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CLINICAL PRACTICE GUIDELINE

'IHPBA-APHPBA clinical practice guidelines': international Delphi consensus recommendations for gallbladder cancer

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Abstract

Background: The Delphi consensus study was carried out under the auspices of the International and Asia-Pacific Hepato-Pancreato-Biliary Associations (IHPBA-APHPBA) to develop practice guidelines for management of gallbladder cancer (GBC) globally.

Method: GBC experts from 17 countries, spanning 6 continents, participated in a hybrid four-round Delphi consensus development process. The methodology involved email, online consultations, and in-person discussions. Sixty eight clinical questions (CQs) covering various domains related to GBC, were administered to the experts. A consensus recommendation was accepted only when endorsed by more than 75% of the participating experts.

Results: Out of the sixty experts invited initially to participate in the consensus process 45 (75%) responded to the invitation. The consensus was achieved in 92.6% (63/68) of the CQs. Consensus covers epidemiological aspects of GBC, early, incidental and advanced GBC management, definitions for radical GBC resections, the extent of liver resection, lymph node dissection, and definitions of borderline resectable and locally advanced GBC.

Conclusions: This is the first international Delphi consensus on GBC. These recommendations provide uniform terminology and practical clinical guidelines on the current management of GBC. Unresolved contentious issues like borderline resectable/locally advanced GBC need to be addressed by future clinical studies.

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Introduction

GBC is the most common biliary tract cancer and ranks sixth most common gastrointestinal malignancy.[1,2] It represents around 80%–95% of all biliary tract cancers.[3] The tendency for patients with GBC to present late in the course of the disease coupled with its propensity for recurring at distant sites despite potentially curative surgery has led to it being considered one of the most lethal solid organ cancers.[2] Unlike other gastrointestinal malignancies, the global incidence of GBC is unevenly distributed and is characterised by significant regional variation. In select areas of high incidence, such as Chile, Bolivia, India, Pakistan, Korea, and Japan, it is a significant source of mortality. More than 64% of GBC cases are detected in Asia, and nearly two-thirds of them occur in low- and middle-income countries (LMIC). The generally low incidence in Western populations has often resulted in studies combining GBC with other biliary tract cancers (cholangiocarcinoma) despite clear differences in their pathophysiology and disease behaviour.[4,5] There is a paucity of prospective studies with virtually no randomized controlled trials exploring management strategies specific to GBC. This has led to variations in management protocols and treatment decisions in various parts of the world. With the rising incidence, mortality, and disease-adjusted life years of GBC globally, there is an urgent need to clarify and disseminate a clear understanding of the epidemiology, pathology, and management strategies guided by the best available evidence to inform practice worldwide.[6]

The International Hepato-Pancreato-Biliary Association (IHPBA) is the premier international organization devoted to education, training, and innovation with the overarching aim of improving the care of patients affected by HPB disorders. Drawing on the rich experience and expertise in managing GBC in Asia and the rest of the world, the IHPBA partnered with the Asian-Pacific Hepato-Pancreato-Biliary Association (APHPBA) to develop an international study group on GBC to formulate these guidelines.

The Delphi technique is an established method for achieving consensus using a systematic process. The key features of the method include iteration, anonymity, statistical group response and controlled feedback being provided.[7] The method aims to generate insights when limited information and evidence is available. The method focuses on the aggregation of responses from a panel of experts and then sharing the same with them to arrive at a consensus. It has been used extensively in clinical research, especially to develop guidelines. The technique has the advantage that it can be administered through different modes. It can use online consensus-building compared to other consensus-building approaches which rely only on in-person communication and discussions. A thorough preparation in identifying the research problem, the format to be used, and the clarity of the Delphi statements is important.[8]

The Delphi method has been used in developing consensus guidelines in many areas of oncology recently.[9–11] It is suited to the development of consensus guidelines for diseases such as GBC owing to its ability to evaluate the current knowledge, resolve controversy, and formulate methodological guidelines and recommendations for action in the absence of high-level prospective evidence.[12,13] The aim of this joint undertaking of the IHPBA–APHPBA was, thus, to recommend clinically and globally relevant practice guidelines for GBC. The conduct and report of this study followed ACCORD guideline checklist for reporting consensus methods in biomedicine developed via a modified Dlephi.[83]

