



## Cohort Study

# Thirty-five cases of gallbladder carcinoma out of 4914 cholecystectomy specimens from a Nepalese tertiary care hospital – A retrospective cohort study



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## ABSTRACT

**Introduction:** The density of gallbladder carcinoma differs in different parts of the world. It is an aggressive tumor with poor prognosis presenting in advanced stages due to paucity of signs and symptoms. This research was conducted to analyze the frequency of incidental and clinically suspected gallbladder carcinoma with clinicopathological correlation.

**Methods:** This is a retrospective cohort study conducted in the Department of Pathology, Manipal College of Medical Sciences, Pokhara, Nepal from January 2005 to December 2020.

**Results:** The study included 35 cases of gallbladder carcinoma compiled over a period of 16 years. There were 11 males and 24 females with a male to female ratio of 1: 2.1. Age ranged from 29 to 75 years with a mean age of  $56.51 \pm 11.38$  years. Incidental carcinoma was observed in 26 (74.28%) cases while clinically suspected carcinoma was identified in 9 (25.71%) cases. Gallstone was associated in 14 (40%) cases of incidental carcinoma. Tumor staging of both incidental and clinically suspected carcinomas showed 13 (37.14%) cases in T1 stage, 15 (42.85%) cases in T2 stage and 7(20%) cases in T3 stage.

**Conclusion:** Our analysis established prevalence of gallbladder carcinoma from 5th to 7th decades with female predominance and higher association of gallstones in incidental carcinoma. The principal histology in incidental carcinoma was well differentiated carcinoma while poorly differentiated carcinoma was encountered only in clinically suspected carcinoma.

## 1. Introduction

Cholecystectomy is a routine procedure performed for various causes and with the advent of laparoscopy; the practice is on the rise. Consequently, there is more probability of coincidental finding of carcinoma of the gallbladder. Carcinoma of gallbladder is a common malignancy standing fifth in line among the most prevalent malignancies of the digestive tract [1]. It accounts for 1.2% of all cancer diagnosis but the picture differs in various part of the world. The reported mortality due to gallbladder carcinoma accounts for 1.7% of all cancer related deaths [2]. Gallbladder carcinoma is a sinister disease principally affecting the elderly female community in their 70s with male to female ratio of 1:5 [3]. By and large gallbladder carcinoma is illusive, so clinical diagnosis becomes challenging. Henceforth, they are incidentally discovered on

evaluation of post-cholecystectomy specimen intended for different clinical suspicion [1].

The objective of the study is to analyze both incidental and clinically suspected gallbladder carcinoma with respect to non-descriptive variables like frequency, age, sex distribution, size of the gallbladder, wall thickness and the tumor size along with histopathological types and staging of the tumor.

## 2. Methods

### 2.1. Study design and setting

A retrospective cohort study was conducted from January/01/2005 to December/30/2020 in a tertiary care hospital from Western region of

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Nepal. This hospital is a major referral site and includes a plethora of specialized health services for the region serving 2.4 million people.

### 2.2. Source and study population

All the relevant data were retrieved from the medial record section and departmental database. The study population included all the patients who were operated between January 2005 to December 2020. The source of study encompassed all the subjects who underwent cholecystectomy irrespective of the modality of the removal i.e. laparoscopic or open surgery. All malignant cases including patients with incidental diagnosis on histopathology and clinically suspected cases of gallbladder carcinoma were included in the study. Patients with incomplete medical records were excluded.

### 2.3. Sample size and sampling procedure

Single population proportion for a finite population was used for determination of sample size for this study. The derived power calculated sample size was  $n = 16$  with a postulation of 95% confidence level, 5% margin of error, and incidence of estimated gallbladder carcinoma (1%) [4]. The study sample comprised of all the cholecystectomy specimens collected over a period of 16 years in a tertiary care hospital of Pokhara, Nepal (N = 4914), the required sample size was obtained by the following calculation.

$$n = N * X / (X + N - 1)$$

where,

$$X = Z_{\alpha/2}^2 * p * (1-p) / d^2$$

n = sample size.

