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Clinical Profile and Outcome of Gall Bladder Carcinoma

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Keywords

Gall bladder cancer, tumor marker carcinoembryonic antigen, tumor marker carbohydrate antigen – 19.9, cholelithiasis.

Abstract

Gall bladder cancer is a well-recognized malignancy of the hepato biliary tract and is the fifth most common malignancy of the gastrointestinal tract. We propose to conduct a study that will help us examine the various presentations of gall bladder cancer in our institution, identify the risk factors in our patient population, and study the pre-operative diagnostic success and treatment outcome.
The study included one year of prospective group from January 1st, 2012 to December 31st, 2012 and ten years of retrospective group from January 1st, 2002 to December 31st,2011. Total of 102 patients were enrolled in this study, out of which 25 patients were placed in the prospective group and 77 patients in retrospective group. Statistical evaluation was performed using the SPSS multivariate analysis. The most common presenting symptom was abdominal pain (98%) followed by jaundice (37.3%), vomiting (32.4%) and weight loss (29.4%). Histologically, the majority of the cases were adenocarcinoma (67.4%), which indicated to the aggressive nature of the disease. In addition, cholelithiasis was present in 75 (73.52%) of patients out of which 11.7% patients had a stone size of more than 2 cm.It was concluded that the gall bladder cancer has a dismal outcome and most of the patients were present at a very advanced stage of the disease. Extensive surgery was also not considered the best prognosis because of the debilitated conditions. Prompt investigation of the patients with symptoms suggestive of benign biliary disease and resulting of removal of all diseased gall bladders containing gallstones may prevent the disease.

Introduction

Maximilian Stoll first described gall bladder cancer in 1788[1] and even after two centuries, the tumor remains characterized as an unfavorable prognosis due to silent progression of its clinical course, limited knowledge of its etiology and poor scientific capability for epidemiological forecasting.[2] While the etiology of carcinoma of the gall bladder remains obscure, it is likely that more than one factor is important in the pathogenesis. Review of literature reveals that although cholelithiasis, genetic factors, malignant transformation of benign neoplasm of the gall bladder, congenital abnormalities, bacterial infections, occupation, xanthogranulomatous cholecystitis, chronic inflammatory bowel disease and previous biliary surgery have been all noted in association with carcinoma of the gall bladder, gall stones remain the sole major risk factor.[3]

Despite the fact that nearly 90% of gallbladder cancer specimens contain stones, however, the incidence of gall

bladder cancer in the population of patients with gall stones is 0.3% to 3%. Another major risk factor is the presence of mucosal polyps. In patients more than 60 years of age, polyp size larger than 10 mm and single polyp has a higher risk of malignant transformation. Calcification of gall bladder wall is reported to be associated with gallbladder cancer, with an incidence ranging from 12% to 61%. Chronic typhoid carriers die of hepatobiliary cancer six time more often than matched controls. Xanthogranulomatous cholecystitis is present in 8.6% of gallbladder cancer. Inflammatory bowel disease also is associated with an increased risk of carcinoma of the biliary tree and in 13% of these cases, the tumor originate in the gall bladder. The female to male ratio for gallbladder cancer is about 3:1 and the incidence of the disease peaks in seventh decade of life. The risk of cancer was more than twice in patients who chewed tobacco. Some chemicals have been implicated in gallbladder carcinogenesis, including methyldopa, oral contraceptives, isoniazid and occupational exposure in the rubber industry.[4]

A history of constant right upper quadrant pain (62%), jaundice (13%), weight loss (7%) and anemia (5%) are signs of advanced disease. The present of a palpable mass also is an ominous finding and predicts a high rate of unrepeatability and advanced disease.[5]

Laboratory investigations reveal anemia, hyperbilirubinaemia and raised levels of alkaline phosphatase. The association of elevated alkaline phosphatase without hyperbilirubinaemia with carcinoma of the gallbladder has been reported and 42% of the patients were found to have resectable lesions. Patients with gallbladder disease in whom an elevated ESR is detected may also represent a high-risk group. Sonography has improved the detection rate for gallbladder carcinoma. Sensitivities range from 70% to 100%. Sonography allows determination of the level of obstruction in cases of bile duct involvement, but only has a detection rate of 30% for peritoneal spread. Multi detector computed tomography (MDCT) is now widely available and has a reported accuracy of up to 84% in determining local extent or the T stage of primary gallbladder carcinoma and 85% in predicting resectability through its ability to delineate hepatic and vascular invasion, lymphadenopathy, and distant metastases. [6]

No treatment option has significantly altered the relentless and fatal course in the majority of patients with carcinoma of gall bladder, although a few long-term survivors have been reported. Fluoropyrimidines (FP), Gemcitabine (Gem) and Platinum compounds are the main drugs used in the treatment of biliary tract carcinoma (BTC). There was no standard chemotherapy to offer to these incurable patients until 2010, when two randomized trials provided evidence that the regimen with Gemcitabin + Cisplatin is an effective therapy for advanced biliary cancer.[7]

Simple cholecystectomy is the appropriate treatment for T1a tumors, but an extended cholecystectomy should be considered for T1b tumors. Extended cholecystectomy consists of en bloc segment 4b and 5 hepatectomy and a lymph node dissection of the porta hepatis for T2 and T3 tumors. Palliative surgery, chemotherapy and radiotherapy are the treatment options for T4 tumors. Squamous and adeno-squamous carcinomas of the gallbladder have poor prognosis. Because these tumors are silent in the initial stage, they are generally diagnosed in advanced stages. Despite recent advances in surgery of the liver and biliary tract, there has been no dramatic improvement in the prognosis of the gall bladder cancer. Five-year survival rate of 1.4 to 4.1% are generally reported. [8]

Aim: To study the clinical profile and outcome of patients presenting with gallbladder cancer.