Table 1 Characteristics of experts participating in the consensus development process

Parameter	No (%)
Region/Countries	
Asia	**(48.9%)**
India	11
Japan	7
Republic of Korea	4
South America	**(22.2%)**
Argentina	4
Chile	3
Peru	2
Colombia	1
Europe	**(15.5%)**
United Kingdom, GB, NI	2
Netherlands	2
Portugal	1
France	1
Germany	1
North America	**(8.9%)**
United States of America	3
Canada	1
Africa	**(4.4%)**
Algeria	1
South Africa	1
Gender	
Male	43 (95.5%)
Female	2 (4.5%)
Professional Background	
Surgeons	34 (75.5%)
Medical Oncologists	9 (20%)
Radiation Oncologists	1 (2.2%)
Pathologists	1 (2.2%)
Others – Scientists from Indian Institute of Public Health	2 (4.5%)

Methods

Study design and development

The whole process from planning to completion of all rounds was completed between May to October 2023. The following steps were undertaken for the Delphi process- identification of the problem area, selection of panel members, controlled feedback through iterative Delphi rounds, consensus criteria, analysis of feedback, and closing criteria.

Identification of problem area

A Core group of experts was constituted initially by the APHPBA. This group identified the problem areas on GBC based on a literature search. A total of 73 clinical questions (CQs) were initially identified and put together in different domains including- Epidemiology (16 CQs), Clinical Pathology (5 CQs), Early and incidental GBC (iGBC) (24 CQs), advanced GBC (20 CQs), and Palliation (8 CQs) (Supplementary Table 1). Five CQs, which were related to molecular testing, systemic therapy, and radiation therapy were removed based on the opinion that these areas are beyond the scope of the current panel which predominantly involved surgeons; leaving a total of 68 CQs to be addressed.

Table 2 Details of the consensus process

Round	No. of questions asked	Consensus achieved, n (%)	Consensus not achieved, n (%)	Number of participating experts in the round (n)
Round 1	68	23 (33.8)	45 (66.2)	45
Round 2	45	10 (14.7)	35 (51.5)	42
Round 3	35	27 (39.7)	8 (11.8)	22
Round 4	8	3 (4.4)	5 (7.4)	33

Selection of panel members

Based on the knowledge, extensive practical experience, and significant scientific contributions in the field of GBC, the core group invited 60 experts from 17 countries representing all continents. Forty five of these experts finally participated in the process. The experts were predominantly surgeons (n = 33, 75.5%). For a balanced view and opinions a few medical and radiation oncologists were also invited (Table 1). The process was monitored and guided throughout by 2 senior scientists from Indian Institute of Public Health with significant experience with this research method and statistics.

Controlled feedback through iterative Delphi rounds

A three-membered core team collaborated with an arbitrator to finalize the CQs. The team converted most of the CQs into statements. Experts rated these statements using a Likert scale (ranging from "strongly agree" to "strongly disagree"). CQs were circulated as an online questionnaire to the pre-identified experts for their anonymous feedback, using the Survey Monkey application (Round 1). Additional comments were sought to examine the reason behind any specific opinion. Based on round 1 analysis, a second round of Delphi was conducted with those CQs for which consensus was not reached. In round 2, the participants were provided with a brief report of the previous round and a summary of the existing literature on each CQ. Additionally, the experts were allowed to post comments against each CQ. Round 3 involved an online discussion on the remaining CQs without a consensus till round 2. Additional evidence was presented by the core team for these CQs before anonymous voting for consensus development. Besides, experts were also asked if they were willing to reconsider their choice if the guideline statement was rephrased. The CQs were modified

Table 3 Consensus statements on GBC epidemiology, risk factors and clinical pathology

