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Original Research Article

A study the burden of carcinoma gall bladder in Hamidia hospital of Bhopal, Madhya Pradesh, India

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ABSTRACT

Background: Gallbladder carcinoma is not an uncommon clinical entity in the Indian scenario, unlike western countries. It is predominantly a disease of females. Therefore, a female especially in forties and fifties with a history of recent onset of constant pain in the right hypochondrium or change in the character of pain should be thoroughly evaluated. Though the association between gallstones and Gallbladder carcinoma is strong. Therefore, every gallbladder should be subjected to routine histopathological examination because with identification of an early gallbladder carcinoma a curative resection may be possible, and these patients have a good survival rate.
Methods: This study is comprising of all patient consecutively admitted for Gall bladder pathology, at Hamidia Hospital, Bhopal, MP during June 2012 to May 2014 on the basis of clinical assessment, USG, FNAC, CT-scan, tumor marker, blood investigation etc.
Results: Present study showed that gallbladder cancer is predominantly a disease of elderly females. Commonly, symptoms are related to associated gallstones. In present study, abdominal pain (91.66%) followed by abdominal mass (79.19%) and anorexia (60.16%). In present study, preoperative imaging of the abdomen (both US and CT) showed the presence of gallstones in 38 (79.16%) cases and a mass in the gallbladder was evident in 44 patients (91.66%).
Conclusions: Though the association between gallstones and Gallbladder carcinoma is strong, the causal relationship between them is not clear. In spite of the advances made in the field of gallbladder imaging, the detection of carcinoma of the gallbladder in early stages remains low.

Keywords: Carcinoma gall bladder, Gall stone

INTRODUCTION

Carcinoma of the gallbladder (GBC), although it has a low overall prevalence, is the most common cancer of the biliary tree and one of the most highly malignant tumors with poor prognosis.[1]

It is the fifth most common gastrointestinal malignancy following colon, pancreas, stomach. and oesophagus.[2] Gallbladder carcinoma is two to six times more common in women than men. Incidence increases with age and more than 75% of patients with this malignancy are older than 65 years. Gallbladder carcinoma is more common in Asians than in blacks and there is some evidence that the incidence is increasing in younger individuals.[3]

High rates of Gallbladder carcinoma are seen in South American countries, particularly Chile, Bolivia, and Ecuador, as well as some areas of India, Pakistan, Japan and Korea. In Chile, mortality rates from GBC are the highest in the world, where it constitutes the most common cancer affecting women and is the leading cause

of death from cancer among women.[4] The risk of Gallbladder carcinoma in patients with gallstones has been reported to have increased four to seven times.[5] The association between an abnormal pancreaticobiliary duct junction, a porcelain gallbladder, and other biliary disorders such as choledochal cyst, primary sclerosing cholangitis, Mirrizi's syndrome and gallbladder cancer has also been recognized.[6] About 1% of all elective cholecystectomies performed for cholelithiasis harbour an occult gallbladder.

METHODS

This study is comprising of all Patient consecutively admitted for Gall bladder pathology, at Hamidia Hospital, Bhopal, MP during June 2012 to May 2014.

Clinical assessment

Most of these patients are asymptomatic while a few presents with clinical features suggestive of benign disease such as right upper abdominal pain interspersed with occasional attack of nausea and vomiting. In one study, 48.2% of patients of carcinoma gallbladder had preoperative diagnosis of symptomatic cholelithiasis. About 1% of patients operated for acute cholecystitis are found to have carcinoma gallbladder. Jaundice, presence of a lump and features of malignant cachexia such as anorexia and weight loss are a feature of extensive disease as is the presence of repeated attacks of vomiting which suggests gastric outlet obstruction due to tumour infiltration.

Investigation

USG

Early carcinoma gallbladder may be detected on abdominal USG as a fixed polypoidal mass projecting in to the lumen of the gallbladder with absence of acoustic shadowing or as an asymmetric thickening of the gallbladder wall.

Advanced tumours also show loss of interface between gallbladder and liver indicating tumour invasion, lymph node and hepatic metastases, dilated bile ducts and ascites.

CT scan

The diagnostic accuracy of CT scan at 60% is lower than that of USG. Its main advantage lies in showing tumour infiltration into adjacent viscera or vessels, lymph node and distant metastases.

FNAC

USG or CT guidance greatly enhances the diagnostic accuracy of FNAC in comparison to a blind FNAC. The reported sensitivity of guided FNAC is 88%.

Blood investigation

Biochemical investigations being nonspecific have little diagnostic value. Elevated serum bilirubin and alkaline phosphatase suggests biliary tract obstruction.

Tumour marker

Tumour markers such as CEA and CA 19-9 are only occasionally elevated.

