

STUDY OF INCIDENTAL CARCINOMA ON ROUTINE CHOLECYSTECTOMY SPECIMENS - A STORY OF A DILIGENT PATHOLOGIST

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ABSTRACT

BACKGROUND

Gallbladder cancer (GBC) is the fifth most common cancer of the gastrointestinal tract and the most common cancer of the biliary tract. Despite advancements in various diagnostic procedures, preoperative diagnosis of GB carcinoma is an exception rather than the rule with most of the cases diagnosed incidentally on histopathological examination.

METHODS

This study includes 1320 cholecystectomy specimens, which were removed, during a period of 3 years in a tertiary care hospital. The clinicopathological findings and radiological findings of all the cases detected as gall bladder cancers were recorded; age, sex, presenting symptoms, presence of gallstones and histological grade and staging of tumours were included. Incidence of IGBC were then studied.

RESULTS

Among the 1320 cholecystectomy specimens, 17 cases were diagnosed to be cases of malignant disease. Out of 17 cases of gall bladder carcinoma 14 (1.06%) cases were incidentally detected on histopathological examination with rest of the 3 cases were already suspicious in preoperative investigations. Among IGBC F:M ratio is 6:1 with median age of patient being 52 years. In our study, more than 80% of cases of gall bladder carcinoma were detected incidentally.

CONCLUSIONS

Histopathological examination of cholecystectomy specimens remains the gold standard for the detection of this occult, yet notorious malignancy since maximum cases of GBC were diagnosed incidentally.

HOW TO CITE THIS ARTICLE: Aggarwal I, Mukerjee G, Mondal R, et al. Study of incidental carcinoma on routine cholecystectomy specimens- a story of a diligent pathologist. J. Evid. Based Med. Healthc. 2019; 6(20), 1514-1518. DOI: 10.18410/jebmh/2019/306

BACKGROUND

Gallbladder cancer (GBC) is the fifth most common cancer of the gastrointestinal tract and the most common cancer of the biliary tract.¹ The prevalence of GBC varies considerably between different geographic areas.

The reports from Indian population-based cancer registries suggest that the GBC is common in Delhi, Cachar, Kamrup where it is the 3rd most common site in females followed by Bhopal, Sikkim and Kolkata where it is the 4th most common cancer in females.²

The clinical manifestations of gall bladder carcinoma are generally indistinguishable from those associated with cholecystitis or cholelithiasis. Cholecystectomy (open/laparoscopic) is performed for patients with gallstone disease and benign gallbladder conditions. With greater

availability of ultrasonography, cholecystectomy has become the commonest surgical procedure performed worldwide. As result of this, there is an increase in the number of patients with incidentally discovered gallbladder cancer (IGBC).

Incidental gallbladder carcinoma (IGBC) is defined as Gallbladder carcinoma diagnosed histopathologically after cholecystectomy done for benign gallbladder disease. It is also known as occult/inapparent/missed Gallbladder carcinomas.³ Most of these patients do not have a radiological or intraoperative suspicion for malignancy.

Despite advancements in various diagnostic procedures, preoperative diagnosis of Gallbladder carcinoma is an exception rather than the rule, occurring in very few patients in most of the studies. Advanced stage of the disease because of delayed diagnosis leads to its poor prognosis except when diagnosed at early stages incidentally during routine cholecystectomies.

The concern whether routine histopathological examination is needed for all cholecystectomy specimens done for benign gallbladder diseases is still debatable.

From this study, we are reporting our experience with gallbladder cancer, which was incidentally diagnosed after cholecystectomy, which was performed for gallstone disease and cholecystitis.

Financial or Other, Competing Interest: None.

Submission 27-04-2019, Peer Review 04-05-2019,

Acceptance 13-05-2019, Published 20-05-2019.

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DOI: 10.18410/jebmh/2019/306

