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Clinicopathological Features of Gallbladder Carcinoma Managed in a Tertiary Level Hospital of Nepal

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ABSTRACT

Introduction

Gallbladder carcinoma is a relatively rare disease in some parts of the world but is common in countries like Chile, Japan, India, and Nepal. Nepal stands as one of the five countries with the highest mortality. However, there are only a few studies published on this matter from Nepal. This study aims to study the demographic and clinicopathological features of gallbladder carcinoma managed in a tertiary level teaching hospital in Nepal.

Methods

A retrospective analysis of all the patients with the diagnosis of gall bladder carcinoma in Tribhuvan University Teaching Hospital from 2018 to 2020 was done. Patient demographics, clinical characteristics, and laboratory parameters including tumor markers were analyzed.

Results

Of the 59 patients, there were 33 (56%) females. The median age at diagnosis was 56 years. Among all, the most common presenting symptom was abdominal pain. Curative resection was done in 18 (30%) of the cases. Metastasis was present in 30% of the cases of which the liver was the most frequently involved organ. The mean carcinoembryonic antigen (CEA) level in unresectable cases was 18.65±22.53 nanograms per milliliter (ng/mL) which was higher than in resectable cases being 6.78±12.75 ng/mL. Similarly, the mean carbohydrate antigen 19-9 (CA 19-9) level in unresectable cases was 604.55±671.28 units/milliliter (U/ml), which was higher than the value in the resectable cases 89.44±273.67 U/ml.

Conclusion

In this study, gall bladder carcinoma was more common in females below 60 years with vague abdominal pain as the most frequent presenting symptom. One-third of the evaluated cases were resectable. Unresectable cases were associated with high CEA and CA 19-9 levels.

Keywords

CA 19-9, CEA, demography, gallbladder carcinoma

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INTRODUCTION

Gallbladder carcinoma is a relatively rare disease in some parts of the world. However, it is common in northern India, Pakistan, Korea and Japan.[1,2] Nepal has an incidence of 6.7 per 100000 population which is lower than Northern India, Chile, and Bolivia.[3] Nepal stands as one of the five countries with the highest mortality attributed to gallbladder carcinoma.[4]

Gallbladder carcinoma increases with age and is seen in patients from 40 to 80 years. It is seen more in females with a female: male ratio of 1.2:1 as shown by a large Asian study of 116,048 patients.[4] Indian and Latin American patients present a decade earlier at 51±11 years in contrast to 71.2±12.5 years in the west.[3]

The diagnosis of gallbladder carcinoma is delayed as the symptom mimics the gallstone disease and peptic ulcer disease and the symptoms are neglected.[2] Therefore, many patients with this aggressive disease present with an advanced stage.[2] This leads to a dismal prognosis in most of the cases.[5] The dismal prognosis can also be predicted by the raised levels of tumor markers, carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA 19-9).[6] The median overall survival is only 6 months for advanced disease.[5]

In this retrospective study, we present information about the demographics, clinical features, and histopathology of all admitted cases of gallbladder carcinoma. In this study we also analyzed the levels of CEA and CA19-9 in patients with gallbladder carcinoma.

METHODS

A retrospective analysis of all cases of gallbladder carcinoma who were admitted in Tribhuvan University Teaching Hospital (TUTH) from April 2018 to March 2020 was done. The case notes of all the patients who were admitted with a diagnosis of gallbladder carcinoma were retrieved and reviewed. Those who had histopathological examination (HPE) or cytological examination suggestive of gallbladder carcinoma were included. All patients who underwent surgery with microscopically margin-negative (R_0) intent were considered curative resections.

The Institutional Review Committee (IRC) approval was taken for conducting the study. In the preoperative period, patients underwent ultrasonography (USG), contrast enhanced computed tomography (CECT), or magnetic resonance imaging (MRI) abdomen and pelvis for diagnosis and staging. In cases of unresectable disease as suggested by imaging, USG or CT guided fine needle aspiration cytology was sent. Patients underwent surgery if the tumor was resectable after clinico-radiological discussion. Gallbladder specimens after surgery were routinely sent for HPE. Based on clinical suspicion and high tumor marker levels, patients underwent staging laparoscopy as decided by the operating team. In cases of any evident intra-abdominal metastasis in the peritoneum, pelvis, liver or other sites, tissue biopsies were taken and sent for HPE. For intraoperative unresectable symptomatic disease, palliative bypass surgery was done. Patient demographics, clinical and laboratory profile, diagnostic modalities, and various curative and palliative treatment variables were analyzed using SPSS software version 20.