CQ No	Consensus statement	Consensus achieved Round	Consensus percentage
Epidemiology, Risk Factors			
7	Globally, there are areas of high epidemiological frequency and areas of low epidemiological frequency.	R1	100
8	Some dietary factors are associated with the carcinogenesis of GBC in certain high-incidence areas.	R3	100
9	Soil/water pollutants have been identified as risk factors in epidemiological studies on GBC.	R2	77
10	Anomalous pancreaticobiliary duct junction (APBDJ) predisposes to GBC.	R1	92
11	Active smoking is an important risk factor for GBC.	**No consensus**	
12	The risk of GBC with porcelain GB is less than previously reported.	R3	94
13	Adenomyomatosis of the GB is not a risk factor for GBC.	R3	100
14	GBC has a strong association with gallstones.	R1	75
15	The risk of malignancy in GB polyps is clinically relevant in polyps more than 1 cm in size.	R1	91
16	GB polyps less than 1 cm can be observed and regularly followed up. They should be operated only if there is a change in the size of the polyp.	R1	92
17	GB polyp more than 1 cm in size should undergo surgery.	R1	86
18	GB polyp patients planned for surgery should undergo cross-sectional imaging (if size is >2 cm or if USG shows suspicious features)	R3	100
19	The laparoscopic approach can be safely offered to patients undergoing surgery for GB polyp.	R1	98
20	Current evidence does not support prophylactic cholecystectomy for patients with asymptomatic gallstones to reduce the risk of GBC.	R3	93
21	Patients with APBDJ should undergo prophylactic cholecystectomy	R3	94
22	Salmonella infection is associated with GBC in the high incidence areas.	R1	80
Clinical Pathology			
23	All cholecystectomy specimens should be mapped and completely examined for incidental GBC in endemic areas.	R1	94
24	Routine pathology examination should be done for all resected GB/cholecystectomy specimens	R3	87
25	All GB specimens during cholecystectomy (open or laparoscopic) should be opened by surgeon and checked for abnormal nodular thickening/mass	R1	82
26	Minimum pathological evaluation of GB specimen includes sections from cystic duct, fundus, and mid body in addition to suspicious areas.	R1	86
27	AJCC staging system is the most optimal for GBC.	R1	87

APBDJ, anomalous pancreaticobiliary duct junction; AJCC, American Joint Cancer Committee.

Table 4 Consensus statements – early and incidental GBC

CQ No	Clinical Question/Revised Question/Consensus Statement	Consensus achieved Round	Consensus percentage
28	It is difficult to distinguish GBC from inflammation in the presence of thickening of the wall and stone disease.	R3	100
29	Prophylactic wedge resection is unnecessary if the liver is not involved during cholecystectomy for gallbladders with irregular wall thickening, cholelithiasis, and no liver invasion.	R3	85
30	Elective surgery for suspected or diagnosed GBC should be carried out under a frozen section cover	R1	80
31	The term iGBC describes preoperatively unsuspected GBC diagnosed incidentally after index cholecystectomy purely as a histopathological surprise	R1	95
32	Intraoperative detection of GBC during LC in a previously unsuspected patient can also be defined as iGBC	R3	92
33	Radical surgery for incidental GBC should be labelled either as Revision Radical Cholecystectomy or Completion Radical cholecystectomy.	R3	92
34	In case of incidental detection of T1a GBC in a cholecystectomy specimen, the patient can be observed without surgical intervention.	R1	91
35	In case of incidental detection of T1b GBC in a cholecystectomy specimen, the patient should be offered revision surgery.	R3	77
36	There is an optimal time for re-operation after detection of GBC after LC.	R2	81
37	If the interval is more than …. weeks, it's not beneficial to offer re operation – Options: 4 weeks/8 Weeks/12 Weeks/ Unknown	**No consensus**	
38	Early-stage GBC should not be biopsied before surgery.	R1	93
39	Radical surgery for per primum (preoperatively detected) GBC should be specified as Radical Cholecystectomy	R3	100
40	Simple cholecystectomy is an adequate procedure for T1a GBC.	R1	84
41	Margin negative wedge resection is an adequate extent of liver resection for T1b GBC	R2	79
42	What is the optimal extent of liver resection in early GBC (T2-3)? 42A – **CS** – Margin negative wedge resection is an adequate extent of liver resection for T2 GBC 42B What is the optimal extent of liver resection in T3 GBC Options: (1) Wedge excision (2) Segment IV B V excision	A – R4 **B – No consensus**	100
43	T1a iGBC does not warrant LN dissection. 12C LN (cystic) if sampled during the index cholecystectomy should be evaluated.	R4	100
44	What is the appropriate extent of lymph nodal clearance in early GBC(T1b)? Options: (1) D0 (#12 c alone) (2) D1 (#12c, #12b) ***(3) D2 (#12a, b,c,p, #8, #13a)*** **CS** – Standard D2 LN dissection involving stations – *(#12a, b,c,p, #8, #13a)* should be performed for pT1b iGBC/GBC	R4	100
45	What is the appropriate extent of lymph nodal clearance in early GBC(T2-3)? Options: (1) D0 (#12 c alone) (2) D1 (#12c, #12b) **(3) *D2 (#12a, b,c,p, #8, #13a)*** **CS** – Standard D2 LN dissection involving Stations – *(#12a, b,c,p, #8, #13a)* should be performed by T2-3 iGBC/GBC	R1	95
46	A routine biopsy of the inter aortocaval (station 16b1) node (Interaortocaval LN sampling and frozen section analysis) should be performed in surgery for GBC for T2 tumors and beyond.	**No consensus**	–

