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SPECTRUM AND MANAGEMENT OF GALLBLADDER CARCINOMA

Medical Science

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ABSTRACT

Aim of this study is to evaluate the gallbladder cancer in terms of its distribution among different age group, sex, location, its clinical presentation, food habit, histopathological finding, its treatment both in terms of surgery or adjuvant therapy and its outcome after 6 months of follow up. This study was help to formulate better screening and management guideline and thus better prognosis.
Both Male and Female 50 Patients with suspicios gall bladder cancer or HPE diagnosed gallbladder cancer attending the General Surgery OPD, IPGME&R and SSKM Hospital, Kolkata from January 2018 to August 2019.
Gallbladder cancer is a lethal disease as it present late in advance stages and it has very vague presentation that make difficulties to suspect gallbladder cancer early. Pain abdomen, abdominal lump, anorexia, jaundice are the common presenting symptoms of gallbladder cancer.
USG is the primary tool to detect and suspect gallbladder carcinoma whereas CT scan being done in suspected and confirmed case to confirm and staging the cases respectively. MRI is done in selective cases where portal and biliary invasion is suspected. PET CT though has high sensitivity not routinely advised.
Obstructive jaundice with Gallbladder cancer remains a dilemma as far as management. These are usually late presented patient and many a time palliative stenting to relieve the jaundice remains the only intervention to do.

KEYWORDS

Gallbladder Cancer, Distribution, Screening And Management

INTRODUCTION

Although overall incidence of carcinoma of Gallbladder (CAGB) is less, it is the sixth most common cancer of the gastrointestinal tract. It is a lethal tumor with poor prognosis due to delayed presentation and early spread [1] .It's age standardized incidence rates of around 2 to 3 per 100,000 populations in both gender separately worldwide [2,3].Though its distribution varies among different gender ,age ,ethnic group, geographical area, socioeconomic status, food habit. CAGB increases with age and is 2 to 3 times higher in women than men.

CAGB has wide geographical variation worldwide. The highest incidence rates (up to 8.0 per 100,000 in men and 22 per 100,000 in women) occur among population in the Indian subcontinent, in the western part of South America which include Colombia and Ecuador and to a lesser extent in East Asia and Eastern Europe. In the United States, the incidence is more among American Indians and in Hispanics.

Multiple risk factors are there for developing CAGB including cholelithiasis, porcelain gallbladder, adenomatous polyp of the gallbladder, chronic salmonella typhi infection, exposure to carcinogen like radon and anatomical variation like Abnormal pancreaticobiliary duct junction (APBDJ).

Chronic inflammation of the gallbladder mucosa due to gallstone is hypothesized to be the major factor that leads to gallbladder cancer. Some molecular changes are emerging as a cause of gallbladder cancer like p53, Kras, P16INK4A and ERBB2/HER2[4].

Gallbladder cancers are mostly adenocarcinomas but other histological type like small cell cancer, squamous cell cancer, lymphoma and sarcoma may also be seen. Gallbladder cancer may be classified according to morphology as infiltrative, nodular, papillary, or a combination of these type. Among them papillary carcinoma has the best prognosis. The clinical feature of gallbladder cancer, especially in early cancer, is non specific. Hence most of the gallbladder cancer is diagnosed at a late stage. This is the main cause of having poor outcome of gallbladder cancer. Besides its anatomical location of gallbladder makes the situation further difficult as at the time of diagnosis most of the gallbladder cancer already involve its vicinity important structure like liver, portal vein.

Aim of this study is to evaluate the gallbladder cancer in terms of its distribution among different age group, sex, location, its clinical presentation, food habit, histopathological finding, its treatment both in terms of surgery or adjuvant therapy and its outcome after 6 months of follow up. This study was help to formulate better screening and management guideline and thus better prognosis.

