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Carcinoma Gallbladder-Epidemiological Trends in a Tertiary Hospital in North India

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Abstract

There is a global rise in cancer both in developed and developing countries including India. The burden is increasing in economically developing countries as a result of population aging and life-style changes. Gallbladder Cancer (GBC) is the commonest cancer of the biliary tract and the most frequent cause of death from biliary malignancies. The incidence of GBC shows prominent geographic, age, race and gender-related difference and is 4-7 times higher in patients with gallstones. This started the genesis of this study to analyze the trends of the presenting symptoms, stage of disease at presentation, management and survival of patients with this disease. In this retrospective study which was conducted in the radiotherapy department of a tertiary hospital in North India, 83 patients (Male: female was 1:2.2, age range 21-95 years, mean 50.95 years) of GBC were recorded over a period of four years. Adenocarcinoma (89.15%) was the commonest histological type. Most of the patients presented in advanced stage (stage 3-53.01% and stage 4-13.25%). Sixteen (19.27%) patients did not receive any treatment due to poor general condition and advanced stage of disease. The median survival was 1 year (range 3 months-6.1 years). The increasing incidence of GBC, presentation at advanced stage and hence associated poor prognosis resulting in high mortality rate is of concern in North India.

Keywords: Cancer; Gallbladder; Biliary tract; Symptoms; Adenocarcinoma

Introduction

Gallbladder cancer (GBC) has a peculiar ethnic, gender and geographic variation in incidence around the globe. Rising incidence rates are being reported from North India. It is 2-6 times more common in women as compared to males. The highest incidence rates worldwide have been reported for females in Delhi, India (21.5/100000) and age adjusted incidence rates among females in Delhi is 7.4/100000 population per year. However, the reasons for high incidence in this population are not well understood [1-6]. Incidence amongst females in Northern India is one of the highest in the world, which is steadily increasing from 10.1/100,000 population in women in 1993 to 19.6/100,000 population in 2006 [7].

Cholelithiasis in presence of chronic inflammation is the most prevalent risk factor (4-7 times increased risk) and this risk increases with stone size. Other risk factors associated are chronic cholecystitis, anomalous pancreaticobiliary duct junctions, gallbladder polyp (solitary and symptomatic polyp greater than 1 cm), porcelain gallbladder, salmonella typhii infection, adenomyomatosis of the gallbladder, certain dietary and environmental factors [1,3,5,8-10].

Tumor stage is the strongest prognostic factor. The 5 year survival rates were 60%, 39% and 15% for patients with stage 0, stage I and stage II disease respectively, whereas corresponding survival rates are only 5% and 1% for patients with stage III and IV respectively as noted in an analysis among 2574 patients in hospital based registries [11]. The prognosis of GBC is poor. Around 90% of the patients present in advanced and unresectable stage and are candidates for palliative treatment only [1,5,12,13]. In this study, we have analyzed the patterns of presentation, surgical and adjuvant treatment given and survival of patients with GBC who presented at our institution over a period of 4 years.

Methods

A retrospective study was carried out at the department of Radiotherapy in a tertiary care hospital of North India from January 2007 to December 2010. Data of 83 patients diagnosed with GBC was analyzed. Identification of patients was done using the patient data register in the radiotherapy department, where patients are referred from adjoining areas of North India including Delhi, Uttar Pradesh, Haryana, Uttra- Khand and Rajasthan.

Based on the clinical investigations including chest X-ray, ultrasound and/or CT-scan of whole abdomen, whole body PET-CT scan (as and when indicated), cytological examination (FNAC), histopathological examination and blood chemistry, confirmation of the diagnosis and staging was done. Clinical data analyses included age, sex, and history of presenting illness, operative procedure (if any), adjuvant treatment and survival. Pathological staging was done according to the TNM staging system using 7th edition of cancer staging manual [14].

Statistical analysis

The descriptive statistics of patients data was presented in terms of frequency and percentage (%) for categorical variables and in terms of range (minimum, maximum), mean, median and standard deviation (SD) for the quantitative variables.

