



Original article

Demographic data and progression-free survival of the patients with biliary cancers receiving palliative chemotherapy in India

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Abstract

Biliary tract cancers are among the sixth most commonly diagnosed alimentary tract cancers. The incidence of this disease is higher among Indians in comparison to other countries. Due to lack of any definitive treatment palliative chemotherapy usually adopted particularly for advanced unresectable gallbladder cancers. The purpose of this study is to gather the demographical data and the various treatment modalities in place in the clinical practice for patients presented with gallbladder complications. Progression-free survival following the palliative chemotherapy was also assessed and presented as mean and 95% CI. Results from this study gathered clinically relevant and important data on the patients presented with gall bladder complications starting from the diagnosis of the disease, treatments implicated, response to the treatment and progression-free survival of the patients on palliative chemotherapy.

Key words: Gallbladder cancer, Palliative chemotherapy, Progression-free survival

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Biliary tract cancers (BTC) is among the sixth most commonly diagnosed alimentary tract cancers in developed countries¹, however among Indians incidence is reported to vary with the geography and overall incidence of BTC among Indians is more than other countries². Among North Indians incidence reported to be more compared to south Indians² and the places near the Gangetic belt have higher incidence of gallbladder cancer. Also, incidence in females reported being almost double in comparison to males¹.

BTC can be Gallbladder cancers (GBC), or bile duct cancer also known as cholangiocarcinomas (CC). Gallbladder cancer (GBC) is the most common BTC and the fifth most common gastrointestinal cancer³. Most biliary tract cancers present in the advanced stage where palliative chemotherapy is the only an option which is basically to improve the symptoms of the disease and to improve the quality of life of the patient. Only in the small proportion of patients who present in early stage, curative surgery can be offered. There is no standard form of chemotherapy for patients with advanced unresectable gallbladder cancers. Most of

the studies have included cholangiocarcinoma along with gallbladder cancers. Without chemotherapy biliary tract cancers have fatal outcome with median survival up to 3-5 months⁴.

Most cancers present in the advanced stage where palliative chemotherapy is the only option. Although BTC are common in India, there is a scarcity of Indian data. The purpose of the present study is to assess the pattern of care of gallbladder and biliary tract cancers in a community care setting. This study will help us know the profile of GBC in India and inform us the treatment modalities for GBC in real time clinical settings in hospitals outside of clinical trials. This study also states the metrics of the treatment-related toxicity and outcomes.

Materials and methods

A retrospective observational study was conducted by recruiting patients with confirmed diagnosis of gallbladder cancer or cholangiocarcinoma from NRI General Hospital and American Oncology Hospital between March 2016 and March 2018. Patients were recruited following inclusion and exclusion criteria and were then followed for another 19 months to capture demographic data on percentage of the patients experiencing the different types of the GBC, symptoms represented with, treatment modalities implicated and response to palliative chemotherapy with different treatment modalities they have undergone following the standard protocols at the discretion of the specialists, researcher had not influenced or had no role in deciding the treatment for the patient. Ethical clearance for the study was obtained from the NRI general hospital and as the nature of the study was a retrospective observational study, consent waiver was obtained. Required data for the study was obtained from the medical records either from hospitals online databases or from the written notes from the patients files. All patients considered for the study had a case record form (CRF), where patients data relevant to the study was captured. A detailed history including symptoms, co-morbid conditions, performance status, blood investigations, imaging study reports, histology of biliary tract cancer were documented. Joint clinic decisions, treatment details and their outcomes including response rates, progression of tumor, survival status and toxicity to chemotherapy were noted.

Selection criteria to include patients in the follow-up study

Inclusion criteria: 1) Patients with confirmed gallbladder cancer or cholangiocarcinoma diag-

nosed based on histological or cytological examinations. 2) Patients who have not undergone prior chemotherapy. 3) Patients who have not undergone radiation therapy. 4) Patients who are more than 18 years of age. 5) Patients who are willing to sign the consent to participate in the study.

