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Challenging the Status Quo: Is Routine Histopathological Examination Necessary after Cholecystectomy?

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Abstract

Background: Routine histopathological examination of gallbladders after cholecystectomy is standard practice in Ireland to detect incidental gallbladder carcinoma (GBC), a rare malignancy with poor prognosis. While comprehensive, this approach may not be cost-effective or sustainable in our low-incidence population. This study evaluates the feasibility of a selective approach of histopathology specimen processing based on well-described risk factors for GBC.

Methods: A retrospective review was conducted of 935 gallbladder specimens submitted for histopathological examination over a five-year period after cholecystectomy at a single institution in Ireland. Clinical, imaging, and histology reports were analysed to identify cases of GBC which were subsequently reviewed in detail to identify clinical, radiological, and macroscopic predictors of malignancy.

Results: Two patients (0.21%) with GBC were identified. Both patients had risk factors, including age >50 years, gallbladder polyps (>1 cm), and abnormal imaging findings. None of the patients had macroscopically abnormal features intraoperatively. These findings align with international evidence supporting the use of selective histopathological examination for cases with identifiable pre-operative risk factors. This approach can reduce the workload on histopathologists and costs without compromising patient outcomes.

Conclusions: Given the low incidence of GBC in our population, adopting a selective approach to gallbladder histopathology processing presents a safe and cost-effective alternative to routine examination. Such a protocol could significantly reduce resource consumption and result in important cost savings to healthcare systems. As evidenced by the experiences in Sweden and the Netherlands, this approach can be implemented nationally while maintaining high diagnostic accuracy without overlooking cases of GBC.

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Introduction

Cholecystectomy is one of the most commonly performed surgical procedures in the world. Approximately 5,000 cholecystectomies are performed annually in Ireland, with laparoscopic cholecystectomy being the gold standard for definitive treatment of symptomatic gallstone disease. The current national practice is routine histopathological analysis of gallbladder specimens after cholecystectomy according to the guidelines of the Royal College of Pathology [1].

The main purpose of routine histopathological examination of gallbladders is to uncover incidental gallbladder carcinoma, which has a reported incidence of up to 0.3% to 0.9% in gallbladder specimens submitted routinely [2] [3,4]. The global distribution of gallbladder carcinoma shows highest incidences in India, Japan, Pakistan, East Asia, Eastern Europe and South America and rare in Northern Europe and America [5,6].

Gallbladder carcinoma (GBC) is a rare and aggressive malignancy with poor prognosis. The 5-year survival rate does not exceed 5%, and when detected in the early stages, this rate is as high as 79%. Due to the non-specific presentation of GBC, it presents diagnostic and clinical challenges. This has led to a widely accepted consensus regarding the histopathological examination of all gallbladder specimens to detect incidental GBC. The diagnosis of gallbladder cancer can significantly alter clinical management by necessitating more extensive hepatic resection and lymphadenectomy in T2 and above tumours.

The management of cholecystectomy specimens, irrespective of preoperative and intraoperative findings on histological examination, has been a point of debate in the literature. A number of authors have advocated for selective histopathology assessment, with some authors reporting their experience with a selective approach adopted nationally in the Netherlands and Sweden [7,8].

In this study, we endeavour to evaluate the incidence of gallbladder carcinoma (GBC) and role of histopathological processing after cholecystectomy at a single institution. We discuss the potential adaptation of a more selective approach in the processing of gallbladder specimens based on risk factors for GBC. Given the low disease incidence in our population, this study raises the question of whether routine histological examination is necessary nationally and in populations with a similar disease incidence.

Materials and Methods

A retrospective review of all histopathological reports of gallbladders after cholecystectomy over a 5-year period from January 2019 to December 2023. Any patient undergoing gallbladder surgery during the timeframe was included, and those cases of confirmed gallbladder carcinoma were selected for further evaluation.

Clinical notes of the selected cases were reviewed for demographic information, presenting symptoms and objective findings on pre-operative imaging and endoscopic procedures. The intraoperative findings were also noted. The majority of patients who undergo cholecystectomy within the cohort underwent pre-operative evaluation with ultrasound (US), CT-abdomen/pelvis, Magnetic resonance cholangiopancreatography (MRCP), with endoscopic ultrasound (EUS) used when abnormal gallbladder or biliary tree morphology was suspected.

The aim of this study was to create a profile of clinical features that could be indicative of a possible underlying gallbladder cancer. Common features shared among patients with preoperative features of concern were reviewed to assess the feasibility of adopting a selective approach in the histological processing of gallbladder specimens.

Results

During the five-year study period, 935 gallbladder specimens were sent for histopathological evaluation after cholecystectomy for benign conditions.

Two (0.21%) cases of histologically diagnosed gallbladder carcinoma were confirmed as primary adenocarcinomas of the gallbladder. Two patients had suspicious lesions on preoperative imaging, with no intraoperative abnormalities in the gallbladder appearance. The female-to-male ratio was 1:1, with ages 66 and 70 years, respectively (Table 1).