N = size of the target population.

Z = 1.96 (95% level of confidence).

P = incidence of estimated gallbladder carcinoma (1%)

d = margin of error = 5%

Therefore, the minimum required sample size is 16.

The study was conducted through a review of record. Consent was obtained from the study subjects. The confidentiality and privacy of the records were ensured.

### 2.4. Data collection tools and procedures

All required data and information for the study was listed and structured. Two days practical training was given to data collectors on the objectives of the study and the procedure i.e. how to review departmental database, registration, medical logbook, the patient's medical record chart and how to maintain the confidentiality of the data. Prior ethical approval of the Institutional Review Committee was obtained before initiation of the study. This study was reported in accordance with the declaration of Helsinki and registered at [www.researchregistry.com](http://www.researchregistry.com) with unique identifying number - 6574. This study is reported according to the STROCSS guidelines [5].

### 2.5. Outcome measures

Detailed summary measures of gallbladder carcinomas with histopathological confirmation were tabulated using descriptive analysis and an exhaustive data was tabulated which included demographic, clinical, radiological and histopathological parameters.

### 2.6. Data processing and analysis

Data was checked for completeness, discrepancies, comprehensiveness, accuracy, missing values and entered into SPSS version 21. Detailed histopathological, demographic, measures of descriptive

analysis such as frequency, percentages, mean and SD values were calculated. A side by side comparison between incidental and clinically suspected cases of gallbladder carcinoma was done. Separate comparison based on histological grading system was prepared which assessed microscopic and gross features.

## 3. Results

### 3.1. Baseline characteristics of the study participants

This is a retrospective cohort study conducted in the Department of Pathology, Manipal College of Medical Sciences, Pokhara, Nepal from January 2005 to December 2020. The study constitutes all gallbladder carcinoma cases compiled over a period of 16 years. All the specifics of the cases including age, sex, clinical history, radiological findings, gross and microscopic features and the final diagnosis were retrieved from the departmental data and medical record section. The compiled data were then comprehensively scrutinized.

The cholecystectomy specimens were fixed in 10% formalin for 24–48 h. Tissue sections were taken from the gallbladder wall, tumor mass or suspected site, processed by standard technique in the Leica Automated Tissue Processor and paraffin blocks were made. The histopathological sections were stained with routine hematoxylin and eosin (H&E) and special stains whenever necessary. The data were analyzed using Microsoft Excel and SPSS 21.0 version.

### 3.2. Demographic data of gallbladder carcinoma

Overall 4914 cholecystectomy specimens were compiled over 16 years. Of the 35 cases of gallbladder carcinoma, 26 were incidental carcinoma and 9 were clinically suspected carcinoma. The demographic distribution, male to female ratio has been represented in [Tables 1 and 2](#).

### 3.3. Association of gallstones to carcinoma

Association of gallstone to gallbladder carcinoma was equivocal in our analysis. Nearly equivalent amount of gallstones were associated with incidental carcinoma while fewer associations were seen with clinically suspected carcinoma ([Table 3](#)).

### 3.4. Histopathological, radiological and clinical evaluation of gallbladder carcinoma

Apart from gallstones; acute and chronic cholecystitis, empyema and obstructive jaundice were also recognized in corporation with incidental carcinoma. 19 cases of well differentiated and 7 cases of moderately differentiated adenocarcinoma were established in incidental carcinoma. Positive margins, lymphatic emboli, perineural infiltration and omental deposits also were identified, contributing to upstaging of the tumor. Stage T2b was the pervasive tumor stage ([Table 4](#)). Grossly, the gallbladder size ranged from 5 to 9.5 cm with a mean of  $6.87 \pm 1.64$  cm and the wall thickness ranged from 0.2 to 2 cm with a mean of  $0.62 \pm 0.52$  cm ([Table 5](#)).

**Table 1**

Distribution of all gallbladder carcinoma cases with respect to gender (n = 35).

