli, A., et al., *Uncommon Presentation of Severe Empyema of the Gallbladder: Case Report and Literature Review.* Am J Case Rep, 2020. **21**: p. e923040.
26. Malik, A., et al., *Laparoscopic cholecystectomy in empyema of gall bladder: An experience at Liaquat University Hospital, Jamshoro, Pakistan.* J Minim Access Surg, 2007. **3**(2): p. 52-6.
27. Seretis, C., et al., *Metaplastic changes in chronic cholecystitis: implications for early diagnosis and surgical intervention to prevent the gallbladder metaplasia-dysplasia-carcinoma sequence.* J Clin Med Res, 2014. **6**(1): p. 26-9.
28. Cockrell, C., J. Teague, and D.E. Axelrod, *Prevention of Colon Cancer Recurrence From Minimal Residual Disease: Computer Optimized Dose Schedules of Intermittent Apoptotic Adjuvant Therapy.* JCO Clin Cancer Inform, 2020. **4**: p. 514-520.
29. Pandey, M., et al., *Carcinoma of the gallbladder: a retrospective review of 99 cases.* Dig Dis Sci, 2001. **46**(6): p. 1145-51.
30. García, P., et al. *Current and New Biomarkers for Early Detection, Prognostic Stratification, and Management of Gallbladder Cancer Patients*. Cancers, 2020. **12**, DOI: 10.3390/cancers12123670.
31. Kanthan, R., et al., *Gallbladder Cancer in the 21st Century.* Journal of Oncology, 2015. **2015**: p. 967472.