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Gastrointestinal Cancer

Pattern of Care and Outcomes of Gallbladder Cancer Patients: Retrospective Study from a High Incidence Region in India

Lakhan Kashyap[1] Arpita Singh[1] Subham Tomar[1] Anuj Gupta[1] Bipinesh Sansar[1] Amit Kumar Chaudhary[1] Bal Krishna Mishra[1] Kuraparthy Sambasivaiah[1] Akhil Kapoor[1]

[1] Department of Medical Oncology, Mahamana Pandit Madan Mohan Malviya Cancer Centre and Homi Bhabha Cancer Hospital, Tata Memorial Centre, Varanasi, Uttar Pradesh, India

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Address for correspondence Akhil Kapoor, DM, Department of Medical Oncology, Mahamana Pandit Madan Mohan Malviya Cancer Centre and Homi Bhabha Cancer Hospital, Tata Memorial Centre, Varanasi 221005, Uttar Pradesh, India (e-mail: kapoorakhil1987@gmail.com).

Abstract

Lakhan Kasyap

Introduction Gallbladder cancer (GBC) is the 20th most common cancer in India with a crude incidence rate of 2.3 per 100,000 persons. Of note, it is relatively common in states which fall in the Gangetic plains. Patients often present in the advanced stage and have an unfavorable prognosis.

Materials and Methods From January to June 2021, 170 treatment-naive GBC (adenocarcinoma) patients who were registered at a tertiary care cancer center in North India, were included. Data were extracted from electronic medical records and was analyzed with SPSS.

Results Median age was 56 years (range 32–77 years) and 65.5% ($n = 112$) were female. Incidental GBC was found in 20% patient ($n = 34$). Majority of patients (79.4%, $n = 135$) had preserved performance status. Advanced GBC was present in 85.8% ($n = 146$) patients (locally advanced = 37.0% and metastatic = 48.8%). Biliary drainage procedure was performed in 24% of patients (68% of patients with obstructive jaundice). More than half of patients (53.5%) were lost to follow-up without any treatment. There were 33 patients (19.4%) who underwent surgery and 20 of them received neoadjuvant chemotherapy. Adjuvant chemotherapy and adjuvant radiotherapy were received by 13 and 2 patients, respectively. Palliative chemotherapy was administered to 46 patients. The most common chemotherapy regimen was gemcitabine-cisplatin. At a median follow-up of 1.7 months (95% confidence interval, 1–2.4 months), 42 patients (24%) progressed and 24 patients (14%) died, with 6 months estimated progression-free survival and overall survival being 60.2 and 79%, respectively.

Conclusion GBC is an aggressive and lethal malignancy predominantly affecting females in the fifth decade with dismal outcomes. Improved access to health care, an aggressive approach in operable cases, and optimization of systemic and adjuvant therapy are the need of the hour.

Keywords

- gallbladder cancer
- high incident region
- outcome
- pattern of care
- retrospective

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Introduction

Gallbladder cancer (GBC) is often diagnosed at advanced stage and carries dismal prognosis.[1,2] GBC is the 20th most common cancer in India with crude incidence of 2.3 per 100,000 persons.[3] However, it is among leading sites of cancer in the northern and northeast part of India.[4] Surgery is the mainstay of treatment in GBC and modest outcomes is reported with systemic chemotherapy alone.[5,6] Also, often surgery is deferred in GBC patients due to either locally advanced disease or medical inoperability secondary to poor nutrition and performance status (PS).[1,5] GBC is an aggressive cancer and 5-year survival among resected patients is 5 to 32% while survival in unresectable/metastatic disease is less than 5%.[7–9] To optimize the outcomes in these patients, it is imperative to identify pattern of care and limitations of treatment in real-world scenario. We present the clinical outcomes and pattern of care of GBC from high-incident area in India.

Materials and Methods

This was a retrospective audit done at Mahamana Pandit Madan Mohan Malviya Cancer Centre, Varanasi, Uttar Pradesh, India. We screened our hospital records from January to June 2021 for suspected GBC patients (patients who presented with gallbladder mass or incidentally detected GBC). ►Fig. 1 shows the consort diagram of the study, out of 200 screened patients, 170 GBC patients were included in the study. Treatment intent and plan of management were formulated after discussion in the multidisciplinary tumor (MDT) board. Based on imaging findings, disease was classified as early stage (node negative, liver invasion $\leq$ 2 cm, and no adjacent organ invasion), or locally advanced (node positive, liver invasion $>$ 2 cm, or adjacent organ invasion).[10] Patients with early stage disease was planned for upfront surgery while patients with locally advanced disease were assessed after neoadjuvant chemotherapy. Patients with metastatic/unresectable disease were planned for palliative chemotherapy. Besides, consultation with pain and palliative care team was taken for all patients with metastatic/unresectable disease.

