

Patterns of Presentation, Treatment, and Survival Rates of Gallbladder Cancer: a Prospective Study at a Tertiary Care Centre

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Abstract

Background India has high incidence of gallbladder carcinoma with regional variation in incidence, the highest in Northern India. This study examines the patterns of presentation, treatment strategies, and survival rate of all patients with gallbladder cancer (GBC) evaluated at our tertiary academic hospital over a period of 2 years.

Methods All patients presented to our institute with established tissue diagnosis of carcinoma gallbladder were accrued in our study over a time period of 2 years. Presentation, treatment modalities, and survival rates were analyzed.

Results One hundred six patients were included: 80 females and 26 males (F: M = 3:1). Median age was 60 years. Eighty patients (75%) had gallstones and 20 patients (21%) had typical history of chronic cholecystitis. The common symptom and sign at presentation were pain in the right upper abdomen (81%) and lump abdomen (49%), respectively. Overall resectability rate was 19.8% (21/106). Eighty-five patients were unresectable or metastatic and treated with palliative intent.

Stagewise distribution at diagnosis was stage I (0%), stage II (4%), stage IIIA (10%), stage IIIB (8%), stage IVA (17%), and stage IVB (61%). Estimated 1-year survival for stages II, IIIA, IIIB, IVA, and IVB was 100, 76, 47.4, 26, and 10.6%, respectively. Significant difference in OS was observed among different stages of GBC (p value <0.001).

Conclusion If proper investigations are done, radical surgery including multi-organ resection can be curative with acceptable morbidity and mortality. Stage at presentation and ability to perform curative resection are the most important prognostic factors predicting survival. Palliative chemotherapy should be considered for metastatic GBC.

Keywords Gallbladder cancer · Multi-organ resection · Palliative chemotherapy · Resectability rate

Introduction

Gallbladder carcinoma (GBC) is the commonest biliary tract cancer having prominent geographic-, age-, race-, and gender-related differences. Gallbladder cancer is up to 25 times more common in some geographical regions compared with others. The incidence of GBC in north and central India is very high—it is the commonest gastrointestinal cancer in women. In Delhi, GBC (incidence rate 6.6) was the fourth most common cancer (following cervix, breast, and ovary) [1]. GBC can be clinically obvious, an unexpected finding at laparotomy, detected incidentally on histologic examination or may be missed only to present with recurrence during follow-up. At presentation, most patients are unresectable because of local invasion, extensive regional lymph node metastasis, vascular encasement, and distant metastases.

Although different associations have been described, gallstones are found to be associated in 70 to 90% of the cases of

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gallbladder cancer. Approximately 0.4% of all the patients who are affected with gallstones eventually develop carcinoma of the gallbladder. The most common histological type of GBC is adenocarcinoma, with a peak incidence in the sixth to seventh decades of life. The clinical pessimism which surrounds gallbladder carcinoma is due to its late presentation and its lack of effective therapy. Besides the exceptional cases detected incidentally at the time of cholecystectomy for gallstone disease, which are usually early stage, the prognosis for most patients is poor. Series from western hemisphere have reported 5-year survival rates of only 5 to 38% [2–4].

The risk of GBC in patients with gallstones has been reported to have increased four to seven times [5]. The association between an abnormal pancreaticobiliary duct junction, a porcelain gallbladder, and other biliary disorders such as choledochal cyst, primary sclerosing cholangitis, Mirrizi's syndrome, and gallbladder cancer has also been recognized. GBC has also been associated with obesity, *Salmonella typhi* infection, ulcerative colitis, cholecystoenteric fistula, chemicals of rubber industry, and adulterated mustard oil. *Helicobacter bilis* and *Helicobacter pylori* have been identified in bile specimens and have been demonstrated to increase the risk of biliary tract carcinoma [6].

The most common symptom for GBC is abdominal pain (73%), followed by nausea and vomiting (43%), jaundice (37%), anorexia (35%), and weight loss (35%) [7]. Constitutional symptoms, ascites, and a palpable mass are all indicative of advanced disease and poor prognosis. Clinical evaluation usually depends on the results of US, computed tomography (CT), and magnetic resonance imaging (MRI). Clinical staging may also be based on open or laparoscopic surgical exploration.