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Table 4 (*continued*)

CQ No	Clinical Question/Revised Question/Consensus Statement	Consensus achieved Round	Consensus percentage
47	If Station 16b1 is positive for lymph node metastasis, quit radical cholecystectomy.	R3	85
48	Staging laparoscopy should be done in all cases of GBC at the time of definitive surgery.	R3	79
49	MIS (laparoscopic/robotic) can be offered in early GBC and should be performed by HPB surgeons/centers experienced in MIS.	R3	79
50	The port sites (including the umbilical port) need not be excised in revision surgery for incidental GBC	R3	92
51	Port site recurrence generally indicates disseminated peritoneal disease	R3	100

iGBC, incidental gallbladder cancer; LC, laparoscopic cholecystectomy; MIS, minimally invasive surgery.

based on the expert suggestions and group consensus. This was followed by round 4 which was a consensus workshop (hybrid mode) during APHPBA 2023 at Bengaluru, India.

Analysis of feedback

All the CQs were analysed by descriptive statistics including frequency and percentage. A consensus recommendation was accepted when the agreement (strongly agree or agree or strongly disagree or disagree) exceeded 75%. The participants' comments were analysed thematically and shared with the experts in successive rounds.

Results

A total of 68 CQs were included in the consensus process. CQs with eventual consensus became consensus statements (CS). After round 1, consensus was developed for 23 (33.8%) CQs. During the successive rounds, the cumulative consensus developed were 48.5% (n = 33) at round 2, 88.2% (n = 60) at round 3 and 92.6% (n = 63) at round 4. Thus, consensus was not achieved for five (7.4%) CQs- two each from the early and advanced GBC section and one in the epidemiology and risk factor section. While initial anonymous response in round 2 could improve the consensus only marginally, the major consensus was developed during the online discussion in round 3 (Table 2). The intent behind each CQ and summary of the current evidence on the topic was presented by the core team representatives followed by comments and suggestions by the experts. Experts sought clarification from core group representatives. Some questions were rephrased based on the discussion and the experts' suggestions in the meeting.

Summary of the recommendations of the consensus process (Tables 3–5)

Epidemiology and risk factors

GBC is known for its significant regional variation. Globally, there are areas of high epidemiological frequency and areas of low epidemiological frequency for GBC ***(CS 7)***. In high-incidence countries like Bolivia, the incidence of GBC is as high as 12.8 per 100,000 population.[14,15]

GBC development has multifactorial aetiopathogenesis. It results due to the combined effects of chronic infection, inflammation, environmental exposure, and genetic susceptibility.[16] Among the various risk factors, experts uniformly agreed on the role of dietary factors, soil, and water pollutants, anomalous pancreaticobiliary duct junction (APBDJ), gallstone disease, and salmonella infection in the development of GBC. ***(CS 8,9,10,14)*** Studies from various high-incidence areas have pointed toward dietary factors which are unique to those areas e.g. – mustard oil, fish, chili pepper, etc. There is regional variation even in proposed offending dietary factors and evidence to support causation is not conclusive for a few of them.[17,18] Experts therefore suggested to agree only that, some dietary factors are associated with the carcinogenesis of GBC in certain the high incidence areas. ***(CS 8)*** The statement intends to suggest general causation and the role of dietary factors amongst other possible factors.

