



Research Article

RADIOLOGICAL AND EPIDEMIOLOGICAL CHARACTERIZATION OF GALLBLADDER MALIGNANCY: A HOSPITAL-BASED STUDY AT TERTIARY CARE CENTRE, NORTH CENTRAL INDIA, 2017

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ABSTRACT

Although, carcinoma of the gallbladder has a low overall prevalence, however, it is an aggressive disease with poor outcomes. Advances in imaging techniques coupled with guided biopsies have improved the preoperative diagnosis of carcinoma gallbladder. Despite achievements in the field of advanced imaging techniques, the high mortality rate of the disease remains.

The present study was conducted in a tertiary centre of North-Central India. All freshly diagnosed cases of carcinoma gallbladder reporting between January-December 2017 were included and findings regarding clinico-epidemiological profile and dual phase contrast-enhanced Computed Tomography (MDCT Scan) about radiological patterns were recorded. The relative proportion of Gallbladder carcinoma was 8.2% with an increasing trend and female preponderance. MDCT Scan revealed advanced radiological features with locoregional and distal spread suggestive of non-operable disease in most cases. Predominant involvement pattern was diffuse or asymmetric gallbladder wall thickening, with the majority of patients showing contiguous hepatic and CBD infiltration.

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INTRODUCTION

Gallbladder cancer is the most common abdominal malignancy among women in the Northern and North-Eastern part of India ^[1]. An incidence rate as high as 4.5 and 10.1 per 100 000 population of males and females, respectively, has been reported by the Indian Council of Medical Research Cancer Registry in some northern parts of India ^[2]. Well- to moderately differentiated adenocarcinoma accounts for the most common form of gallbladder carcinoma.

The incidence of carcinoma gallbladder varies widely within India. Carcinoma gallbladder is much more common, especially in women, in north and central India than in the west and south. Though the overall age-adjusted incidence rates of carcinoma gallbladder in India are low (1.0 for men and 2.3 for women per 100000 population), the incidence in women in Delhi in north India and Bhopal in central India is as high as 6.6 and 5.2, respectively, which is much higher than 0.6 in Chennai and 0.8 in Bangalore in south India ^[3]. National cancer registry program of Indian Council of Medical Research in its consolidated report of hospital-based cancer registries 2012-2014 revealed that the relative proportion of

carcinoma gallbladder varied from as high as 13.6% at Dr. B. Borah Cancer Institute, Guwahati to as low as 0.5% at Regional Cancer Centre, Thiruvananthapuram. Gender differences demonstrated a marked predominance of women over men worldwide. Women are affected 2-6 times more often than men ^[4]. Nervi *et al.* reported that increased risk of Carcinoma gallbladder is gender-related, risk being 2.8 times higher among women than for men. Also, the disease has increased incidence with increasing age in women with gallstones, as shown by a study that 10/217 women with gallstones in the 50- 59, 12/243 in the 60-69 and 13/183 in the 70-79 years age group had Carcinoma gallbladder ^[5].

Predisposing risk factors of carcinoma gallbladder include cholelithiasis, chronic biliary infections (*Salmonella typhi*, *Opisthorchis viverrini*), primary sclerosing cholangitis, and porcelain gallbladder ^[6]. Size of the gallstones may also be a risk factor, as patients with stones larger than 3 cm have a significantly greater risk of developing carcinoma ^[7]. Other factors that increase the risk of gallbladder cancer include obesity, a high-carbohydrate diet, smoking, and alcohol use ^[8]. Gallbladder polyps are associated with a risk of malignancy ^[9]. The choledochal cyst has been implicated as a risk for malignancy ^[10]. Anomalous pancreaticobiliary duct junction is a rare congenital malformation of the biliary tract, in which the pancreatic duct drains into the biliary tract outside the duodenal wall ^[11]. More prevalent in Asians (particularly

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Japanese patients), this anomaly carries a heightened risk of developing biliary tract cancer; 3-18% develop gallbladder cancer [11-13].