Surgery is the only potential curative treatment for GBC, but the majority of patients present with advanced-stage tumors (stage IV) and are not amenable to surgical resection. Increasing number of GBC patients are now being recognized as *incidental GBC*; only few of them (T1a) may be cured by cholecystectomy. For patients with T1b, T2, and T3 incidental GBC, re-resection is generally recommended. The extent of the hepatic resection should be dictated by the ability to achieve a microscopically negative (R0) margin. Routine resection of the common bile duct is unnecessary, but should be undertaken in the setting of a positive cystic duct margin [8].

The role for surgery in patients with stages II and III disease remains controversial, but most hepatobiliary surgeons believe that an aggressive surgical approach improves survival for these patients. Although no data from prospective, randomized studies are available, resection of the gallbladder, adjacent liver, regional lymph node dissection with or without the extrahepatic bile ducts is the operative approach recommended for resectable GBC [9].

Published studies on the role of adjuvant therapy in the management of GBC are sparse and generally limited to small

retrospective series. However, several reports have evaluated the role of adjuvant chemotherapy or chemoradiotherapy and have shown significantly better 5-year survival rate for patients receiving adjuvant chemotherapy [10, 11]. There is a paucity of randomized controlled studies on the role of palliative chemotherapy for GBC and most included patients with other biliary tract malignancies. However, currently the most patients with unresectable/metastatic GBC having good performance status and organ reserve are being strongly considered for combination palliative chemotherapy [12–15]. Palliation of obstructive jaundice can be best done with biliary stenting; surgery is rarely advised for palliation. Most of the available literature has been reported from developed countries which have a sociocultural and health setup, which is different from that of a developing country such as India. This study was aimed at defining the disease profile in the Indian population and analyzing the outcomes of various treatment strategies in this endemic area of GBC.

Methods

This study was conducted at Malignant Disease Treatment Centre of a tertiary care centre of India. All patients presented to this hospital with established diagnosis of carcinoma gallbladder were accrued in our study over a time period of 2 years (May 2013 to April 2015). All relevant information of study subjects including demography, investigations, indoor and outdoor treatment details, and their follow-up data were recorded. Study subjects were assessed clinically and radiologically for resectability, operability, and fitness for therapy. Imaging included ultrasonography and triple phase CECT abdomen and supplemented with MRI/MRCP, FDG-PET scan, and upper GI endoscopy/ERCP in selected patients. Select patients with high index of suspicion for peritoneal disease underwent staging/diagnostic laparoscopy.

Those who were found to have provisionally resectable disease underwent exploratory laparotomy. Major vascular encasement, peritoneal disease, presence of liver metastasis, and N2 nodal metastasis, detected preoperatively or intraoperatively, were deemed unresectable and merited consideration of palliative chemotherapy if qualify for the same. Palliation of surgical obstructive jaundice and gastric outlet obstruction were done by interventional approach wherever feasible. Those in whom this approach failed and had considerable life expectancy, surgical palliation was done.

Outcome

Short-term outcomes (mortality, morbidity, hospital stay) and long-term outcomes (disease-free survival (DFS) and OS) following surgery were calculated and analyzed. Stage distribution (AJCC 7th edition) of resected patients was as follows:

stage II (3), stage IIIA (9), stage IIIB (8), and stage IVA (1). Minimum follow-up of operated patients was 1 month and maximum follow-up was 24 months. For survival analyses, surviving patients were censored on April 30, 2015. Unresectable/metastatic patients were considered for different kinds of palliative therapy and were actively followed up by means of outpatient review, postal, and/or telephonic communication as applicable and feasible.

Data Analysis

The descriptive statistics is presented using mean (with SD) and median (with range) for quantitative variables, and categorical variables are presented in frequencies along with respective percentages. The statistical comparisons for quantitative variables were done by using Student's *t* test. For categorical variables, chi-square test or Fisher's exact test was used according to the nature of data. For survival analysis, Kaplan-Meier survival curve was plotted to see the survival pattern in different subgroups, and log-rank test was used for comparison of survival. All statistical analyses were performed by using SPSS software (Version 22, SPSS Inc., Chicago, IL, USA). The *p* value less than 0.05 was considered statistically significant.

Results

Age and Sex Distribution

A total of 106 GBC patients included in this report: 80 females and 26 males (F: M = 3:1). The youngest patient in this study was 28-year-old female and the oldest one was 80-year-old male. Median age of presentation of GBC was 60 years for both male and female (Table 1). By applying *t* test, mean age for female and male was calculated as 58.0 and 60.6 years, respectively, with no significant difference in age of presentation.