Methods

This study was conducted in the Department of General Surgery, Christian Medical College and Hospital, Ludhiana, India. The study included a one-year prospective group from January 1st, 2012 to December 31st, 2012 and a ten-year retrospective group from January1st, 2002 to December 31st, 2011, which comprised of patients with a histopathological diagnosis of gall bladder carcinoma.

Inclusion Criteria:

All patients of histologically proven diagnosis of carcinoma of gallbladder.

Methodology:

In the prospective group, patients were enrolled after they signed a written informed consent; a detailed history was recorded from the patients as per the protocol. Total 102 patients were enrolled in this study out of which 25 patients comprised the prospective group and 77 patients in retrospective group. All patients enrolled in the study underwent a complete clinical history and physical examination, complete blood counts, liver function tests, a chest radiograph, ultrasound abdomen. Investigations like CECT

abdomen, MRCP, and ERCP was done as deemed necessary on individual basis. Patients were staged by physical examination and radiological evaluation according to the criteria established by the American Joint Committee on Cancer.

Following staging, the patients were planned for the most appropriate treatment modality. The detailed clinical profile including presenting symptoms, clinical examination findings, investigation, treatment received and outcome as per protocol.

The records of the patients in the retrospective group were obtained from the medical records department and data with regard to the clinical presentation; examination findings, investigation, treatment detail and outcome were recorded as per the protocol.

The patients in the retrospective group were contacted by post-card or telephonically based on the details available. In the prospective group, patients were followed up every month for 6.

Statistical evaluation was performed using the SPSS multivariate analysis and the clinical profile and outcome were analyzed in both prospective and retrospective groups.

Results

Distribution according to Gender

During our study period,out of the total 102 patients 24 (23.3%) were male and 78 (76.7%) were female. The male to female ratio is 1: 3.29. (Table 1)

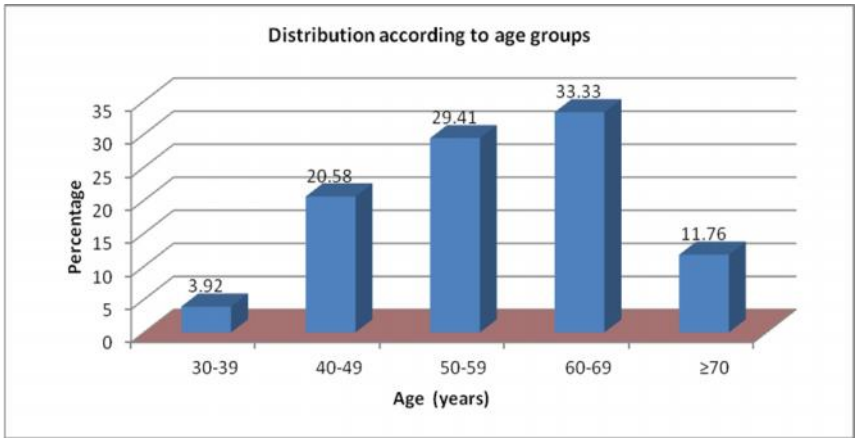
Table 1: Distribution according to Gender

Gender	No. (N)	Percentage (%)
Male	24	23.3
Female	78	76.7

Distribution according to age groups

The age at presentation with a diagnosis of gall bladder carcinoma ranged from 30 to 90 year with the majority of patients (33.33%) belonging to the age group of 60-69 years followed by, 50-59 years group (29.41%) and 40-49 years group (20.58%). The mean age at presentation is 56.16 years. (Figure 1)

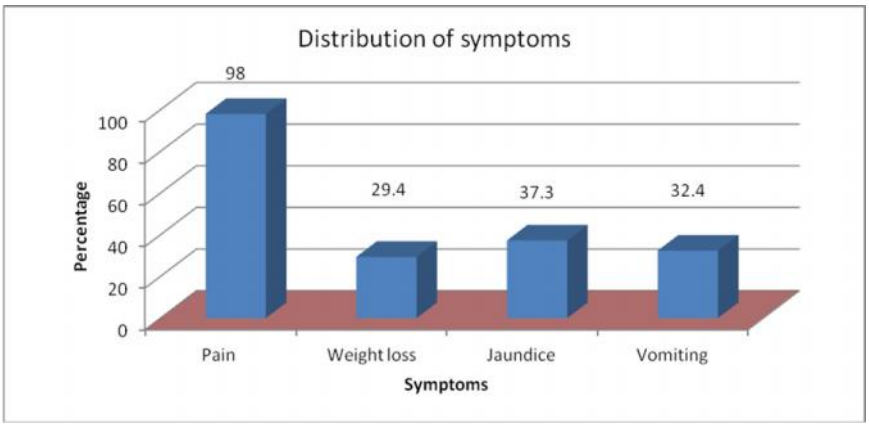
Figure 1: Distribution according to age groups



