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REVIEW

Gallbladder cancer: Progress in the Indian subcontinent

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Abstract

Gallbladder cancer (GBC) is one of the commonest biliary malignancies seen in India, Argentina, and Japan. The disease has dismal outcome as it is detected quite late due to nonspecific symptoms and signs. Early detection is the only way to improve the outcome. There have been several advances in basic as well as clinical research in the hepatobiliary and pancreatic diseases in the West and other developed countries but not enough has been done in GBC. Therefore, it is important and the responsibility of the countries with high burden of GBC to find solutions to the many unanswered questions like etiopathogenesis, early diagnosis, treatment, and prognostication. As India being one of the largest hubs for GBC in the world, it is important to know how the country has progressed on GBC. In this review, we will discuss the outcome of the publications from India highlighting the work and the developments taken place in past several decades both in basic and clinical research.

Key Words: Gallbladder cancer; India; basic research; Clinical research; Surgery; Therapeutics

Core Tip: This review is important to know the work done on gallbladder cancer from the country with high incidence of the disease and struggling to do its best. Research outcome may help to compare with the work being done in rest of the world and for the future collaborative research to find way for early diagnosis and to improve the treatment outcome of this aggressive disease.

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INTRODUCTION

Gallbladder cancer (GBC) is the most common and most aggressive malignancy of the biliary tree. Early diagnosis is crucial for better prognosis of this dreaded disease. However nonspecific clinical presentations often hinder the accurate diagnosis of GBC at an early stage. GBC remains a highly lethal disease, with only 10% of all patients are upfront resectable. People diagnosed with early GBC typically have a 5-year survival rate of 30%-40%, whereas individuals with locally advanced lesions have a one-year survival rate of around 10%[1].

India carries one of the most substantial burdens of this condition, with its peak incidence among women in northern India reaching 21.5 cases per 100000 individuals. The substantial morbidity and mortality from GBC significantly hinder global cancer control efforts, particularly in high-risk populations. Currently, effective strategies to reduce GBC mortality are lacking.

Chile has the highest incidence of GBC globally, with 9.7 new cases per 100000 inhabitants each year. This is followed by Bolivia (8.1 per 100000 inhabitants), South Korea (6.5 per 100000 inhabitants), Laos (4.7 per 100000 inhabitants), and Japan (4.7 per 100000 inhabitants)[2]. In the United Kingdom, GBC accounts for less than 1% of all new cancer cases. In contrast, United States has significantly lower incidence rate compared to global trends, with rates of 1.4 per 100000 among women and 0.8 per 100000 among men.

Despite of large case load of GBC in Indian subcontinent, the extent of advancement in clinical and basic research related to the etiology, pathogenesis, diagnosis, prevention, and treatment of GBC remains unclear. This review seeks to evaluate India's progress in various aspects of GBC research and provide a comprehensive summary of GBC studies conducted across the Indian subcontinent. In this review, we have endeavored to encompass all the significant research conducted in India on GBC.

METHODOLOGY

We systematically reviewed published literature from India on gall bladder (GB) cancer between year 2000 to 2023 from online search engine PubMed and Medline using the search terms gallbladder, etiopathogenesis, prevention, Indian studies, basic research, epidemiological studies, clinical studies, and bullion operators like AND, OR, NOT. The secondary sources retrieved from these publications were identified through a manual search and assessed for relevance. Publications have been categorized in detail covering the areas of epidemiology, basic and clinical work. The result has been discussed in detail.

RESULTS

We have categorized the research published from 2000 to 2023 into five distinct areas: Demography and Etiopathogenesis, Clinicopathogenesis, Genetics and Polymorphism, Diagnostics and Imaging, Surgical Approaches and Resection, and Multimodality Therapy.

STUDIES ON DEMOGRAPHY AND ETIOPATHOGENESIS

Epidemiology

India has a high incidence of GBC and accounts for approximately 10% of the global burden of this disease. There is a pronounced regional disparity in GBC incidence across India, with considerably higher rates observed in the northern and northeastern regions compared to southern states. For instance, GBC incidence in North India (8.9/100000) is approximately 10 times greater than that in Chennai (0.8/100000). According to data from the National Cancer Registry, Delhi exhibits a similar Age-Standardized Rate (ASR) for GBC comparable to that of Chile. According to a study by Dutta *et al* [3], the ASRs for GBC in northern India and northeastern India are 11.8 per 100000 population and 17.1 per 100000 population, respectively. These rates are comparable to the high incidence areas of Bolivia (14/100000) and Chile (9.3/100000). Phadke *et al*[4] conducted a study to calculate the Annual Percentage Change (APC) in age-adjusted incidence rates of a specific health condition. They found significant APC, in the high-risk regions of Cachar [7.0 (P = 0.02)], Delhi [4.0 (P = 0.04)], and Kamrup [4.3 (P = 0.02)]. Meanwhile, in the low-risk regions of Bengaluru and Pune, the APC was 5.7 (P = 0.04) and 3.4 (P = 0.04), respectively. S *et al*[5] discovered that GB cancer incidence among women in Kamrup urban (ASR 16.2) was second highest after Chile[5]. Some epidemiological studies have also shown that, the population living in high-risk regions is associated with an elevated risk of developing GBC. Mhatre *et al*[6] from Tata Memorial Hospital

(TMH) in Mumbai conducted a study revealing demographic disparities in GBC. The study revealed 4.82-fold higher odds (95%CI: 3.87-5.99) of developing GBC among individuals born in high-risk regions compared to those born in low-risk regions. Additionally, there was a dose-response relationship observed between GBC risk and length of stay in high-risk regions, showing a lifetime exposure odds ratio (OR) of 5.58 (95%CI: 4.42-7.05) with a significant *P* value (≤ 0.001). Notably, the risk of GBC persisted even among individuals who migrated from high-risk to low-risk regions. All these studies indicate a higher disease burden of GBC in India.

Demographic risk factors

Numerous risk factors contribute to the development of GBC in Indian patients, particularly in high-risk regions, notably in the northern and northeastern states where many studies have been conducted. The Sutlej, Ganges, Yamuna, and Brahmaputra rivers, originating from glaciers in the northern Himalayas, flow east and became contaminated downstream by industrial and human waste. Several studies have explored the hypothesis that increased pollution of these rivers contributes to the risk of GBC in the North Indian population. Gupta *et al*[7] found that exposure to benzene hexachloride, dichlorodiphenyltrichloroethane, and high concentrations of cadmium in the Ganga River contribute to development of GBC. Several studies have shown an increase in *Helicobacter pylori* (*H. pylori*) and coliform counts in drinking water in the rivers mentioned above. Several studies have also shown that *Salmonella typhi* (*S. typhi*) and *H. pylori* , transmitted through fecal contamination, are linked to the development of GBC[8,9]. Evidence suggests that *Helicobacter* species may increase the risk of GBC, with ORs ranging from 2.7 to 12 in different studies from India. Tewari *et al*[10] found that *S. typhi* is significantly associated with GBC compared to gallstone disease (GSD; 33% *vs* 0%).