Table 1 Age and sex distribution for all patients with gallbladder cancer (*n* = 106)

Age group (years)	Female	Male	No. of patients
≤30	3	1	4
31–40	5	1	6
41–50	9	3	12
51–60	26	6	32
61–70	27	10	37
>70	10	5	15
Total	80	26	106

Obesity

We tried to find out association of GBC with obesity as risk factor in our population, as reported in western literature. No definite conclusion could be drawn; in fact, majority of our patients had normal BMI (58%); only 29% GBC patients were overweight and obese.

Stone Disease

Gallstone disease is a major risk factor for GBC. In our patient population, 80 patients (75%) had gallstones and 20 patients (21%) had typical history of chronic cholecystitis.

Clinical Presentation

The common presenting symptoms were pain in the right upper abdomen, weight loss, jaundice, and lump abdomen. Other features were vomiting, anorexia, dyspepsia, and abdominal distension. The most common clinical sign at presentation was lump abdomen (49%) followed by icterus and pallor. Other findings observed were ascites, presence of supraclavicular lymph nodes, and skin nodules (Tables 2 and 3).

Site of Origin

Most common site of origin of GBC was fundus (39%), followed by body (19%) and neck (17%). In 25% of patients, the epicenter of growth could not be delineated by CECT abdomen as the entire gallbladder fossa was occupied by mass lesion.

Treatment

Out of 106 patients with GBC, 32 patients were found to be resectable based upon preoperative evaluation. However, 11 patients were either unresectable or metastatic based upon intraoperative findings. Overall resectability rate was 19.8% (21/106). Overall surgical morbidity rate among GBC patients (*n* = 21) who underwent curative resection was 42.8% (9/21)

Table 2 Various modes of clinical presentation of GBC (*n* = 106)

S. No.	Presenting complaints	No. of cases	% of cases
1	Pain abdomen	86	81
2	Weight loss	39	37
3	Jaundice	33	31
4	Lump abdomen	17	16
5	Vomiting	21	20
6	Anorexia	20	19
7	Dyspepsia	11	10
8	Abdominal distension	2	2

Table 3 Clinical signs of GBC at presentation (*n* = 106)

S. No.	Signs	No. of cases	% of cases
1	Lump abdomen	46	43
2	Jaundice	34	32
3	Pallor	18	17
4	Ascites	13	12
5	SCLN	13	12
6	Skin nodules	2	2

and mortality rate was 4.7%. Mean DFS and mean OS for resected patients were 19.9 months (SE 1.42, 95% CI) and 21.1 months (SE 1.36, 95% C.I.). Eleven patients got treated by adjuvant CCRT followed by adjuvant chemotherapy, five patients with adjuvant CCRT, and three patients received only adjuvant chemotherapy. Two patients were unwilling to have any form of adjuvant treatment.

Eighty-five patients were unresectable or metastatic and treated with palliative intent. A total of 65 patients received palliative chemotherapy, either combination chemotherapy or single agent chemotherapy. Twenty patients, either unfit for chemotherapy or unwilling for the same, were advised for best supportive care. Median OS was 35.6 weeks (SE, 2.6; 95% C.I.) for patients who received palliative chemotherapy, whereas median OS for those who received best supportive care alone was 13 weeks for best supportive care (BSC) group (SE, 2.02; 95% C.I.). Log-rank test was used to compare OS between BSC and CT groups. Statistically significant difference in OS was seen (*p* value <0.001).

Palliative Procedures Done for GBC

A total of 65 palliative procedures were done in this cohort, mostly nonsurgical interventions. Surgical palliation was required in only three patients (Table 4).

Stagewise Distribution and Survival Pattern

Most of the GBC patients presented in advanced stage (Fig. 1). Most common stage at presentation was stage IVB (61%). Estimated 1-year survival for stages II, IIIA, IIIB, IVA, and IVB was 100, 76, 47.4, 26, and 10.6%, respectively (Fig. 2). By using log-rank test, significant difference in OS

Table 4 Various palliative procedures done for GBC patients (*n* = 106)

S. No.	Nonsurgical	No. of cases	Surgical	No. of cases
1	Biliary stenting	38	Segment III bypass	1
2	Duodenal stenting	4	Triple bypass	1
3	Ascetic tap	19	Gastrojejunostomy	1
4	Hemostatic RT	1		
Total		62		3

was observed among different stages of GBC (*p* value <0.001).