Distribution of symptoms

The most common symptom at presentation was pain (98%) followed by Jaundice (37.3%), vomiting (32.4 %) and weight loss (29.4%). (Figure 2)

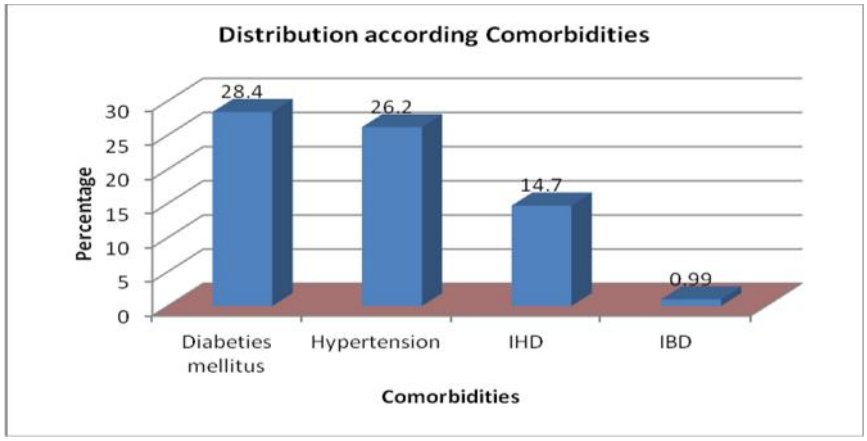
Figure 2: Distribution of symptoms



Distribution according Comorbidities

Most common comorbidities associated with gall bladder carcinoma was Diabetes mellitus (28.4%) followed by hypertension (26.2%), ischemic heart disease (14.7%), and inflammatory bowel disease (0.99%). (Figure 3)

Figure 3: Distribution of comorbidities



Distribution according to family history

In our study 5 patients (4.90%) had family history of gall bladder carcinoma while 97 (95.09%) had no history of gall bladder carcinoma in the family. (Table 2)

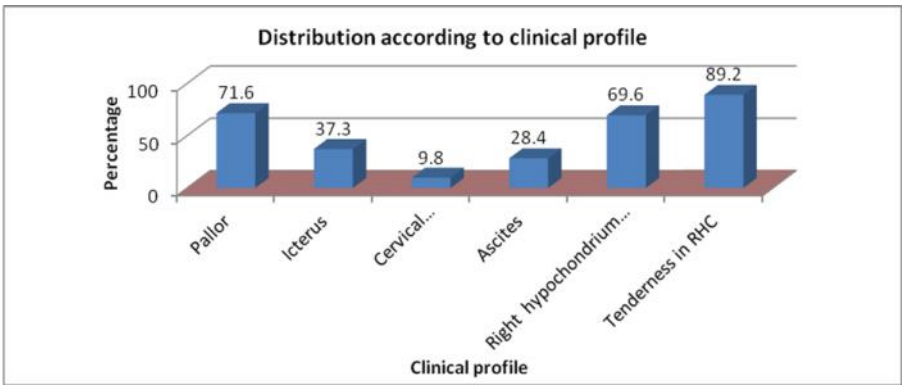
Table 2: Distribution according family history

Family history	No. (N)	Percentage (%)
Yes	5	4.90
No	97	95.09

Distribution according to clinical profile or features

The most common clinical feature at presentation was tenderness in right hypochondrium region (89.2%) followed by pallor (71.6%), right hypochondrium mass (69.6%), icterus (37.3%), ascites (28.4) and cervical lymphadenopathy (9.8%). (Figure 4)

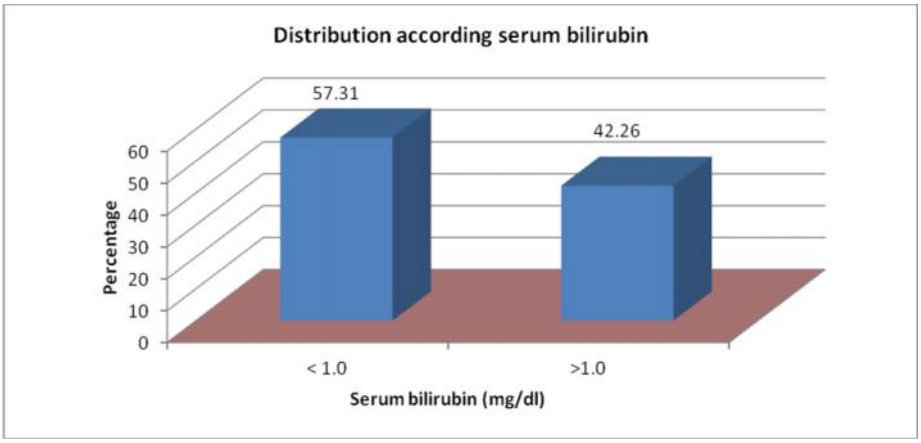
Figure 4: Distribution according to clinical profile