Many studies were conducted to find the other demographics risk factors for this dreaded disease. Mhatre *et al*[11] discovered that there is an increased risk of GBC associated with higher parity and a shorter reproductive lifespan. Same authors in another study reported that consumption of mustard oil was associated with increased risk of GBC[12]. In a gallstone-matched study, Mishra *et al*[13] identified several factors associated with GBC, notably age 50 years or older, low literacy, below-poverty-line socioeconomic status, infrequent bowel habits, history of hypertension, use of antihypertensive medications, non-vegetarian diet, cooking with firewood, consumption of hand pump water, and high coffee intake[13]. Gallstones are the most significant risk factor for GBC, present in 60%–90% of GBC patients compared to 20%–25% of an age-matched population[14]. Several studies conducted in the early 2000s explored the relationship between gallstones and GBC. Mhatre *et al*[15] identified that the presence of gallstones is associated with an elevated risk of developing GBC. Dutta *et al*[16] found that the presence of gallstones was an independent determinant associated with a younger age of patients with GBC (OR 4, 95%CI: 1.5-11; *P* = 0.006). Sharma *et al*[17] identified that the duration of symptom for gall stone disease is a significant risk factor for GBC. Conversely, Narang *et al*[18] found that ,a higher number and larger size of gallstones, along with the presence of cholesterol in gallstones, may also elevate the risk of developing GBC. Singh *et al*[19] reported that as the size of gallstones increases, there is a progression in the gallbladder mucosa response, transitioning from cholecystitis and hyperplasia to metaplasia, ultimately into carcinoma. Studies conducted in India highlighted the composition of bile and its role in gallbladder carcinoma. Sharma *et al*[19] discovered that patients with GBC had a substantial decrease in lipid species and an increase in bacterial taxa in their bile. The summary of other relevant publications on demography and etiopathogenesis is presented in Table 1[20-37].

STUDIES ON MOLECULAR PATHOGENESIS-GENETICS AND POLYMORPHISM

Our current understanding of the genetic and molecular changes associated with GBC remains limited. GBC, like other tumors, is driven by multiple genetic alterations. Several studies in India have aimed to elucidate the genetic mutations and molecular pathogenesis underlying gallbladder carcinoma. Studies from Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, have identified *KRAS*, *PIK3CA*, and *EGFR* are the some of commonly mutated genes in GBC. A summary of genes related to different stages of pathogenesis is illustrated in Figure 1. Iyer *et al*[38] identified *ERBB2* alterations in early-stage GBC and proposed that anti-EGFR therapy (Afatinib) could be a promising therapeutic option. Kazmi *et al*[39] studied the role of *KRAS* and found that K-ras codon 12 mutations were highly prevalent in GBC and were associated with bad prognoses in resected GBC. Gupta *et al*[40] identified a new protein called Survivin, which was significantly associated with GBC, suggesting its role in the pathogenesis of GBC. Many studies were conducted regarding single gene expression and Global gene expression in GBC.

Studies on single gene expression

Many studies were conducted in India exploring single gene expression in GBC. Kumari *et al*[41] found that that C-erbB2 positive tumors exhibited a longer median survival compared to C-erbB2 negative tumors. Misra *et al*[42] studies p53 protein overexpression in gallbladder carcinoma. Singh and colleagues reported that MASPIN and THBS1 have an important epigenetic role in GBC[43]. Tekcham *et al*[44] identified downregulation of *PTEN* in GBC. Rai *et al*[45] found that the expression of CCKAR was significantly higher in GBC compared to GSD.

Studies on global gene expression

Several studies have also investigated global gene expression in GBC. Yadav *et al*[46] conducted a study on targeted gene sequencing of GBC and identified 184 somatic mutations and 60 germline mutations in cancer driver genes such as *SMAD4*, lysine methyltransferase 2C (*KMT2C*), and tumor protein p53. Kumari *et al*[47] used high-throughput methods and detected mutations in *P53*, *STK11*, *RICTOR*, *TSC2*, as well as *FGF3-TACC* fusion and *FGF10* amplification using next-generation sequencing platform.

Table 1 Studies on etiopathogenesis of gall bladder cancer

Serial No.	Sample size	Findings	Ref.
1	GBC (214) controls (214)	Biomass burning was recognized as a significant risk factor for GBC	Shridhar *et al*[20]
2	GBC (200); Gall stone disease (200) controls (200)	Residence in the Gangetic belt, consumption of tea, tobacco, joint family structure, chemical exposure, fried food, and high levels of secondary bile salts are risk factors of GBC	Jain *et al*[21]
3	GBC (54)	Cholelithiasis is a predisposing factor for GBC	Bhattacharjee and Nanda[22]
4	GBC (1291)	Exposure to high soil arsenic levels and proximity to river ganga are risk factors for GBC	Madhawi *et al*[23]
5	GBC (333)	Smoking, cholelithiasis, alcohol consumption, typhoid in the past, post-menopausal women are risk factors for GBC	Tyagi *et al*[24]
6	GBC (63)	Poor hygiene and water supply, malnutrition, cholelithiasis, tobacco and alcohol consumption are modifiable risk factors for GBC	Khan *et al*[25]
7	GBC (122); controls (122)	Education, intake of vitamin C, parity, and type of fuel used were significant factors for GBC	Panda *et al*[26]
8	GBC (49)	About 75% of patients diagnosed with GSD showed detectable H. pylori DNA in their gallbladder tissue	Bansal *et al*[27]
9	GSD (330)	As the stone size increases, gallbladder mucosa changes progress from cholecystitis to carcinoma	Mathur *et al*[28]
10	GBC (n = 11), Chronic cholecystitis (n = 23), Xantho-granulomatous cholecystitis (n = 11)	The cholesterol content in gallstones of GBC was significantly lower compared to that in benign gallbladder diseases	Srivastava *et al*[29]
11	GBC (390)	Chronic bacterial infection of bile is considered an etiological factor in the development of gallbladder carcinoma	Sharma *et al*[30]
12	GSD (101)	*H. pylori* colonizes regions of gastric metaplasia within the gallbladder	Misra *et al*[31]
13	GBC (328); controls (328)	Females, consumption of mustard oil, Family history, low socioeconomic status and drinking water from hand pump were the risk factors for GBC	Kumar *et al*[32]
14	GBC (27), GSD (196)	High prevalence of salmonella typhi in gall bladder carcinoma	Vaishnavi *et al*[33]
15	GBC (38)	Higher levels of biliary nitrate associated with the gallbladder carcinogenesis	Shukla *et al*[34]
16	GBC (n = 30); controls (n = 30)	Decreased levels of selenium (Se), zinc (Zn), and vitamin E are associated with an increased risk of gallbladder carcinoma	Shukla *et al*[35]
17	GBC (n = 30); controls (n = 30)	Significantly high biliary benzene hexachloride and dichloro diphenyl trichloroethane associated with gallbladder carcinogenesis	Shukla *et al*[36]
18	150 GBC	Gall stones associated with development of metaplastic, dysplastic and neoplastic mucosal changes of gall bladder mucosa	Gupta *et al*[37]

GSD: Gallstone disease; GBC: Gallbladder cancer; *H. pylori*: *Helicobacter pylori*.

Loss of heterozygosity (LOH) is frequently observed in GBC. In GBCs this change is commonly seen as the loss of one copy of a gene (heterozygous allelic loss) in multiple chromosomal regions. This phenomenon has been extensively studied and is known as LOH. Priya *et al*[48] observed LOH in *FHIT* gene. Jain *et al*[49] detected LOH at 8 Loci, that is 3p12, 3p14.2, 5q21, 9p21, 9q, 13q, 17p13, and 18q for tumor suppressor genes (*DUTT1*, *FHIT*, *APC*, *p16*, *FCMD*, *RB1*, *p53*, and *DCC* genes). There are few studies that examined the aberrant promoter methylation gene. Pandey *et al*[50] from Lucknow studied candidate genes and identified *GSTT1, NAT2, APOB,* and *MTHFR* mutations. Numerous other studies on genetics and polymorphisms have been published, and some of them are summarized in Table 2[51-93].

STUDIES ON CLINICOPATHOLOGICAL ASPECT OF GBC

In this section, we have described clinicopathological parameters including presenting symptoms, screening methods, histopathological findings, prognostic factors, and tumor characteristics.