The exact pathogenesis remains unclear, although pooling of carcinogens in conditions causing biliary stasis or malignant degeneration of metaplastic changes after chronic inflammation is suggested mechanisms [14]. Clearly, the most significant risk factor for gallbladder cancer is the presence of chronic inflammatory state of the gallbladder, usually as a result of gallstones. Most of the variance in geographic and racial gallbladder cancer rates can be explained by the varying incidence of gallstones in the populations. Histologically, the most common type of gallbladder cancer is adenocarcinoma. Other types, such as adenosquamous carcinoma, oat cell carcinoma and sarcomas are also seen.

Cholelithiasis is a well-established risk factor for the development of gallbladder carcinoma and gallstones are present in 74%-92% of affected patients [15,16]. Gallstones cause chronic irritation and inflammation of the gallbladder, which leads to mucosal dysplasia and subsequent carcinoma [17]. Porcelain gallbladder is an uncommon condition in which there is diffuse calcification of the gallbladder wall, and 10%-25% of patients with this condition have gallbladder carcinoma [18].

The clinical presentation of the gallbladder cancer is difficult to separate from that of biliary colic. Gallbladder cancer is either detected early as an incidental finding when cholecystectomy is performed for symptomatic cholelithiasis, or late, when the tumor has invaded the bile duct or has metastasized intraabdominally. Indeed, in 15-20% of patients, carcinoma of the gallbladder is discovered in patients operated for cholelithiasis, either intraoperatively or postoperatively on histology. In only 20% of the patients, the disease is confined to gallbladder at diagnosis. The majority of the patients thus have locoregionally advanced or metastatic disease at first presentation [19,20]. Clinical manifestations of gallbladder carcinoma include right upper quadrant pain, anorexia, weight loss, and jaundice.

Imaging of carcinoma gallbladder can be done by ultrasound or computed tomography (CT) scan. Ultrasonography has a limited role in the detection of early lesions and disease staging. Therefore, CT scan is used as the modality of choice for evaluation of suspected malignant gallbladder lesion. Gallbladder carcinoma may appear at any of these imaging techniques as a mass completely occupying or replacing the gallbladder lumen, focal or diffuse asymmetric gallbladder wall thickening, or an intraluminal polypoid mass lesion [21].

Mass Occupying or Replacing the Gallbladder- This pattern being the most common, may be present in 40-65% of patients with gallbladder carcinoma at initial detection [21]. On sonography, CT, or MRI, the presence of a large gallbladder mass that nearly fills or replaces the lumen, often directly invading the surrounding liver parenchyma, is highly suggestive of gallbladder carcinoma [22]. On CT or MRI, intense irregular enhancement may occur at the periphery of large primary gallbladder carcinoma lesions during the early arterial phase. Contrast enhancement may be retained in fibrous stromal components of gallbladder carcinoma during the portal venous and delayed phases aiding differentiation from large central hepatocellular carcinomas, which have a greater tendency to wash out contrast material in these phases.

Focal or Diffuse Asymmetric Wall Thickening - Gallbladder carcinoma may present as focal or diffuse asymmetric wall thickening in 20- 30% of cases [23]. Gallbladder wall thickening can have an expansive differential diagnosis. However, at contrast-enhanced CT and MRI, diffuse symmetric wall thickening suggests a nonneoplastic process, whereas asymmetric, irregular, or extensive thickening which may have marked enhancement during the arterial phase that persists or becomes isodense or isointense to the liver during the portal venous phase should heighten suspicion of gallbladder carcinoma [24].

Intraluminal Polypoid Mass Lesion- The initial detection of gallbladder carcinoma as a polypoid lesion occurs in 15-25% of cases. Malignant lesions are usually larger than 1 cm in diameter and may have a thickened implantation base. The differential diagnosis of a polypoid gallbladder lesion includes adenomatous or hyperplastic cholesterol polyps as well as uncommon tumors [25].

Local or Distant Spread -The most common route of dissemination for carcinoma of the gallbladder is a direct invasion of the liver. The commonest mode by which gallbladder carcinoma spreads to adjacent organs is a direct extension, followed by lymphatic and vascular extension [26]. Intraperitoneal, intraductal, and neural spread of tumor also occur. The liver is the organ most frequently involved by direct contiguous spread (65% of cases), followed by the colon (15%), duodenum (15%) and pancreas (6%). Extension of the primary tumor into the liver is well depicted by CT and MR imaging. There may be non-visualization of gallbladder and adjacent hepatic margins (hepatization of gallbladder).