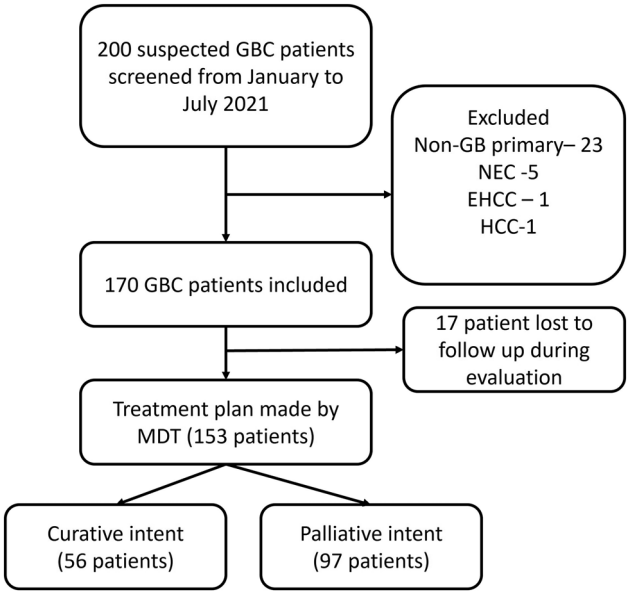

Fig. 1 Consort diagram depicting patient selection. EHCC, extrahepatic cholangiocarcinoma; GB, gallbladder; GBC, gallbladder cancer; HCC, hepatocellular carcinoma; MDT, multidisciplinary tumor board; NEC, neuroendocrine carcinoma.

Electronic medical records of these patients were used to extract demographic, treatment, and outcome data. Patients were censored at last follow-up. Progression was defined as development of a new site of disease, increase in extent of baseline disease, or death due to any cause. Progression-free survival (PFS) was calculated from date of diagnosis (date of histopathology or date of registration when former was not available) to date of progression while overall survival (OS) was calculated from date of diagnosis to date of death. Demographics and treatment characteristics were reported as simple percentage and proportion. Kaplan–Meir survival statistics was used for estimating PFS and OS. Between groups, proportions were compared with chi-squared test while continuous data was compared with Mann–Whitney *U* test. SPSS version 24 (IBM Corp. Released 2016; IBM SPSS Statistics for Windows, Version 24.0, IBM Corp, Armonk, New York, United States) was used for statistical analysis.

Results

Patient Characteristic

Median age of the patients was 56 years (range 32–77 years) and 112 (65.5%) patients were female. All the patients were residents of districts in Gangetic plains. Common presenting complaints were abdominal pain (80.7%), jaundice (17.5%), vomiting (15.2%), and abdominal mass (8.2%). Baseline characteristic is summarized in ►Table 1. Tissue diagnosis was available in 145 patients (84.8%) and histology was adenocarcinoma. Around half of the patients (83, 48.5%) had metastatic disease and a third (63, 36.8%) of the patients had locally advanced disease at presentation.

Treatment Characteristic

After MDT discussion, planned treatment intent was curative in 56 (32.7%) patients while it was palliative in 97 (56.7%) patients. Treatment could be initiated as planned in 79 (46.5%) patients. Of 60 patients (35% of all) with obstructive jaundice, 41 patients (24%) underwent biliary drainage procedures. Incidental GBC after cholecystectomy was found in 34 (20%) patients. Out of these 34 patients, 19 (55.8%) were lost to follow-up before any treatment. Of remaining 15 patients, 4 patients underwent revision cholecystectomy and 11 patients received chemotherapy due to interim disease progression (4 with neoadjuvant and 7 with palliative intent). Overall, 13 patients (7.6%) underwent upfront surgery (radical cholecystectomy or revision cholecystectomy) and all of them received adjuvant chemotherapy. After neoadjuvant chemotherapy, 20 (11.7%) patients underwent surgery. Palliative chemotherapy could be given to 46 patients (47% of 97 patients with palliative intent treatment).

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Table 1 Baseline patient characteristics

Baseline characteristic	Frequency (%)
Median age (range)	56 y (range 32–77 y)
Female	112 (65.5)
Performance status (ECOG)	
1	135 (79.4)
2	24 (14.1)
3	8 (4.7)
Not available	3 (1.8)
Stage	
Early stage	17 (10.0)
Locally advanced	63 (37.0)
Metastatic	83 (48.8)
Unknown	7 (4.2)
Obstructive jaundice	60 (35.0)
Tumor marker	
Median CEA	3.4 ng/mL
Elevated CEA [(> 3 ng/mL (nonsmoker)/> 5 ng/mL (smoker)]	70.1
Median 19–9	54.3 U/mL
Elevated CA 19–9 (> 37 U/mL)	65.5
Median hemoglobin (NR = 12–15 g/dL)	11.3 g/dL
Hemoglobin (below LLN)	62
Median albumin (NR = 3.5–5.2 g/dL)	3.6 g/dL
Albumin (below LLN)	37

Abbreviations: CA 19–9, carbohydrate antigen 19–9; CEA, carcinoembryonic antigen; ECOG, Eastern Cooperative Oncology Group; LLN, lower limit of normal; NR, normal range.