Distribution according serum bilirubin

In our study 42.26% of our patients presented with raised serum bilirubin levels above the upper limit of normal range. (Figure 5)

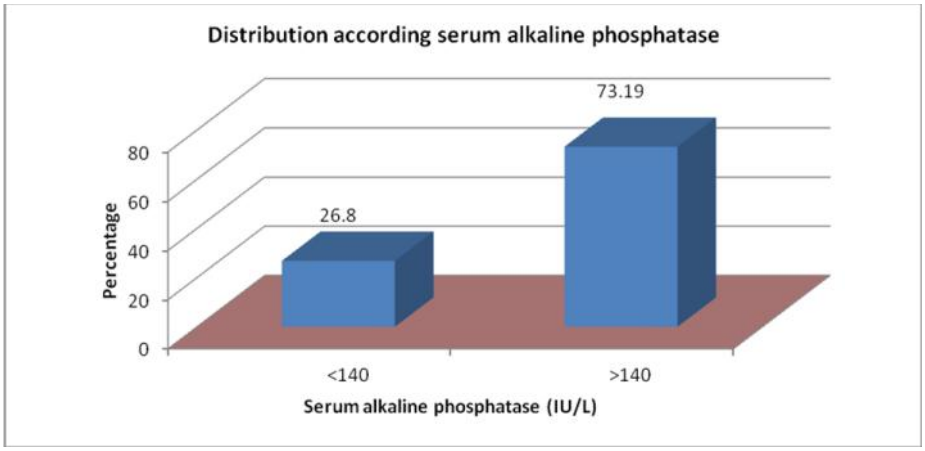
Figure 5: Distribution according to S.bilirubin level



Distribution according serum alkaline phosphatase

In our study 73.19% of our patients presented with raised serum alkaline phosphatase levels above the upper limit of normal range (20 to 140 IU/L). (Figure 6)

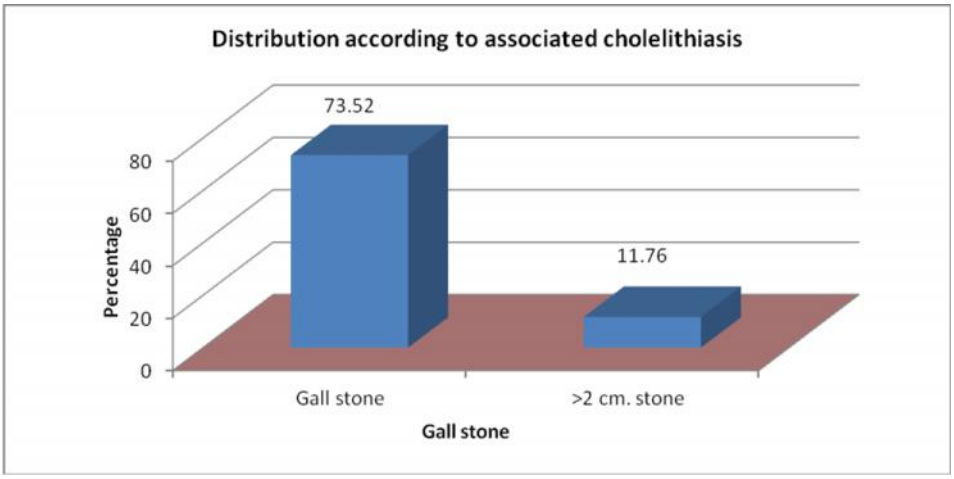
Figure 6: Distribution according to serum alkaline phosphatase level



Distribution according to associated cholelithiasis

All patients included in the study underwent ultrasonographic examination, which revealed gall stones in 75 (73.52%) patients. Out of this 11.7% patients had a stone size of more than 2 cm. (Figure 7)

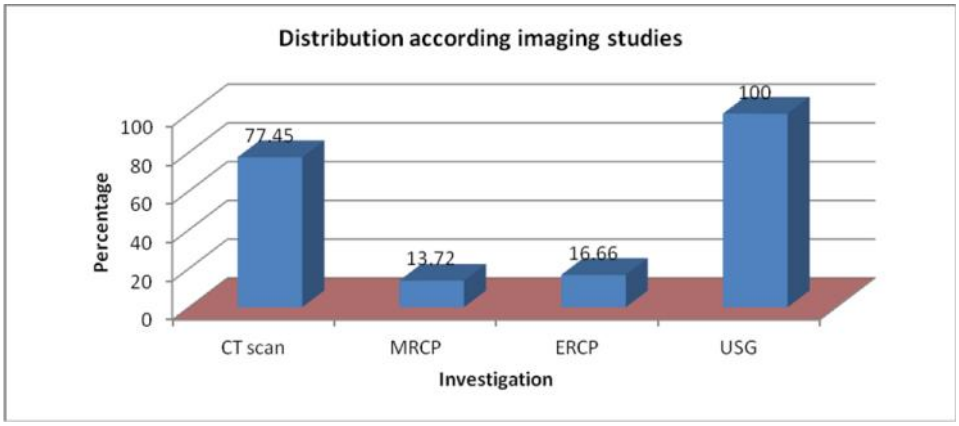
Figure 7: Distribution according cholelithiasis