Symptomatology

Patients with GBC typically present with pain in the right upper quadrant and epigastrium region of the abdomen, with or without changes in the character of the pain. They may also exhibit symptoms such as jaundice, features of GOO

Table 2 Studies on genetics and polymorphism in gall bladder cancer

Serial No.	Sample size	Findings	Ref.
1	-	IGF-MAPK cascade, p38 MAPK pathway, p53 pathway, and FAS signaling pathway as highly enriched among dysregulated miRNAs in GBC	Saxena *et al*[51]
2	-	*PARP1 rs1136410* (A/G) associated with early onset of GBC	Anjali *et al*[52]
3	GBC (29), controls (29)	*VEGF-A* expression can be used as potential prognostic biomarker in GBC	Singh *et al*[53]
4	-	Studied the prognostic significance of the oxidative stress marker 8-OH-dG and genes associated with the BER pathway	Singh *et al*[54]
5	GBC (25)	In gallbladder cancer patients, mutations were identified in both P53 and codon 12 of KRAS	Shukla *et al*[55]
6	-	Mutations in the sorcin gene associated with poor overall survival in GBC	Shabnam *et al*[56]
7	GBC (523), controls (274)	Studied the *TERT-CLPTM1L* and *8q24* Genetic Variants in GBC	Yadav *et al*[57]
8	GBC (50)	Individual and repetitive mutations of shh gene in GBC can be used as diagnostic marker	Dixit *et al*[58]
9	GBC (50)	Overexpression of Her2/neu and Ki67 in gallbladder cancer associated with lymph node metastasis	Pujani *et al*[59]
10	GBC (541), controls (307)	*KRAS rs61764370* polymorphism is significantly associated with GBC	Kazmi *et al*[60]
11	-	Studied Epigenetic silencing of *APC* in advanced GBC.	Tekcham *et al*[61]
12	GBC (24)	Found 7 hypermethylated or down-regulated (*e.g.*, *FBN1*, *LPP*, and *SOD3*) and 61 hypomethylated or up-regulated markers (*e.g.*, *HBE1*, *SNRPF*, *TPD52*) for GBC	Sharma *et al*[62]
13	Cases (50)	The level of *EGFR* expression correlates with the aggressiveness of the disease	Kumar *et al*[63]
14	GBC (52)	Tγδ17 could serve as a potential predictive biomarker in GBC	Patil *et al*[64]
15	GBC (30)	The *MTHFR A1298C* polymorphism associated with development of GBC	Dixit *et al*[65]
16	GBC (37)	Telomere dysfunction and alterations are the earlier events in progression of GBC	Poojary *et al*[66]
17	GBC (148), controls (256)	*CYP-17* gene polymorphism is associated with risk of gallbladder cancer	Dwivedi *et al*[67]
18	-	*LXR-β* polymorphisms associated with GBC	Sharma *et al*[68]
19	GBC (195), controls (300)	Vascular endothelial growth factor single nucleotide polymorphism associated with GBC	Mishra *et al*[69]
20	GBC (35)	mitochondrial D-loop mutation associated with GBC	Maurya *et al*[70]
21	GBC (410), controls (210)	Estrogen and progesterone receptor sequence associated with increased risk of *GBC*	Srivastava *et al*[71]
22	-	*KRAS p.Q25H* polymorphism associated with development of GBC	Parmanik *et al*[72]
23	GBC (230), controls (230)	Caspase-8 polymorphisms associated with GBC	Srivastava *et al*[73]
24	GBC (51)	p53 mutation are early events in the evolution of GBC	Agrawal *et al*[74]
25	GBC (185), controls (195)	*CYP7A1* haplotype associated with GBC	Srivastava *et al*[75]
26	GBC (230), controls (230)	The role of pre-microRNA variants in GBC uncertain	Srivastava *et al*[76]
27	GBC (62)	Most common alteration in the p53 was frameshift mutation at codon 271	Nigam *et al*[77]
28	GBC (40)	High LOH in *CDH1* associated with pathogenesis of GBC	Priya *et al*[78]
29	GBC (212), controls (219)	Studied the *DNMT3B -579* G > T promoter polymorphism	Srivastava *et al*[79]
30	GBC (233), controls (260)	Angiotensin I-converting enzyme insertion/deletion polymorphism associated with GBC	Srivastava *et al*[80]
31	GBC (126), controls (190)	Role of DNA repair pathways GB carcinogenesis	Srivastava *et al*[81]
32	GBC (171),	Patients with *ABCG8* variant allele are at a higher risk of GBC	Srivastava *et al*[82]

	controls (221)		
33	GBC (185), controls (200)	Complement receptor polymorphism associated with pathogenesis of GBC	Srivastava and Mittal[83]
34	GBC (173), controls (204)	Single nucleotide polymorphisms of DNA repair genes *OGG1* and *XRCC1*; associated with low risk for GBC	Srivastava *et al*[84]
35	GBC (144), controls (210)	Role of *CCR5+/Delta32* polymorphism associated with risk of GBC	Srivastava *et al*[85]
36	GBC (124), controls (166)	*IL-1* gene polymorphisms associated with GBC	Vishnoi *et al*[86]
37	GBC (142), controls (217)	*CYP1A1 C* allele frequency associated with GBC	Pandey *et al*[87]
38	-	*CYP7A1* polymorphism associated with GBC	Srivastava *et al*[88]
39	-	The X (+), D haplotype of *APOB* is associated risk for development of GBC	Pandey *et al*[89]
40	-	NAT2 slow acetylator phenotype associated with risk of GBC	Pandey *et al*[90]
41	GBC (129), controls (208)	*LRPAP1* polymorphism associated with GBC	Pandey *et al*[91]
42	GBC (39)	Mutation in codon 12 of the K-ras oncogene associated with GBC, which indicate role of chronic inflammation in gallbladder carcinogenesis.	Singh *et al*[92]
43	GBC (117), controls (137)	The apoB-XbaI gene polymorphism associated with GBC	Singh *et al*[93]

GBC: Gallbladder cancer; GB: Gallbladder.

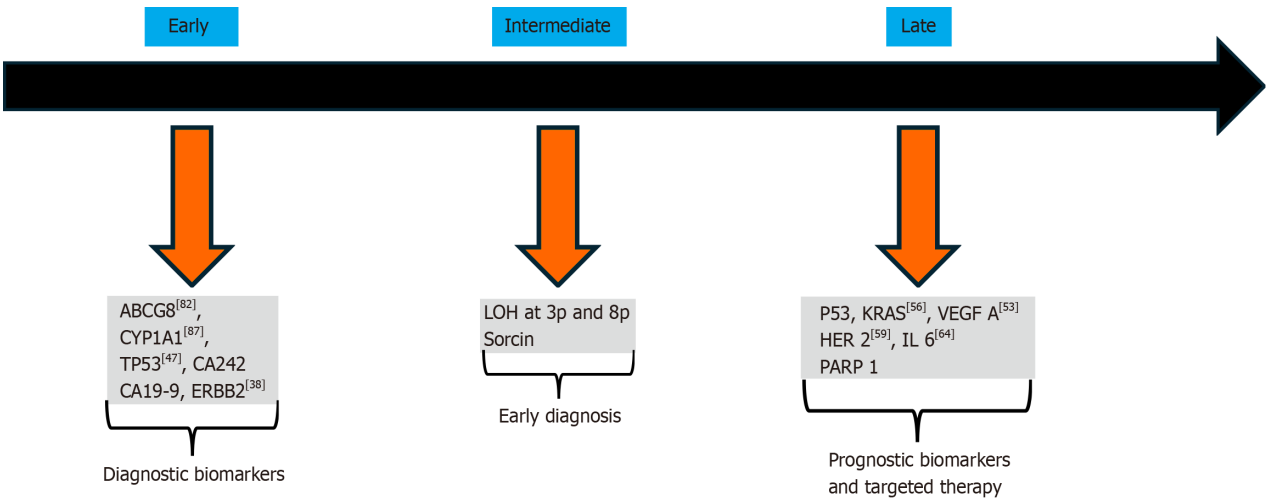

Figure 1 Genes involved in gallbladder cancer pathogenesis at various stages.