A third of patients (14, 30.4%) could complete the planned number of chemotherapy cycles in the palliative setting. The chemotherapy regimen used in (neo)adjuvant and the palliative setting is summarized in ►Table 2. Most common chemotherapy regimen was gemcitabine and cisplatin. Two patients received adjuvant radiotherapy.

Table 2 Chemotherapy regimen

Chemotherapy regimen	Neoadjuvant ($n = 20$)	Adjuvant ($n = 13$)	Palliative (46)
Gem-Cis	13 (65%)	9 (69%)	28 (61%)
Gem-Ox	2 (10%)	2 (16%)	6 (13%)
CAPOX	–	1 (7.5%)	4 (9%)
mFOLFOX-7	–	–	1 (2%)
Details NA	5 (25%)	1 (7.5%)	7 (15%)

Abbreviations: Gem-Cis, gemcitabine and cisplatin; Gem-Ox, gemcitabine and oxaliplatin; CAPOX, capecitabine and oxaliplatin; mFOLFOX-7, modified infusional 5FU and oxaliplatin, NA, not available.

Table 3 Comparison of patients who received treatment versus those lost to follow-up

Patient characteristic	Treatment received ($n = 79$)	Lost to follow-up ($n = 91$)	*p*-Value
Median age (y)	55	57.5	0.25
PS 2 or higher (%)	9 (11.5)	23 (25)	0.02
Comorbidities present (%)	24 (30)	32 (35)	0.51
Metastatic disease (%)	30 (38)	45 (49.4)	0.13
Obstructive jaundice (%)	10 (12.6)	20 (22)	0.11
Median hemoglobin (g/dL)	11.2	11.3	0.92
Median albumin (g/dL)	3.7	3.6	0.06
Median 19–9 level (U/mL)	41.8	61.8	0.62

Abbreviation: PS, performance status.

Treatment Compliance

Out of 170 patients, 91 patients (53.3%) were lost to follow-up before initiation of treatment. ►Table 3 compares the cohort of patients who received treatment (cohort A) with those who were lost to follow-up (cohort B). Cohort B had significantly higher number of patients with poor PS (Eastern Cooperative Oncology Group Performance Status 2 or higher) than cohort A (25% vs. 11.5%; *p*-value = 0.02). Cohort B had numerically higher number of patients with metastatic disease (49.4% vs. 38%), obstructive jaundice (22% vs. 11.2%), and comorbidities (35% vs. 30%). Cohort B patients also had higher CA 19–9 at diagnosis (median 61.8 vs. 41.8 U/mL).

Outcomes

At a median follow-up of 1.7 months (95% confidence interval [CI], 1–2.4 months), disease progression and death occurred in 42 (24%) and 24 (14%) patients, respectively. Median PFS was 7.3 months (95% CI, 6.7–7.9 months) and the estimated PFS at 6 months was 60.2% (95% CI, 49–71.4). Median OS was not reached while the estimated OS at 6 months was 79% (95% CI, 70.8–87.2). After disease progression only 14 patients (33%) could receive second-line chemotherapy. Most common chemotherapy regimen in the second line was irinotecan. ►Figs. 2 and 3 show PFS and OS curves, respectively.

Discussion

India accounts for 10% of global GBC incidence and it is prevalent in the northern and northeastern part of the country.[11] In our study, all patients were residents in Gangetic plains which may be partly due to proximity of our center in this region and partly a reflection of high incidence of GBC in the region.[12] Majority of patients in our study were

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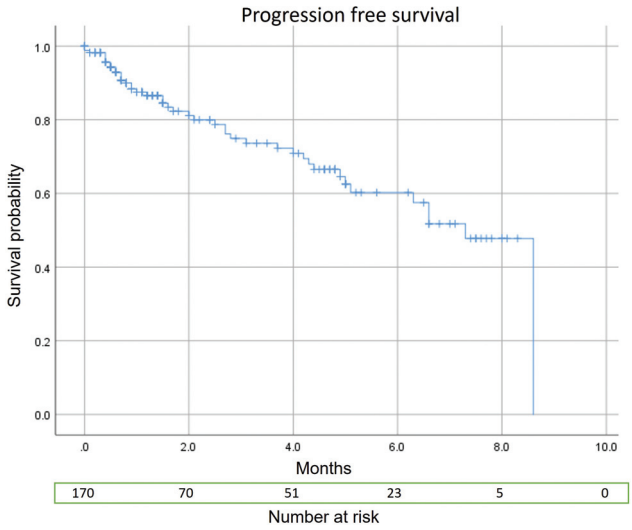

Fig. 2 Progression-free survival.