Results

Out of 6414 registered cases in the department of Radiotherapy, 83 patients were diagnosed with GBC during 2007-2010. Amongst 83 patients, 26 (31.32%) were male and 57(68.67%) patients were female (Table 1). Majority of the patients were residents of Delhi, Uttar

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Pradesh, Haryana, Uttrakhand, Bihar and Rajasthan and there was a marked female preponderance (2.2:1). The median age was 55 years in males (range, 30-95 years) and 49.5 years (range, 21-74 years) in females. The highest incidence (68.67%) was found in the age group of 30-60 years with the sixth decade as the peak age of presentation. Financially 35 (42.17%) patients were from lower income group with 20 (24.09%) patients below poverty line.

Cholelithiasis was reported in 66 patients (79.51%) and was thus a prominent risk factor. The following radiological and pathological findings were observed: liver infiltration in 17 patients (20.48%), abdominal lymphadenopathy in 52 patients (62.65%) and ascites was present in 22 patients (26.50%), mediastinal lymphadenopathy in 5 patients (6.02%) and supraclavicular and cervical lymphadenopathy in 4 (4.81%) patients each. Pleural effusion, perineural invasion, metastasis to lung, bone, vessels and adnexa were seen in one patient each.

Most common histology reported was adenocarcinoma in 74 patients (89.15%), rest other being papillary carcinoma (3.61%), squamous carcinoma (2.40%), adenosquamous carcinoma (2.40%), mucinous carcinoma (1.20%) and malignant mesothelioma (1.20%). TNM staging was as follows: stage I-11 patients (13.25%), stage II-17 patients (20.48%), stage III-44 patients (53.01%) and stage IV-11 patients (13.25%).

The most common presentation (Table 2) was pain abdomen (100%) followed by nausea and vomiting (75.90%), appetite loss (68.67%), lump abdomen (59.04%), jaundice (49.40%), weight loss (44.58%), fever (27.71%), and ascites (26.50%). Majority of the patients had locally advanced stage of the disease and about 15% of the patients had distant metastasis at the time of presentation.

Surgery

Forty-three patients (51.80%) underwent surgery followed by adjuvant chemotherapy (Table 3). The median overall survival in this group was 12 months (range, 3-73 months).

Six patients (7.22%) who were FNAC proven cases of carcinoma of the gallbladder underwent upfront surgery (Extended cholecystectomy in two cases and laparoscopic cholecystectomy in four cases), following which they received adjuvant chemotherapy with Gemcitabine (1250 mg/m^2) on days 1 and 8 in combination with cisplatin (60 mg/m^2) on day1, every 21 days up to 6 cycles or as per tolerance. Median survival in this group was 10.5 months (range 8-22 months) (Table 3).

Thirty seven patients (44.57%) initially underwent open cholecystectomy for cholecystitis and histopathology revealed a diagnosis of carcinoma of gallbladder incidentally. Four of these patients then underwent a second surgical procedure. 26 patients received combination chemotherapy with Gemcitabine and cisplatin with the same schedule as above in the adjuvant setting. Median survival in this group was 12 months (range, 3-73 months). 11 patients who were deemed unfit for combination chemotherapy received Gemcitabine (1250 mg/m^2) alone on day 1, 8 and 15 every 21 days interval. Median survival in this group was 5 months (range 3-9 months) (Table 3).

Palliative and supportive care

Forty cases (48.19%) were deemed inoperable either because of locally advanced disease or due to poor general condition of patients; median survival in this group was 4.5 months (range 1.5-6 months) (Table 3).

Twelve patients (14.45%) who were deemed inoperable at the time of laparotomy were given palliative chemotherapy with 5-fluorouracil (550 mg/m^2) weekly. Median survival in this group was 3 months (range 3-4 months).

Palliative radiotherapy to portal nodes was given to twelve inoperable patients (14.45%) with a dose of 20 Gy in 5 fractions over 1 week on cobalt-60 machine and treated with anterior-posterior portals. Radiation fields encompassed the tumor bed and regional lymphatics and the fields were verified using ultrasonography. Patients in this group had median survival of 4.5 months (range 3-6 months).

Characteristics	Frequency	Percentage
Age (Years)		
0-30	2	2.41
30-60	57	68.67
60-90	24	28.91
Sex		
Male	26	31.32
Female	57	68.67
Place of Residence		
Rural	51	61.45
Urban	32	38.55
Socio Economic Status		
BPL	20	24.09
LIG	35	42.17
MIG	25	30.12
HIG	3	3.61
BPL – Below poverty line, LIG – Low Income group, MIG–Middle Income Group HIG – High Income Group		

Table 1: Age, sex and demography.