Treatment

The treatment depends primarily upon the stage of the disease at presentation. The only potentially curative therapy is surgical resection. Unfortunately, the overall resection rates at presentation range from 10-30% only. Broadly management guidelines can be divided into three clinical groups.

- Incidentally discovered carcinoma gallbladder during laparotomy or after cholecystectomy for benign disease
- Carcinoma gallbladder suspected or confirmed preoperatively on diagnostic workup
- Advanced carcinoma gallbladder diagnosed clinically or by preoperative investigations

Incidentally discovered carcinoma gallbladder

Carcinoma gallbladder is incidentally discovered during cholecystectomy for benign diseases in 12-36% of patient. If the disease is so extensive as to preclude curative resection then a biopsy along with the appropriate palliative procedure may be carried out. Most authors feel that simple cholecystectomy is adequate if the tumour has not invaded beyond the muscle layer reporting 5 years survival rates of nearly 100%. argue against this approach. They have reported a 100% 5 years survival for lesions confined to mucosa and muscularis treated by extended cholecystectomy as against 71% and 92% 5 years survival rates respectively for patients treated by simple cholecystectomy alone ($p<0.05$).[8] These authors have showed that occult carcinoma gallbladder which penetrates only the mucosa or muscle coat carries a 100% 5 years survival whereas if the serosal layer is invaded the 5 years survival decreases to 91% if resection margins are negative on re-exploration and to 43% with positive resection margins. This underlines the importance of a preoperative or at least a preoperative diagnosis. In a respectable carcinoma recognized intraoperatively, extended resection including a wedge of liver and hepatoduodenal lymphatic tissue may improve the duration of survival for patients with gallbladder cancer invading beyond the mucosa (stage I and II) but not invading contiguous structure (Stage III and IV). This extended or radical cholecystectomy means enbloc removal of the gallbladder bed. The lymphatics surrounding the portal vein, hepatic artery, porta-hepatis and the nodes behind the 2nd part of duodenum, head of

pancreases and coeliac axis are also dissected. The extent of liver resection ranges from a non-anatomical wedge resection to removal of segments IV and V Segments IV, V and VIII and even right hepatic lobectomy.[9] Patients with disease confined to the gallbladder are treated by extended or radical cholecystectomy but for disease extending beyond the gallbladder extended or radical cholecystectomy offers little, if any, survival advantage.[10,11] Reported a 5 years survival of 29% after extended cholecystectomy in patients with transmural (T3, T4) tumour invasion and lymph node involvement as compared to no survivors after simple cholecystectomy in this group of patient.[12] Advocate more extensive surgery such as excision of bile ducts, more extensive liver resections and even pancreaticoduodenectomy to further increase survival rates.[13] The criteria for respectability can vary but presence of multiple peritoneal or liver metastases, distant metastases, extensive involvement of hepatoduodenal ligament, encasement or occlusion of major vessels and poor performance status are contraindications for surgical resection. In patients not fit for tumour resection, some form of palliative procedure such as a surgical bilioenteric bypass or endoscopic/percutaneous stenting in patients with obstructive jaundice may be done. In the presence of tumour invasion of the umbilical fissure of the liver, segment III bypass is not possible, and recourse has to be taken for an alternative approach such as the Longmire procedure.[14] Advances in endoscopic and radiologically guided percutaneous stenting have made operative bypass procedures in patients with unresectable cancer largely redundant. For patients with distal common bile duct obstruction an endoscopically placed stent provides good palliation whereas the percutaneous approach does the same for more proximal obstructions.

Radiotherapy

Radiotherapy has been used primarily as an adjuvant treatment following surgery. The 3 years cumulative survival rate was 10.1% for patients receiving intraoperative radiotherapy after resection surgery whereas it was nil for a similar group of patients undergoing resection alone. However, carcinoma gallbladder is not only relatively radioresistant but also the proximity of sensitive normal tissues limits the delivery of large doses of radiotherapy.

Chemotherapy

5-Fluorouracil (5-FU) either alone or in combination has been widely used but without much success. It offers no survival benefit, however hepatic arterial infusion of mitomycin C with or without systemic 5-FU was associated with increased survival rates.[15]

Prognosis and survival

The stage at presentation is the most important prognostic determinant. Presently, the overall survival carcinoma gallbladder is extremely discouraging have shown 2 years survival is 45% for stage I, 15% for stage II, 4% for stage III and 2% for stage IV.[16] Medical survival is 19, 7, 4 and 2months for stage I, II, Ill and IV disease respectively. Surgery offers the best chances of cure.