The role of smoking was deliberated extensively. Though smoking is accepted as a general risk factor for solid organ cancers there was no consensus to associate active smoking as a specific independent risk factor for GBC. ***(CS11)***

Prophylactic cholecystectomy

Recent studies find the association between porcelain gallbladder and GBC to be lower than historical reports.[19,20] There are reports of occasional coexistence of GBC with focal adenomyomatosis however literature does not suggest a direct association between adenomyomatosis and GBC.[21,22] Experts agreed that the risk of GBC with porcelain GB is less than previously reported ***(CS 12)*** and adenomyomatosis is not a risk factor for GBC. ***(CS 13)***

Though it was agreed that GBC has a strong association with gallstones, ***(CS 14)***[23,24] experts suggested that current evidence does not support prophylactic cholecystectomy for patients with asymptomatic gallstones to reduce the risk of GBC. ***(CS 20)***

Table 5 Consensus statements on advanced GBC

CQ No	Clinical Question/Revised Question/Consensus Statement	Consensus achieved Round	Consensus percentage
52	Do you agree with the concept of 'Borderline resectable' GBC?	R2	81
BR/LA GBC definition-			
53	Patients with a tumor contiguous liver involvement >2 cm Options: (1) Borderline (locally advanced) resectable (2) Locally advanced unresectable (3) Resectable	**No consensus**	
54	Patients with Involvement of bile duct causing obstructive jaundice (Type I/II block on MRCP/ERCP/PTBD) Options: ***(1) Borderline (locally advanced) resectable*** (2) Locally advanced unresectable (3) Resectable	R2	76
55	Patients with Radiological/Endoscopic involvement of antropyloric region of stomach, duodenum, hepatic flexure of colon or small intestine. Options: (1) Borderline (locally advanced) resectable (2) Locally advanced unresectable (3) Resectable	**No consensus**	
56	Patients with Impingement/involvement (≥180-degree) of one or more of the following blood vessels: common hepatic artery and right & left hepatic artery. main portal vein and right & left portal vein Options: (1) Borderline (locally advanced) resectable ***(2) Locally advanced unresectable*** (3) Resectable	R3	92
57	Patients with a suspicion of regional lymph node metastases (enlarged nodes- 4 or more by imaging studies). **Options: *(1) Borderline (locally advanced) resectable*** (2) Locally advanced unresectable (3) Resectable	R3	93
58	Patients with oligometastatic (one or two? small liver metastasis). (1) Borderline (locally advanced) resectable ***(2) Metastatic – unresectable*** (3) Resectable	R2	77
59	Patients with incidental GBC accompanied with any one of the following factors: 1. Residual/Recurrent mass in GB fossa/liver bed 2. Histologically confirmed N1 nodes as per nodal criteria. 3. Involvement of bile duct causing OJ (Type I/II Block) ***(1) Borderline (locally advanced) resectable*** (2) Locally advanced unresectable (3) Resectable	R2	82
60	Patients with a tumor requiring HPD for margin negative resection should be treated as locally advanced GBC	R2	79
61	Patients with a tumor requiring portal vein reconstruction for margin-negative resection should be treated as locally advanced GBC	R1	83
62	Patients with a tumor requiring right hemi hepatectomy for margin negative resection should be treated as locally advanced GBC	R2	87
63	Borderline resectable GBC are likely to benefit from NACT	R3	87
66	How is response to NACT/RT best determined? **Options: *(1) PET/CT*** (2) MRI (3) CECT	R3	75
67	Current evidence does not support HPD for advanced GBC	R3	100
68	Current evidence does not support vascular resection and reconstruction with major hepatectomy for GBC.	R3	100
69	Adjuvant chemotherapy should be advised to all resected GBC patients- with pT2 and/or N+ disease and beyond	R3	100
71	What is the optimal follow-up schedule and testing for patients resected for GBC? Options: ***(a)* 3 months *interval*** (b) 6 months interval (c) 1 year interval	R1	77
72	The PET scan is a recommended modality to stage locally advanced GBC.	R3	100

