ORIGINAL RESEARCH PAPER

Surgery

KEY WORDS: Adinocarcinoma, Carcinoma gallbladder, Cholelithiasis, Haldwani, Sushila Tiwari.

HISTOPATHOLOGICAL PROFILE OF CARCINOMA GALLBLADDER

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ABSTRACT

Carcinoma gallbladder is one of the most common and aggressive primary hepatobiliary malignancy with poor prognosis, and predominantly affects females and older persons. Most gallbladder carcinomas are adenocarcinomas. Among them, the pancreatobiliary is the most common subtype, followed by intestinal type. Usually in most patients carcinoma gall bladder is diagnosed at advanced stage of the disease because of the poorly defined gall bladder muscularis. **Aims:** This study was conducted to identifying common histological variant of carcinoma gallbladder at our centre along with analyse of clinical presentation and radiological findings of this disease. **Methods:** An observational prospective analytic study was done to identify the common histological variants of carcinoma gallbladder at Dr. Sushila Tiwari Govt. hospital attached to GMC Haldwani over a period of 2 years from September 2011 to August 2013. **Results:** There were total 66 patients registered during this time span for carcinoma gallbladder, out of these, 44 were female and 22 were male. Single predominant age group was 61-70 years (33.33%) with mean age 53.56 ±12.62 years. Abdominal lump and pain were most common presenting complaints. Adenocarcinoma was most dominant variants found in more than 90% of patients. **Conclusions:** Reporting of every specimen must be encouraged to identify true incidence of various histological variants, which helps future clinical researches on histology based targeted therapy

INTRODUCTION

Although uncommon, carcinoma of the gallbladder is one of the most common and aggressive primary hepatobiliary malignancy with poor prognosis, and predominantly affects older persons with long-standing cholelithiasis. GB epithelial tumors tend to behave similarly to other GI adenocarcinomas. [1,2]

Incidence varies geographically with higher rates in certain areas of Latin America (Colombia, Peru, and Ecuador), Japan, and Eastern Europe (Poland, the Czech Republic, Slovakia, Hungary, and the former East Germany. In North America, high rates of gallbladder cancer have been noted in Hispanic and American Indian populations.[3]

Population based data revealed that incidence of gall bladder carcinoma is high in northern India 5-7 / 105 and 0-0.7 / 105 females in Southern India. High incidence area comprising UP, Bihar, Orissa, West Bengal and Assam are being noticed.4. The highest incidence of carcinoma of gall bladder in India has been seen along Ganges delta. [5]

The overall age adjusted incidence rates of gallbladder carcinomas in India are 1.0 for men and 2.3 for women per 100,000 population, With great regional variations.[6]

Patients with GB carcinoma have an overall mean survival rate of 6 months, and the 5-year survival rate is 5%.[7,8]

GB carcinoma has a female preponderance influenced with Life-style, parity, menstrual and reproductive factor. 9 The female-to-male ratio is [3:1.10]

The greatest incidence of GB carcinoma is in persons older than 65 years.[11]

It has been reported that in approximately 1% of all elective cholecystectimies performed for cholelithiasis harbor an occult gall bladder cancer.[12]

Most gallbladder carcinomas are conventional adenocarcinomas. Among them, the pancreatobiliary is the most common subtype, followed by intestinal type. Papillary variant of adenocarcinoma is the second most common subtype affecting the gallbladder. However, its true incidence is yet unknown. Both pancreatobiliary and papillary cancers have good prognoses. Other variants, mucinous adenocarcinoma, and adenosquamous carcinoma of gallbladder are very rare.[13]

In affected patients, 60% of GB tumors occur in the fundus, 30% in the GB body, and 10% in the GB neck.4 Gallbladder carcinoma usually forms an infiltrating, gray white mass. Some carcinomas cause diffuse thickness of the gallbladder wall while some are polypoidal or adenomatous in appearance.[14]

Usually in most patients carcinoma gall bladder is diagnosed at advanced stage of the disease because of the poorly defined gall bladder muscularis that allows early spread into the perimuscular tissue and, frequently, beyond the gall bladder to involve the liver and extrahepatic biliary ducts.

This study was conducted to identifying common histological variant of carcinoma gallbladder at our centre along with analyse of clinical presentations and radiological findings of this disease.

MATERIALS AND METHODS

An observational prospective analytic study was done to identify the common histological variants of carcinoma gallbladder at our centre. This study was approved by the medical ethics committee of Govt. medical college Haldwani.

All diagnosed cases of carcinoma gall bladder were included in study for a period of 2 years from September 2011 to August 2013.

Gall bladder carcinoma was diagnosed according to the definition formulated by the World Health Organization in 2010.15 The diagnosis included type I diagnosis (histopathological findings) and type II diagnosis (clinical and imaging examination).
The results were analyzed using SPSS 20.