(gastric outlet obstruction), and an incidentally detected mass on imaging. In a study conducted by Pandey *et al*[94] the most common symptoms observed were weight loss (reported in 201 patients, 99%) followed by loss of appetite (reported in 197 patients, 97%). Other observed symptoms included pain in the right hypochondrium (reported in 143 patients, 70%), a mass in the right hypochondrium (reported in 107 patients, 53%), jaundice (reported in 79 patients, 39%), and nausea and vomiting (reported in 21 patients, 10%).

Histopathological types

Many patients in India who undergo cholecystectomy do not routinely have their gallbladder specimens sent for histopathology due to financial burden. However, Agarwal *et al*[95] found that patients whose cholecystectomy specimens were sent for histopathological examination (HPE) experienced earlier management if GBC was found in the specimen, achieved a better R0 resection rate, and had longer overall survival (OS) compared to those in whom specimens were not sent. Histologically most of the GBCS are adenocarcinoma whereas most common architectural pattern observed was sheets and acini, with a predominance of columnar cells[96]. Yadav *et al*[97] classified GBC based on fine needle aspiration cytology (FNAC) into various subtypes, including Adenosquamous, mucinous, signet ring, squamous, small cell, mixed adenoneuroendocrine, undifferentiated carcinomas, as well as spindle and giant cell subtypes.

Role of FNAC

Chandra *et al*[98] have introduced a classification system based on FNAC, which includes the following categories: Category 1 (inadequate), Category 2 (negative for malignancy), Category 3 (atypical cells), Category 4 (highly atypical cells suggestive of malignancy), and Category 5 (positive for malignancy). Yadav *et al*[99] reported 28 cases of neuroendocrine tumors (NETs) of the gallbladder. They classified these tumors into three categories based on their differentiation: Well-differentiated (grades 1 and 2), small cell carcinoma (grade 3), and mixed adenoneuroendocrine carcinoma. A positive diagnosis of NET was confirmed by the presence of TTF-1 in the nucleus. Kamboj *et al*[100] published 19 cases of NEC of GB and described the aggressive nature of diseases. Krishnani *et al*[101] reported that FNAC demonstrated a high sensitivity of 90.63% and specificity of 94.74% in detecting carcinoma. For locally advanced or metastatic GBC, preoperative histopathological confirmation is mandatory before initiating chemotherapy. Goyal *et al*[102] concluded that FNAC can be a precise and reliable method for diagnosing GBC in these settings. Shukla *et al*[103] found that the diagnostic accuracy of ultrasonography (USG)-guided FNAC was 95%. This is significantly higher compared to a diagnostic accuracy of 60% on blind aspiration.

Xanthogranulomatous cholecystitis

Xanthogranulomatous cholecystitis (XGC) is malignant masquerade of GBC. Shukla *et al*[104] defined the pathological features of XGC, proposing that they include the presence of foam cells, histiocytes, bile, multinucleate giant cells, and a mixed population of inflammatory cells in varying proportions. These features are observed in a background of pink and granular debris.

Immunohistochemistry

Some immunohistochemistry (IHC) based study also published to diagnosis and prognosticate the disease. Some studies based on IHC have also been published to aid in the diagnosis and prognosis of the disease. Study conducted by Shukla *et al*[105], revealed that although it is a common occurrence in females, GBC does not express hormone receptor. Yadav *et al*[106] suggest that the overexpression of MMP9 and the loss of membranous beta-catenin may be indicative of poor clinical outcomes and advanced disease. Jain *et al*[107] found significant overexpression of KRT7 and SRI in node positive GBC patients compared to node negative GBC patients. This finding may have important implications for the diagnosis and treatment of GBC.

Analysis of cancer-derived extracellular vesicles (EVs) is an emerging method employed to identify potential biomarkers for disease detection and prognosis. Priya *et al*[108] studies GBC cell line- derived EVs and found 16 proteins including haptoglobin which can be served as circulating biomarkers for early detection of GBC. Akhtar *et al*[109] studied specific proteins (MPO, MMP9, and DEFA1) associated with neutrophil degranulation possess signal sequences. They proposed that these proteins could serve as promising circulating markers for early detection of GBC. Priya *et al*[110] studied plasma-derived biomarker that can help in the early detection of GBC. According to their findings, NT5E and ANPEP biomarkers are associated with advanced-stage GBC, while the MME biomarker is linked with early-stage GBC. These studies could be significant in improving the diagnosis and treatment of GBC, allowing for earlier detection and better patient outcomes.

Prognostic markers

Numerous studies have been conducted to identify prognostic markers for GBC. Mishra *et al*[111] found that presence of Higher TNM stage, adjacent organ infiltration, nodal involvement, and jaundice predict poor survival. Negi *et al*[112] found that lymph node (LN) ratio is a strong predictor of outcome after curative resection (CR) for GBC. Shah *et al*[113] found that LN micro metastasis did not correlate with survival. Balachandran *et al*[114] found that Adjuvant therapy, R0 resection and extended cholecystectomy associated with improved survival in patient with GBC. Some other pathological studies are described in Table 3[115-126].

STUDIES ON DIAGNOSTICS AND IMAGING

GBC presents significant diagnostic challenges due to its often-asymptomatic nature in the early stages and nonspecific symptoms as it progresses. Early diagnosis of GBC is crucial for improving patient outcomes. Various imaging modalities are critical for detecting and characterizing gallbladder lesions. USG is frequently chosen as the initial imaging modality for its accessibility and capability to visualize gallbladder abnormalities. Computed tomography (CT) and magnetic resonance imaging (MRI) offer detailed information on tumor extent, invasion of adjacent structures, and the presence of distant metastases. Endoscopic ultrasound (EUS) is a valuable tool for staging GBC due to its high sensitivity in detecting small lesions, assessing local tumor invasion, and facilitating biopsy when necessary. Additionally, positron emission tomography (PET) imaging can help evaluate distant metastases and guide treatment decisions.