Distribution according imaging studies

Most common investigation was ultrasound (100%) followed by CT scan (77.45 %), ERCP (16.66 %) and MRCP (13.72%). (Figure 8)

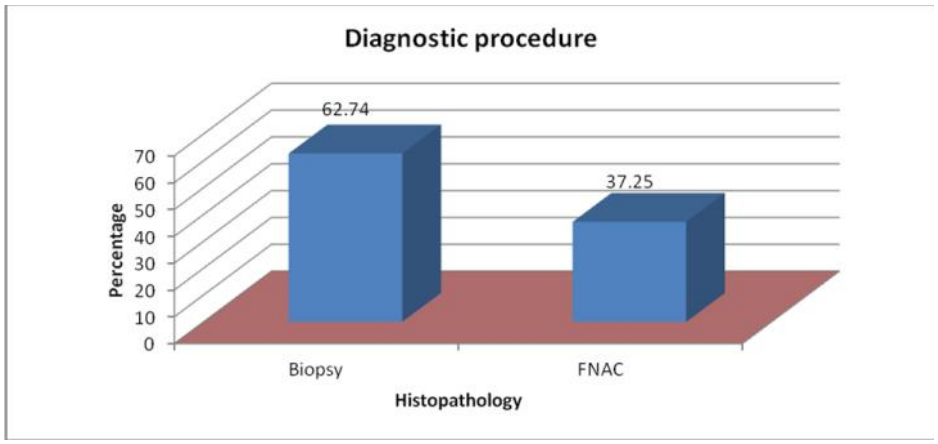
Figure 08: Distribution according imaging studies



Distribution according histopathology procedure

In our study pathological diagnosis was confirmed by biopsy in 62.74% and FNAC in 37.25%. (Figure 9)

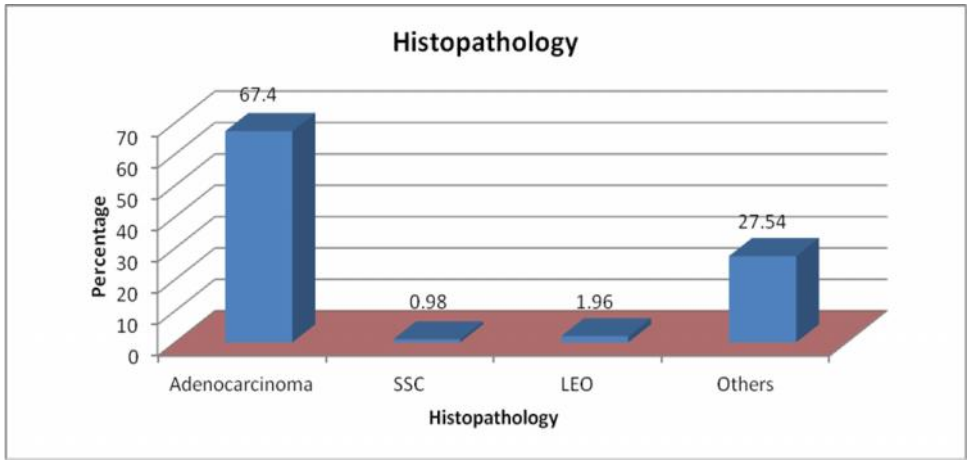
Figure 09: Distribution according histopathology procedure



Distribution according histopathology type

Adenocarcinoma was the most common pathological type found in (67.4%) patients, followed by squamous cell carcinoma (0.98%), leiomyoma (1.96%). Of the 38 patients who had FNAC, 30 patients (27.54 %) did not have a specific histological diagnosis with the report only showing malignant cells. (Figure 10)

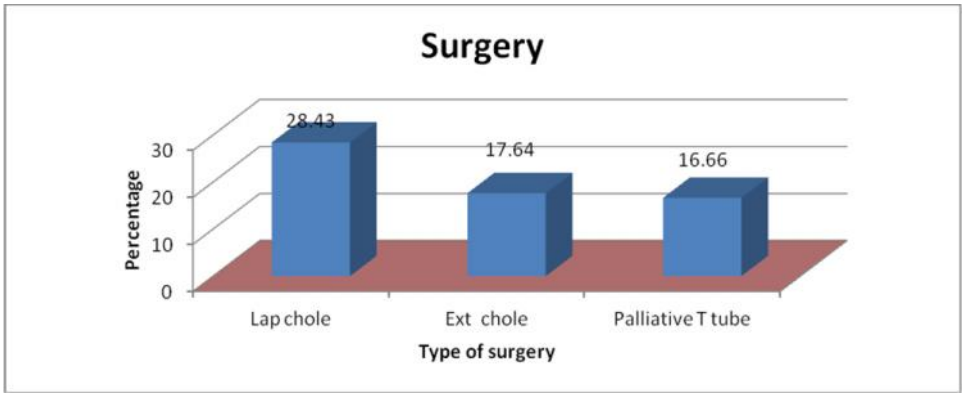
Figure 10: Distribution according histopathology type



Distribution according surgery

Cholecystectomy was done on (28.43%) patients, followed by extended cholecystectomy were performed in (17.64%). Biliary drainage as a palliative procedure was done in 16.66%. (Figure 11)