Diagnosis		Gender		Total n (%)
		Male n (%)	Female n (%)	
Gallbladder carcinoma	Incidental carcinoma	9 (34.61)	17 (65.38)	26 (74.28)
	Clinically suspected carcinoma	2 (22.22)	7 (77.77)	9 (25.71)
Total		11 (31.42)	24 (68.57)	35 (100)

**Table 2**  
Distribution of all gallbladder carcinoma cases in different age groups.

Diagnosis		Age-group (years)						Total	Mean age (years)
		21–30	31–40	41–50	51–60	61–70	71–80		
Gallbladder carcinoma	Incidental carcinoma	1	–	8	6	9	2	27	55.53 ± 11.58
	Clinically suspected carcinoma	–	1	1	2	5	–	9	59.33 ± 10.93
Total		1	1	9	8	14	2	35	56.51 ± 11.38

**Table 3**  
Association of gallbladder carcinoma with gallstones (n = 35).

Diagnosis			Frequency (n)		Percentage (%)
Gallbladder carcinoma	Incidental carcinoma	with gallstone	14	26	74.28
		without gallstone	12		
	Clinically suspected carcinoma	with gallstone	1	9	25.71
		without gallstone	8		

Chronic cholecystitis was related to most of the clinically suspected carcinoma. Infiltration of right lobe of liver, common bile duct (CBD) and pancreas were also illustrated on radiological evaluation. Microscopic examination affirmed well differentiated, poorly differentiated, mucin secreting adenocarcinomas and adenosquamous carcinomas with well differentiated adenocarcinoma being more prevalent. Positive margins, lymphovascular embolus, perineural infiltration, emboli and positive nodes were also recognized. T2b and T3 were the most common tumor stages. The gallbladder size ranged from 5 to 9 cm with a mean of  $7.83 \pm 1.65$  cm; the wall thickness ranged from 0.2 to 1.3 cm with a mean of  $0.5 \pm 0.34$  cm and the tumor size ranged from 0.2 to 6 cm with a mean of  $2.3 \pm 1.97$  cm (Table 6).

#### 4. Discussion

Carcinoma gallbladder is ranked 22nd amongst the most prevalent cancer and 17th amid the most precarious cancer world wide as stated by GLOBOCAN 2018 data. It attributes to 1.2% of all cancer diagnosis and 1.7% of all cancer related deaths [6]. Cholelithiasis, chronic inflammation, carcinogen exposure, *Helicobacter pylori* infection coupled with geographic, ethnic and sex distribution are recognized as some of the vital elements in carcinogenesis. Genetic link also cannot be overlooked as a fourth of gallbladder carcinomas are regarded as familial [2, 7,8].

Carcinoma of gallbladder is two to six times more pervasive in women than males with female hormone estrogen being related to surge in saturation of cholesterol in bile, thus in turn expanding the liability of gallstone formation [2,9,10]. Male preponderance of gallbladder carcinoma have also been dictated by other researches with M:F ratio ranging from 1:2.6 to 1:5, while Singh et al. acclaimed female involvement in toto [7,8,11,12]. In keeping with the stats, our review also exhibited M:F ratio of 1:2.1.

Presumably due to gradual progression, gallbladder carcinoma manifests itself with advancing age, being more evident after the age of 60 years [2,8]. The age spectrum extending from low as 38 to as high as 85 years with mean age of 51.3–55.8 years have been depicted in numerous researches [1,12–14]. We also had similar observation with age stretching from 29 to 75 years with mean age of  $56.51 \pm 11.38$  years;  $55.53 \pm 11.58$  years for incidental carcinoma and  $59.33 \pm 10.93$  years for clinically suspected carcinoma.

The disease expresses itself as nausea, vomiting, pain in right hypochondrium and occasionally as a mass with particular symptoms being more distinguished than other [13,14]. We also had identical

presentations with clinical diagnosis encompassing cholelithiasis, empyema, obstructive jaundice, acute and chronic cholecystitis.