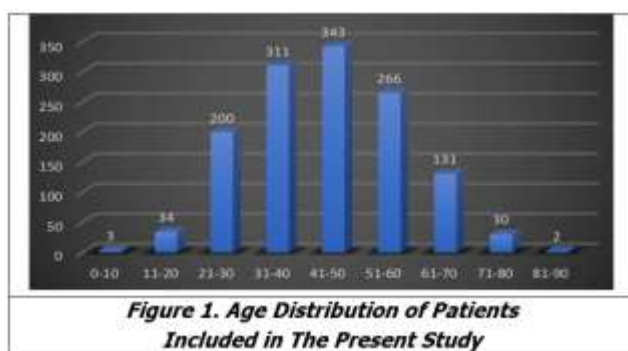


METHODS

This retrospective study was based on 1320 gallbladder specimens obtained from cholecystectomy procedures conducted at a tertiary teaching hospital IQ city medical college and NH Hospital in Durgapur, during a period of three years. The gross examination was done after fixing the specimens with 10% formalin. Gross morphological findings of size, external surface, thickness of wall, mucosa, presence of stones and lymph node were noted. For each specimen, three sections were obtained for entire thickness of wall each from fundus, body and neck of specimen. Sections from lymph nodes were also taken wherever found. Supplementary sections were taken after regrossing in cases of incidental gallbladder carcinoma. Routine tissue processing was done. 4-6-micron thickness sections were obtained from paraffin-embedded tissue followed by routine Haematoxylin & Eosin staining and detailed microscopic evaluation were done for various lesions of Gallbladder. American Joint Committee on Cancer (AJCC) staging system was used for staging gallbladder carcinoma. The main objective of the study is to find out the incidence of incidental gallbladder carcinoma

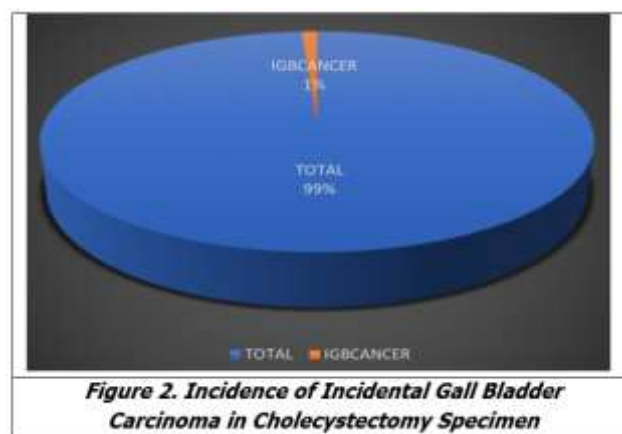
RESULTS

Over a period of three years, 1320 patients were admitted in surgery department for cholecystectomy, and all the specimens were received in pathology department. Out of these 352 were male (13%) and 968 were female (87%) with a female to male ratio of 2.75:1. The age ranged from 10 to 83 years, with most of the patients were in the age group of 41-50 years (26%). (Figure 1)

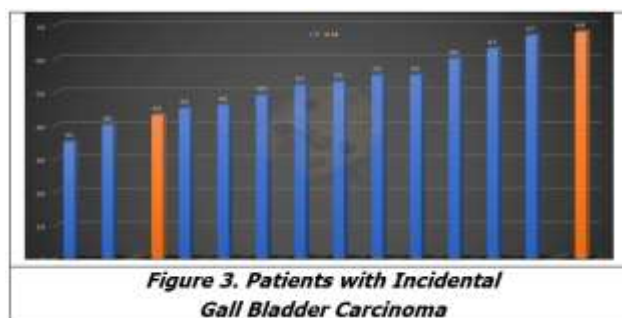


Majority of the patients presented with pain in right hypochondrium associated with nausea and vomiting. Almost all of the patients included in the study primarily had cholelithiasis.

Among the 1320 cholecystectomy specimens, 17 cases were diagnosed to be a case of malignant disease. Out of 17 cases of gallbladder carcinoma 14 (1.06%) cases were incidentally detected on histopathological examination with rest of the 3 cases were already suspicious in preoperative investigations. (Figure 2) Other cases were benign in nature with different type of conditions. Benign conditions of gallbladder were mostly chronic cholecystitis frequently associated with ulceration of mucosa, prominent Rokitansky-Aschoff's (RA) sinus, cholesterosis and xanthogranulomatous changes.



Out of 14 patients that were incidentally diagnosed as gall bladder carcinoma 12 were female and 2 were male (F:M::6:1). Minimum age of presentation was 35 year and maximum age of presentation was 68 years with mean age of presentation 52 years. (Figure 3) Clinically and radiologically no patients had any suspicion of malignancy.



Ultrasonography revealed stones in almost all patients. On gross examination thickening of gall bladder wall was noticed in 10 cases and polypoid tumour mass with delicate papillary projections observed in 4 cases.

Sites involved by tumour were fundus, body and neck of gallbladder. On microscopic examination, 7 cases showed features of well differentiated adenocarcinoma, 6 cases were of moderately differentiated adenocarcinoma and 1 case showed features of poorly differentiated carcinoma.

According to AJCC staging system, tumour cells were seen infiltrating the muscularis propria in 2 cases (pT1b) and perimuscular connective tissue without involving serosa in the 12 cases (pT2). Lymphovascular invasion and perineural invasion were seen in 2 cases and 4 cases, respectively. Cystic duct margin was found to be involved only in one case.

The details of the 14 cases of incidental gallbladder carcinoma has been described in Table 1.