Case 1

The first patient is a 66-year-old female with a significant medical history of a prior left laparoscopic nephrectomy and adrenalectomy for multifocal renal carcinoma (with metastasis to the left adrenal gland) and prior right hemicolectomy for colon adenocarcinoma. She had no genetic abnormality recorded. She had a past medical history of left MCA stroke and drug-induced acute pancreatitis. She is an ex-smoker with a previous 45 pack year history, a BMI of 30.9. A gallbladder polyp was noted incidentally on surveillance imaging for her prior cancer diagnoses. She was asymptomatic.

Preoperative imaging: Abdominal ultrasound revealed gallbladder polyps measuring up to 15 mm and dilated common bile duct up to 12 mm. MRCP: dilated common bile duct with increased intrahepatic biliary duct dilatation. A tubular filling defect in the lumen of the distal common bile duct is atypical for calculus. Distended gallbladder with fundal mural thickening and multiple mural cysts consistent with adenomyomatosis.

Table 1: Demographic features of patients with confirmed gallbladder carcinoma.

Case	1	2
Age	66	70
Sex	F	M
Preoperative Imaging Findings	15mm gallbladder polyps, 12mm dilated CBD	Irregular thickening of gallbladder wall with a 15x13mm polyp
Preoperative Diagnosis	GB polyps	GB polyp & possible adenomyomatosis
Operation	OC	LC
Intraoperative Findings	Small adhesions to GB	No abnormalities
Histology	pT2N0M0	PT2N0M0
Survival (Months)	46 (alive)	48

CBD: Common Bile Duct; GB: Gallbladder; OC: Open Cholecystectomy; LC: Laparoscopic Cholecystectomy

An open approach to cholecystectomy was chosen due to prior laparotomies, and no abnormalities were reported by the operating surgeons regarding the appearance of the gallbladder at the time of surgery. The histopathology results revealed a moderately to poorly differentiated adenocarcinoma, pT2, perineural invasion, and negative lymph node with R0 section. The patient was discussed at a multidisciplinary meeting and was found to be a candidate for adjuvant chemotherapy. At the most recent follow-up at 46 months; she had no evidence of recurrent or metastatic disease.

Case 2

The second patient is a 70-year-old man who presented with an incidental finding of a gallbladder polyp on imaging for the investigation of deranged liver enzymes. His past medical history included prostate cancer, ulcerative colitis, type 2 diabetes mellitus, hypothyroidism, primary sclerosing cholangitis (PSC), and cirrhosis (Child Pugh A). He was a lifelong non-smoker and had a BMI of 31.1. He had symptoms of weight loss and longstanding deranged liver enzymes due to cirrhosis and PSC.

Preoperative Imaging: Ultrasound and CT showed irregularly thickened gallbladder fundus with a 15 mm × 13mm polypoid area concerning for adenomyomatosis. After review at a multidisciplinary meeting, he underwent a laparoscopic cholecystectomy. No abnormality was observed with the gallbladder by the operating surgeons. The histopathology results showed a moderately differentiated gallbladder adenocarcinoma, pT2, high-grade dysplasia, perineural invasion, and lymphovascular invasion. No gallstones were present, and a thickened gallbladder wall of 3 mm with a fibrotic (porcelain) appearance was observed.

The consensus from the multidisciplinary discussions was that this patient was not a candidate for completion of liver segment IVb/V resection due to the history of PSC and cirrhosis. The patient went on to have adjuvant chemotherapy treatment. The patient showed disease recurrence at 39 months. He was commenced on second line chemotherapy. The patient passed away from hepatorenal syndrome from advanced liver cirrhosis and disease burden of recurrence at 48 months (Table 2).

Table 2: Summary of clinical features of the 2 cases of gallbladder carcinoma.

Clinical features of tissue diagnosed gallbladder carcinoma
Weight loss
RUQ and/or epigastric pain
Deranged liver function tests
Primary sclerosing cholangitis
BMI (30.9 both cases)
Ex-smoker (case 1- 40 pack year)
Age >60

Discussion

Laparoscopic cholecystectomy is a commonly performed procedure in general surgical departments for various biliary tract disorders, most notably, symptomatic cholelithiasis and cholecystitis. Despite the low incidence of GBC, all gallbladder specimens, regardless of macroscopic appearance and preoperative clinical features, undergo routine histopathological examination according to the Royal College of Pathologists Guidelines [1].

There is documented geographic and ethnic variability in the distribution of GBC worldwide, which parallels the frequency of cholelithiasis. The highest incidence rates were found in Eastern Europe, East Asia, and Latin America, with the lowest rates in North America and most of Europe [9]. The geographical variations have been attributed to differences in environmental exposure, genetic predisposition and regional intrinsic risk factors that predispose to carcinogenesis [10].

This malignancy continues to have a poor prognosis, with a 5-year survival rate of less than 5% and a median survival time of 6 months. Most long-term survivors have early-stage carcinomas confined to the gallbladder. The risk factors commonly associated with GBC include gallbladder polyps greater than 1.5 cm, porcelain gallbladder, gallstones, age >50 years, empyema, genetic predisposition, geographical/ethnic factors, Salmonella infection, and chronic cholecystitis. GBC is 2-6 times more prevalent in females [10,11].

