Primary Gall Bladder Carcinoma: A one year prospective study at a tertiary care center.

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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. Association between gallstones and Gallbladder carcinoma is strong. Its carcinogenesis follows a progression through a metaplasia-dysplasia-carcinoma sequence. An early diagnosis is essential as this malignancy progresses silently with a late diagnosis, often proving fatal. 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 was a prospective study done on 22 cases of gall bladder carcinomas over a period of 1 year from 1st November 2017 to 1st November 2018.

Results: Present study showed that gallbladder cancer is predominantly a disease of elderly females. In present study, abdominal pain 18 cases (81.81%) followed by anorexia 15 cases (68.18%) and dyspepsia 14 cases (63.63%) was the most common presenting symptom present. Cholelithiasis was found in only 5 (22.72%) of our patients. Adenocarcinoma was the most common histopathologic variant found in 20 cases (90.90%) followed by squamous cell carcinoma 2 cases (9.09%).

Conclusions: Every gallbladder should be subjected to routine histopathological examination because with early stage disease a curative resection may be possible, and these patients have a good long-term survival. JMS 2018; 21 (2):91-94

Keywords: Carcinoma gall bladder, Gall stone, abdominal pain, Adenocarcinoma.

INTRODUCTION

Carcinoma of the gallbladder is a rare malignancy accounting for approximately 7,100 new cases and 3,500 deaths per annum in the US. It is the most common biliary tract malignancy and the fifth most frequent gastrointestinal malignancy^[1]. In India, the prevalence of GBC varies on geographical distribution whereas it is higher in North India compared to South India^[2]. In an analysis of various cancers from Kashmir, gall bladder cancer was found to have a percentage prevalence of 2.2% with a female preponderance^[3].

Gallbladder carcinoma is two to six times more common in women than men^[4,5]. Incidence increases with age and more than 75% of patients with this malignancy are older than 65 years^[6].

The aetiology of gall bladder cancer has been a source of

speculation. The incidence of gall bladder cancer parallels the prevalence of gall stone disease; large and long standing gall stones being associated with the higher risk of gall bladder cancer^[7,8]. The risk of gall bladder cancer in patients with gall stones has been reported to have increased 4-7 times^[6]. Increasing stone size augments the risk of gallbladder cancer; stones more than 3 cm carry a tenfold increased risk when compared with smaller stones^[9]. Its clinical presentation is nonspecific and the majority of patients have advanced disease at presentation. The overall prognosis has remained dismal with a 5-year survival of 10% due to the late detection of the disease while the median survival for patients with suspected cancers is 9.2 months, and for those with incidentally diagnosed cancers, 26.5 months^[1,7]. The dismal prognosis, in part, relates to the gallbladder lacking a serosal layer adjacent to the liver, enabling hepatic invasion and metastatic progression. Improved imaging modalities are helping to diagnose patients at an earlier stage. The last decade has witnessed improved outcomes as aggressive surgical management and preoperative adjuvant therapy has helped prolong survival in patients with gallbladder cancer^[10].

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METHODS

This was a prospective study carried out in the Department of Pathology, Sher-i-Kashmir Institute of Medical Sciences, Soura over a period of 1 year from 1st November 2017 to 1st November 2018. A total of about 480 cholecystectomies were received during this period. Of these, 15 cases proved to be malignant on histopathology and these were included in our study. 3 review biopsies and 4 usg guided biopsies were also included in the study. Therefore total number of malignant lesions in our study were 22. The age, sex, relevant clinical and radiological details were recorded for each case. The specimen was processed as per standard procedure. 4-5mm thick sections were cut on microtome and stained by hematoxylin and eosin stain. The stained slides were studied in detail microscopically; and Immunohistochemistry was done wherever necessary.

RESULTS

A total of 22 patients with gall bladder carcinoma were observed during this 1 year period. Males constituted 4 patients (18.18%) and females constituted 18 patients (81.81%). Male to female ratio was 1:5. The age of patients ranged from 39 years to 80 years. (mean of 56.31). The peak age of presentation was the fifth decade of life.

Most common abdominal symptom was abdominal pain in about 18 patients (81.81%) followed by anorexia in 15 patients (68.18%) and Dyspepsia in 14 patients (63.63%) (Table 1)

Table 1: Clinical presentation of patients

SYMPTOMS	NO OF CASES	PERCENTAGE
Abdominal pain	18	81.81%
Anorexia	15	68.18%
Dyspepsia	14	63.63%
Jaundice	2	9.09%
Weight loss	14	63.63%

Cholelithiasis was found in only 5 (22.72%) of our patients. Gross morphology was studied in 15 patients. Tumor configuration was polypoidal in 7 cases (46.66%) followed by infiltrative lesion in 6 cases (40%) and gall bladder wall thickening in 2 cases (13.33%). Majority of lesions were found in the fundus of gall bladder 6 cases (40%) followed by 5 cases (33.33%) in body of gall bladder. In two cases

lesion was found in neck of the gall bladder and whole body (13.33%). Table 2

Table 2: Gross Morphology in 15 patients

Site of lesion	Tumor configuration	No of patients	Percentage
Fundus /body/Neck	polypoidal	7	46.66%
Fundus or body	infiltrative	4	26.66%
Whole GB	Infiltrative	2	13.33%
GB wall thickening		2	13.33%
Total		15	100%