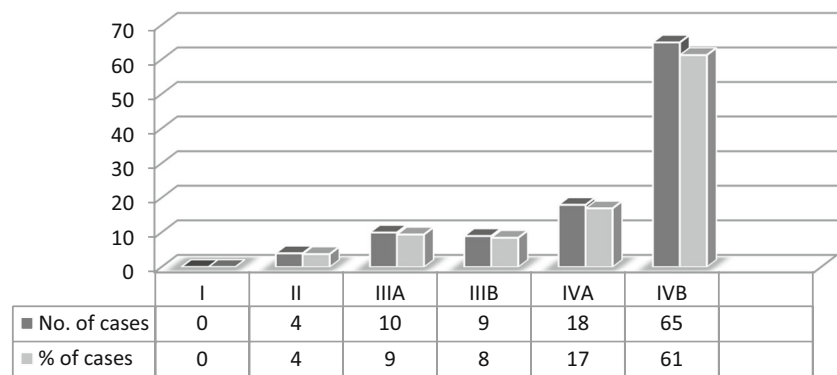
Discussion

Gallbladder cancer is the most common malignant lesion of the biliary tract and the fifth most common among malignancy of the digestive tract [16]. It is a highly fatal disease with poor prognosis. This is largely attributed to advanced stage of disease at presentation, which frequently precludes a curative resection. There is limited knowledge about biology and natural history of this disease, and considerable uncertainty remains regarding its optimal diagnostic and therapeutic management. Even with the numerous diagnostic tests available, gallbladder cancer is frequently diagnosed in advanced stages due to its non-specific presentation and intricate anatomical location. Surgical resection is the only potentially curative treatment for GBC. However, the resectability rate has been reported to range between 30 and 40%, and 5-year survival for cancers of the gallbladder lies between 0 and 10% in most reported series. Role of adjuvant therapy and palliative chemotherapy has not been well studied, and present recommendations for their utilization in management of GBC are based upon small studies.

Gallbladder cancer occurs more frequently in women (female to male ratio = 3:1). The incidence increases progressively with age, both in males and females. It is most commonly diagnosed in the seventh decade of life [2, 3, 17, 18]. In the present study, the mean age at presentation was 58.5 years (range 28 to 80 years) with no significant difference between female and male. This early age of presentation in this cohort may be attributed to the fact that this institute caters medical care to a specific population subgroup (armed forces personnel and their families), which may not reflect the general population. Female to male ratio in this study was 3:1 which is in sound agreement with published literature [19, 20].

Gallstones are considered the most important *risk factor* for gallbladder cancer. Gallstones associated with gallbladder cancer have been reported in 61–90% of patients [21]. However, the incidence of GBC in a population with gallstones varies from 0.3 to 3% only. In this study, 75% patients had evidence of gallstones, quite in accordance with literature. Several life style factors such as obesity, smoking, tobacco

Fig. 1 Stagewise distribution of GBC patients ($n = 106$) according to AJCC cancer staging manual, 7th edition



chewing, and alcohol consumption have been implicated [22, 23] but, in this small study population, it is difficult to derive any possible association.

The most common symptom of GBC reported in this study was pain in the right upper abdomen (91%). Other common symptoms reported were weight loss (41%), jaundice (35%), anorexia (21%), and vomiting (22%). Similar observations have been made by Taner CB et al. (2004) who reported that pain abdomen was presenting symptom in 73%, followed by nausea and vomiting (43%), jaundice (37%), anorexia (35%), and weight loss (35%) [24]. Various other studies relating to GBC viz. Muhammad A et al. (2005) [19] and Zang BH et al. (2003) [25] had shown similar symptomatology. Special mention to be made that this study reported higher incidence of supraclavicular lymph node metastasis (14%) which may be because of more advanced disease at presentation.

Surgery remains the only treatment modality associated with a benefit in terms of survival in GBC. In the last decade, several studies have documented an increase of 5-year

survival rates from 5 to 12 up to 38%. It is well known fact that palliative chemotherapy or radiotherapy is not very effective for GBC and survival benefit if any is limited to months. In this context, an aggressive surgical approach for locally confined disease is justified. However, what is most disconcerting is the lack of consensus across the world on what constitutes an aggressive surgery for a given stage of the disease. Being a relatively uncommon disease around the world, hardly any of the approaches have been evaluated in evidence based manner. The complex location of gallbladder, coupled by morbid anatomy due to cancer, poses a great difficulty to assess resectability even intraoperatively. Before taking any irreversible step, one must be very sure that R0 resection can be achieved with an acceptable morbidity. In our experience, encased hepatic artery or portal vein (and their left branches) or fixity of hepatoduodenal ligament is considered contraindication for resection. In the present series, we have not proceeded with any non-therapeutic resection for such an advanced disease considering very high morbidity and mortality, besides oncologic concern of margin positive resection.