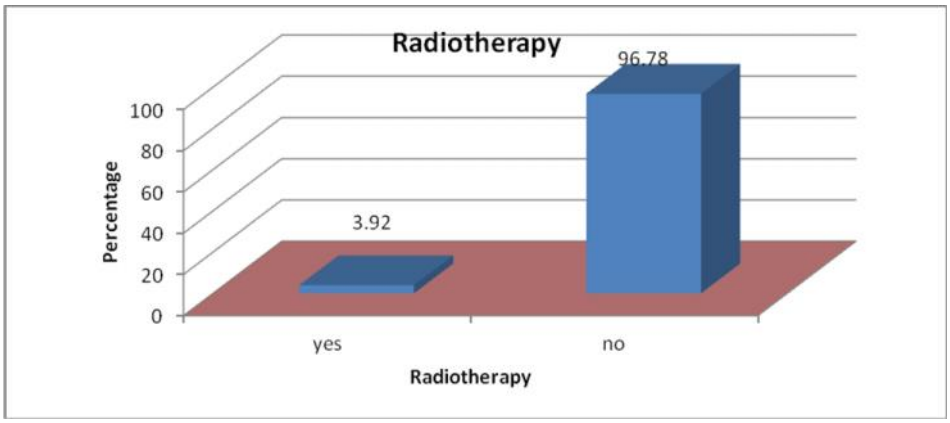
Figure 11: Distribution according surgery



Distribution according radiotherapy

In our study only 3.92% patients were received radiotherapy. (Figure 12)

Figure 12: Distribution according radiotherapy



Distribution according recurrence after surgery / Distribution according type of recurrence after surgery

In our study out of the 47 (46.07%) patients who underwent surgery, 12 (25.53%) patients presented with recurrence constituting a local recurrence rate of 17.02% and systemic 8.51(%). (Table 3/Table 4)

Table 3: Distribution according recurrence after surgery

Recurrence	No. (N)	Percentage (%)
Yes	12	25.53
No	35	74.46

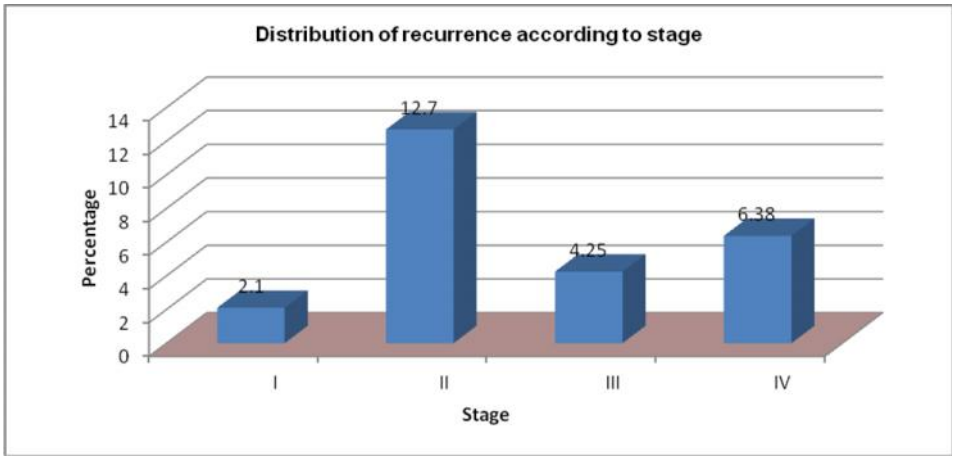
Table 4: Distribution according type of recurrence after surgery

Type of recurrence	No. (N)	Percentage (%)
Local	8	17.02
Systemic	4	8.51

Distribution of recurrence according to stage

Most common recurrence after surgery in stage II (12.7%) followed by IV (6.38%), III (4.25%) and I (2.1%). (Figure 13)

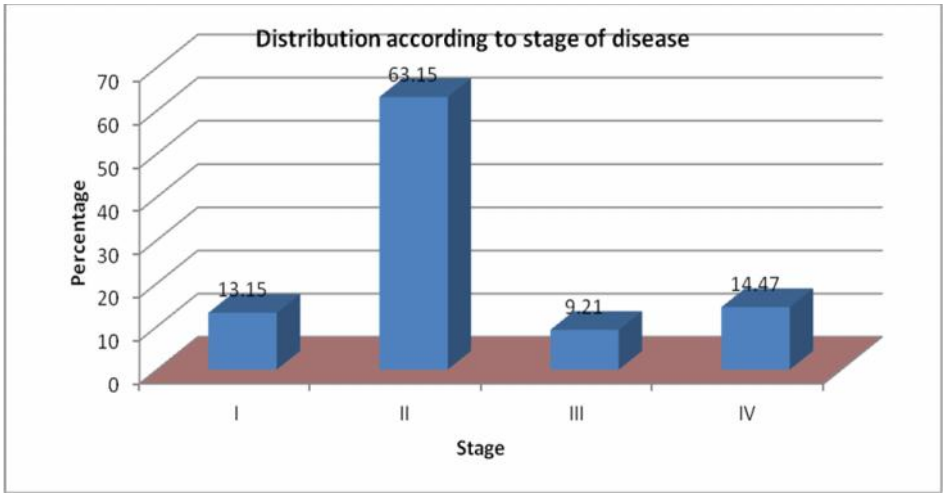
Figure 13: Distribution of recurrence according to stage