RESULTS

During this 2 years study period a total of 48 patients with gallbladder carcinomas were observed (Table 1). Males contributed 11cases (22.91%) and females 37 cases (77.09%), with a male to female ratio of 1:4. The age of the patients ranged from 35-82 years (mean 55 years). The peak age of presentation was the fifth decade of life (Table 2). On the basis of economic status, patients were divided into three groups: Poor (62.6%), Middle class (22.2%) and Upper class (15.2%). The most common presenting features were pain in right hypochondrium and epigastrium in 44 patients (91.66%) and abdominal mass in 38 patients (79.19%) (Table 3). The symptoms were present for an average duration of 4.8 months prior to presentation. Laboratory investigations revealed anemia, (Hb<10g/d1) in most of the patients and leukocytosis (TLC>10, 000/mm3) in 21.2% patients (Table 4).

Table 1: Distribution of age of patients.

Age	No.	%	Male	Female
10-20	-	-	-	-
21-30	-	-	-	-
31-40	2	4.16%	1	1
41-50	8	19.66%	2	6
51-60	25	52.08%	6	19
61-70	7	14.52%	2	5
71-80	4	8.32%	0	4
81-90	2	4.16%	0	2
Total	48	100%	11	37

Table 2: Distribution of symptoms and sign.

	No. of cases	Percentage
Symptoms		
Abdomen pain	44	91.66 %
Anorexia	29	60.66 %
Dyspepsia	27	56.25 %
Weight loss	22	39.28 %
Jaundice	16	33.33 %
Nausea and vomiting	15	31.25 %
Malaise	13	27.08 %
Pruritis	12	25 %
Signs		
Abdomen mass	38	79.19 %
Icterus	18	37.50 %
Ascities	11	22.91 %
Cachexia	8	19.66 %
Fever	5	10.41 %

Preoperative imaging of abdomen (including US and CT) performed in all the patients showed: Gallstones in 38 patients (79.19%). There was evidence of lymph node enlargement in 13 patients (27.08%) and involvement of liver in 26 patients (42.85%).

Table 3: Lab, parameters of patients.

Lab parameter	Mean	Range
Hb (gm/c11)	8.1	4.2 - 12.8
Serum bilirubin (mg/dl)	2.8	0.4 - 25.3
Serum ALP (IU/1)	938.6	79 - 2255
Total proteins (gm/dl)	6.9	4.8 - 8.3
Serum albumin (gm/dl)	3.5	1.9 - 5.2

Table 4: Ultrasound and CT scan findings.

Ultrasound	CT scan
GB mass lesion -40	GB mass lesion -44
GB wall Thickening -1	GB wall Thickening -3
Invasion of Liver -12	Invasion of Liver -20
Liver Metastasis -10	Liver Metastasis -14
Lymph node Involvement-4	Lymph node Involvement - 18
Ascitis -8	Ascitis -12
Peritoneal Metastasis -0	Peritoneal Metastasis -6
Gall Stones -38	Gall Stone -38

Table 5: Stages of patients.

Stage	No. of cases
Stage I	6
Stage II	8
Stage III	7
Stage IV	27

Table 6: Gross morphology in 15 resected specimens.

Site	No.	Percentage
GB mass lesion	12	80 %
Body	5	33.33 %
Fundus	3	20 %
Infundibulum/Neck	2	13.33 %
Whole GB	2	13.33 %
GB wall Thickening	2	13.33 %
Area could not be specified	1	6.66 %
Total	15	100 %

Surgical exploration was performed in 15 patients Gallbladder resection was done in 6 patients (including incidentally diagnosed gallbladder carcinomas in 2 patients and only biopsy, with or without bypass and biliary drainage in 8 patients. In 30 patients, (62.50%) diagnosis of malignancy was achieved by fine needle aspiration cytology (FNAC), both direct and image guided. FNAC was inconclusive in 3 patients due to inadequate material or presence of necrotic material only. Findings on gross and histopathological examination of the resected surgical specimens are showed (Table 5,6).

Table 7: Histopathological findings in surgical specimen.

Histopathological variant	No.	Percent %
Adenocarcinoma (NOS)	28	82.35°A
Well differentiated		
Moderately differentiated	17	
Poorly differentiated		
Papillary adenocarcinoma	2	5.88 %
Mucinous adenocarcinoma	1	2.94 %
Squamous cell carcinoma	3	8.82 %
Total	34	

Staging of the patients was done according to MCC TNM 6th edition: Stage I in 6 patients (12.50%), stage II in 8 patients (16.66%), stage III in 7 patients (14.5%) and stage IV in 27 patients (56.25%). Surgical resection of gallbladder (cholecystectomy/ radical cholecystectomy) was performed in all the stage I patients and stage II patients. All stage II patients and stage III patients were given chemotherapy besides surgical resection. In 17 stages III and IV patients, surgical exploration with only biopsy and chemotherapy, with or without bypass and biliary drainage was done. Diagnostic laparoscopy was performed in 8 patients, among them 4 were found to be inoperable. In 15 patients with inoperable disease, either chemotherapy or symptomatic treatment only was given. Three patients died before receiving any treatment.