Exclusion criteria: 1) Patients who have started to started chemotherapy. 2) Patients who have started to undergone radiation therapy. 3) Patients not willing to sign the consent to participate in the study. 4) Patients who are less than 18 years of age at the time of recruiting for the study.

Statistical analysis

Statistical analysis was performed in SPSS version 24. Depending on the type of the data variables were either categorical or metric. For categorical variables summary data was calculated and presented as percentages and for metric variables as arithmetic mean.

Progression free survival (PFS) will be defined as the time from registration until tumour progression or death or last follow up occurred. All time-to-event curves for PFS were estimated according to the Kaplan–Meier method. A p-value less than 0.05 is statistically significant, where applicable.

Results

In a total of 219 patients, 76 were male patients (35 %) and 143 were female (65%) with a mean age of 53 years (SD= 10.7; Range of 25-80 years), BMI of 1.61 (SD= 0.13; Range 1.41- 1.81) and Weight of 56.52 kgs (SD= 11.13; Range 38-85).

Majority of the patients were diagnosed with gallbladder cancers (92%) and the adenocarcinoma (96%) was the main histological outcome for the patients. Fine needle aspiration cytology (FNAC) was the most used technique to study the histology of the tissues and CT scan (66%) followed by PET CT scan (32%) were the popular imaging techniques used for diagnosis whereas MRI (2.7%) was least preferred.

In terms of the symptoms, patients presented with abdominal pain (80%) was the mostly reported symptoms followed by the clinical presentation of gallstone (32%) and other symptoms or pre-existing conditions were fever (4%), Anorexia (11%), vomiting (4%), GB mass (4%), weight loss (9.6), jaundice (22%), dyspepsia (3%), hypertension (14), diabetes (12), ischemic heart disease (IHD) and Ascites (3%). About 67% of the patients were presented with metastasis at different sites of which Liver metastasis (35%) and Lymph node metastasis (37%) were most common.

After the initial assessment of the symptoms and confirmed diagnosis for GBC, treatment modalities implemented were variable. Majority of the patients started with palliative chemotherapy (70%) and about 12% of the patients underwent surgical procedures. Table 2 presents the various treatment modalities implemented for the patients diagnosed with GBC.

Combination treatments with Gemcitabine and Cisplatin (48%) was most preferred first-line palliative chemotherapy followed by Gemcitabine and Oxaliplatin (40%) monotherapy with either Gemcitabine (1 %) or Capecitabine (1%) were least preferred. Response to the treatment with some clinical benefit was noted in about half of the patients (46%), however only two patients (2%) achieved complete response. Table 3 presents the Response to treatment with first-line palliative chemotherapy.

Out of 219 patients, 154 received palliative chemotherapy, patients who were lost to follow-up or who didn't proceed for chemotherapy after initiation were excluded from the study. After a median follow up of 19 months mean progression-free survival (PFS) in all the patients (including gallbladder & cholangiocarcinoma) was 5.5 months (95% CI 4.5 - 6.5 months) (Fig 1).

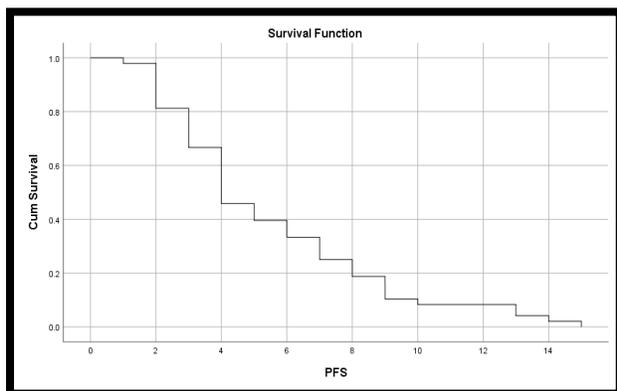


Fig 1. Progression-free survival of the patients on the palliative chemotherapy

Discussion

The purpose of this study is to gather the demographical data and the various treatment modalities in place in the clinical practice for patients presented with gallbladder complications. Progression-free survival following the palliative chemotherapy was also assessed and presented as mean and 95% CI.