Distribution of patients according to stage of disease

The maximum numbers of patients were diagnosed at stage II (63.15%) followed by stage IV (14.47%), stage I (13.15%) and stage III (9.21%). (Figure 14)

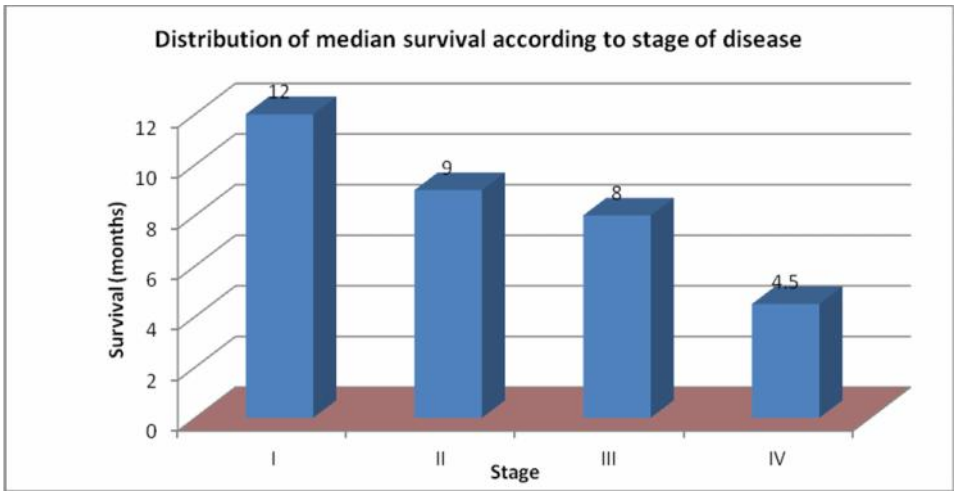
Figure 14: Distribution of survival rate according to stage



Distribution of median survival according to stage of disease

The median survival rate of stage I (12 months) followed by II (9 months), III (8 months) and IV (4.5 months). The maximum survival were 5 years and 2 months in stage I followed by 4 years in stage II, one year in stage III and one year and 10 months in stage IV. (Figure 15)

Figure 15: Distribution of medium survival according to stage of disease



Distribution according survival rate

Total 68 patients (66.66%) were followed up in our study and 24 patients were (33.33%) lost follow up. One-month survival rate 23.52%, 1 to 3 months 27.94%, 4 to 6 months 11.76% and 7 to 12 months survival rate 23.52. (Table 5)

Table 5: Distribution according survival rate

Months	No. (N)	Percentage (%)
< 1	16	23.52
1-3	19	27.94
4-6	8	11.76
7-12	16	23.52
13-24	4	5.88
25-36	2	2.94
37-48	2	2.94
49-60	1	1.47

Discussion

The geological incidence, ethnic differences and cultural variation of this disease suggest major environmental influences, rendering etiology of gall bladder cancer, which is obscure at present.

Age at presentation

In our study, age at presentation ranged from 32 to 90 years, with majority of patients belonging to the age group of 60-69 years [mean=56+16 (in years)]. The age at diagnosis ranged from 30-86 years in a study by Kapoor VK et al (2007) with mean age of 57.7 years which is similar to our study.[9]

Gender wise distribution

In our study out of 102 cases, 24 (23.3%) were male and 78 (76.8%) were female patients and male to female sex ratio 1: 3.30. This is in accordance with reports by Bhurgri et al (2002)[10]where the ratio was 1:3.

Symptoms

The most common symptom at presentation was pain (98%) followed by Icterus (37%), vomiting (32 %) and weight loss (29%). According to Albores-Saavedra et al (1986) the most common presenting symptoms were right upper quadrant pain (92%), jaundice (37.3%), weight loss (32%) and vomiting (31%).[8]

Comorbidities

The most common comorbidities associated with GBC were diabeties mellitus (28.4%) followed by hypertension (26%), ischemic heart disease (14%), and inflammatory bowel disease (0.99%). According to Tyagi BB et al (2008)[2], diabeties mellitus was seen in 21%, Ischemic heart disease was seen in 16.5% of cases.

Family history of gall bladder carcinoma

In our study 5 patients (4.90%) had family history of gall bladder carcinoma while 97 (95.09%) had no history of gall bladder carcinoma. Our figures are similar to Family-Cancer Database (2009)[11] the risk to offspring from parental gall bladder cancer was 5.05%

Clinical profile

Most common sign associated with gall bladder carcinoma was pallor (71%) followed by icterus (37.3%), and cervical lymphadenopathy (9.8%). According to Alborez-Saavedra (1986)[8] common signs were Icterus (30%), pallor (20%), and cervical lymphadenopathy (12%). Our study differs in that majority (71%) of our patients presented with pallor.

The most common finding on abdominal examination was tenderness in right hypochondrium region (89.2%) followed by mass in right hypochondrium region (69.6%), gall bladder mass in (66.7%) and ascites (28.4%). Our findings are in accordance with those of Alborez-Saavedra and Henson (1986)[8] where the most common sign was tenderness in the right upper quadrant (75%). Other signs were ascites (20%), duodenal obstruction (10%), palpable mass and hepatomegaly.