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Table 5 (*continued*)

CQ No	Clinical Question/Revised Question/Consensus Statement	Consensus achieved Round	Consensus percentage
73	Palliative cholecystectomy has no clinical benefit in metastatic GBC.	R2	82
74	Palliative surgery (biliary bypass, gastric bypass) has a very limited clinical benefit in the era of stenting.	R3	100
75	Palliative chemotherapy has a role in patients with unresectable GBC.	R1	92
76	Biliary stenting is an effective method for relieving obstructive jaundice in locally advanced GBC.	R1	100
77	Biliary stenting is an effective method for relieving obstructive jaundice in metastatic GBC.	R1	98

HPD, hepatopacreaticoduodenectomy; NACT, neoadjuvant chemotherapy.

Cancer risk reduction achieved with prophylactic cholecystectomy does not justify the risk of surgery in the general population. Even studies in high risk populations suggest that multiple factors contribute to GBC risk reduction and cholecystectomy rates in the population may not be solely responsible for GBC risk reduction.[25] APBDJ was recommended as an indication for prophylactic cholecystectomy. ***(CS 21)***

Approach to GB polyps

The risk of malignancy in GB polyps is clinically relevant in polyps larger than 1 cm in size. ***(CS 15)*** GB polyps less than 1 cm can be observed and regularly followed up. They should be operated only if there is a change in the size of the polyp. ***(CS 16)*** Any GB polyp larger than 1 cm should undergo surgery. ***(CS 17)*** GB polyp patients planned for surgery should undergo cross-sectional imaging if the size of the polyp is >2 cm or if the USG shows suspicious features such as associated asymmetrical wall thickening or coexistence of gallstones ***(CS 18)*** Though there are no specific studies on this aspect, the risk of coexistent cancer in a polyp is significant if there are suspicious features on USG or if the polyp is more than 2 cm.[26,27] Experts suggested the selective use of cross-sectional imaging in GB polyps for these clinical situations. Experts also recommended that the laparoscopic approach can be safely offered to patients undergoing surgery for GB polyp. ***(CS 19)***[28]

Clinical pathology

It was clearly recommended that early and resectable GBC patients should not undergo preoperative biopsy ***(CS 38)***. Elective surgery for suspected or diagnosed GBC should be carried out under frozen section cover. ***(CS 30)*** Though, it is difficult to distinguish early GBC from inflammation in the presence of thickening of the wall and stone disease ***(CS 28)***, gallbladder specimens during cholecystectomy must be opened by the surgeon and checked for abnormal nodular thickening or mass and these cholecystectomy specimens should be sent for histopathological examination ***(CS 25)***. Significant variation reflected in the discussion on the practice of pathologic evaluation of GB specimens after a cholecystectomy for a presumed benign indication. It is a routine in few countries and is performed selectively in others to reduce the burden on healthcare infrastructure in view of low risk of GBC in absence of suspicion on gross examination.[29,30] There can be medicolegal implications for not evaluating the excised GB specimen and there is a risk of missing potentially curable iGBCs, which is reported after about 0.7–0.9% cholecystectomies.[31] It was unanimously accepted that routine pathology examination should be done for all resected GB specimens. ***(CS 24)*** Minimum pathological evaluation of GB specimens should include sections from the cystic duct, fundus and mid-body in addition to suspicious areas. ***(CS 26)*** Whereas, it was recommended that gallbladder specimens should be mapped and completely examined for incidentally detected GBC in endemic areas. ***(CS 23)*** AJCC/UICC system was recommended to be the most optimal for staging GBC. ***(CS 27)***[32]

Definitions radical and extended cholecystectomy

Literature has previously used the terms 'radical cholecystectomy' and 'extended cholecystectomy' to describe oncologic operation for GBC. These terms are considered interchangeable. Terms 'completion' or 'revision' are usually prefixed to these to describe surgery for iGBC. For the sake of uniformity, experts agreed that radical surgery for GBC should be labelled as 'Radical Cholecystectomy' ***(CS 39)*** and it includes -

1) A form of liver resection – essential to achieve margin negative resection – en bloc with the primary tumour. Extent of liver resection can vary depending upon the tumour extent – No liver resection for T1a/Wedge Excision/Segment IVb-V Resection/Major hepatectomy.
2) Complete HDL lymphadenectomy – (T1b onwards)

It was suggested that the term 'extended' should be used to mean resection beyond the routine extent and should not be used to describe the standard radical operation for GBC or iGBC.