Symptom	Frequency	Percentage
Pain	83	100
Nausea & Vomiting	63	75.9
Appetite Loss	57	68.67
Weight loss	37	44.58
Lump abdomen	49	59.04
Fever	23	27.71
Jaundice	41	49.4
Ascites	22	26.5

Table 2: Symptoms at Presentation.

Treatment Offered	No. of Patents	Duration/Prior Treatment	Outcome/Survival
	(N=83)	**(Months)**	**Median (Months)**
Surgery (Cholecystectomy)	**43 (51.80%)**	**(5.2-6)**	**12 (3-73)**
Extended	2 (2.40%)	-	10.5 (8-22)
Laparoscopic	4 (4.80%)	-	10.5 (8-22)
Open	37 (44.57%)	-	-
Adjuvant Chemotherapy	**43 (51.80%)**	**(4.2-5)**	**12 (3-73)**
Dual agent	32(38.55%)	-	-
Single agent	11(13.20%)	-	5(3-9)
Palliative and Supportive	40 (48.19%)	-	**4.5 (1.5-6)**
Chemotherapy	12(14.45%)	-	3(3-4)
Radiotherapy	12(14.45%)	-	4.5(3-6)
ERCP & CBD Stenting	6(7.20%)	-	3(1.5-4)

Table 3: Treatment and Outcomes.

Sixteen patients (19.27%) did not receive any treatment because of poor general condition. Six of them (7.22%) underwent endoscopic retrograde cholangiopancreatography (ERCP) and common bile duct (CBD) stenting as palliative procedure. Median survival was 3 months (range 1.5-4 months).

Discussion

Gallbladder carcinoma is the commonest malignancy of the biliary tract system and the incidence is the highest in northern and central India. In developing countries it usually presents at an advanced stage due to which the chances of curative resection are minimal [1,4,6,12,13,15].

In a New Delhi based study, the incidence rate of GBC was 1/1, 00,000 in males and 3.3/1, 00,000 in females in the period of 1987-96. Female to male ratio (F/M) was 3.3 [8]. Results from our study showed that gallbladder cancer is predominantly a disease of females, with an overall male to female ratio of 1:2.2. These results were consistent with the results of other studies, where the ratio was reported to be 1:3, 1:3 and 1:2.5 respectively [16-19].

In our study, the median age of presentation was 55 years in males and 49.5 years in females. The mean age was 50.95 years (21-95 years), with the sixth decade as the peak age of presentation. Similar results were observed in other studies from India [15,18,19]. In contrast, studies from west reported the mean age of 67 years and the peak age of incidence in 7th decade of life [17,20].

The commonest factor implicated in gallbladder carcinogenesis is chronic gallstone disease which is well documented. In our study too, we observed that 79.51% of patients had a history of gallstones which is comparable to data from USA and from India [19,20].

GBC either remains asymptomatic for a long time or presents with very non-specific symptoms. Commonly, symptoms are related to the associated gallstones [21]. In our study, the most common presentation was pain abdomen (100%) followed by nausea and vomiting (75.90%), appetite (68.67%) and weight loss (44.58%), lump abdomen (59.04%), jaundice (49.40%), fever (27.71%), and ascites (26.50%). Similar observations were reported in other studies [2,22]. Clinical signs mimic benign gallbladder disease until the invasion of surrounding structures gives clue to the correct diagnosis [23].

Adenocarcinoma is the most frequent histologic subtype of malignant gallbladder neoplasms, representing approximately 90-95% of all cases. In contrast, squamous cell or 'epidermoid' carcinoma and adenosquamous carcinomas are rare [24]. In our study, adenocarcinoma constituted the most common (89.15%) histologic type followed by papillary carcinoma (3.60%), squamous cell carcinoma (2.40%), adenosquamous carcinoma (2.40%) with one case each of mucinous carcinoma and malignant mesothelioma. Histopathology findings were comparable to those seen in other studies [2,17].

Thirty seven cases of incidental GBC (44.57%) were observed in the current study: liver infiltration was present in 17 patients (20.48%), abdominal lymphadenopathy in 52 patients (62.65%), mediastinal lymphadenopathy in 5 patients (6.02%) with cervical and supraclavicular lymphadenopathy in 4 (4.81%) patient each. Pleural effusion, perineural invasion, metastasis to lung, bone, vessels and adnexa were seen in one patient (1.20%) each with stage III being most frequent (53.01%).