Age/ Sex	Macroscopic Finding	Microscopic Diagnosis	Site	Cystic Duct Margin	Lymphovascular Invasion	Perineural Invasion	TNM Staging
49/F	Thickened wall 0.7 cm	Moderately differentiated adenocarcinoma	Fundus, Body	Not involved	Present	Not seen	pT2NxMx
60/F	Thickened wall 0.6 cm	Moderately differentiated adenocarcinoma	Fundus, Body	Not involved	Not seen	Not seen	pT2NxMx
55/F	Thickened wall 0.5 cm	Moderately differentiated adenocarcinoma	Fundus, Body	Not involved	Not seen	Not seen	pT2NxMx
68/M	Irregular mucosa with small papillary projections	Well differentiated adenocarcinoma	Neck	Not involved	Not seen	Not seen	pT1bNxMx
35/F	Irregular mucosa with small papillary projections	Well differentiated adenocarcinoma	Fundus	Not involved	Not seen	Not seen	pT2N0Mx
63/F	Thickened wall 0.8 cm	Moderately differentiated adenocarcinoma	Fundus, Body, Neck	Involved	Present	Present	pT2NxMx
45/F	Thickened wall 0.5 cm	Well differentiated adenocarcinoma	Fundus	Not involved	Not seen	Not seen	pT2N1Mx
53/F	Thickened wall 1 cm	Moderately differentiated adenocarcinoma	Fundus, Body	Not involved	Not seen	Present	pT2NxMx
43/M	Thickened wall 0.8 cm	Moderately differentiated adenocarcinoma	Fundus, Body	Not involved	Not seen	Present	pT2aNxMx
52/F	Thickened wall 0.4 cm	Well differentiated adenocarcinoma	Fundus, Body	Not involved	Not seen	Not seen	pT2N0Mx
67/F	Irregular mucosa with small papillary projections	Well differentiated adenocarcinoma	Fundus, Body, Neck	Not involved	Not seen	Not seen	pT1bNxMx
55/F	Irregular mucosa with small papillary projections	Well differentiated adenocarcinoma	Fundus, Body, Neck	Not involved	Not seen	Not seen	pT2aN0Mx
40/F	Thickened wall 1 cm	Well differentiated adenocarcinoma	Fundus, Body	Not involved	Not seen	Not seen	pT2N0Mx

Table 1. Histological Findings of Patient with Incidental Gall Bladder Carcinoma

DISCUSSION

Adenocarcinoma of the gallbladder represents 80%–95% of biliary tract cancers. Carcinoma of the gallbladder is more frequent in females than males (3-4:1 ratio), and over 90% of the patients are 50 years of age or older at the time of diagnosis.^{4,5} In our study median age of the presentation with GBC is 52 years. Present study also revealed female preponderance of gall bladder carcinoma with F:M ratio of 6:1. Review of literature from different states from the country also showed female preponderance. (Table 2)

Cholelithiasis is a well-known risk factor for gallbladder cancers.⁶ We also found the presence of gallstones in 70% of Incidental gall bladder carcinoma. Gallstones cause mucosal irritation and chronic inflammation setting a stage for the development of dysplasia and subsequently carcinoma. This transformation requires many years to occur, therefore most cases of GBC are seen in the elderly patients.⁷

However, while most of the patients of GBC will have a history of cholelithiasis, only 1% of the patients with gallstones develop GBC.⁸

Other conditions said to be associated with an increased risk of gallbladder carcinoma are cholecystoenteric fistula, porcelain gallbladder, Primary sclerosing cholangitis, obesity, segmental adenomyomatosis, familial adenomatous polyposis/Gardner syndrome and anomalous connection between the common bile duct and the pancreatic duct.

Many of the latter cases present at an advanced stage. Although almost half of gallbladder carcinomas are found incidentally at cholecystectomy as GBC either remains asymptomatic for a long time or it presents with very non-specific symptoms like pain in the abdomen, vomiting, anorexia, jaundice, a gallbladder mass and fever.

Incidental Gallbladder Carcinoma (IGBC) is the carcinoma of the gallbladder which is suspected for the first-time during cholecystectomy or which is found on the histological examination of the gallbladder. With the increasingly widespread acceptance of Laparoscopic cholecystectomy and the difficulties in diagnosing GBC preoperatively, the number of cases of Incidental gall bladder carcinoma during and after Laparoscopic cholecystectomy has increased. Our study also showed incidence of Incidental gall bladder carcinoma to be 1%, which was in concordance with the previous literatures from different region of the country where incidence of Incidental gall bladder carcinoma ranges from 0.4-7.1%. (Table 2)^{9,10} Highest incidence (7.1%) of Incidental gall bladder carcinoma in India was found in study done by Acharyya et al in 2012 in Bankura district of West Bengal.⁹

Table 2 also showed that in many of the studies from different part of the country all the cases of gall bladder carcinoma were detected incidentally rather preoperatively.