Results from this study gathered clinically relevant and important data on the patients presented with gall bladder complications starting from the diagnosis of the disease, treatments implicated, response to the treatment and progression-free survival of the patients on palliative chemotherapy.

Table 1: Clinical presentation of the patients

Item	% (n)
<i>Disease diagnosed</i>	
Gall bladder cancer	92.2 (202)
Hilar cholangiocarcinoma	2.7 (6)
Intrahepatic cholangiocarcinoma (ICC)	3.7 (8)
Distal cholangiocarcinoma	1.4 (3)
<i>Histological findings</i>	
Adenocarcinoma	96 (210)
Adenocarcinoma with squamous cell differentiation	1.8 (4)
Sarcomatoid carcinoma	0.9 (2)
Poorly differentiated carcinoma with neuroendocrine differentiation	0.5 (1)
<i>Technique used for histopathology</i>	
FNAC	57.5 (126)
Biopsy	16.9 (37)
Operated specimen	21.0 (46)
Brush cytology	1.8 (4)
Ascitic fluid cytology	1.4 (3)
Bile cytology	0.5 (1)
<i>Presence of metastasis at different sites</i>	
Liver metastasis	67.1 (147)
Lymph node metastasis	34.7 (76)
Bone metastasis	37 (81)
Bone metastasis	3.2 (7)
Lung metastasis	5.9 (13)
Peritoneal metastasis	13.7 (30)
<i>Imaging used at staging</i>	
CT scan	65.8 (14)
PET CT scan	31.5 (69)
MRI	2.7 (6)
<i>Symptoms and preexisting conditions</i>	
Abdominal Pain	79.5 (174)
Fever	4.1 (9)
Anorexia	11.4 (25)
Vomiting	4.1 (9)
Gallstones	32.0 (70)
GB mass	11.0 (24)
Weight loss	9.6(21)
Jaundice	21.5 (47)
Dyspepsia	3.2 (7)
Hypertension	14.2 (31)
Diabetes	12.3 (27)
IHD	3.2 (7)
Ascites	3.2 (7)
<i>Stage of disease</i>	
Non metastatic	29.2 (64)
Single site metastasis	43.3 (95)
Metastasis at 2 sites	18.1 (40)
Metastasis at 3 sites	6.2 (14)
Metastasis at 4 sites	3.2 (7)

Table 2: Treatment modalities

Item	% (n)
Treatment implemented	
Surgery	11.9 (26)
Adjuvant chemotherapy	0.9 (2)
No JC done	2.3 (5)
Neoadjuvant chemotherapy	10.0 (22)
Palliative chemotherapy	70.3 (154)
Radiochemotherapy	0.9 (2)
Best supportive care (BSC)	3.7 (8)
Palliative chemotherapy regimens (N=154)	
Gemcitabine and Cisplatin	47.9 (74)
Gemcitabine and Oxaliplatin	39.8 (60)
Gemcitabine	0.8 (1)
Capecitabine	0.8 (1)

Table 3: Response to treatment with first-line palliative chemotherapy (N=113)

Item	% (n)
Complete response	1.1 (1)
Partial response	11.6 (13)
Stable disease	14.2 (16)
Progressive disease	32.3 (36)
Objective response	13.2 (15)
Clinical benefit	27.5 (31)

Number of females with the gallbladder complications where almost doubled that of the males in this study which implicates the higher incidence among females and is in coincidence with other reported studies^{1,5-9}. In our present study majority number of patients were from Uttar Pradesh (20.1 %), Bihar (19 %), West Bengal (18.8 %) and Maharashtra (13.3%). This study also demonstrates the higher incidence of GBC in Gangetic belt as it was reported in various Indian studies^{7,10}.

Most of histological types of gallbladder cancers were adenocarcinomas (95.3 %) similar to what has been reported in other studies^{11,12}. The common symptoms at presentation were pain (79.5%) and jaundice (21.5%). These presenting symptoms is similar to that reported from other countries^{11,13} and as well as from India¹⁴. Metastasis at different sites was found in 67 % of patients, however majority of patients (43%) had metastasis at single site and lymph node metastasis followed by liver metastasis were the mostly noted metastasis sites¹⁵. Clinicians found to relay more on Fine needle aspiration cytology (FNAC) to study the histology of the tissues and CT scan (66%) followed by PET CT scan (32%) were the popular

imaging techniques for diagnosis whereas MRI (2.7%) was least preferred.