Radiological clue of early stage of gallbladder carcinoma is ambiguous with findings coinciding with acute or chronic cholecystitis comprising of thickened gallbladder wall and gallstones [14]. Amidst the 9 clinically suspected carcinoma of gallbladder in our observation, radiological imaging revealed liver infiltration in 22.2% of the cases; similar findings were published by Batra Y et al. who encountered 23% of such incidents [13]. Apart from that we encountered 33.3% of subjects with CBD and 11.1% with pancreatic infiltrations on imaging.

We identified 35 (0.71%) specimens of gallbladder carcinoma encompassing 0.52% of incidental and 0.18% of clinically suspected carcinoma. A total of 26 (74.28%) cases of incidental carcinoma involving 9 (34.61%) males and 17 (65.38%) females; 9 (25.71%) cases of clinically suspected carcinoma comprising 2 (22.22%) males and 7 (77.77%) females were established. Roughly 0.23–3.30% of cholecystectomy samples turn out as carcinoma [8,13]. Out of 291 cholecystectomy specimens, Batra Y et al. exhibited 6 (2%) cases of incidental carcinoma [13]. Khoo JJ et al. in their study of 1122 cholecystectomy specimens, ascertained 9 (0.8%) cases of gallbladder carcinoma with 77.77% of incidental and 22.22% of clinically suspected carcinoma. Of the 7 cases of incidental carcinoma, 3 were males and 4 females while a case each of clinically suspected gallbladder carcinoma were disclosed in their study [4].

Macroscopic findings of gallbladder carcinoma can be varied. Talreja V et al. identified 9 (0.92%) cases of incidental carcinoma exhibiting thickened wall in 8 cases, polypoidal growth and mucosal epithelial ulcer in a case each [12]. Islam MJ et al. noted 12 (2.21%) cases of incidental gallbladder carcinoma; all without any gross abnormality [7]. Jha V et al. found 20(0.41%) cases of incidental carcinoma in 4800 cholecystectomy specimens with mucosal ulceration in 2 (10%), wall thickening in 11 (55%) and no abnormality in 7 (35%) samples [15]. Similarly Sujata J et al. detected 6 (0.96%) cases of incidental carcinomas with gallbladder wall thickening of >3 mm in 4(66.66) cases [14]. Our search on gross examination of the incidental gallbladder carcinoma demonstrated, gallbladder size spanning from 5 to 9.5 cm and wall thickness from 0.2 to 2 cm (14 cases). We also unearthed 2 cases of incidental carcinoma on microscopic examination of polypoidal lesion and a tiny papillary projection of gallbladder mucosa. Likewise the size varied from 5 to 9 cm and wall thickness ranged from 0.2 to 1.3 cm in the 9 clinically suspected carcinoma of the gallbladder.

Gallstones are disclosed in 54–97% of gallbladder carcinoma [8]. All six cases of incidental carcinoma of gallbladder were associated with gallstones in the review published by Sujata J et al. [14] Talreja V et al. encountered only 6 (54.54%) association of gallbladder carcinoma with multiple gallstones [12]. Jha V et al. acclaimed 14(70%) cases with gallstones [15]. We encountered the incidence of gallbladder carcinoma to gallstones to be 42.85%.

Most frequent histological type is adenocarcinoma representing approximately 90% of cases and is further classified into papillary, tubular and mucinous types. Prevalence of other histological types, anaplastic, squamous and adenosquamous carcinoma are nominal [16]. In majority of cases described by Barcia JJ et al., gallbladder carcinoma were moderately to poorly differentiated adenocarcinoma and a case of mucinous carcinoma with extensive infiltration of the gallbladder wall [1]. Sujata J et al. enumerated 2(33.3%) cases of well differentiated, 3 (50%) cases of moderately differentiated and 1(16.6%) case of poorly

**Table 4**  
Diagnostic correlation with clinical diagnosis, microscopic findings and tumor staging in incidental carcinoma cases (n = 26).