The armamentarium of surgical procedures mainly comprised liver resection, common bile duct resection, lymph node dissection in the hepatoduodenal ligament and especially practiced in Japan-concomitant pancreatoduodenectomy or lymph dissection of the interaortocaval compartment. Most of our surgical patients belong to advanced stage GBC (stages III and IV) with only three patients of stage II. The initial results of this study are encouraging with acceptable morbidity and excellent survival with curative intent radical resection. With the follow-up of 1 to 24 months, the mean DFS of 19.9 months and mean overall survival of 21 months were calculated. There was a significant difference in OS between surgically resected patients and those who could not undergo curative resection (p value <0.0001). Longer follow-up data is needed to compare our survival results with other contemporary series.

The role of *adjuvant therapy* is again an object of debate and controversy in optimal management of biliary tract malignancies. Isolated locoregional failure has been reported in approximately 15% patients with GBC and systemic failure with or without locoregional recurrence occurred in 85%

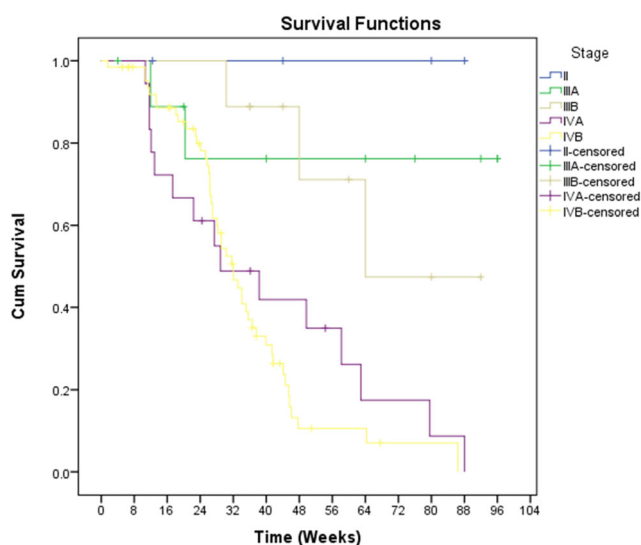


Fig. 2 Kaplan-Meier survival curves for different stages of GBC ($n = 106$). Significant difference in OS was observed among different stages of GBC (p value <0.001)

patients of GBC [26]. Because of poor survival after curative resection due to frequent local relapse and distant metastases, the role of adjuvant therapy has been widely explored.

There is large number of retrospective series which had reported a modest potential OS benefit with adjuvant CCRT [27]. In a retrospective series of 73 patients with gallbladder cancer treated between 1985 and 2004 at Mayo Clinic, Gold DG et al. (2009) suggested that adjuvant CCRT may obtain a statistically significant improvement in OS only for patients with lymph node involvement [28]. Another study from South Korea suggested an improved OS only in patients with locally advanced tumor (T3/T4) or with R1 resection [29]. Unfortunately, the retrospective nature of most of these studies, the small sample size, the lack of correction for multiple comparisons, patient selection bias; heterogeneity in terms of patients' characteristics, treatment regimens, tumor site and stage; long-lasting accrual periods, different surgical, radiotherapy and radiological techniques in different historical periods, and other confounding factors do not allow to draw any firm conclusion on the role of CCRT.

Chemotherapy has also been used in GBC with little or no survival benefit demonstrated. Park et al. [30] in a retrospective study reported that overall survival (OS) was not significantly different among the adjuvant therapies ($p = 0.180$), but DFS was ($p = 0.033$). Overall, the chemotherapy group had a better prognosis, although there were no significant differences. They concluded from this study that adjuvant therapy is an effective treatment option for resected GBC.