On histopathology adenocarcinoma was the most common histopathologic variant found in 20 cases (90.90%) followed by squamous cell carcinoma 2 cases (9.09%). Table 3

Table 3 : Histopathological findings in surgical specimens/biopsies

Tumor Type	No of Cases	Percentage
Well differentiated adenocarcinoma	7	31.81%
Moderately differentiated adenocarcinoma	9	40.90%
Poorly differentiated adenocarcinoma	2	9.09%
papillary adenocarcinoma	2	9.09%
squamous cell Carcinoma	2	9.09%
TOTAL	22	100%

Complete TNM staging was done in 15 cases only as 3 cases were review biopsies and 4 cases were usg guided biopsies. 3 patients (20%) had stage II disease, 5 (33.33%) had stage IV disease. 7 patients (46.66%) had stage III disease. Table 4

Table 4 : TNM Staging In 15 Patients

STAGE		PERCENTAGE
I	-	
II	3	20%
III	7	46.66%
IV	5	33.33%
TOTAL	15	100%

DISCUSSION

Maxmillan Destoll is credited with the first report of gall bladder carcinoma (GBC) on the basis of two autopsies in

1777^[11]. Since then, the primary carcinoma of the gall bladder has remained a uniformly fatal neoplasm. The reasons being, a) its late presentation b) early spread by lymphatic, hematogenous and direct route c) high propensity to seed the peritoneal surfaces and d) lack of effective adjuvant therapy.

The present study revealed the mean age of the patients to be 56.31 years, with a range of 39-80 years and fifth decade as the peak age of presentation. Similar results were observed in other studies from India^[12]. Results from present study showed that gallbladder cancer is predominantly a disease of elderly females; with an overall male to female ratio of 1:5. 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^[13]. In the present study, abdominal pain (81.81%) followed by anorexia (68.18%) and dyspepsia (63.63%) were the most common presenting features. Consistent results were reported in other studies^[1,14].

The etiology of gall bladder carcinoma is unknown but there is a clear worldwide association between chronic cholelithiasis and gall bladder carcinoma. The risk of developing cancer among patients of untreated cholelithiasis has been estimated to be 0.2-0.5% over a 20 year period.^[14] However in our study gall stones were found in 4 patients only. Other risk factors that increase the risk of gall bladder carcinoma include, a number of genetic, dietary factors, endo and exobiotics. Chronic inflammation and infection have been associated with the development of gall bladder carcinoma.^[15] Chronic inflammation cause DNA damage, which provokes repeated tissue proliferation and restoration attempts. This response involves the release of cytokines and growth factors and, thus, predisposes cells to oncogenic transformation. It has been found that higher intake of energy and carbohydrates possibly increase the risk of gall bladder carcinoma and adequate intake of fruits and vegetables probably reduce the risk of GBC as they contain potentially anticarcinogenic agents^[16].

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. 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.^[1,14]

Pathologically GBC usually presents as a mass lesion. It may however form a localized wall thickening or a polypoidal growth. Approximately 60% of tumors originate in the fundus, 30% in the body and 10% in the neck(12). Our study had also comparable results.

Microscopically adenocarcinomas account for 90% of Gall bladder carcinomas and they may be well moderately or poorly differentiated. There are several histological variants of adenocarcinoma i.e. papillary, intestinal, mucinous, signet ring cell and clear cell. In our study we had 20 cases(90%) of adenocarcinomas and 2 cases of squamous cell carcinoma(10%).

Early stage gallbladder cancer can mimic cholecystitis, when presenting with biliary-type abdominal pain that warrants cholecystectomy. Such incidental gallbladder cancers are detected histologically after the fact in 0.3%–3% of laparoscopic cholecystectomies performed for cholelithiasis. In other cases, treatment options usually focus on curative resection, which can be compromised by the extent of tumor invasion. Indeed, primary tumor invasion (T) is the most important subset of the American Joint Committee on Cancer staging criteria; it determines the surgical approach^[10] Patients may require cholecystectomy with wedge resections involving segment IVb and V of the liver as well as portal lymphadenectomy^[17]

Adjuvant chemotherapy and or radiotherapy for patients with Gall Bladder Carcinoma has not altered the dismal prognosis The overall outcome of this disease is dismal with the 5year survival rate being less than 5% with a median survival of 5 to 8 months^[18].

CONCLUSION

Gallbladder carcinoma although a rare entity in western countries is not an uncommon clinical entity in the Indian scenario. 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 investigated and evaluated. 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 early stage disease a curative resection may be possible, and these patients have a good long-term survival.

Acknowledgements:

Authors acknowledge the immense help received from the scholars whose articles are cited and included in references of this manuscript. The authors are also grateful to authors / editors / publishers of all those articles, journals and books from where the literature for this article has been reviewed and discussed

Financial support:

None

Conflict of interest: None

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