MATERIALS AND METHODS

a. Study setting: General Surgery OPD, Curzon Ward, Victoria Ward and Main OT complex, SSKM&H
b. Place of study: Dept. of General Surgery, IPGMER and SSKM hospital, Kolkata.
c. Study population: Both Male and Female Patients with suspicios gall bladder cancer or HPE diagnosed gallbladder cancer attending the General Surgery OPD, IPGME&R and SSKM Hospital, Kolkata from January 2018 to August 2019.
d. Sample size: 50 patients, attending the General Surgery OPD of SSKM&H, Kolkata will be chosen after informed consent.
e. Inclusion criteria:
Patients with diagnosed case of GBC by
a. Imaging Modality
i. Ultrasonography
ii. CT scan
iii. MRI (optional) and with b. Histological or Cytological diagnosis by Biopsy

f. Exclusion criteria:
a) Patient not willing to be part in this study
b) Patient having inadequate reports and left the study

Statistical analysis:
Data were entered in MS Excel and codified. Statistical analysis was done using SPSS 20.0 for Windows. Frequency distribution tables were made to express proportions of different variables. Chi-Square test was used to show association between categorical variables. Unpaired t test was used to show mean of normally distributed continuous variables.

RESULT AND ANALYSIS

In our study the age range was found to be between 36 years and 78 years with a mean age of 56. The maximum incidence occurred in

above 61 years of age group then the age group between 51 years to 60 years. Inference: Increasing age was significantly associated with high mortality at 6 months. Distribution of patients according to sex(N=50) inference: Female gender was significantly associated with high mortality at 6 months. Inference: A non significant numerical mortality preponderance was observed among residents of Extra Gangetic area.

It was found that 1= Cholelithisasis, 2= CaGB, 3= GB Lump, 4= Intestinal obstruction 1= Cholelithiasis+ GB Lump 2- Cholelithiasis+ GB wall Thickening 3= GB SOL 4- NA 5= GB Mass+ Liver SOL 6= Cholelithiasis+ GB mass+ Liver sol 7= Cholelithiasis 1= Heterogenous GB Mass 2= GB Mass with hepatic decreased attenuation+LN 4= Not Available 5= GB+livermets+LN CT Diagnosis Inference: Presence of metastasis at diagnosis was significantly associated with high mortality at 6 months.

We found that 1= Stage A 2= Stage 2A 3=Stage 2B 4= Stage 3A 5= Stage 3B 6= Stage 4A 7= Stage 4B 8= Stage 0 1= Mucinous adenoCa 2= WellDiff AdenoCa 3= Moderately diff Adeno 4= Poorly diff 5= Sq Cell Ca Inference: Radiological inoperability was significantly associated with high 6 months mortality. 1= Extended Cholecystectomy 2=open cholecystectomy 3= No surgery done 1= Alive & Asymptomatic 2= Alive & Progressive 3= Died

DISCUSSION

Age

Gallbladder cancer is a highly lethal cancer which arises from gallbladder mucosa. In 2018, about 219,000 people were estimated to have been diagnosed with gallbladder cancer. This constitutes 1.2% of all cancer diagnoses [2]The incidence greatly varies in different age group and even .In our study 50 patients have been evaluated. We got the patients having age starting from 36 upto 78 years of age. This study is showing maximum GBC occurs in 6th decade of life (50%) and then age group between 51-60 years of age group. A single centre study regarding epidemiological factors of Gallbladder cancer in Eastern India showed that the peak incidence was in 41–50 years age group. Thirty-one patients (49.20 %) were in this age group. Gall bladder carcinoma is significantly higher for the patients older than 40 year [5].Here in our study it is corresponding that gall bladder cancer increases with age. Increased age group also showed higher mortality (64%).p value is 0.018.

Sex

Out of 50, 31 patients were female and 19 patients were male.so higher no of gallbladder cancer has been seen in our study. In a study by Duffy et al in 2008 women are two to six times more commonly affected than men [6]. The female hormone estrogen is known to increase the saturation of cholesterol in bile, thus increasing the risk of gallstone formation. This pathogenesis is believed to be the primary culprit behind the greater risk of gallbladder cancer among females [7].So other study also corresponds with our study.