'Extended radical cholecystectomy' describes Radical cholecystectomy with any of the following

1) Liver resection beyond segment IVB-V, involving 3 or more segments i.e. major hepatectomy
2) Extrahepatic biliary tract resection
3) Extrahepatic adjacent organ resection: duodenum, colon, etc
4) Vascular resection
5) Extended LN (lymph node) dissection: Celiac LN, paraaortic LN, others.

The term "iGBC" describes preoperatively unsuspected GBC diagnosed incidentally after index cholecystectomy purely as a histopathological surprise. ***(CS 31)*** Experts also recommended that in an uncommon clinical scenario when a GBC is detected intraoperatively by a frozen section analysis during a cholecystectomy, in a previously unsuspected patient, should also be defined as iGBC. ***(CS 32)*** Similar to the terminology of perprimum GBC, experts recommended that radical surgery for iGBC should be termed either revision radical cholecystectomy or completion radical cholecystectomy. ***(CS 33)***

Principles of surgery

iGBC – Five-year survival in cases of pT1a-iGBC approaches 100% in most studies. Experts recommended that incidentally detected pT1a GBC patients can be observed without surgical intervention ***(CS 34)***. For pT1b iGBC, five year survival figures drop to 84.8 %. The incidence of LN positivity and residual disease has been reported to be around 9.9%.[33,34] pT1b patients should be offered completion surgery. ***(CS 35)*** It was discussed that indication can be selective in patients with advanced age, high risk for general anaesthesia or significant comorbidities where potential benefits may outweigh the risks associated with re-surgery. This potential exception was not added as a specific recommendation.

Routine port-site excision fails to reduce disease recurrence, does not improve survival and results in incisional hernias in up to 8% of patients. Port site recurrence generally indicates disseminated peritoneal disease. ***(CS 51)***[35,36] It was recommended that the port sites (including the umbilical port) need not be excised in revision surgery for iGBC. ***(CS 50)***

There was no consensus on the ideal timing for surgery after diagnosis for iGBC. ***(CS 36)*** There was no consensus about the approach to the patient presenting late (more than 12 weeks) after index cholecystectomy. Though most experts believed that surgery should be offered to the delayed presentations there was no consensus on cut-off time for not offering surgery to these patients.

Extent of liver resection

CQ 42 involved the statement on optimal extent of liver resection for T2 and T3 GBC. CQ was subdivided into individual statements for T2 and T3 disease (42A and 42B) as per suggestions received in round 3. Experts unanimously agreed that a margin-negative wedge should be considered adequate for T2 GBC ***(CS 42A)***. For T3 GBC, however, experts were divided. Forty-six percent experts considered margin-negative wedge excision an