Author	Year of Study	Place of Study	Sample Size	No. of GBC	No. of IGBC	F:M
Sangwan et al	2015	Haryana	530	10	10	4:1
Munshi et al	2015	Kolkata (WB)	500	09	09	3.5:1
Mohanty et al	2016	Orissa	1927	17	17	2:1
Bharathi et al	2017	Andhra Pradesh	252	04	03	3:1
Waghmare & Kamat	2014	Mumbai	270	07	07	All females
Sharma et al	2016	Lucknow	822	07	07	All females
Kalita et al	2013	Delhi	4115	25	18	1.14:1
Acharyya et al	2012	Bankura (WB)	631	45	45	4:1
Kumar et al	2016	Uttarakhand	502	13	07	3.3:1
Kumar et al	2015	Chennai	100	03	02	All females
Sharon W	2016	Imphal	480	07	07	2.5:1
Singh & Jaiswal	2017	Pune	1123	07	06	1.3:1
Jha et al	2019	Delhi	4800	20	02	4:1
Raina et al	2016	Hapur (UP)	464	03	03	All females
Sujata et al	2013	Delhi	622	06	06	All females
Present study	2019	Durgapur (WB)	1320	17	14	6:1
Table 2. Incidence of IGBC in Different Studies						

The ultrasonographic findings in early stage GBCs are subtle, with considerable overlaps with the findings of acute and chronic cholecystitis. Thus, preoperative USG was not useful in raising a high degree of clinical suspicion of malignancy. Similarly, gross examination did not reveal significant findings in all cases of IGBC in our study.

Grossly, gallbladder carcinoma may present as a diffusely growing (70%) or nodular, polypoid, or papillary mass (30%). When diffuse, the gross distinction from chronic cholecystitis may be difficult; it is also important to note that a significant minority of gallbladder cancers are not apparent grossly,^{11,12} indicating the need for microscopic examination of every excised gallbladder. This finding is also apparent in our study where diffuse involvement of gall bladder was found in more than 70% of the cases of GBC, as all were missed and diagnosed preoperatively as a case of chronic cholecystitis.

The vast majority arise in the fundus (70%–80%), with approximately one-third arising in the body and the remaining 10% in the neck.¹²

Present study also showed fundus involvement in 13 cases with tumour remains in fundus in 2 cases, spread to body in 11 cases and GBC arising from neck in only 1 case.

Microscopically, more than 90% of gallbladder cancers are adenocarcinomas, showing varying degrees of differentiation which correlates with our study.^{11,12}

Stage of carcinoma at presentation plays a critical role in prognosis of disease. For Tis and pT1a tumours, simple cholecystectomy is sufficient with 5-year survival rate being almost 100%. However, for pT1b tumours, radical resection is recommended. For pT2 tumors, the 5-year survival rate improves from 20% to 70% if simple cholecystectomy is followed by radical cholecystectomy after the diagnosis of IGBC.³ Results of this study showed 12 out of 14 cases of IGBC in pT2 stage and 2 case in pT1 stage. Therefore, histopathology should be done for all surgically resected gallbladders, as it is the only tool, which can detect IGBC accurately which improves patient's survival as compared to GBC.

Despite availabilities of newer diagnostic tools and careful macroscopic examination, a significantly large

proportion of these cases are still missed even at tertiary care centre.

The Royal College of Pathologists suggests a histopathological examination of all cholecystectomy specimens as normal gross morphological features may be misleading.¹³

Literature is based on need of routine histopathology of all gallstones related cholecystectomy specimens. Recently few studies have refuted its usefulness in all cases stating that it not only overburdening our pathologists but also cost ineffective due to low incidence of incidental gallbladder carcinoma.^{14,15}

In present study, also we missed 14 out of 17 cases of gall bladder carcinoma, which is significant in number. Therefore, cases of missed incidental carcinoma cannot be justified by increased cost and pathologist's workload and a routine histopathology of all cholecystectomy specimens should be advised beyond doubt.

CONCLUSIONS

Gallbladder cancers are one of the most common tumours of gastrointestinal tracts and are known to have a poor prognosis. Incidence of IGBC is low and is usually early stage cancer with a better 5-year survival rate as compared to GBC. Radiology and macroscopic findings usually fail to raise suspicion of malignancy (IGBC) in cholecystectomy specimens. Thus, histopathological examination of cholecystectomy specimens is the gold standard for the detection of occult malignancy.

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