Ultrasound is an essential diagnostic tool used for investigating medical conditions in patients. It can detect various abnormalities such as masses, ascites, metastasis, liver infiltration, and involvement of surrounding structures. It is considered as the primary investigation method in most cases. Gallbladder adenocarcinomas can appear as one of three morphologies in USG: Intraluminal mass, diffuse mural thickening, or a mass that replaces the gallbladder. Gallstones are commonly present along with mass in 60%–90% cases. Some retrospective studies were conducted to determine the accuracy of USG in diagnosing GBC. In a study conducted by Pandey *et al*[94], a mass lesion in the gallbladder was found in 87% of the 177 patients examined *via* abdominal sonography. The masses were classified as either intraluminal (59%) or

Table 3 Clinico pathological studies

Serial No.	Sample size	Findings	Ref.
1	GBC (50)	Her2 neu, p53, p16, survivin, COX-2, and EZH-2 expression associated with GBC	Gupta *et al*[115]
2	GBC (200), Dysplasia (32), CC (100)	HER-2/neu overexpression seen in patients with GBC	Jain *et al*[116]
3	GBC (128)	HER 2 and Ki-67 can be used as a prognostic biomarker for gallbladder carcinoma	Halder *et al*[117]
4	-	Combination of ALU247 and cfDNA provides good sensitivity, specificity in diagnosis of GBC	Kumari *et al*[118]
5	-	Proposed a scoring system for XGC	Rajaguru *et al*[119]
6	GBC (34)	Quantitative analysis of cfDNA may aid in early diagnosis	Kumari *et al*[120]
7	GBC (39), cholelithiasis (30), and control (25)	Overexpression of survivin is associated with poor prognosis	Nigam *et al*[121]
8	(GSD, n =30; GBC, n = 39) healthy control (n = 25)	Expression of survivin in peripheral blood could be useful both in the diagnosis and prognosis of GBC	Nigam *et al*[122]
9	GBC (80)	P53 expression is positively correlated with increasing tumor grade, whereas beta-catenin nuclear expression is associated with tumor grade and depth of invasion	Ghosh *et al*[123]
10	9 case of Squamous cell carcinoma	Ultrasound-guided fine-needle aspiration is a useful minimally invasive investigation in the preoperative diagnosis of squamous cell carcinoma of the gallbladder	Gupta and Gupta[124]
11	GBC (55), vontrols (8)	Assay of CA242, CA19-9, CA15-3, and CA125 can be used as marker of carcinoma of the gallbladder	Shukla *et al*[125]
12	GBC (40)	Intraoperative bile cytology can be used for diagnosis of in situ and early invasive GBC	Arora *et al*[126]

GBC: Gallbladder cancer; CC: Chronic cholecystitis.

infiltrative (41%), with irregular margins and higher echogenicity compared to the liver. Infiltrative lesions were more common at the gallbladder neck and fundus. In study by Batra *et al*[127] mass replacing GB was most common findings (73%) on USG followed by presence of gall stone along with mass (54%). Chhabra *et al*[128] demonstrated a new combined type of GBC when GBC present as both thickening and mass replacing GB. Rana *et al*[129] proposed sonographic "Cervix Sign" for GB neck malignancy. The role of USG for screening of GBC is controversial. In a pilot study conducted by Patel *et al*[130] which included 778 patients from high-risk areas, 4 cases of GBC were detected. Anadure *et al*[131] found 6 GBC among 978 high risk healthy participants. Despite showing positive outcomes, it is challenging to conduct screenings for the Indian population due to practical difficulties in real life.

It's quite challenging to differentiate between malignant and benign Thick-walled GB (TWGB). Many studies were conducted in this regard. Gupta *et al*[132] a recommended scoring system called Gallbladder Reporting and Data System can be used to evaluate gallbladder wall features in ultrasound scans. This system considers various factors such as layered appearance, interface with the liver, symmetry and extent of involvement, intramural features like cysts and echogenic foci. By using this system to risk stratify GB lesions; Surgeon can make more informed decisions about treatment options. Gupta *et al*[133] propose an imaging-based algorithm for gallbladder wall thickening. They suggest that diffuse asymmetrical thickening or focal thickening, discontinuous mucosa or breach in mucosa, loss of layered pattern in the gallbladder, high mean systolic velocity in color Doppler, and high shear velocity in Doppler are more indicative of malignant gallbladder wall thickening. Kapoor *et al*[134] proposed that elastography effectively distinguishes between benign and malignant gallbladder wall thickening. Combining this technique with sonography enables early-stage diagnosis of gallbladder carcinoma, highlighting its value as a diagnostic tool. Kalage *et al*[135] suggested a Multiparametric MRI to distinguish between benign thick walls and malignant thick walls. This approach includes Diffusion-weighted, dynamic contrast-enhanced perfusion, intravoxel incoherent motion, and diffusion tensor sequences. The study found that the Multiparametric MRI technique had a 90% sensitivity and 88% specificity for diagnosing Malignant TWGB, whereas conventional Contrast enhanced MRI had 80% sensitivity and 88% specificity.

Recently some authors studied the utility of EUS fine-needle aspiration (FNA) for evaluation of gallbladder mass. Singla *et al*[136] demonstrated that EUS-FNA is a highly sensitive tool for evaluating gallbladder mass lesions associated with obstructive jaundice. However, due to the low negative predictive value of the test, further evaluation is necessary for cases where FNA results are negative.

CT scan

CT is the diagnosis modality of choice for staging the disease. Kalra *et al*[137] discovered that MDCT exhibited a sensitivity of 72.7%, a specificity of 100%, and an accuracy of 85% in assessing the resectability of GBC. To diagnose

hepatic and vascular invasion by the tumor, CT showed a 100% correlation with surgical findings. According to the study conducted by Kumaran *et al*[138] CT scan has an overall accuracy of 93.3% in staging of GBC. Therefore Dual-phase helical CT is a comprehensive method that can be used for preoperative staging of GBC to determine if it is resectable. Soundararajan *et al*[139] proposed CT can be routinely used to determine gastro-intestinal tract involvement on GBC.

Role of PET–CT

GBC are not pet avid tumors. Standard guidelines do not advocate routine pet scan in GBC. In India Many studies were published exploring the utility of PET-CT in GBC. According to a study conducted by Patkar *et al*[140] found that PET-CT can detect metastatic disease in 46.6% of patients that could not be confidently detected using standard cross-sectional imaging. Goel *et al*[141] found that PET-CT altered the management plan in approximately 25% of resectable GBC cases and 30%-35% of locally advanced cases. Shukla *et al*[142] studied role of PET-CT in incidental GBC and found that MDCT had a sensitivity and positive predictive value (PPV) of 42.8% each for determining residual disease, while PET-CT showed a sensitivity of 28.5% and PPV of 20%. In patients diagnosed incidentally with GBC and no metastatic disease, PET-CT and MDCT appear to offer complementary roles in clinical assessment. Goel *et al*[143] found that, the patients with PET-negative pT1b tumors showed no residual disease, in contrast to PET-positive patients (0% *vs* 33%, $P = 0.028$). They proposed that PET-negative pT1b patients could be monitored closely due to the low risk of relapse. Kumar *et al* [144] investigated the efficacy of PET-CT in detecting tumor recurrence in GBC. Their study demonstrated that PET/CT exhibited a high sensitivity (97.6%) and specificity (90%) for detecting tumor recurrence. These findings suggest that PET-CT can be a valuable tool in the detection of tumor recurrence, Residual tumor in incidental GBC and in cases with suspicious of distant metastasis.

Tumor markers

In patients with GBC Sinha *et al*[145]discovered a significant association between serum levels of tumor markers (such as CA19-9, CEA, CA125, and CA242) and GBC. Agrawal *et al*[146] suggested that CA19-9, CA125 and CEA may serve as predictors of resectability in GBC. They found that elevated levels of CA19-9 and CA125 associated with poorer prognosis in affected patients. The role of different imaging modalities in the diagnosis of GBC is illustrated in Figure 2. Some other studies on diagnostics and imaging modality are described in Table 4[147-157].

STUDIES ON SURGICAL APPROACH AND RESECTION

In this section, we have described various landmark studies published in the literature from India regarding the surgical approaches for GBC. Staging laparoscopy is highly accurate in identifying peritoneal deposits and sub centimetric metastases over liver surface and should be considered for all patients of GBC undergoing surgery. Agarwal *et al*[158] found, staging laparoscopy prevented laparotomy in 23% of patients with GBC. They suggested performing routine staging laparoscopy for GBC patients undergoing surgery. Another study by Agrawal *et al*[159] reported that staging laparoscopy prevented a nontherapeutic laparotomy in 43% of patients initially deemed resectable based on pre-operative imaging. Both of these studies underscored the importance of staging laparoscopy and advocated for its mandatory use in GBC.