The CT findings of tumor invasion into the hepatoduodenal ligament include well-defined nodular masses caused by discrete lymph nodes; matted masses due to confluent adenopathy; mixed, well-defined, and confluent masses in various locations along the hepatoduodenal ligament; and infiltrating, enhancing areas of soft-tissue attenuation obscuring the portal vein margins. Infiltrative tumor growth with spread along the cystic duct to the common bile duct (CBD) may happen and appear as loss of fat planes around CBD. Infiltration of CBD leading to intraductal spread of tumor results in obstruction with upstream dilatation of CBD or intrahepatic biliary radicles (IHBR).

Lymphatic metastases progress from the gallbladder fossa through the hepatoduodenal ligament to nodal stations near the head of the pancreas. There is portal or periportal lymphadenopathy noted. The cystic and pericholedochal lymph nodes are the most commonly involved at surgery and are a critical pathway to the involvement of the celiac, superior mesenteric, and para-aortic lymph nodes retroperitoneal lymph nodes [27]. The masses produced by lymph node metastasis around the distal common bile duct and pancreatic head may mimic a pancreatic head carcinoma. Vascular involvement in form of infiltration of the hepatic artery, portal vein and their branches can be visualized in contrast-enhanced dual phase MDCT. Hematogenous metastases are most commonly seen in the liver. Pulmonary, skeletal, cardiac, pancreatic, renal, adrenal, and cerebral metastases occur less frequently. Hematogenous metastases to the liver are well depicted by CT and MR imaging.

The objective of the present study is to describe the epidemiology of gallbladder cancer among freshly diagnosed patients at a tertiary care oncology centre and to describe findings of dual phase MDCT scan regarding involvement pattern and disease extent at the time of diagnosis in patients of gallbladder cancer reporting to a tertiary hospital.

MATERIALS AND METHODS

The study was conducted in an oncology centre of a tertiary care hospital in North Central India. The hospital has a dependent population of serving Armed Forces personnel, their families, ex-servicemen and their families from the state of Uttar Pradesh, Bihar, Jharkhand, Madhya Pradesh, Chhatisgarh and Uttarakhand with an estimated number of one million. All cases of freshly diagnosed histologically /surgically proven cases of carcinoma gallbladder reporting between January 2017 to December 2017 to an oncology centre in a tertiary care institute were included in the study after having obtained a written informed consent. Only freshly diagnosed cases are included in the study. Post cholecystectomy patients and known case of carcinoma gallbladder on follow up were excluded from the study. A pretested semi-structured questionnaire was filled up for each case. The questionnaire has two parts. The first part recorded socio-demographic and clinical data about each case which included age, gender, presenting signs and symptoms, the presence of cholelithiasis, size and location of the lump, if any etc. The second part recorded the radio-imaging findings which included dual phase contrast-enhanced Computed Tomography (MDCT Scan) findings of radiological patterns, adjacent organ involvement patterns with the locoregional and distant spread.

We also analyzed the data of a total number of cases of freshly diagnosed malignancy and carcinoma gallbladder for the year 2015, 2016 and 2017 and calculated relative proportions of carcinoma gallbladder for each year.

Sample size and Sampling technique. Considering the prevalence of least common radiological presentation of Ca Gallbladder of Intraluminal Polypoid mass lesion as 15%, 5% as of level of significance and 10% as a margin of error, the sample size was calculated to be 49. A purposive sampling technique was used for this study by including all cases qualifying the inclusion criteria. The data were analyzed using SPSS version 24.0 for calculating the frequencies and proportions.