DISCUSSION

Gallbladder cancer is the most common cause of death from biliary malignancies.[17] It is usually detected at an advanced stage due to its non-specific symptoms.[18] Gallbladder cancer ranks among the first five common cancers in females in Delhi, India. In the endemic zone of West Bihar and Eastern Utter Pradesh, it is the third most common malignancy of the alimentary tract.[19]

The commonest factor implicated in the gallbladder carcinogenesis is gallstones. In present study, gallstones were present in 79.16 % of cases with gallbladder cancer which is comparable to a study from MD Anderson Hospital in which 51 (88%) patients had gallstones.[20] Other study from India reported presence of gall stones in 70% gallbladder cancer patients. In a study from United States, it was found that 74% females and 26.7% males had a previous history of gallstone disease, while on pathological examination of resected specimen's gallstones were found in 69% males and 83% females, suggesting a high incidence of silent gallstones among male carcinoma patients.[21] Another study found gallstones in 41 out of 56 patients of southwestern American Indian origin, an incidence of 73.2%. In a study from Chile, an area of high incidence of gallbladder carcinoma, gallstones were found in 53 out of 54 potentially respectable gallbladder carcinoma patients. The above studies favour a casual association between gallstones and gallbladder carcinoma. In epidemiological

study 2,583 patients with documented cholelithiasis were followed for a mean of 13.3 years.[22] When these results were clubbed with another study the incidence of carcinoma in silent gallstone patients dropped to 0.4%.[23]

The present study revealed the mean age of the patients to be 55 years, with a range of 32-82 years and fifth decade as the peak age of presentation. Similar results were observed in other studies from India.[24] Results from present study showed that gallbladder cancer is predominantly a disease of elderly females; with an overall male to female ratio of 1:3.3. These results were consistent with the results of other studies where it was reported to be 1:3, 1:3 and 1:2.5 respectively. In another study, a male to female ratio of 1:1 was seen.[25]

Most of the patients in present study had a poor socioeconomic background, similar to that of one study.[26] Gallbladder Carcinoma either remains asymptomatic for a long time or presents with very non-specific symptoms. Commonly, symptoms are related to associated gallstones.[27] In present study, abdominal pain (91.66%) followed by abdominal mass (79.19%) and anorexia (60.16%) were the most common presenting features. Consistent results were reported in other studies. Clinical signs mimic benign gallbladder diseases until the invasion of surrounding structures give clue to correct diagnosis.[28]

The laboratory investigations in present study revealed anemia (hemoglobin, <10gm/dl) in 172 (86.9%) patients; hyperbilirubinemia (serum bilirubin, >2mg/dl) in 37.4%; and elevated levels of alkaline phosphatase (>100IU/m1) in 64.5% of the patients. Comparable findings were reported in other studies.[29] Abnormal serum alkaline phosphatase and gamma glutamyl transferase may be elevated in the absence of jaundice.

CT is better at detecting lesions than US. Both US and CT may fail to show local gastrointestinal and omental infiltration and peritoneal deposits.[30] In present study, preoperative imaging of the abdomen (both US and CT) showed the presence of gallstones in 38 (79.16%) cases and a mass in the gallbladder was evident in 44 patients (91.66%).

There were no false positive cases in present study. Similar results were observed in other studies.[31] FNAC (direct as well as image guided) suggested malignancy in 88.2% of cases. The sensitivity of image guided FNAC was higher than that of direct FNAC. Other studies found similar results.[32]

Adenocarcinomas are the most frequent histological subtype of the malignant gallbladder neoplasms, representing approximately 90-95% of all cases. In contrast, squamous cell or 'epidermoid' carcinomas and adeno-squamous carcinomas are rare. Adenocarcinoma, not otherwise specified, constituted the most common (87.7%) histological type followed by papillary (6.9%) and mucinous (3.8%) adenocarcinoma. Histopathology revealed comparable findings in other studies. Seven cases of incidental Gallbladder Carcinoma (3.5%) were observed in the current study: three cases had polypoidal mass, 2 had wall thickenings only and 2 cases mucosal irregularity, with gall stones in three cases.

CONCLUSION

Gallbladder carcinoma is not an uncommon clinical entity in the Indian scenario, unlike western countries. It is predominantly a disease of females. Therefore, a female especially in forties and fifties with a history of recent onset of constant pain in the right hypochondrium or change in the character of pain should be thoroughly evaluated. Though the association between gallstones and gallbladder carcinoma is strong, the causal relationship between them is not clear. In spite of the advances made in the field of gallbladder imaging, the detection of carcinoma of the gallbladder in early stages remains low. Therefore, every gallbladder should be subjected to routine histopathological examination because with identification of an early gallbladder carcinoma a curative resection may be possible, and these patients have a good long-term survival.

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