TWGB

Surgeons around the world do not widely accept laparoscopic cholecystectomy for TWGB due to the risk of malignancy. Srikanth *et al*[160] in their study proposed that laparoscopic cholecystectomy can be performed in patients with diffuse TWGB. However, there is an increased risk of to open cholecystectomy. Kapoor *et al*[161] proposed an approach of anticipatory extended cholecystectomy for TWGB (Luckow Approach).

Role of 16b1 node

After staging laparoscopy, the usual first step is the sampling of interaortocaval (IAC) LNs. GBC involving the 16b1 (IAC) LN is considered to be metastatic. Agarwal *et al*[162] studied the role of routine frozen-section HPE of the 16b1 LN in the management of GBC. They recommended the routine sampling of the 16b1 node during surgical procedures to prevent non-therapeutic radical resection. Their study found that routine 16b1 LN biopsy prevented such resections in 18.6% of patients. When 16b1 nodes tested positive, Agarwal *et al*[162] treated them along with systemic disease, and abandoned surgery when these nodes were found to be positive. Ghosh *et al*[163] from SGPGIMS, Lucknow echoed the same finding, they found that the median survival for IAC node positive group and patients with distant metastasis were same. However, Aggarwal *et al*[164] advocated that certain cases of GBC with IAC node metastasis may be eligible for CR followed by adjuvant therapy. However, their study was limited by a small sample size.

Extent of resection

According to previous studies, only 10% of patients with GBC are deemed resectable. For Tis and T1a lesions, a simple cholecystectomy with negative margins at the cystic duct is typically effective and can achieve cure rates ranging from 85% to 100%. However, gallbladder lesions classified as T1b and higher often come with nodal metastases, necessitating radical resection. This typically involves en bloc hepatic bed resection (which may include removing 2-3 cm of liver wedge or performing a formal segment IVb and V resection) along with regional lymphadenectomy. The surgical goal is R0 resection, aiming to achieve negative cystic duct margins (CDMs). In cases of positive margins, revision of the duct

Table 4 Studies on diagnostic methods and imaging

Serial No.	Sample size	Findings	Ref.
1	-	PET-CT can be used to rule out metastatic disease and for post-therapy surveillance for recurrence in patients of GBC	Bisht *et al*[147]
2	GBC (38)	Potential utility of CT texture-based radiomics analysis in patients with GBC.	Gupta *et al*[148]
3	GBC (141)	Raised levels of serum CA19-9 beyond 20 units/mL should be used for prognostication purposes after EC	Agrawal *et al*[149]
4	GBC (141)	NMR-based methods can be used as a diagnostic modality for GBC	Sharma *et al*[150]
5	GBC (41)	CEA expression may help in diagnosis of GBC	Mondal *et al*[151]
6	GBC (203)	Discontinuous mucosal lining, diffuse wall thickening, intramural nodules, and cholelithiasis may indicate XGC rather than gallbladder carcinoma	Sureka *et al*[152]
7	GBC (74)	Duodenal involvement significantly decreases resectability but does not preclude resection	Kalayarasan *et al*[153]
8	XGC (31)	Mass-forming XGC mimics GBC	Agarwal *et al*[154]
9	GBC (117)	CA 242 is a promising tumor marker for GBC and performs better than CEA and CA19-9.	Rana *et al*[155]
10	GBC (15)	Dynamic MRI with MRCP is a reliable method of showing gall bladder carcinoma.	Kaza *et al*[156]
11	GBC (60)	Color Doppler USG together can improve pickup rate of GBC	Pradhan *et al*[157]

PET: Positron emission tomography; CT: Computed tomography; GBC: Gallbladder cancer; MRI: Magnetic resonance imaging; MRCP: Magnetic resonance cholangiopancreatography.

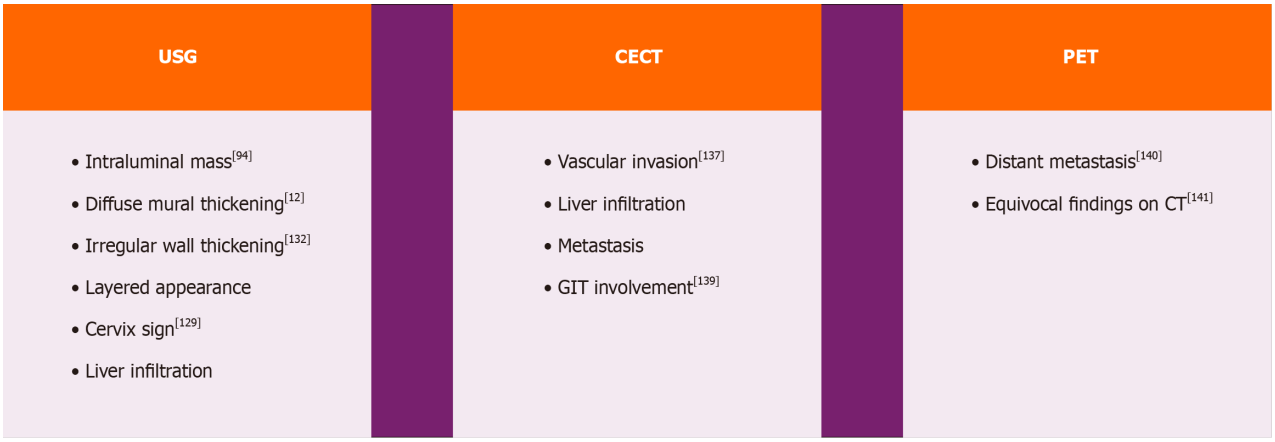

Figure 2 Role of diagnostic modalities in gallbladder cancer. USG: Ultrasonography; CECT: Contrast-enhanced computed tomography; PET: Positron emission tomography.

margin or extrahepatic bile duct (EHBD) excision may be necessary. Studies published in India exploring the ideal surgical approach for GBC have not yet provided concrete recommendations.

Singh *et al*[165] found that CR is the only chance of cure, aggressive surgical approach and improve OS. Wagholikar *et al*[166] advocated that simple cholecystectomy is effective only for GBC limited to the mucosa. However, patients diagnosed with pT1b tumors should undergo extended cholecystectomy. The study proposes that for cases where incidental GBC extends to the muscularis layer, early reoperation to complete an extended cholecystectomy is recommended.

There has been considerable debate regarding the optimal approach to liver resection in GBC, specifically whether anatomical segment IVb and V resection is superior to non-anatomical wedge excision of the liver. There are some studies regarding the same with conflicting results. Pottakkat *et al*[167] demonstrated that the extended criteria for radical resection (Segment 4b and 5) are highly effective, achieving R0 status in over 80% of GBC patients and yielding acceptable long-term outcomes. Nag *et al*[168] from GB Pant Hospital, New Delhi, discovered that there was no significant difference in mean recurrence-free survival (RFS) between segment 4b and 5 resections compared to wedge resection, with 58.2 months *vs* 42.3 months, respectively (P = 0.264). The OS was also similar between both of these groups. Therefore, they concluded that segment 4b and 5 resections were not superior to wedge resection. Tewari *et al*[169] from Banaras Hindu University (BHU) found that wedge resection of the gallbladder achieves adequate oncological clearance in early GBC.

Margin status

Studies have shown that the surgical margin status is the most important factor in determining the overall outcome of liver resection surgeries, rather than the type of resection performed. Behari *et al*[170] found similar results, with patients who underwent R0 resections having significantly better survival rates than those who underwent R1 resections (median 25.8 months *vs* 17.0 months; $P = 0.03$). Hence, the primary objective should be to achieve complete removal of the disease with clear histologic margins.