Residence

In our study (58%+24%=) 82% patient of gall bladder cancer patient resides in either gangetic and extended gangetic belt (According to National geography of India , 6th edition-Both 24 Parganas, Howrah, Hooghly, Nadia and Kolkata districts are considered as pure gangetic belt and after adding Malda, Murshidabad, Burdwan it becomes extended Gangetic belt. And rest of the West Bengal is considered as Non gangetic belt). The quality of evidence for these factors is limited as they come from small case-controlled studies and requires further larger multi centric studies. The high-risk regions extend from the states of Jammu and Kashmir, Punjab, Haryana, Himachal Pradesh, Uttarakhand, UP, Bihar, Bengal, Assam and Manipur. A large part of these states is based along the major rivers of the country namely Sutlej, Ganges, Yamuna and Brahmaputra. These rivers arise from the glaciers and flow from the northern Himalayas towards west and east and have become polluted due to human waste and industrial pollutants. As the Ganges flows towards east, the pollutants concentration as well as bacterial contamination have been found to steadily rise which may account partially for high incidence in this gangetic region of the country. It is also an agricultural driven community. The Ganges supports a very densely populated human civilization on its banks, especially the poorer sections, which subsist on the river for its daily water needs. Untreated sewage, industrial waste and agricultural effluents unfortunately get added to the water along its course [8]. The fecal coliform count steadily rises as the river flows towards the east [9]. Salmonella typhi (S. TYPHI) and Helicobacter pylori (H. PYLORI) are feco- orally transmitted organisms which have been known to be associated with pathogenesis of GBC and are likely to be increased as the river flows downstream [10,9,11]. In North, North east and eastern India, mustard oil is the staple cooking oil in contrast to coconut oil, sesame or groundnut oil in south and west India. Mustard oil has irritant property on the gut and is often adulterated with butter yellow which is known carcinogen

Socio-economic Status

In my study 70% patient of gallbladder cancer have literacy rate of below class X and 62% patients have monthly family income lower than 10,000.

Lower socio-economic status is indirectly a result of illiteracy and poor education standards. This leads to unemployment and decreased livelihood capacity influencing preventive aspects of Gall bladder cancer [12]

Gallstones and lower socio economic status are independent determinants for early onset of gall bladder carcinoma.[9]

Sign and Symptoms

The clinical presentation of GBC is often vague or delayed relative to pathologic progression, contributing to advanced staging and dismal prognosis at the time of diagnosis. The clinical presentation is nonspecific, may include abdominal pain, weight loss, fever, and jaundice, and any of these can be seen in cholecystitis and other benign gallbladder conditions as well as in other abdominal malignancies[8,13]

In our study we found pain abdomen was found as major presenting complaint(50%).Besides it 20% patient presented with abdominal lump,14% presented with jaundice and 16% presented with anorexia. Shukla[14] reviewed 315 patients and reported pain to be the commonest symptom (85 %) followed by icterus (60.3 %), lump and loss of appetite (40 % each).

So all the previous study showing pain abdomen was major presenting feature of gallbladder carcinoma as our study also suggest. But other features are exactly not corresponding with our study that might be due to different etiology behind developing gallbladder cancer.

Cholelithiasis

In our study 74%(n=37) patient had gallstone. It is significantly higher number than patient not having gallstone. Prashanta Kumar Bhattacharya et al [15]has shown that About 74.1% (n = 40) of our patient cohort had gallstones. Test of proportion showed that the proportion of patients with cholelithiasis was significantly higher than those without stones ($Z = 10.39$; $P < 0.0001$). Corrected Chi-square test showed that there was no significant association between the age of patient and risk of cholelithiasis ($P = 0.54$).