MDCT Protocol Dual-phase MDCT was performed in all patients on an MDCT scanner (Philips, 16 slice). The patients were fasting for 4-6 hr. Water (1.5-2 L) was used as an oral contrast. Initial 10-mm contiguous, non-contrast axial sections of the upper abdomen were obtained. One hundred milliliters of nonionic iodinated contrast (300 mg I/mL) was then injected at a rate of 4.5 mL/sec through a 16-gauge IV cannula using a pressure injector. Scanning was performed using a pitch of 1.5:1, a scanning time of 0.5 sec/rotation, a table speed of 7.5 mm/rotation, 250-300 mAs, and 120 kVp. Using a bolus-triggered technique by placing the cursor in the aorta at L1/L2 level and setting the threshold at 50 HU, hepatic artery phase images were obtained in a craniocaudal direction. Portal venous phase images were obtained in a caudocranial direction with a scan delay of 40 sec after the initiation of contrast injection. Images were acquired in both phases in a single breath-hold with a slice thickness of 2.5 mm and a

reconstruction interval of 1.25 mm. The rest of the abdomen and pelvis were then scanned in the axial mode by taking 10-mm-thick sections.

RESULTS

A total of 71 cases of freshly diagnosed histologically/surgically proven cases of carcinoma gallbladder were included in the study. The mean age of the cases was 60.9±8.9 years (Mean±SD), ranging from 39 to 80 years. The most affected age group was >60 years of age which accounted for about half (48%) of the cases. Females accounted for 52 (73%) cases reflecting approximately 3 times female preponderance over males.

Out of 863 freshly detected any site cancers for the year 2017, 71 cases were of gallbladder cancer accounting for 8.2% of relative proportion among all cancers. Similar figures for the year 2016 and 2015 are tabulated in table-1.

Table 1 Total number of freshly diagnosed cancers of all site and carcinoma bladder and its relative proportion

Year	All cancers	Carcinoma Gallbladder n (%)
2015	766	47 (6.1)
2016	752	60 (7.9%)
2017	863	71 (8.2%)
Total	2381	178 (7.4%)

Table 2 Dual-phase MDCT pattern of involvement in carcinoma gallbladder (n=71)

Pattern of involvement	Number of cases n (%)
Asymmetric Gallbladder wall thickening	35 (49.3%)
Intraluminal polypoidal Mass lesion Gallbladder	21 (29.6%)
mass replacing gallbladder	14 (19.7%)
Porcelain Gallbladder	1 (1.4%)
Total	71

Table 3 Radiological findings in Carcinoma Gallbladder Cases (n=71)

Associated Radiological Finding	n	(%)
GB sludge / cholelithiasis	71	100.0%
Obliteration of fat plane with liver / Infiltration of adjacent liver parenchyma	65	91.5%
Locoregional or Periportal lymphadenopathy	56	79.0%
Intra hepatic biliary radicles dilatation	43	60.6%
Omental thickening/ caking or Ascites	17	23.9%
Hepatic Metastasis	15	21.1%
Retroperitoneal/ mesenteric/ abdominal lymph nodes	14	19.7%
Loss of fat planes with CBD/ infiltration of CBD	41	57.8%
Abdominal deposits	6	8.5%
Hepatic flexure /sigmoid colon infiltration/involvement	5	7.0%

All 71 (100%) patients were found to have gallbladder calculi or tumefactive sludge which was confirmed by corroborative ultrasound.

The pattern of involvement of gallbladder in these cases included focal or diffuse asymmetric thickening of the gallbladder wall (49.3%) as the commonest pattern. This was followed by a pattern of an intraluminal polypoid mass lesion in gallbladder (29.6%). The pattern of a mass lesion in the gallbladder fossa replacing the gallbladder partially or completely (19.7%) was least common (Table 2). The patterns are depicted in Figure 1,2 and 3.

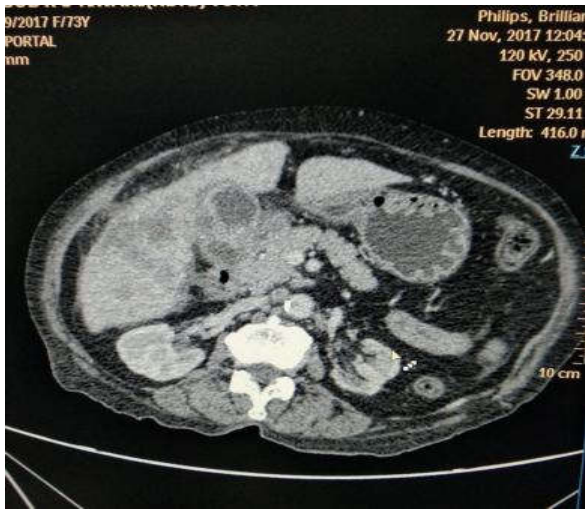


Figure 1 Asymmetric wall thickening of the gallbladder with obliteration of fat planes with the adjacent liver. Multiple metastases are also noted in the visualized liver.