Frozen section of CDM

Routine use of CDM frozen section analysis is controversial. Some study from India refuted this practice. Jajal *et al*[171] suggest that routine CDM frozen analysis may not be necessary in patients with resectable GBC who do not have jaundice. They found that a positive CDM has comparable survival outcomes to a negative CDM, with similar R0 resection rates and tumor stages. Some authors suggest that routine resection of the common bile duct during surgery may aid in lymphadenectomy and increase LN yield. However, a study by Behari *et al*[170] from India found that EHBD resection does not offer significant survival benefits.

Standard lymphadenectomy

The standard lymphadenectomy for GBC involves removing LNs located along the hepatoduodenal ligament, common hepatic artery, and peri-pancreatic region (stations 8, 12, and 13). Pandey *et al*[172] from BHU proposed this systemic regional lymphadenectomy in GBC gives a good lymph nodal yield and better outcome. Negi *et al*[112] suggested that the retrieval and examination of at least 6 nodes can have a positive impact on the quality of staging and disease-free survival (DFS) in node-negative patients. Goel *et al*[173] from TMH found that for individuals diagnosed with T1b GB cancer, the likelihood of nodal positivity is approximately 21%. Therefore, they recommended that radical surgery, including comprehensive periportal lymphadenectomy, should be considered the standard of care.

Excision of extra-hepatic bile duct

Some authors believe that the presence of obstructive jaundice is a sign of inoperability. Agarwal *et al*[174] conducted a study on 51 patients with GB cancer and obstructive jaundice. Of these 51 patients, 14 underwent resection with curative intent, resulting in a resectability rate of 27.45%. Despite being jaundiced, these patients were able to undergo successful resection. They found a mortality rate of 7.14% and a morbidity rate of 50%. The mean DFS was 23.46 months, with a median of 26 months and a range spanning from 2 to 62 months. Among patients who underwent resection, 50% survived beyond two years. They concluded that Biliary obstruction in GB cancer is not signs of inoperability and resection results in prolongation of survival[174]. Pandey *et al*[172] found that EHBD resection to achieve R0 resection is safe, associated with acceptable postoperative morbidity, and may increase survival. A positive CDM, direct infiltration of the hepatoduodenal ligament, and densely adherent peri-choledochal LNs were the indicators of EHBD resection. K *et al*[175] studied 59 GBC patients who had jaundice. Total of 61.7% and 84%, respectively, of patients underwent CR and non-CR had common bile duct involvement ($P = 0.062$). They found that Patients with GBC and jaundice have better significant survival after CR.

Extended resection in GBC

There are some reserves among surgeons for extended resection in carcinoma GB. As operative techniques improve and new technology develops, there is an increasing trend in extended resection. Commonly performed extended procedures are segmentectomy 4B + 5, extended right hepatectomy, median sectorectomy and hepatopancreaticoduodenectomy. Pottakkat *et al*[167] studied the outcomes of extended resection in GBC and identified postoperative complications in 60% of patients. They achieved acceptable R0 resection (83%) and survival rates. But Behari *et al*[170] could find that only 43% of GBC undergoing extended resection could achieved R0 resection. Singh *et al*[176] from Rajiv Gandhi Cancer institute first to explore PVE followed by extended hepatectomy in GBC. In their study on 14 patients following Neo adjuvant chemo therapy (NACT) and portal vein embolization. Seven (50%) underwent CR (extended hepatectomy). The median OS was 27 months for resectable patients and 15 months for unresectable patients.

Agarwal *et al*'s[177] study, which examined the duodenum's involvement in GBC, revealed that, of the 43 patients with duodenal involvement, 26 had R0 resection (61.9%). Of these, 16 had duodenal sleeve resection (61.54%), 9 had distal gastrectomy with resection of the first part of the duodenum (34.62%), and 1 patient had hepato-pancreatoduodenectomy (HPD; 3.85%). They concluded that duodenal infiltration does not serve as a sign of unresectability or a reason to undergo HPD. For the majority of these patients, a distal gastrectomy combined with resection of the first segment of the duodenum, or a duodenal sleeve resection can accomplish an oncologically appropriate R0 resection[178].

With surgeons now willing for extended resection, further some studies published for resection in presence of metastasis. Patkar *et al*[179] from TMH propose a potential role for aggressive treatment of advanced GBC with limited metastatic burden, such as microscopic disease in the station 16b1 node, low-burden peritoneal disease with deposits smaller than 1 cm in adjacent omentum or diaphragm, isolated N2 disease, or a solitary discontinuous liver metastasis in adjacent liver parenchyma.

Minimally invasive surgery in GBC

With advance laparoscopic and robotic surgery now getting prominence, Agarwal *et al*[180] found that laparoscopic radical cholecystectomy is safe and feasible for selected patients with GBC, and the outcomes are comparable to those of open radical cholecystectomy. Nag *et al*[181] found laparoscopic hepatic bisegmentectomy is safe and feasible. Palanisamy *et al*[182] from GEM hospital published their study and suggested that laparoscopic radical cholecystectomy

may serve as a viable and feasible option for managing GBC, providing effective oncological clearance. Additionally, it offers the typical benefits associated with minimal access procedures. Goel *et al*[183] from TMH suggested robotic radical cholecystectomy is safe and feasible and the short-term results are compared with Open radical cholecystectomy.

Incidentally detected GBC

Incidentally detected carcinoma GB is another debatable topic. Some studies have been published on incidentally detected gallbladder carcinoma from India. Shukla *et al*[184] studied the factors influencing operability in incidentally detected GBC and found that stage is the most important factor in determining resectability. They found that as the T-stage of the disease progressed, the probability of finding residual disease increased, while operability decreased. They also found that incidence of lymph nodal disease is higher for pT1b cancers. Wagholikar *et al*[166] suggested that, incidental GBC extending up to the muscularis requires completion extended cholecystectomy. Although there are no prospective clinical trials, it is widely believed that complete resection of residual disease leads to improved survival. Multiple studies have shown a survival advantage with CR, thereby supporting re-resection in incidental GBC beyond pT1b. Patkar *et al*[185] from TMH, found contrasting results in their study on 425 patients of PT2 of GBC out of which 118 (27.7%) and 307 (72.23%) patients were in the upfront operated GBC and incidental GBC groups, respectively. They found that incidentally detected pT2 GBCs have significantly worse outcomes compared to similarly staged patients undergoing an upfront radical cholecystectomy**.** Some other studies on surgical management are described in Table 5[186-189].

STUDIES ON MULTIMODALITY THERAPY.

Despite improvement in surgical techniques, survival and resection rate of GBC remained the same. Gradually multi-modality therapy evolved with the aim of improving survival. Patkar *et al*[190] published the experience of TMH, Mumbai with largest cohort of 1307 patients with GBC. They advocated peri-operative chemotherapy both in adjuvant and neo adjuvant settings in properly selected patients. We will first discuss adjuvant therapy followed by neoadjuvant therapy and advances made in these fields.

Studies on adjuvant therapy in GBC

The role of adjuvant therapy on increasing survival in GBC is controversial. To date, there have been only a few randomized studies conducted in India exploring the role of adjuvant radiotherapy (RT) or chemo RT (CRT) in resected GBC.

