Clinicopathological Study of Gall Bladder Cancer with special Reference to Gall Stones: 12 years Experience in Tertiary Care Center in Nepal

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ABSTRACT

INTRODUCTION: Gall bladder cancer is most common cancer of the biliary tree and one of the highly malignant tumors with poor prognosis. Although its incidence is low in west, it is common in our part of the world. There are very few studies regarding gall bladder cancer in Nepal. The incidence of gallstones in patients with gall bladder cancer is high. The aim of the study was to evaluate the clinicopathological aspect of the disease in patients with gallbladder cancer and to Asses the incidence of gallstones in patients with gall bladder cancer.

METHOD: This was a retrospective study carried out in GI Surgery unit of National Academy of Medical Science, Bir Hospital, Kathmandu, Nepal. All patients diagnosed as gallbladder carcinomas during 12 years period from 2002 to 2014 were included in this study. Their clinical characteristics, laboratory data, tumor histopathology reports were obtained and analyzed using SPSS17.

RESULT: Total of 47 patients who met inclusion criteria were included in the study. Male to Female ratio was 1:1.8. Age ranged from 32 to 72 years with mean age of 54. Most common presenting symptom was Pain abdomen (93.6%) followed by weight loss (51.1%) and Jaundice (46.8%). Most common finding on examination was Icterus (42.6%) followed by palpable gall bladder (34%) and Hepatomegaly (29.8%). Gall Stones were seen in 37 (72.3%) patients. Most common histopathology was Adenocarcinoma (93.6%).

CONCLUSION: Most of the patient with gall bladder cancer remained asymptomatic until late. Pain abdomen was most common presenting symptom and icterus was most common findings. There was strong association between gall bladder cancer and gallstones. There should be high index of suspicion if patient with gallstones has constant pain in right hypochondrium and has jaundice.

KEY WORDS: Gall bladder cancer, Gallstones, Nepal

INTRODUCTION:

Gallbladder cancer has geographic and ethnic variation throughout the world and is a highly fatal malignant tumor. The poor prognosis of this disease is due to the anatomic position of the gallbladder and the nonspecific symptoms and signs.[1,2]Gall bladder cancer, although it has a low overall prevalence, is the most common cancer of the biliary tree and one of the most highly malignant tumors.[3]The disease clinically mimics benign gallbladder diseases and usually presents late in its course. Preoperative diagnosis of carcinoma of gallbladder is the exception rather than the rule, occurring in fewer than 20.0% of patients.[4]

Globally, there is a prominent geographic variability in gallbladder carcinoma incidence. High rates of gall bladder cancer are seen in South American countries, particularly Chile, Bolivia, and Ecuador, as well as some areas of India, Pakistan, Japan and Korea[5].There were very few studies done in Nepal on gall bladder cancer. The incidence of gall bladder cancer parallels the prevalence of gallstone disease; large and longstanding gallstones being associated with a higher risk of gall bladder cancer. The risk of gall bladder cancer in

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patients with gallstones has been reported to increase four to seven times[6].

The aim of this study was to evaluate the clinicopathological aspect of the disease in patients of gallbladder cancer.And to assess the incidence of gall stones in patients with gall bladder cancer.

METHOD

This was a retrospective study carried out in GI Surgery unit of National Academy of Medical Sciences, Bir Hospital, Kathmandu, Nepal.All patients diagnosed as primary gall bladder cancer including incidentally diagnosed gallbladder carcinomas during 12 years period from 2002 to 2014 were included in this study. Patients without a confirmed histological diagnosis and patients with history of any previous malignancy were excluded from the study. A total of 47 gall bladder cancer patients were treatedin GI Surgery unit of this hospital during this study period. Their clinical characteristics, laboratory data, tumor histopathology reports and treatment givenwere obtained. Statistical analyses were conducted using SPSS. Descriptive statistics were calculated for all variables. Incidence of gallstones in patient with gall bladder cancer is assessed.

RESULT

Total 47 patients who met inclusion criteria were included in the study. 28 (59.6%) were Female and 19 (40.4%) were Male. Age ranged from 32 to 72 years with mean age of 54.

Gall Stones were seen in 37 (72.3%) patients during radiological investigation.

Most common presenting symptom was Pain abdomen (93.6%) followed by weight loss (51.1%) and Jaundice (46.8%) (Table 1). Most common findings on examination was Icterus (42.6%) followed by palpable gall bladder (34%) and Hepatomegaly (29.8%) (Table 2).