RESULTS

Total 66 patients with gallbladder carcinoma were registered. Out of these 22 were male (33.33%) and 44 cases were females (66.67%), with a male to female ratio of 1:2. The age of the patients ranged from 30-82 years (mean 53.56 ± 12.62 years) (Table 1). Most of the patient were adult (more than 83% of them are above 40 years), the single predominant age group was 61-70 years (33.33%). The youngest patient was a female of 30 and oldest patient was a male of 82 years.

The most common presenting features were abdominal lump in 54 patients (81.8%) and pain in right hypochondrium and epigastrium in 46 patients (69.7%) (Table 2). The symptoms were present for an average duration of 3 months prior to presentation. There was evidence of lymphadenopathy (left supraclavicular node) in 4 patients (6.1%) and involvement of liver in 36 patients (54.5%).Jaundice were present in 27 patients (41%).

Imaging of abdomen (including US and CT) performed in all the patients showed: Gallstones in 53 patients (80.3%), gallbladder mass in 50 patients (75.8%) which was associated with gallstones in 40 patients (60.6%) (Table 3).

In our series out of 66, 10 patients were incidentally diagnosed after cholecystectomy, around 15 % and representing around 1 % of the total cholecystectomies performed at our centre during period of study.

Extended cholecystectomy with major liver resection were done only in 12 cases. Most of the patient were inoperable and present late during course of their disease and they were treated with either chemotherapy or palliative measures. Staging of the patients was done according to AJCC TNM 6th edition: Stage I in 11 patients (16.7%), stage II in 10 patients (15.2%), stage III in 9 patients (13.6%) and stage IV in 36 patients (54.5%).

Most common histological variant in this study was adenocarcinoma in 61 patients (92.42%) (Fig. 1 and 2) followed by its papillary variant in 2 patients (3%) (Table 4).

DISCUSSION

Carcinoma gall bladder occurs in elderly patients at around 60 years or more. Solan 2 Jackson et al16 reported an average age of 69 years, however around 33.33 % of our patients were also belonged to this age group [a single largest group in range of 10 years (61-70) with the mean age in our series was 53.56 ± 12.62 years. The mean age reported in various major series from north India was also around 50 years (Pandey M, Aryya NC, Sukla VK 2001).17 In our study very small no. of patients are above 70 years (only 2 patient), whereas in some other studies (Nakayoma 1991)18, this no. is higher. This may be due to difference in life expectancy in our country and developed country.

Some observers feel that the carcinoma of gall bladder occurs a decade earlier in females, but in our patients male and female age groups were same. The enhanced susceptibility to cancer may result from impairment of gene and immune functions associated with later stages of life span.

The male female ratio is 1:2 demonstrating predominance of female patients in this area though in the literature male and female ratio has been reported is 1:2 to 1:3 (Carriga MT, Henson DE).19 The incidence in women was 2-6 times that of men, making gall bladder cancer one of the few neoplasm that had female predominance (Diehl A K 1980, Pichler JM & Crichlow R W 1978, Strom BL 1985, Mohandas KM, Jagannath P 2000 and Kapoor VK 2002).[20,21,22,23,24]

Researchers reported that the incidence of gall bladder cancer in females is two to three times higher than that in males. This may be because of higher incidence of gall bladder stones in women which lead to cronic cholycystitis and then carcinoma gall bladder (Diehl A K 1980, Pichler JM & Crichlow R W 1978, Strom BL 1985).[20,21,22]

The commonest factor implicated in the gallbladder carcinogenesis is gallstones. In our study, gallstones were present in 80.3% of cases with gallbladder cancer which is comparable to a study from MD Anderson Hospital (Perpetuo et al.)25 in which 51 (88%) patients had gallstones. Other study from India (Pandey et al.)17 reported presence of gall stones in 70% gallbladder cancer patients.

The accuracy of clinical diagnosis even at late stage is not more than 45% (Kaushik SP.).26 The poor clinical recognition of carcinoma gall bladder has been thought of be due to its symptomless primary stages. Associated symptoms in the early stages are attributed to concomitant benign gall bladder disease.
In our study abdominal lump and pain were the most common presenting symptom (81.8% and 69.7 % respectivly), which is comparable to Perpetuo et al, Chao (1978), Greager (1991) and North et al (1998).25, 27, 28 Jaundice in our study was present in 41 % of the patient which almost same as Perpetuo et al25 44 %, Chao and Greager 27 46 %. Anorexia and weight loss in our study was present in 35 % of cases which agree with other series, Perpetuo et al 25 77 %, Chao and Greager 27 28 %.