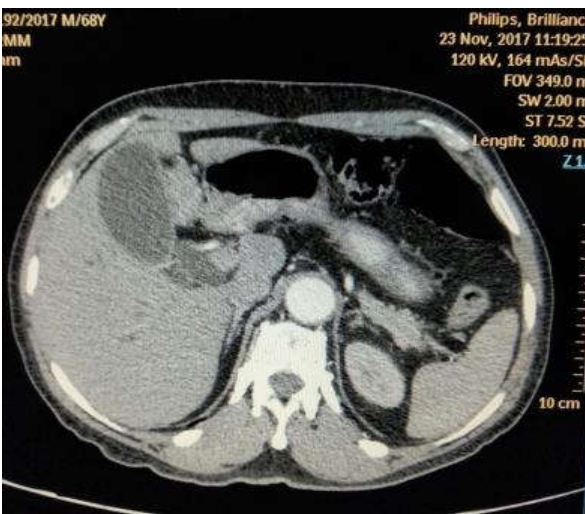


Figure 2 There is an intraluminal polypoid small mass lesion noted in the region of the neck of gallbladder.

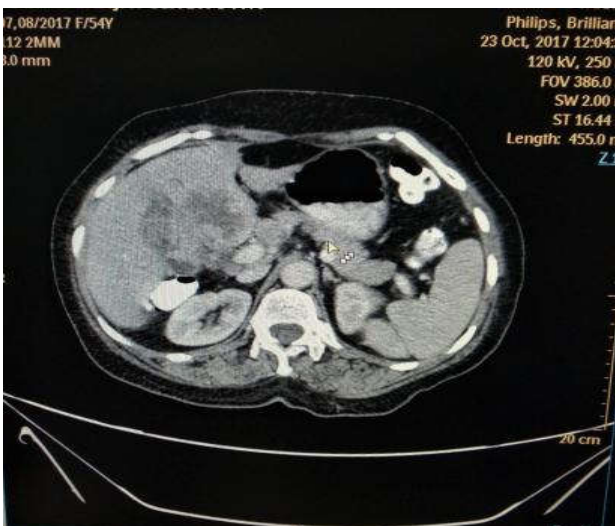


Figure 3 There is complete replacement of the gallbladder by a mass lesion which is seen infiltrating into adjacent liver with no intervening fat planes. (Hepatization of gallbladder). Multiple lymph nodes are also noted at porta.

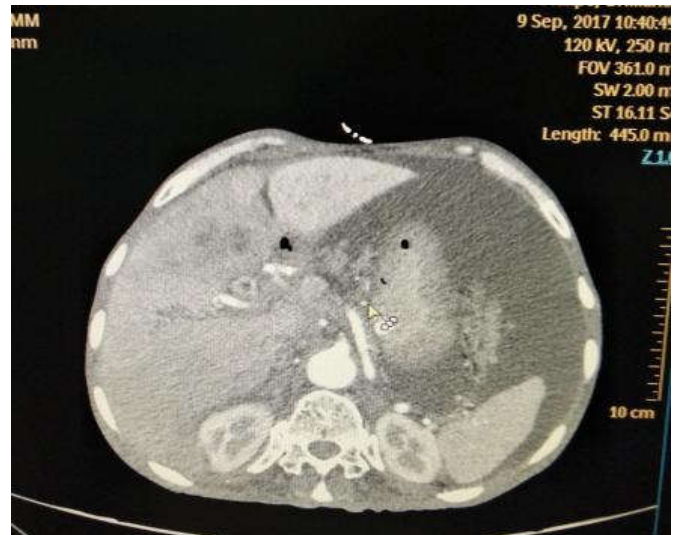


Figure 4 There is thickening of CBD wall with enhancement. Locoregional lymphadenopathy is noted. Multiple liver metastases are noted. There is transient hepatic attenuation difference noted in the left lobe of the liver.