In our study, the two cases of incidental gallbladder carcinoma had known risk factors for gallbladder cancer: gallbladder polyps, thickening of the gallbladder wall, and age >60 years. Both tumours were classified as T2N0M0, and both patients received adjuvant chemotherapy. None of the cases were eligible for further resection.

There is an ongoing debate in the literature on whether traditional routine histopathological processing is feasible globally, given what is known of the prevalence and incidence of GBC. Several studies have suggested a move towards a more selective approach, taking into account the risk factors of GBC without compromising patient outcomes.

Arguments in favour of the routine approach state a desire for diagnostic completeness and fear of medicolegal implications for potentially missed diagnoses of GBC where patients would be deprived of additional treatment [12,13].

Supporters of routine analysis often come from areas with an increased prevalence of GBC [14-20]. A retrospective study conducted by Agarwal et al. in patients diagnosed with GBC after cholecystectomy reaffirmed that early diagnosis through histological evaluation was associated with a better prognosis. Given the aggressive nature of the tumour and its higher incidence in their cohort, these authors

Table 3: Indications for additional histopathological examination of gallbladders in the literature.

Suspicious features for GBC as reported in the literature	
Preoperative	**Intraoperative**
Risk factors:	Severe adhesions
· Gallbladder polyps >10 mm	
· Porcelain gallbladder	Macroscopic gallbladder features
· Primary sclerosing cholangitis	· Thickened or fibrotic wall
· Mirizzi syndrome	· Irregular mucosa
· Chronic cholecystitis	· Masses
Clinical features:	Surgeon's suspicion of GBC
· Weight loss	
· Jaundice	
· Age ³60	
Preoperative imaging	
· Gallbladder wall thickening	
· Contracted gallbladder	
· Unusual gallbladder appearance on imaging	
Bazoua et al. [23], Corten et al. [33], Cha et al. [34]	

emphasized the need to maintain the traditional approach. Similarly, Kozan et al. evaluated the histopathology results of 2,723 gallbladders at a Turkish institution and underscored the importance of routine assessment in understanding the wide spectrum of pathologies of the gallbladder including pre-malignant lesions [17].

Although proponents of the routine approach argue that most incidental GBCs are detected histologically rather than through intraoperative findings, advocates of selective examination contend that suspicious cases of GBC typically exhibit noticeable signs that can be identified by the operating surgeon intraoperatively [21]. Macroscopically, GBC can present in various forms, including infiltrative, papillary, nodular, or mixed types, and these characteristics are often observed on gross examination of gallbladder specimens [22].

The selective approach argues that GBC is uncommon in cases where the gallbladder appears macroscopically normal and no risk factors are present [23-30]. They further suggest that if a gallbladder with malignancy appears normal or shows only subtle suspicious findings during surgery, the disease is likely at an early stage, such as Tis or T1a, which requires no further treatment beyond simple cholecystectomy. In cases with unequivocal macroscopic features, the specimen was sent for histopathological evaluation. A systematic review by Khan et al. [21], compared the macroscopic features of 486 gallbladders with confirmed GBC that underwent selective versus routine pathology. They found that many macroscopic features of malignancy that were not noticed by surgeons involved in routine histology were noticed and suspected by those using the selective approach. In a study in China involving 14,369 gallbladder specimens, Deng et al. [24] found that 44 of 46 patients with incidental gallbladder cancer had macroscopic abnormalities, and the two cases with a macroscopically normal gallbladder were diagnosed as having pTis and pT1a disease which did not require further resection [24].

These studies emphasize the importance of intraoperative macroscopic examination, which could be enhanced with guidance from pathologists to improve the quality of assessment before

specimens are submitted for histopathological examination. This approach substantially reduces the chances of missing incidental GBC, decreases the workload on histopathologists, and lowers the costs of processing the specimens while maintaining patient safety.

Studies from low incidence countries (UK, Sweden and the Netherlands) highlight significant cost savings from adopting a selective approach. In Sweden, routine histological assessment of specimen would incur high costs with minimal life-years gained [31], while the UK saved €12,200 over five years and the Netherlands could save approximately €1,6 million annually [8,32] (Table 3).

Conclusion

In an era where sustainability in operating theatres is prioritized, adopting a selective approach to histopathological examination offers a practical balance between cost efficiency and maintaining quality patient-centred care. The successful national implementation of selective specimen processing in Sweden and the Netherlands demonstrates the viability of this approach. Tools such as the risk assessment model developed by Corten et al. [35] could be adapted for use in Ireland and other countries with lower disease incidence.

Establishing international guidelines to support this practice would help reduce costs and workloads in histopathological specimen processing. Furthermore, having standardised guidelines could alleviate the potential medicolegal burden associated with implementing the selective approach, providing clarity and consistency for surgeons. This review hights the need for continued dialogue and action to revise specimen handling protocols in the operating rooms.

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