RESULTS

The demographic profile of patients is illustrated in Table 1. The majority of the patients (63%) were less than 60 years of age suggesting an increased number of younger patients to be affected by gall bladder carcinoma. The median age at diagnosis was 56 years. There were more females (56%) as compared to males (44%). Most of the patients were from the Terai and Hilly regions (98%) and people from the Himalayan region were only 1.69%.

The patients in this study presented with a variety of symptoms. Figure 1 illustrates the symptom profile of patients. Among all, the most common presenting symptom was abdominal pain followed by jaundice and weight loss. Pain usually occurred over the right upper abdomen and was vague. Pain was present in 63% of patients. Jaundice

Table 1. Demographic characteristics of patients with gallbladder carcinoma (n=59)

Characteristics	Frequency (%)
Age (years)	
Mean ± SD	57.79±11.89
Median	56
Age Distribution	
≤60 years	37 (63)
>60 years	22 (37)
Sex Distribution	
Male	26 (44)
Female	33 (56)
Co-morbidities	
Diabetes mellitus	9 (15)
Hypertension	12 (20)
Hypothyroidism	4 (7)
Others	8 (14)
None	26 (44)
Geographical area	
Terai	27 (45.56)
Hills	31 (52.54)
Mountain	1 (1.69)

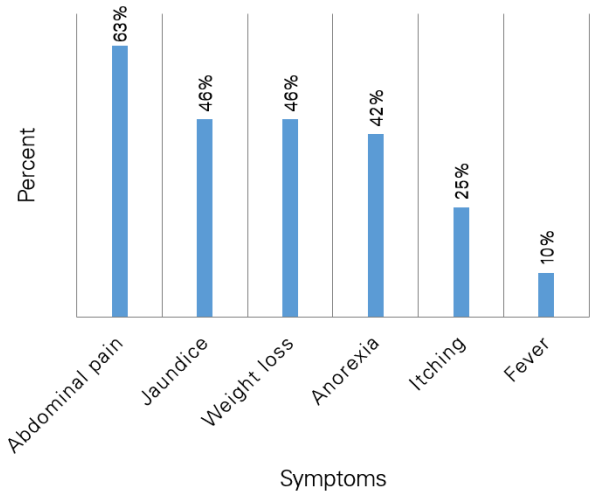

Fig 1. Various symptoms at presentation

Table 2. Preoperative evaluation for resectibility (n=59)

Resectibility	Frequency (%)
Unresectable disease	32 (54)
Resectable	27 (46)
Unresectable by Staging laparoscopy	4
Unresectable by surgical dissection	5
Surgical dissection*	18

**Surgery done were extended cholecystectomy 16, Right extended hepatectomy 1, and extended cholecystectomy with pancreaticoduodenectoimy 1*

and weight loss each were present in 46% of the patients. The onset of the first symptom was within mean duration of 40.24±37.36 days. Thus, it took on an average of 1.5 months for the patients to seek health care after they developed these non-specific symptoms.

Resectability in this study was considered with the help of preoperative imaging (Table 2). The preoperative availability of the most commonly used two imaging (USG and CECT) together was 100%. These preoperative imaging predicted resectability in almost half i.e. 27(46%) of the cases. Further, staging laparoscopy revealed unresectable disease in four more cases, thereby, predicting unresectability in 4/59 (6.7%) of cases. On exploration, surgical resection could not be done in five more cases. Among these nine unresectable disease found intraoperatively, palliative surgical bypass was done in five cases. Thus, curative resections could be done in only 18(30%) cases including one right extended hepatectomy and, one extended cholecystectomy with pancreaticoduodenectomy. No cases of completion surgery for incidental gallbladder carcinoma was performed during the study duration.

Table 4. Pathological features and metastasis (n=59)

Features	Frequency (%)
Histopathological variants	
Adenocarcinoma	55 (93.2)
Others#	4 (6.8)
Location of GB Mass	
Fundus	17 (29)
Body	3 (5)
Neck	9 (15)
Diffuse/GB fossa	8 (14)
Non-specified	22 (37)
Metastasis in unresectable disease*	
Liver	12 (52)
Nodal	4 (17)
Omental	2 (9)
Peritoneal	2 (9)
Duodenal	2 (9)
Lung	1 (4)
Metastasis in regional nodes	23 (40)

**Total sites of metastasis seen were 23, Number of patients with metastasis were 18(30%)*
 # Other diagnoses were papillary invasive carcinoma, intracystic papillary neoplasm with invasive carcinoma.

The median value of total bilirubin level in this study was 42 micromol/litre with a range of 7- 570 micromol/litre. The serum CEA and CA19-9 values (Table 3) were increased in both resectable and unresectable cases. The elevation of tumor markers was more in the unresectable cases as compared to the resectable ones.