Table 1. Distribution of symptoms

Symptoms	No. of Patients	Percent
Pain Abdomen	44	93.6
Weight Loss	24	51.1
Jaundice	22	46.8
Anorexia	19	40.4
Nausea and Vomiting	18	38.3
Pruritus	14	29.8
Fever with chills	8	17

Table 2. Distribution of Signs

Signs	No. of Patients	Percent
Icterus	20	42.6
Palpable gallbladder	16	34
Hepatomegaly	14	29.8
Abdominal tenderness	12	25.5
Ascites	10	21.3

Laboratory investigation revealed mean Hemoglobin of 11.58 mg% ranging from minimum of 8.2 and maximum of 15.3 mg%. Likewise, TotalBilirubin was elevated in most of the patient ranging from 0.4 to 35.9 mg/dL with meanbilirubin of 9.92 mg/dL. Hyperbilirubinemia were present in 22 (46.8%) of patients. Serum Alkaline Phosphatase (ALP) wasraised with mean ALP of 600.5 Units (Table 3).

Table 3. Laboratory parameters

	Minimum	Maximum	Mean
Hemoglobin	8.2	15.3	11.587
Total Bilirubin	0.4	35.9	9.927
Serum ALP	4.1	5390.0	600.540
Total Protein	4.4	9.4	7.044
Serum Albumin	2.0	5.3	3.589

Surgeries were performed in 29 patients. Six (12.8%) had undergone cholecystectomies all of which were incidental findings on cholecystectomies patients either staged T1a or has lost the follow up. 14 (29.8%) had undergone Extended Cholecystectomies. where as Palliative bypass surgery were done in nine (19.1%) Patients. 18 (38.3) patients were managed conservatively (Table 4).

Table 4: Treatment

	Frequency	Percent
Cholecystectomy	6	12.8
Extended Cholecystectomy	14	29.8
Palliative Bypass surgery	9	19.1
Non operative palliation	18	38.3
Total	47	100.0

Most common histopathology was Adenocarcinoma (93.6%). Most of them were either well differentiated adenocarcinoma (45.45%) or Moderately differentiated adenocarcinoma (43.45%). Few were poorly differentiated adenocarcinoma (11.36%). There were two cases of Papillary Adenocarcinoma and one case of Mucinous adenocarcinoma (Table 5).

Table 5. Histopathology report		
HPE	Frequency	Percent
Adenocarcinoma	44	93.6
Papillary Adenocarcinoma	2	4.3
Mucinous Adenocarcinoma	1	2.1
Total	44	100

DISCUSSION

The prevalence of gallbladder cancer shows great geographical variation. Though an uncommon malignancy in western world, including USA, UK, Canada, Australia and New Zealand[7]. Gall bladder Cancer is common malignancy in Northern India and It is second most common malignancy after Gastric cancer in our GI surgery unit. Majority of the patients with gall bladder cancer remains asymptomatic or have vague complaints in the early stage of the disease, and by the time they become symptomatic, the tumor is in the advanced stage[8-10].

One of the most common factors implicated in gall bladder cancer carcinogenesis is gallstone. In our study, gall stones were present in 72.3% of patients which is comparable to study by Pandey et al. from Calcutta, India where70% of patients with gall bladder cancer had gall stones.[11] In a similar study by Hamdani et al. from India, gallstones were present in 86% of patients with gall bladder cancer.[5]Likewise, a study from MD Anderson Hospital (perpetuo et al., 1978), 88% of patients with gall bladder cancer had gall stones.[12] Yet another study by De Aretxabla et al. from Chile, gallstones were found in 53 out of 54 potentially resectable Gall bladder cancer patients.[13]

Shrestha et al. reviewed 668 cases of cholecystectomies in Nepal Medical College Teaching Hospital during five years period from 2003 to 2007. 22 (3.3%) patients had primary carcinoma of gallbladder.[14] In a similar study done by Ghimire et al. in Fishtail Hospital and Research Center, Pokhara, Nepal,where they retrospectively reviewed 783 cases of Cholecystectomies between 1998 to 2009 and found incidental carcinoma of gallbladder to be 1.28%.[15]

The pathogenic mechanism underlying the relationship of gallstones to gallbladder cancer is unknown. Size and duration of gallstones seem to play a role, and the concept that gallstones initiate neoplastic transformation directly has been proposed. Two large studies have reported a spectrum of atypical changes, including carcinoma *in situ,* in gall- bladder epithelium in patients with cholelithiasis.[16,17]It has been recently observed that dysplastic lesions of the gallbladder may progress to advanced cancer over a period of 15 years.[18]

At the molecular level, it has been shown that chronic inflammation of the gallbladder may lead to an allele-specific mutation, particularly loss of heterozygosity of the p53 gene and excessive expression of p53 protein, which may result in malignant transformation.[19,20] What initiates or promotes the initial inflammatory or metaplastic process remains unclear, although gallstones are strong candidates.