Only one patient out of 71 was found to have carcinoma gallbladder developing into an extensive porcelain gallbladder (1.4%) in histopathological examination. Majority of lesions in these patients (91.5%) show loss of fat planes with adjacent liver with many of them showing infiltration (Table 2). A similar picture was noted in the relation of the lesion with the common bile duct. In few patients thickening and enhancement of CBD were noted (Figure 4). There was IHBR dilatation noted in 60.6% of cases. Contiguous Spread to hepatic flexure was observed in 5% of patients. Vascular involvement is noted in 22% of cases, affecting predominantly left branch of portal vein.

Periportal lymphadenopathy was noted in 79% of patients. Mesenteric and retroperitoneal lymphadenopathy was noted in 20% of cases suggesting distant lymphatic spread.

A significant number of patients (24%) show mesenteric and omental deposits and associated ascites, which categorize them as non-operable. Hematogenous spread causing hepatic metastasis is noted in 22% of patients. 9.5% of patients showed multiple pulmonary nodules suggestive of pulmonary metastases.

DISCUSSION

The study highlights the significant proportion of cancers are attributed to Gallbladder carcinoma among all freshly diagnosed cancer cases of all organs together, which is towards the higher side of national average and much higher than the western world.

The relative proportion of gallbladder carcinoma in our study for the year was 8.2%, which also showed a steady increasing trend from 6.1% in 2015 through 7.9% in 2016 to 8.2% in 2017. This relative proportion is much higher than most of the figures reported by southern hospital-based registries, however it is less than the figures reported by North eastern hospitals such as Assam Medical College and Dr. B. Borah Cancer Institute, Guwahati.

The pattern of involvement of gallbladder in these cases included focal or diffuse asymmetric thickening of the gallbladder wall (49.3%) as the commonest pattern. This was followed by a pattern of an intraluminal polypoid mass lesion

in the gallbladder (29.6%). The pattern of a mass lesion in the gallbladder fossa replacing the gallbladder partially or completely (19.7%) was least common. This pattern is different from the western studies where mass replacing the gallbladder is predominant involvement pattern. A study done by Franquet T *et al* in 50 patients of gallbladder carcinoma showed 44% of the lesions as mass replacing the gallbladder [23]. Levy *et al* in 2001 mention structural changes induced by growth of the tumor as either complete occupation or replacement of the gallbladder lumen by the mass (in 40-65% of published cases); or focal or diffuse parietal thickening (20-30% of cases), or intraluminal polyp (15-25%) [21]. Rodríguez-Fernández A *et al* in 2006 also mention similar rates [22]. This discrepancy in the pattern of involvement of gallbladder carcinoma may be population specific and further studies in the Indian population are required to confirm this finding.

Only one patient out of 71 was found to have carcinoma gallbladder developing in extensive porcelain gallbladder (1.4%) in histopathological examination. The western literature mentions comparatively high rates of association of porcelain gallbladder with gallbladder carcinoma, approximately 10%-25% of patients as described by Berk RN, Armbruster TG, Saltzstein SL [18]. This shows the lesser prevalence of this entity in carcinoma gallbladder compared to western literature and probably reflect that this entity does not have any strong association with gallbladder carcinoma in India.

There is a very strong association of cholelithiasis or tumefactive sludge with gallbladder cancer, with 100% of the patients showing these findings in our study compared to 74%-92% of affected patients in the western population [16].

The findings of MDCT showing spread of disease is comparable with western studies, where it was noted that the carcinoma gallbladder is in advanced stage at the time of diagnosis.

CONCLUSION

This study concludes that the North and Central India (Uttar Pradesh, Madhya Pradesh, Uttarakhand, Jharkhand, Chhatisgarh and Bihar) are exhibiting a significant relative proportion of gallbladder cancer among all cancers, with an increasing trend. The presentation of the disease is showing advanced radiological features with locoregional and distal spread and extent suggestive of non-operable disease in the majority of the cases. Predominant involvement pattern is diffuse or asymmetric gallbladder wall thickening, with the majority of patients showing contiguous hepatic and CBD infiltration. No specific association of porcelain gallbladder was noted with carcinoma gallbladder. Contrast-enhanced Dual phase multidetector CT scan has proven to be an excellent modality for evaluation of carcinoma gallbladder and mapping the disease extent.

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