Table 4 reveals that the most common anatomic location of mass was in fundus followed by the neck region. On histopathological examination,

Table 3. Comparison of tumor markers between resectable and unresectable cases (n=59)

Tumor markers	Resectable (n=18) Mean ±SD (Median)	Unresectable (n=41) Mean ±SD (Median)	p value
CEA	6.78 ±12.75 (2.48)	18.65 ±22.53 (7)	0.03
CA19-9	89.44 ±273.67 (14)	604.55±671.28 (388)	0.02

adenocarcinoma was the most common finding seen in 93% of patients. Advanced metastatic gallbladder carcinoma was seen in 18 (30%) cases. Of these metastatic cases, the most common site of metastasis was liver.

DISCUSSION

Gallbladder carcinoma is not an uncommon disease in Nepal.[3,7] The incidence of gallbladder carcinoma increases with age, and the median age at diagnosis in the present study was 56 years which aligns with the median age shown by previous national and international studies as 55-67 years.[6,8,9] The average age of diagnosis in the US population was found to be 72 years whereas the patients from India present a decade earlier at 5th- 6th decade of life 3. Patients younger than 60 years occupied a majority of the spectrum (63%) of the disease in our study similar to a study from Qatar(75%).[10] The reason for early age at presentation may be the presence of multiple risk factors in our part of the world.[7,11]

Nepal is divided into three ecological regions- Terai, Hills, and Mountains. Most of the patients in this study were from Terai and Hilly region of Nepal (98%), whereas there were only few gallbladder carcinoma cases from Mountain region. Terai being close to the northern belt of India can be expected to have more cases of gallbladder carcinoma. However, in this study, more patients were from the hilly region when compared to Terai region. The reason may be that people from Terai are seeking treatment from nearby hospitals and cancer centres.

Females are at upto six times higher risk of gallbladder carcinoma than males which is different in different parts of the world being highest in Hispanic women.[12] The ratio, in general, is lower as suggested by recent data from Asia studying 116,048 patients which shows the female: male ratio to be 1.2:1.[4] This finding mirrors the disease occurrence among females in our study (55%). Earlier studies on gallbladder carcinoma have noted increased incidence among females as high as 70-77%, suggesting a link between gallbladder carcinoma and hormone levels.[2,13]

The patients often presented with vague pain in the right upper abdomen (63%). The three most common symptoms were pain abdomen followed by weight loss (46%) and jaundice (46%), which is in accordance with other studies with a range of weight loss (30%-47%) and jaundice (30% -60%).[14,15] However, pain abdomen was more frequent in other studies which showed pain abdomen in more than 80% of cases of gallbladder carcinoma (81-85%).[14,15] Another study from Nepal showed pain abdomen in most of their patients (93.6%).

USG and CECT were done in majority of the cases in our series, however, such investigations do not seem to detect the disease at an early stage.

Radical curative surgery could be offered to only few (30%) patients, whereas surgical bypass was done in 8% of patients and nonsurgical treatment was offered to the majority of patients. Similar number of curative surgeries (23%) were done in other centers as well.[9]

The majority (93%) of the resected specimen revealed adenocarcinoma of gall bladder which is similar to the biopsy reports of other studies done for carcinoma gall bladder (84.31%).[15] The most common location of the tumor was fundic similar to the study by Dubey et al.[2] The second and third most common locations were the neck and diffuse types. The tumor location was in the body of gall bladder in only a few (5%) cases in our study when compared to 26% in the study by Dubey et. al.[2] The fundus of the GB is a common site possibly due to higher mucosal contact time as it is the dependent part in biped erect human beings.[3]

Eighteen patients (30%) had advanced metastases at the time of diagnosis. Twenty-three (40%) patients had regional lymph node metastasis. Thus total metastatic disease in this study was 70%. Among the total 21 metastatic sites in 18 patients, the most common metastasis was seen in the liver (52%) followed by nodal (17%), peritoneal (9%). A seven years' experience in Qatar revealed an increased rate of metastatic (regional plus advanced) gallbladder carcinoma (71%) with liver being the commonest site of metastasis in 42% of their cases.[10]

CEA and CA19-9 are the most frequently used tumor markers in gallbladder carcinoma. Both of these were elevated in this study. However, the mean CEA and CA19-9 levels were significantly higher in unresectable disease as compared to the resectable disease. Some studies even found that high levels of CA19–9 above 70–100 IU/ml are highly associated with unresectable disease suggesting the use of PET-CT in workup when the CA19–9 is> 72 and CEA >5 to identify the possible occult metastasis preoperatively.[6]

CONCLUSION

Gall bladder carcinoma was more common among females of age less than 60 years. Vague abdominal pain was the most common symptom, making the diagnosis difficult. About one-third of cases were resectable. Unresectable cases were associated with high CEA and CA 19-9 levels.

CONFLICT OF INTEREST

None declared.

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