On the other hand, Maringhini *et al.* carried out the first prospective epidemiological study designed to assess the risk of gallbladder cancer in patients with gallstones. A total of 2,583 residents of Rochester, Minnesota, who had gallstones were followed for 31,000 person-years. Gallbladder cancer developed in five (0.19%) patients after a median follow-up of 13.3 years,which is contrary to all the findings.[21]Another study by Wenekert et al. in 1976 showed the incidence of carcinoma in silent gallstone patients dropped to 0.4%.[22]

Gallstones have traditionally been regarded as an etiological factor for gallbladder cancer. Despite some epidemiological data to support this, experimental models have failed to replicate the carcinogenetic process.[23]It is thus difficult at the present time to firmly conclude whether gallstones are the cause or mere innocent by-standers in the causation of gallbladder cancer. They may however, be regarded as cofactors. In light of the high incidence of gallstones in regions reporting gallbladder cancer, the role of prophylactic cholecystectomy needs to be further assessed to define specific circumstances in which such a procedure could be justifiable.[23]

In our study, Patients were mostly female (59.6%). Patient's age of presentation range from 32-74 years with mean of 54 years. Kapoor et al.[7], Hamdani et al.[5] and Shukla et al.[24] from India observed similar results in their studies.

Gall bladder cancer patient may remain asymptomatic until late. Most common presenting symptom in our study was Pain abdomen (93.6%) followed by weight loss (51.1%) and Jaundice (46.8%). And most

common findings during examination were Icterus (42.6%) followed by palpable gall bladder (34%) and Hepatomegaly (29.8%). In a similar study by Shrestha et al. most common presentation was Pain abdomen (75%) followed by Jaundice (10%) and Palpable mass (10%).[14] Hamdani et al. has similar findings with most common presentation being pain Abdomen (89.9%) followed by abdominal mass (76.3%) and anorexia (60%).[5] Similar findings were seen in a study by Gupta et al.[25]In a study by Pandey et al. The most common presenting symptom was pain in the abdomen (82.8%), followed by anorexia (41.4%) and significant weight loss (39.4%)[11]

Laboratory investigation revealed hyperbilirubinemia in most of the patients with mean total bilirubin of 9.92 mg/dL ranging from 0.4 to 35.9 mg/dL. Serum Alkaline Phosphatase (ALP) was raised with mean ALP of 600.5 U/L. Findings were comparable to other studies by Shukla et al.[24] and Hamdani et al.[5]

Surgeries were performed in 29 patients. Six (12.8%) cholecystectomies. 14 (29.8%) had under gone Extended Cholecystectomy with curative intent where as Palliative bypass surgery were done in Nine (19.1%) of Patients. In 18 (38.3%)patientsnon operative symptomatic management was done. The results were comparable to study by Pandey et al. where Cholecystectomies were done in (12.1%), Extended cholecystectomy in 10.1%, Palliative surgery were done in 45.4% of patients whereas nonoperative management is done in 30% of the patients.[11]

Most common histopathology was Adenocarcinoma (93.6%). Papillary adenocarcinoma and Mucinous adenocarcinoma were rare only in 4.1 and 2.3% respectively. Similar findings were noted in studies by Hamdani et al.[5]

There are several limitations to this study. Because of its retrospective design, there are potential for bias in data gathering. We were not able to extract the size, number and type of stones. The study population was from a single medical center, and the results may be less generalizable than those from multicenter studies.

CONCLUSION

In Conclusion, Gall bladder cancer although rare in west, It is common in our part of the world. Most of the patient remains asymptomatic until late. It carries worst prognosis among all GI and Hepatobiliary malignancy. There was strong association between gall bladder cancer and gallstones, unfortunately, there are no widely accepted or widely used guidelines regarding which patients should undergo surgery.Pain abdomen was most common presenting symptom and icterus was most common findings. Sothere should be high index of suspicion if patient with gallstones has constant pain in right hypochondrium and has jaundice. Cure is possible only if the diagnosis is made at early stage.

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