Our study reported much higher findings (44.57%) of incidental carcinomas detected after elective cholecystectomy than most other series, which reported a much lesser percentage of incidental carcinomas 3.5% and 1.4% respectively [2,25]. However, our results were comparable with the results of a retrospective review of 435 patients in which 123 patients (47%) were diagnosed with incidental GBC during laparoscopic cholecystectomy [26].

Patients were referred to us from civil/general hospitals and other private centers from all over North India. Most of our patients were from weaker socio-economic backgrounds and presented with advanced disease. Therefore, there needs to be increased awareness amongst general practitioners, surgeons, pathologists and radiologists–both in public and private sectors regarding the need for early diagnosis of GBC and the necessity of radical or extended cholecystectomy in incidentally detected GBCs in order to optimize survival.

A high level of suspicion for possible GBC needs to be kept in mind while dealing with patients presenting with gall bladder thickening or a polypoidal lesion more than 1 cm in size. Patients who are suspected to have gall bladder carcinoma at initial presentation should not undergo laparoscopic cholecystectomy, but should preferably be treated with radical cholecystectomy [1,13].

If the cancer is identified incidentally, the pathologist should report on the T stage, location of the tumor with respect to liver bed or peritoneal surface and histology of the cystic duct margin. These patients should be examined further and should have radical surgery if the tumor is found to be pT1b or beyond. The guidelines also recommend intraoperative staging and procurement of frozen section of gall bladder for biopsy prior to definitive resection [1,13,27].

Surgeons need to be particularly cautious in managing patients with incidentally detected gall bladder cancers after laparoscopic cholecystectomy. If the gall bladder is removed laproscopically, a protective bag should be used to prevent tumor spill and seeding. At the time of cholecystectomy, surgeons should routinely report on gall bladder wall violation and whether or not the specimen was bagged prior to removal. In case the gall bladder was torn at initial procedure or if no bag was used while removing gall bladder during laparoscopy, it is necessary to resect the extraction or the port sites even though the benefit is not conclusively proven- this can provide additional staging information and help in estimating recurrence risk besides being beneficial in terms of cancer control [1,13,27,28].

The optimal resection in GBC (stage Tia-T2) consists of cholecystectomy with a limited hepatic resection (segments IVB and V) and portal lymphadenectomy to encompass the tumor with negative margins. Lymphadenectomy should include lymph nodes in the porta hepatis, gastrohepatic ligament and retroduodenal regions without routine resection of the bile duct if possible. Simple cholecystectomy is adequate treatment for patients with T1a tumors with long term survival rates approaching 100%. Cholecystectomy combined with hepatic resection and lymphadenectomy is associated with an improved survival for patients with T2 or higher tumors [13,28,29].

In a recent single center randomized study of 81 patients with unresectable GBC chemotherapy with a combination of gemcitabine and oxaliplatin improved median OS (9.5 months) compared to best supportive care (4.5 months) or 5-fluorouracil alone (4.6 months) [12]. Gemcitabine and cisplatin combination also provided OS benefit in another study of 410 patients [30]. We suggest that a combination of gemcitabine and platinum compounds should be the preferred chemotherapeutic option in advanced GBC. In our study too, single agent 5FU did not demonstrate greater benefit as compared to local palliative radiation therapy (median survival 3 months *vs.* 4.5 months)

in locally advanced cases of GBC with poor general condition. However, palliative radiation therapy does seem to be a reasonable option in patients unable to tolerate combination chemotherapy.

Conclusion

The incidence of gallbladder cancer is showing increasing trends in North India and most of the patients present with advanced stages. There is also a very high proportion of incidentally detected GBC, which is not treated adequately. Any findings on ultrasonography suggestive of a neoplastic process should be evaluated with detailed imaging studies. Patients with imaging characteristics suggestive of gallbladder cancer should be referred to a tertiary care center for the assessment for radical resection of the tumor. Incidentally found gallbladder cancer during or after cholecystectomy should be resected on the lines of malignancy without delay. The benefit of radical resections for gallbladder cancer is well established in literature. High index of suspicion and improved ability to diagnose would lead to better outcomes. Gemcitabine and platinum combinations are advised for locally advanced disease. Palliative radiation therapy may be another option for patients unfit for chemotherapy.

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