Another beautifully crafted systematic review and meta-analysis published in Journal of Clinical oncology (February 2012) supports adjuvant therapy for biliary tract cancers [31]. This meta-analysis showed that those receiving CT or CCRT derived statistically greater benefit than RT alone (p value = 0.02). The greatest benefit for adjuvant therapy was in those with LN-positive disease (p value = 0.004) and R1 disease (p value = 0.002).

Given the lack of guidelines based on high level of evidence, biliary tract tumors receive heterogeneous management around the world. A survey of therapeutic strategies recommended in the clinical practice in 2001–2002, reported that adjuvant CCRT was widely adopted in the majority of American centers (71%), followed by Asian/Pacific centers (55%), but only by 29% of European institutions. This scenario may have changed in more recent years with a trend towards possibly increasing use of adjuvant treatment due to the numerous positive experiences reported in the literature in the last decade [29].

In the present study, as most of patients belonged to locally advanced GBC, 90% of our surgically treated patients received some form of adjuvant therapy, mostly adjuvant CCRT. The impact of adjuvant therapy in this series needs to be evaluated with adequate follow-up. In the initial observations, only three of our patients had recurrence; two of them had received adjuvant CCRT followed by adjuvant chemotherapy. Both these patients had significant metastatic lymph nodes of hepatoduodenal ligament. As

a concluding remark, we can say that a multi-institutional worldwide effort to conduct well-designed phase III trial and to expand biological knowledge of the disease is necessary to clarify the role of adjuvant therapy in GBC.

Gemcitabine and platinum compounds are emerging as commonly used drugs for *palliation*, either as a single agent or in combination. The study by DC Doval et al. using gemcitabine and cisplatin reported 38% response rates and 4.8 months of median survival [13]. In the present study, a total of 65 patients received palliative chemotherapy, either combination chemotherapy or single agent chemotherapy. Twenty unresectable patients were treated with BSC. Overall median survival in our study with palliative chemotherapy was 35.6 weeks, significantly superior to BSC (p value <0.001).

There is no universally suitable *palliative surgical procedure*, and the choice of operation must take into account the general risk to the patient, the likely effect of surgery. The goal of palliation should be relief of pain, jaundice, and bowel obstruction and prolongation of life. These should be achieved as simply as possible, given the aggressive nature of this disease. With the advances in ancillary interventional branches, the need for surgical palliation is gradually decreasing. This fact is quite evident from this series where only three patients needed surgical palliation in the form of biliary bypass and GI bypass procedures. Most of the patient can now be best palliated with nonsurgical approach. In this study cohort, 38 patients underwent biliary stenting either by percutaneous stent or by endoscopic stent whichever was possible. Endoscopic duodenal stenting for gastric outlet obstruction was done in four patients.

Most of the GBC patients presented in advanced stage. Most common *stage at presentation* was stage IVB (61%). Estimated 1-year survival for stages II, IIIA, IIIB, IVA, and IVB was 100, 76, 47.4, 26, and 10.6%, respectively. Short follow-up period of this study, especially for surgically managed patients and changing TNM stage grouping, makes it difficult to compare these observations with previously published literature. Very few reports are available with 1-year survival data. In a retrospective review by Principe A et al. (2006), 1-year survival for different stages (AJCC 6TH Edition) with aggressive surgical approach was reported [20]. Overall, 1-year survival for stage IA–IB (present stages I and II), stage IIA–IIB (present stage IIIA and IIIB), and stages III–IV (present stage IVA–IVB) was 67, 63, and 50%.

As evident from this present study and several others, stage at presentation and ability to perform curative resection are the most important prognostic factors predicting survival. Highly significant statistical difference was observed among different stages of disease (p value <0.001). Other important factors include male sex, old age, histopathological type, regional lymph node metastasis, vascular invasion, presence of biliary infiltration, and adjuvant treatment [32, 33].

In conclusion, GBC is a highly lethal and aggressive disease with a poor prognosis. However, if proper investigations are done,

radical surgery including multi-organ resection can be curative with acceptable morbidity and mortality. Most patients present in advanced incurable stage (80%) and may be a candidate of palliative treatment alone. Palliation for obstructive jaundice and gastric outlet obstruction associated with GBC can best be achieved with ancillary interventional branches with only occasional need of surgical palliation. Stage at presentation and ability to perform curative resection are the most important prognostic factors predicting survival. Palliative chemotherapy should be considered for unresectable/metastatic GBC patients if they are fit for the same. Palliation of obstructive jaundice and gastric outlet obstruction should be done using interventional procedure wherever feasible.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

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