The number of patients with GBC in our study having associated with gallstones on imaging was 32 %. This is a lower than that reported by Pandey et al¹⁶ as 63.6% and Batra et al¹⁴ as 54% from India. However, this discrepancy was also noted with other reports where a lack of correlation between gallstones and GBC reported¹⁷⁻¹⁹.

Following confirmed diagnosis for GBC majority of patients (70%) were started on palliative chemotherapy. Combination chemotherapy was preferred to single drug treatment in 88% of the patients who underwent palliative chemotherapy. Mostly preferred combination chemotherapy used by clinicians were Gemcitabine and Cisplatin (in 48% of patients on palliative chemotherapy) followed by Gemcitabine and Oxaliplatin which was used in about 40% of cases. On the other hand, surgery was opted only for about 12% of the patients for the treatment of GBC. These findings are in accordance with the previous reports²⁰.

Metastatic gall bladder cancer and cholangiocarcinomas (biliary tract cancers-BTC) are managed either with systemic chemotherapy or offered best supportive care (BSC). Most of the studies done in this setting were small and had a mixture of gall bladder and cholangiocarcinoma. Various combination chemotherapy regimens used in phase 2 clinical trials in the treatment of metastatic cholangiocarcinomas have shown median survival ranging from 6 months to 15.2 months^{21,22}. Only two phase 3 trials have been conducted till date in the setting of metastatic BTC, both of which have shown Gemcitabine-Cisplatin combination compared to Gemcitabine alone to be associated with a significantly greater median overall survival and median progression free survival^{23,24}. In ABC02 trial of Gemcitabine/ cisplatin vs. Gemcitabine alone in 410 patients with advanced/metastatic biliary tract cancers showed a 3 month OS and PFS benefit of combination arm. Hence gemcitabine/cisplatin is considered as standard option for advanced biliary cancer.

BTC are relatively common in India but rare in the Western world. Most cancers present in the advanced stage where palliative chemotherapy is the only option. Although BTC are common in India, there is a scarcity of Indian data. A single center, open label, three armed RCT from AIIMS, India, compared best supportive care (BSC), 5-FU plus folinic acid (FUFA) and, gemcitabine plus oxaliplatin (Gem-Ox) in management of unresectable GBC⁴. The median OS in BSC, FUFA and gem- Ox arms was 4.5, 5.3 and 9.3 months respectively and the

median PFS was 2.8, 3.5 and 8.5 months respectively.

Majority of patients on first-line palliative chemotherapy responded to the treatment and had either clinical benefit or stable disease or complete or partial or objective response to the treatment, however about 32% of the patients showed progression of the disease. Among the patients with gall bladder cancer who underwent upfront surgical resection, 11 of 23 patients had relapse of the disease within a median of 9 months (5.7 to 12.2 months). These are similar to the rates reported by Jarnagin et al²⁵.

Among patients who were treated with first-line palliative chemotherapy, the objective response rates (ORR) in our study was 15.1 % and in addition 25.8 % had stable disease. This was lower compared to GERCOR study (ORR=36%) and the study from India by Sharma et al (ORR=30.8%)^{4,22}. Our median progression-free survival (PFS) of 5.5 months was lesser than other studies (Sharma et al–PFS=8.5, GERCOR- PFS =5.7), while ABC02, a large phase 3 trial with gemcitabine and cisplatin reported objective response of 38% with survival of 11.7 months²⁴. Overall survival was not calculated in our study group since a large number of patients were lost to follow up. The patients were not contacted to inquire about their disease or death status as it is a retrospective study. In our study there were no statistically significant differences in the rate of response between the gallbladder and cholangiocarcinoma subgroups (results not reported), the similar results were demonstrated in ABC02 trial²⁴.

Conflict of interest: Nil

Acknowledgements: Nil

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