CT is better at detecting lesions than US. CT has a low sensitivity for detecting lymph node metastasis, although its positive predictive value is more than 90%. Both US and CT may fail to show local gastrointestinal and omental infiltration and peritoneal deposits (Shiwani, 2007)29. In our study, imaging of the abdomen (both US and CT) showed the presence of gallstones in 53 (80.3%) cases and a mass in the gallbladder was evident in 50 patients (75.8%). Hepatic involvement was picked up accurately in almost all the patients; however, the pickup rate for lymph nodes was rather low; peritoneal deposits were not picked up in any case. There were no false positive cases in our study. Similar results were observed in other studies (Piehler et al. 1978; Pandey et al. 2001)[21,17.]

FNAC (direct as well as image guided) suggested malignancy in 93% of cases. The sensitivity of image guided FNAC was higher than that of direct FNAC. Other studies (Zargar et al. 1991; Pandey et al., 2001)30, 17 found similar results.

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 adenosquamous carcinomas are rare (Roa et al. 2011)[31].

The histological appearance of the tumor in our series was mostly adeno carcinoma gall bladder (92.3%) (Table 4). Out of all 66 confirmatory biopsies only two was papillary carcinoma, one mucinous, one squamous and one was adenosquamous carcinoma. Nearly same findings were reported by Carriga and Henson (1995).[19]

As most of patients presented late and more than 90% of them were adenocarcinoma, it was not possible to comment on their prognosis outcome merely on the basis of histological variant in this series.

In our series out of 66, 10 patients were incidentally diagnosed after cholecystectomy, around 15 % and representing around 1 % of the total cholecystectomies performed at our centre during period of study.

Our results were comparable with a study from Malaysia (Khoo et al.)32 where 9 cases of incidental GBC were reported. In their series Malik et al., 2009 33 reported 6.15% incidental carcinomas whereas Shreshtra et al.34 found the frequency of incidental primary gallbladder carcinoma to be 1.4% (i.e. 8/570 cases).

CONCLUSION

Gallbladder cancer is not an uncommon clinical entity in our scenario, unlike western countries. It is predominantly a disease of females. 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 specimen 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.

It was found that increasing numbers of patients were being referred to our hospital in recent past, thus increasing the number of cases per year. This fact may be attributed to the increasing awareness of this disease amongst general physicians and general

surgeons working in the peripheral areas and small medical facilities within the city.

Carcinomas gallbladder are considering among the leading causes of cancer related mortality in South East Asia, including India. Reporting of every specimen must be encouraged to identify true incidence of various histological variants, which helps future clinical researches on histology based targeted therapy.

Table:-1 Distribution of Age of Patients (N=66)

Age	No.	Percentage	Male	Female
21-30	1	1.51	_	1
31-40	10	15.2	5	5
41-50	19	28.77	3	16
51-60	12	18.17	3	9
61-70	22	33.33	9	13
71-80	1	1.51	1	_
81-90	1	1.51	1	_
Total	66	100	22	44

Table:-2 Clinical Features of gall bladder cancer

Characteristic		No of patients	%
Pain abdomen		46	69.7
Icterus		27	41
Right Upper abdominal lump		54	81.8
Liver (Hepatomegaly)		36	54.5
Weight loss		23	34.8
Lymphadenopathy (Left Supraclavicular)		4	6.1
Ascites		14	21.2
Anemia		21	31.8
Features of Obstruction	Gastric outlet	5	7.6
	Colonic	2	3
Pedal edema		20	30.3

Table: - 3 Radiological findings of patients in the Study

Radiology finding (CT/USG)	No. of patients	%
Cholelithiasis	53	80.3
GB Mass	50	75.76
GB Mass Without infiltration of adjacent organs	20	30.3
GB Mass With infiltration of adjacent organs	30	45.5
Cholelithiasis with GB Mass	40	60.61
GB Polyp	4	6.06
Thick walled GB	10	15.2
Others (Choledocholithiasis, Pseudopancreatic cyst etc.)	5	7.6

Table: - 4 Cyto / Histopathological findings of Patients

Histopathology	No. of patients	%	
Adenocarcinoma	Well differentiated	15	22.7
	Moderately differentiated	29	44
	Poorly differentiated	17	25.8
Papillary adenocarcinoma		2	3
Mucinous adenocarcinoma		1	1.5
Squamous Cell Carcinoma		1	1.5
Adeno-Squamous Cell Carcinoma		1	1.5
Total		66	100

Figure 1 (Normal Gall Bladder Epithelium)

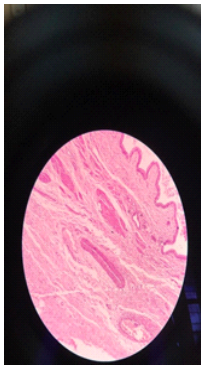
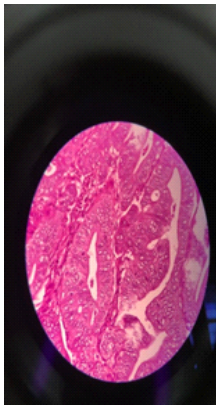


Figure 2 (Adenocarcinoma Gall Bladder)



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