The risk of a patient with GBCA having gallstones was 8.48 times more among females as compared to males (OR = 8.48; 95% CI 2.16–33.19; P = 0.0009). Chi-square test showed a significant association between gender and cholelithiasis ($P = 0.0009$).

Nearly 45% (n = 18) of our patient cohort had a single stone, whereas 55% (n =22) had multiple stones. This difference was not found to be statistically significant ($Z = 1.41$; $P = 0.1585$). Test of proportion showed that significantly higher number of patients had stone size <3 cm (70%, n = 28) as compared to those with stone(s) ≥3 cm ($Z = 5.65$; $P < 0.0001$). Incidentally, multiple stones were mostly <3 cm in diameter while single stones were ≥3 cm in size, the association was statistically significant ($P < 0.0001$)

We have not studied on number of gallstone and it's diameter as parameter but only gallstone as a whole a parameter which as per other previous study showing major GBC is associated with gallstone.

DIAGNOSIS

In the diagnosis of GBC, differential diagnosis and determination of the local extension of tumor are important. For these purposes, imaging modalities such as endoscopic ultrasonography (EUS), CT, MRI, and magnetic resonance cholangiopancreatography(MRCP) are useful. EUS has good sensitivity in differentiating benign gallbladder diseases from GBC

ULTRASOUND

Ultrasound can depict a focal intraluminal, wall involvement, or large mass-like lesion replacing the gallbladder. The tumor usually has

irregular and sometimes ill-defined margins, with heterogeneous echotexture and predominantly low echogenicity. Hyperechoic foci with posterior acoustic shadowing may be seen within the mass, possibly reflecting gallstones or gallbladder wall calcifications - porcelain gallbladder

In our study 32%(n=16) patient diagnosed by ultrasound as GB SOL,14%(n=7) patient showed only cholelithiasis and after cholecystectomy they were diagnosed incidentally with GBC.12%(n=6) patient only showed asymmetrical wall thickening. GB mass with liver SOL is seen 12% patient(n=6).

CT SCAN

If GBC is confirmed, thin-slice spiral CT can contribute valuable information on local spread.[15].Although CT is inferior to ultrasound in depicting mucosal irregularity, mural thickening, and cholelithiasis, it is superior for evaluating the thickness of portions of the gallbladder wall that are obscured by gallstones or mural calcification on ultrasound. CT may show focal or irregular mural thickening; the images should be carefully inspected for bile duct dilation, local invasion, metastases, and adenopathy.

We in our study found 42% patient(n=21), in their CT scan GB mass with hepatic decreased attenuation with lymphnode. In 24% (n=12) cases CT Scan finding was heterogenous GB mass.

On MRI, GBC usually shows hypo- to isointense signal characteristics. An all- in-one protocol supplementing MRI with cholangiographic (MR cholangiopancreatography) and contrast-enhanced arterial and portal phase 3D angiographic (MR angiography) images may be up to 100% sensitive for bile duct and vascular invasion, yet sensitivity falls to 67% for hepatic invasion and 56% for lymph node metastases.[16]

In this study much focused was not given on MRI. For few cases where biliary invasion was suspected MRI was done (16% cases)

METASTASIS

In our study 40% patients (n=20) were diagnosed with liver metastasis. It means a large number of patients presented in an advance stages. Most of these patients were radiologically inoperable. This amounts a large no 28%(n=14).Six patients more(12%) has been found to be inoperable after exploring.

CYTOLOGY/BIOPSY

Other than radiology histological diagnosis was also done in our study. And in case of all incidental finding of GBC diagnosis was done by histopathology of resected gallbladder. In 14 cases (28%) GBC diagnosed as incidental finding in this study.

In our study mostly adenocarcinoma was diagnosed (92%).In 8% cases (n=4) squamous cell carcinoma was found. Among adenocarcinoma mo derately differentiated was the major type 42% (n=21).