Ostwal *et al*[191] from TMH, Mumbai in their study of 242 resectable stage II and III GBC patients found that patients undergoing R0 resections receiving adjuvant Gemcitabine and cisplatin bases chemotherapy have high completion rates and good tolerance. Kattepur *et al*[192] found that adjuvant chemotherapy reduces distant failure rates but did not improve OS in completely resected GBC patients. They found that lymphovascular invasion important predictor of RFS in T2N0 patients. Some centers tried RT in adjuvant setting. Mahantshetty *et al*[193] from TMH suggested adjuvant RT along with CT improve survival in GBC after resection. Authors used 5 FU bases regimen in their cohort of patients. Choudhary and Asthana[194] studied the effect of adjuvant treatment, including RT, CT, or CRT, following CR and found improved survival compared to surgery alone but the difference was not statistically significant. Agrawal *et al*[195] found that Adjuvant CRT followed by adjuvant chemotherapy improves outcomes in patients with R1 and node-positive disease. There is only one Randomized control trial available that examines the function of CT and RT in adjuvant situations.

The GB-GECCOR trial, a phase II multicenter study, investigated two treatment arms: CAPE-RT (consisting of 2-4 cycles of capecitabine followed by RT: 45 Gy over 25 fractions concurrent with capecitabine: 825 mg/m^2 twice daily, followed by 2-4 additional cycles of capecitabine) *vs* GC (gemcitabine at 1000 mg/m^2 and cisplatin at 25 mg/m^2 administered on days 1 and 8, every 3 wk) following resection. The DFS rate for the GC group was 88.9% *vs* 77.8% for CAPE-RT group. These outcomes support the application of both regimens as appropriate care[196].

Unresectable and metastatic diseases

The appropriate regimen for unresectable and metastatic disease has not yet been defined. Many studies have been published studying different therapies in these settings. Many studies shown that Gemcitabine/cisplatin combination well tolerated and in advanced unresectable GBC[197-199]. Chatni *et al*[200] studied infusion chemotherapy with cisplatin and fluorouracil. Sharma *et al*[201] studied the gemcitabine and oxaliplatin regimen in unresectable GB cancer and found a survival benefit. Same authors studied the efficacy of chemotherapy compared to best supportive care and reported that chemotherapy improved OS and progression free survival (PFS) in unresectable GBC. Ali *et al*[202] in their comparative study between Cisplatin-5-Fluorouracil and Gemcitabine-Cisplatin and found overall more benefit in Gemcitabine-Cisplatin arm. Singh *et al*[203] advocated use of Gemcitabine based regimen in metastatic and advanced GBC which improved PFS.

Currently there is no "standard" second-line therapy after failure of first-line gemcitabine and cisplatin in patients with GBC. Ramaswamy *et al*[204] found that CAP-IRI is a well-tolerated second-line chemotherapeutic regimen in advanced GBC. In GB-SELECT trial they found that single agent irinotecan can be used as second line treatment in palliative setting. Some other important study on Adjuvant therapy in metastatic disease are described in Table 6[205-214].

Table 5 Studies on surgical approaches and resection

Serial No.	Sample size	Findings	Ref.
1	GBC (521)	Surgical resection improves survival in GBC with jaundice	Goel *et al* [186]
2	GBC (97)	Radical cholecystectomy with wedge resection of the liver oncological equivalence compared to formal segment IVb/V excision	Patkar *et al* [187]
3	GBC (20)	The technique of LHBRL is safe and feasible for patients with GBC	Nag *et al* [188]
4	07 incidental GBC	Re-exploration and aggressive resection followed by adjuvant chemotherapy for incidental gallbladder carcinoma are safe and provide hope for long-term survival	Kaman *et al* [189]

GBC: Gallbladder cancer; LHBRL: Laparoscopic hepatic bisegmentectomy with regional lymphadenectomy.

Table 6 Studies on adjuvant therapy on gall bladder carcinoma

Serial No.	Sample size	Findings	Ref.
1	GBC (176)	CT followed by CTRT improves outcomes in patients with limited volume disease	Alam *et al*[205]
2	GBC (550)	CT followed by cCTRT appears to improve survival in responders with good PS	Alam *et al*[206]
3	GBC (38)	Her2neu directed therapy significantly improved survival	Das *et al*[207]
4	GBC (66)	FOLFOX-4 is an effective and well-tolerated regimen as a second-line treatment	Dodagoudar *et al*[208]
5	GBC (87)	CAP-IRI is a well-tolerated second-line chemotherapeutic regimen in advanced GBC	Ramaswamy *et al*[209]
6	GBC (121)	Reduced dose intensity of chemotherapy in GBC	Gangopadhyay *et al*[210]
7	GBC (210)	Use of gem-platinum in Indian patients associated with slightly worse outcomes	Sirohi *et al*[211]
8	-	Autologous immune enhancement therapy associated with, an improvement of the quality of life	Bhamare *et al*[212]
9	GBC (104)	Adjuvant chemoradiation improve survival	Mallick *et al*[213]
10	-	Chemoradiation improve survival in locally advanced GBC	Engineer *et al*[214]

GBC: Gallbladder cancer; CTRT: Chemo-radiotherapy; cCTRT: Consolidation chemoradiation.

STUDIES ON NEOADJUVANT TREATMENT

Surgical resection is the only potential cure for GBC. However, many patients are present with locally advanced state, making it difficult to perform curative surgery. Neoadjuvant therapy can effectively downstage tumors in these patients and help assess disease biology to identify the most suitable candidates for surgery. TMH has taken a step ahead and started using NACT as an option in locally advanced GBC. Chaudhari *et al*[215] introduced the TMH criteria for neoadjuvant chemotherapy in locally advanced or borderline resectable GBC, leading to curative surgical resection in a significant percentage of patients. Agrawal *et al*[216] demonstrated the benefit of neoadjuvant chemo-RT in locally advanced GBC. In their study they have reported Radiologic downstaging of liver involvement is 40.5% and lymphadenopathy is 67.5%[216].

A group of investigators is presently carrying out a prospective clinical experiment called POLCA-GB at TMH in Mumbai. This experiment aims to assess the efficacy of chemotherapy administered alone (four cycles of gemcitabine-cisplatin or gemcitabine-oxaliplatin) *vs* chemotherapy administered in combination with radiation treatment (RT) contemporaneous with gemcitabine, followed by two rounds of gemcitabine-cisplatin or gemcitabine-oxaliplatin chemotherapy. This trial aims to enable potentially CR by downstaging locally advanced GBC. The trial is now in the recruiting stage[217]. Few other series from India have demonstrated a benefit of gemcitabine-platinum based neoadjuvant therapy in GBC described in Table 7[218-221].

CONCLUSION

This review has found significant work and efforts made by India in addressing GBC over the past two decades. India has produced a substantial number of quality research publications on GBC-epidemiology, etiopathogenesis, pathology, surgery, and multimodal treatment approaches. Country has progressed well on surgical management and multimodal

Table 7 Studies on neo-adjuvant therapy on gall bladder carcinoma

Serial No.	Sample size	Findings	Ref.
1	GBC (510)	Surgery and peri-operative systemic therapy associated with improved survival	Patkar *et al*[218]
2	GBC (28)	Locally advanced GBC may benefit from neoadjuvant chemoradiation	Engineer *et al*[219]
3	GBC (37)	Neoadjuvant chemotherapy in patients with locally advanced gallbladder cancer	Sirohi *et al*[220]
4	GBC (21)	Resection after neoadjuvant chemotherapy improve survival	Selvakumar *et al*[221]

GBC: Gallbladder cancer.

treatment strategies. However, there remains a lack of specific research on etiopathogenesis, early diagnosis, preventive measures, and emerging treatments such as immunotherapy. The coming decades should prioritize efforts towards screening strategy in high-risk zone, early detection, and the development of well-defined treatment protocol/ policy. Collaborative international research would be useful to achieve and overcome the deficient areas.

FOOTNOTES

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