Diagnosis	No of cases	Clinical Diagnosis						Microscopic Findings					Tumor staging												
		Cholelithiasis		Chronic cholecystitis		Acute cholecystitis		Empyema		Obstructive Jaundice		L. Emboli		PNI		Margin positive		Omental Deposit		T1		T2		T3	
Adenocarcinoma	19	14	2	3	-	-	-	-	-	-	4	-	4	-	2	9	-	-	-	2	9	-	6	2	
Moderately differentiated	7	-	4	-	2	2	1	1	1	1	-	3	1	1	-	-	-	-	-	-	-	-	5	2	
Total Incidental Carcinoma	26	14	6	3	2	2	1	1	1	4	3	1	4	3	2	9	-	-	1	2	9	-	11	4	

PNI - Perineural infiltration, L. Emboli- Lymphatic Emboli.

**Table 5**

Correlation of gallbladder size and gallbladder wall thickness in incidental carcinoma cases (n = 26).

Diagnosis	GB size		Wall thickness	
	Range	Mean	Range	Mean
Well differentiated adenocarcinoma	5-9	6.2 ± 1.367	0.2-2	0.6474 ± 0.537
Moderately differentiated adenocarcinoma	6.3-9.5	8.54 ± 1.08	0.2-1	0.571 ± 0.534
Total Incidental Carcinoma	5-9.5	6.87 ± 1.64	0.2-2.0	0.62 ± 0.52

differentiated carcinoma among the incidental carcinomas [14]. Talreja V et al. recorded 4 (44.44%) cases of well differentiated carcinoma and 5 (55.55%) cases of moderately differentiated carcinoma [12]. Comparable to these findings, we uncovered 19(54.28%) cases of well differentiated and 7(20%) cases of moderately differentiated incidental adenocarcinoma. Amongst the clinically suspected carcinoma, 4 (11.42%) were well differentiated adenocarcinoma, 2(5.71%) were poorly differentiated adenocarcinoma, 2 (5.71%) mucin secreting carcinoma and 1(2.85%) case of adenosquamous carcinoma.

We ascertained incidental gallbladder carcinoma that disclosed perineural infiltration in 4 and lymphovascular emboli in 1 subject. Apart from that positive margin was observed in 3 samples with omental deposit in one subject. We also chanced upon 2 clinically suspected gallbladder carcinoma infiltrating the liver and CBD with a case demonstrating pancreatic intrusion. Besides that, lymphovascular emboli were detected in 2, perineural infiltration in 1, positive margin in 3 and lymphnodal metastasis in one specimen. Similarly Shrestha R et al. distinguished metastasis in liver (4 specimen) and other organs; viz pancreas (2 cases), duodenum, colon and omentum (1 case) and ovary (1 case) [17]. Among the 6 cases of incidental carcinoma Sujata J et al. established one case presenting with infiltration of the liver bed and positive resected margin [14].

Further insight into our research revealed lower staging of tumors in incidental gallbladder carcinoma compared to clinically suspected carcinoma. The tumor staging of incidental carcinoma presented 4 (15.38%) cases in T3 stage, 11 (42.30%) cases in T2b, 9(34.61%) cases in T1b and 2 (7.69%) cases in T1a stage. In cases of clinically suspected carcinoma, T2b and T3 stage was witnessed in 3(33.33%) cases each and T1a, T1b and T2a was detected in 1(11.11%) case each. Islam MJ et al. in their series observed 12 cases of incidental carcinomas comprising of 9 (75%) cases in stage T1 and 3 (25%) cases in stage T2 and none showed distant metastasis [7]. Likewise, Sujata J et al. recorded 3(50%) cases in stage T1a, 1 (16.6%) case each in stage T1b, T2 and T3 [14]. Several other analysis have also recorded T1a cases of incidental gallbladder carcinoma to vary from 15 to 22.22%, T1b ranging from 20 to 75% and T2 cases stretching from 10 to 60% of cases [12,15,17].