Serum bilirubin

There were a total of 56 patients (57.7%) where serum albumin level was less than 1 mg/dl and 41 (42.261%) whose serum level was above 1 mg/dl. According to Rao I et al (2006)[12] serum bilirubin less than 1 mg/dl in 65 %.

Alkaline phosphatise (ALP)

In our study 73.19% of our patients presented with raised serum alkaline phosphatase levels above the upper limit of normal range. According to De Groen et al (1999)[13] serum alkaline phosphate less than 100 IU/L was seen in 26 %.

Cholelithiasis

All patients included in the study underwent ultrasonographic examination which revealed gall stones in 75 (73.52%) patients. Stone size more than 2 cm was seen in 12 (11.7%) patients and gall bladder wall thickness more than 4 mm in (17.64 %) patients. According to Shrikhande et al (2010)[14] gallstones were found in 70% to 98% of patients with GBC, with a stone size more than 2 cm in 14.90%.

Radiological imaging

The most common investigation performed in our institution was ultrasound (100%) followed by CT scan (77.45 %), ERCP (16.66 %) and MRCP (13.72%). According to Furukawa et al (1998) CT scan was done for diagnosis of gall bladder carcinoma in (89.8 %).[15]

Histological diagnosis

In our study pathological diagnosis was confirmed by histopathology in 62.74% and FNAC in 37.25%. Watanabe et al (2000)[16] reported histologic diagnosis in (88.9%). Diagnostic accuracy for malignant and benign diseases was 100% and 83.3%, respectively.

Histopathological type

Adenocarcinoma was the most common pathological type found in (67.4%) patients, followed by leiomyoma (1.96%), squamous cell carcinoma (0.98%). The 30 patients (27.54 %) were showed malignancy in FNAC. Watanabe[16] study reported adenocarcinoma (88%) as the most common histology, followed by adenosquamous (4%), squamous (4%), small cell (3%), and neuroendocrine (1%).

Stage

The maximum numbers of patients were diagnosed at stage II (63.15%) followed by stage IV (14.47%), stage I (13.15%) and stage III (9.21%). In a study published by Mishra S etal (2003)[17] 16%, 18%, 38% , 28 % were diagnosed with stages I, II, III and IV disease.

Surgical treatment

Cholecystectomy was done on (28.43%) patients, followed by extended cholecystectomy in (17.64%). To relieve obstruction, palliative surgery was performed in (16.66%). In 2002, Puhalla H et al

(2002)[18] reported that extended cholecystectomy surgery was done in 17% to 47% of patients. Malik (2006)[19] in his series reported stenting of common blie duct to relieve obstruction in 29.8% of patients followed by ERCP in 13.9% and PTC 15.9% patients.

Adjuvant radiation therapy

In our study only 3.92% patients received radiotherapy. This is in concordance with the norms of practice where there is limited role for radiotherapy in gall bladder cancer.

Recurrence

In our study 25.53% patients showed recurrence of disease after surgery. Out of this 17.02% had local recurrence and the remaining 8.5% had distant metastatic disease. Ricardo et al (2009)[20] found that 1.1% in T1a and 9.3% in T1b and overall recurrence rate was 79%.

Survival

Sixty eight patients (66.66%) were on regular follow up while the remaining 24 patients were lost to follow up. In our study 16 patients (23.52%) were alive at the end of the year and 4 (5.88%) had 2 year overall survival. Only one patient (1.47%) survived for than 5 years. The median survival in ours series was 10 months. In a study published by Shirai Y et al (1992)[21] in patients undergoing curative surgery, the median survival time was 19 months, 8 months in patients undergoing chemotherapy and radiotherapy and 3 months for those patients who received no additional treatment other than biliary drainage procedure.

Conclusion

The study concluded that the gall bladder cancer has a dismal outcome for most of the patients that are in advanced stage of the disease. Clinical symptoms are not useful in finding of the disease at an early stage. In bladder cancer, extensive surgery was also not an alternative due to the debilitated condition and the advanced stage of the disease in the patients. Palliative surgical procedure can also be considered but are highly associated with mortality. The most common presenting symptom was abdominal pain (98%) followed by jaundice (37.3%), vomiting (32.4%) and weight loss (29.4%). Histologically, the majority of the cases were adenocarcinoma (67.4%), which indicated to the aggressive nature of the disease. Presence of hepatic metastases and involvement of porta hepatis lymph nodes indicate the advanced stage of the disease at the time of diagnosis. Most common stage at time of diagnosis was stage II (63.15%) followed by stage IV (14.47%), stage I (13.15%) and stage III (9.21%). The majority of the patients had too advanced off lesion to be treated and underwent only palliative procedures for biliary or gastrointestinal obstruction. In addition, cholelithiasis was present in 75 (73.52%) of patients out of which 11.7% patients had a stone size of more than 2 cm. Therefore, it was determined that the disease may be prevented by prompt investigation of patients with symptoms suggestive of benign biliary disease and by removal of all diseased gall bladder containing gallstones. A curative resection may be possible in such cases detected in the “preclinical stage” and long-term survival may be expected.

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