MANAGEMENT

As Gallbladder carcinoma present late and very less chemoradio sesnsitivity surgical management is the principal effective management in gallbladder carcinoma. GBC is characterized as an aggressive and highly lethal disease, and surgery is the only option for the treatment. A more aggressive surgical approach, including resection of the gallbladder, liver, and regional lymph nodes, is advisable for patients with T1b to T4 tumors. Aggressive resection is necessary because a patient's GBC stage determines the outcome, not the surgery itself. Therefore, major resections should be offered to appropriately selected patients. Patients with advanced tumors or metastatic disease are not candidates for radical resection and thus should be directed to more suitable palliation.

Complete surgical resection remains the only potentially curative treatment for primary adenocarcinoma of the gallbladder. Several basic concepts of surgical management of this illness are straightforward, whereas others remain controversial. Aggressive surgical therapy of GBC is becoming more common as large institutional series demonstrate longer survival times from more extensive resections.] Long-term survival is possible in early stage of gallbladder carcinoma. Surgery for gallbladder carcinoma has the potential to be curative only in local or regional diseas. According to Yuman Fong et al in 2000 [17] Unresected gbc is a rapidly fatal disease. radical resection can provide long term survival even for large tumour with extensive liver invasion.

Long term survival can be achieved for patients presenting after prior noncurative surgical exploration.

In our study Surgical inoperability was significantly associated with high 6 months mortality. Furthermore extended cholecystectomy patient had significantly higher 6 months survival than those who received only open cholecystectomy.(p value 0.004).

MORTALITY

In our study we tried to focus different parameter and its association with mortality.

Clinical inoperability was significantly associated with high 6 months mortality. Among total 24(100%) inoperable patient 16 (66.7%) died which marks as significant association(p-value 0.001)

27 (100%) patients underwent palliative stenting from which 8(29.6%) patient died . So non significant mortality preponderance was found among those study subjects who received palliative stenting(p value 0.055).It might be due to fact that palliative stenting usually was given to advanced cases which might mask the beneficial effect of palliative stenting.

Those patients who received chemotherapy had significant high mortality at 6 months interval.36% patient of mortality was found among chemo receiving patient than 14% non chemo recipient patients. That may also signify that advance stage itself increase mortality. Anyway in this study it has been established that chemotherapy can not improve mortality dramatically.

In this study we evaluated mortality according to stage and found advancing stage was significantly associated with high 6 months mortality (p value 0.004).

Non modern treatment, negligence in attending modern medical system is also hindering better mortality outcome. We evaluated the gap (in month) in attending modern treatment facilties and its association with mortality. And we found more the gap more is the 6 months mortality.

CONCLUSION

On the basis of our study we can draw the following conclusion:

Average age of Gallbladder carcinoma in India is 56 of years though it may occur even in 3rd decade and 7th decade also.

Female sex has more incidence than male.
Gangetic and extended gangetic belt has higher incidence rate.
Poor educational qualification and poor monthly income individuals are more affected. Low socio-economic status patients even contact modern medical system late and this causes poorer outcome.

The single most common associated factors with GBC is Gallstone. Though simple gallstone as an etiological factor for developing Gallbladder cancer has not been established.

Gallbladder cancer is a lethal disease as it present late in advance stages and it has very vague presentation that make difficulties to suspect gallbladder cancer early. Pain abdomen, abdominal lump, anorexia, jaundice are the common presenting symptoms of gallbladder cancer.

USG is the primary tool to detect and suspect gallbladder carcinoma whereas CT scan being done in suspected and confirmed case to confirm and staging the cases respectively. MRI is done in selective cases where portal and biliary invasion is suspected. PET CT though has high sensitivity not routinely advised.

Obstructive jaundice with Gallbladder cancer remains a dilemma as far as management. These are usually late presented patient and many a time palliative stenting to relieve the jaundice remains the only intervention to do.

Radical/Extended cholecystectomy is the surgery of choice and followed by chemotherapy completes the treatment and these are the

only treatment available till date.

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