Majority of gallbladder carcinoma are diagnosed in their advanced stages with histological subtype, grade, and stage of the tumor at the time of presentation contributing to its prognostic value [18]. As a consequence of its late diagnosis; the overall mean survival rate for patients with gallbladder carcinoma is 6 months, with a very poor 5-year survival rate of 5% [16,18].

### 5. Strength and limitation of the study

The study encompassed a large target population over a period of 16 years in a single tertiary care hospital. The study shows the importance of histopathological evaluation of all resected gallbladder specimen irrespective of clinical suspicion. The limitation of this study includes the fact that it was a single centre study and may not represent the entire population, further this was a retrospective cohort study, and so many predictive variables could not be assessed in the study.

**Table 6**  
Diagnostic correlation with clinical diagnosis, radiological and pathological findings in clinically suspected carcinoma (n = 9).

Diagnosis	No of cases	Clinical Diagnosis			Radiological Findings			Gross Findings			Wall thickness (cm)			Tumor size (cm)			Microscopic Findings			Tumor staging		
		Cholelithiasis		Chronic cholecystitis	Obst Jaundice	Rt lobe liver infiltration	CBD	Pancreas	GB size (cm)	Range	Mean	Range	Mean	Range	Mean	L. Emboli	PNI	Margin positive	LN positive	T1	T2	T3
		Cholelithiasis																				
		Cholelithiasis	Cholelithiasis	Cholelithiasis	Cholelithiasis	Cholelithiasis	Cholelithiasis	Cholelithiasis	Cholelithiasis	Cholelithiasis	Cholelithiasis	Cholelithiasis	Cholelithiasis	Cholelithiasis	Cholelithiasis	Cholelithiasis	Cholelithiasis	Cholelithiasis	Cholelithiasis	Cholelithiasis	Cholelithiasis	
Adenocarcinoma	4	1	3	-	1	1	1	6-9	8.1 ± 1.43	0.2-0.5	0.37 ± 0.15	0.2-3.8	2.07 ± 1.68	-	-	1	-	1	1	1	1	
Well differentiated																						
Poorly differentiated	2	-	2	-	1	1	1	5-9	7 ± 2.82	0.5-1.3	0.9 ± 0.56	1.3-6	3.65 ± 3.3	1	1	1	-	-	-	1	1	
Mucin secreting	2	-	1	1	-	-	-	6-9	7.5 ± 2.12	0.3-0.7	0.5 ± 0.28	1.5-4	2.75 ± 1.76	1	-	-	1	-	-	-	1	
Adenosquamous Carcinoma	1	-	1	-	-	1	1	9	9	0.2	0.2	0.2	0.2	-	-	1	-	-	-	-	1	
Total	9	1	7	1	2	3	1	5-9	7.83 ± 1.65	0.2-1.3	0.5 ± 0.34	0.2-6	2.3 ± 1.97	2	1	3	1	1	1	1	3	

CBD- Common bile duct, L. Emboli- Lymphatic Emboli, PNI – Perineural infiltration, LN – Lymphnode.

**6. Conclusions**

From our research we have perceived that incidental carcinomas are more frequent than clinically suspected carcinoma with female preponderance in both the events. More association of gallstones was observed in incidental carcinoma. Higher stage is witnessed in clinically suspected than incidental carcinoma with adenocarcinoma being the predominant histological type ranging from well to poor differentiation.

**Participation selection**

All the cases of gallbladder carcinoma were taken into study irrespective of their age and sex over a period of 16 years.

**Dissemination**

This work will be published in a peer-reviewed journal and presented at national level meetings.

**Ethical approval**

Ethical approval was granted from the Institutional Review Committee - MEMG/IRC/434/GA.

**Sources of funding**

None.

**Author contribution**

DG – Study concept, design and paper writing. AKJ – Data collection and data analysis. AG – Data interpretation and editing paper writing. MKS – Data interpretation and editing paper writing.

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**Guarantor**

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**Declaration of competing interest**

None.

**Appendix A. Supplementary data**

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.amsu.2021.102753>.

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