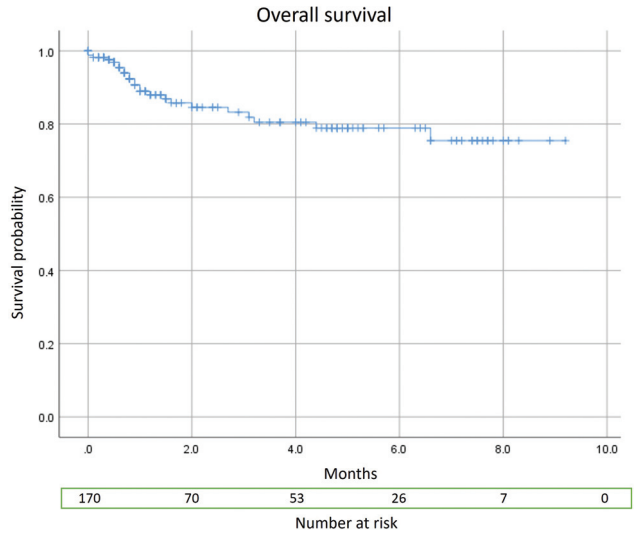

Fig. 3 Overall survival.

diagnosed in mid-fifties which is consistent with other studies from India.[1,5,11] GBC has female predilection as is reflected in our study with two-thirds patients being female.

Majority of the patients presented in the advanced stage in our study. The GBC often presents with vague symptoms which leads to delay in diagnosis. This was consistent with reported literature.[13] In our study, less than half of the patients could undergo treatment as planned in MDT. Patients with compromised PS were less likely to come up for treatment.[14] Moreover, there seems to be association of comorbid condition, metastatic disease, obstructive jaundice, and raised CA 19–9 with treatment noncompliance. Patients with metastatic disease and higher CA 19–9 often have significant disease-related symptoms which may compromise their nutrition and overall general condition. Besides, third of patients in our cohort had obstructive jaundice which led to treatment delay and further deterioration in PS. Even in patients with incidentally detected GBC, more than half were lost to follow-up and among those who received treatment majority had interim disease progression thus precluding surgery. There was high attrition after initial workup. Possible reasons were logistics of access to health care, financial constraints, and lack of awareness.[15] Surgery could be performed in only 20% ($n = 33$) of patients due to locally advanced disease in the majority of patients.[16] Poor nutrition as reflected in low baseline albumin in third of patients, also led to compromise in chemotherapy intensity with only a third of patients completing planned chemotherapy cycles.[17] Most of the patients received gemcitabine-based chemotherapy (gemcitabine and cisplatin or oxaliplatin), this is consistent with reported literature and efficacy of gemcitabine-based regimen in biliary tract tumors.[18–20] Due to heterogeneous patient cohort (metastatic as well as nonmetastatic), analysis of prognostic variables could not be done.

In our study, around 40% ($n = 66$) of the patients relapsed ($n = 42$) or died ($n = 24$) within 6 months and estimated OS at 6 months was 79%. Other studies have reported median survival of 12 to 15 months and 4 to 5 months in locally advanced and metastatic GBC, respectively.[1,21,22] This reflects dismal prognosis of advanced GBC.[1,5,9,16] A third of patient could receive second-line treatment after relapse in our study. Frequently, post-relapse deterioration in PS precludes any cancer-directed treatment in GBC patients. Single-agent chemotherapy has shown benefit with limited toxicity in this scenario.[23,24]

Our study reiterates the poor outcome of GBC patients. There is need to identify these patients at early stage which calls for institution of screening in high incidence area. The nutritional optimization and supportive care can improve the treatment compliance and overall outcomes. Telephonic follow-up and financial support in low-income region during the treatment may help in reducing attrition.[25] Strength of our study is relatively large sample size and sample being representative of high incidence region. However, there were some limitations, follow-up duration was short, there was poor documentation of chemotherapy-related toxicity, and outcomes post-relapse and progression was not available.

In conclusion, GBC is an aggressive cancer often diagnosed in advanced stage with female predilection and carries dismal prognosis. Screening in high-risk areas, multimodality treatment in locally advanced disease, and optimization of adjuvant treatment is the need of the hour.

Conflict of Interest

None declared.

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