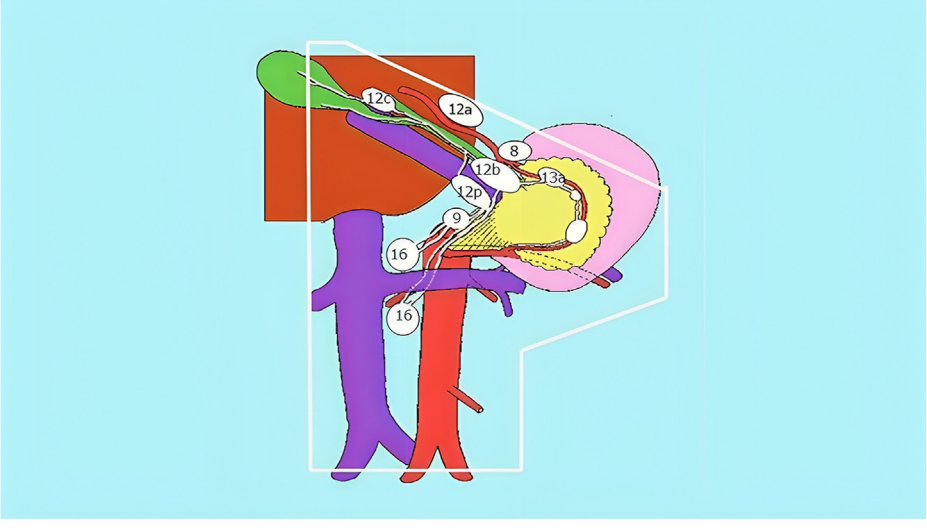

Figure 1 Standard lymph node dissection for gallbladder carcinoma. The standard dissection involves the lymph nodes in the hepatoduodenal ligament (12c, 12b, 12a, and 12p), the lymph nodes along the common hepatic artery (8), and the posterior pancreatoduodenal lymph nodes (13). 8: lymph nodes around the common hepatic artery; 9: lymph nodes around the celiac trunk; 12c: the cystic lymph nodes; 12b: the pericholedochal lymph nodes; 12a: lymph nodes around the proper hepatic artery; 12p: lymph nodes around the portal vein; 13: the posterior superior pancreaticoduodenal lymph nodes; 14: lymph nodes around the superior mesenteric artery; 16: the paraaortic lymph nodes

adequate procedure. The rest of the experts suggested an en-bloc segment IVB-V resection. As there was no consensus on this aspect both procedures were considered acceptable for T3 GBC. Experts however specifically made a disclaimer that the term segment IVB-V resection should only be used if systematic anatomic resection of these two segments is performed. Larger wedge excision should not be documented as a segment IVB-V resection.

Extent of LN dissection

pT1a is generally an incidental diagnosis post laparoscopic cholecystectomy and simple cholecystectomy is considered an adequate procedure. ***(CS 41)*** 12c (cystic LN) if sampled during the cholecystectomy should be evaluated. However, LN dissection is not mandatory for pT1a iGBC. ***(CS 43)***

For all other patients with resectable GBC or iGBC standard D2 LN dissection should be performed and it includes station 8, all station 12 (12a,b,c,p), and station 13a lymph nodes. ***(CS 44 45)*** (Fig. 1).

There was no consensus on routine intraoperative frozen section analysis of 16b1 (interaortocaval) LN station as practiced in some centers. ***(CS 46)*** Experts however uniformly agreed that 16b1 station should be considered metastatic (M1) disease and if it is found positive, surgery should be abandoned. ***(CS 47)***

Minimally invasive surgery (MIS) for GBC

Diagnostic laparoscopy detects peritoneal and liver surface metastasis in more than 25% of patients.[37,38] This upstaging prevents futile laparotomy in a significant proportion of patients and it was recommended that diagnostic laparoscopy should be done in all cases of GBC at the time of definitive surgery to rule out metastatic disease. ***(CS 48)***

Several studies have shown non-inferiority of laparoscopy and benefit in perioperative outcome parameters at least in early GBC.[39–42] Experts recommended that Minimally invasive surgery (MIS – laparoscopic/robotic) can be offered in early GBC. It was specifically recommended that these resections should be performed by HPB surgeons at centers experienced in MIS. ***(CS 49)*** Currently there is no evidence to support the MIS approach in advanced GBC and it cannot be recommended as a routine.

Borderline resectable/locally advanced GBC (BR/LA-GBC)

Most experts agreed to the concept of BR-GBC. In this consensus, 'BR' and 'LA resectable' GBC were considered similar terms. 'LA unresectable' was grouped separately. CQs were provided with the clinicoradiologic situations that could be considered 'BR/LA' and experts were expected to classify them into one of the above options.

Non metastatic GBC patients with type 1 or type 2 perihilar blocks and patients with significant regional lymphadenopathy were unanimously classified as BR-GBC.***(CS 54)*** Similarly, iGBC with any one of the following factors:1. Residual mass in GB fossa 2. Histologically confirmed nodal disease or radiologic N2 nodes 3. Involvement of bile duct causing obstructive jaundice (Type I/II Block) was also classified as BR/LA potentially resectable cancer. ***(CS 59)*** Impingement or involvement of common hepatic artery and its branches and portal vein and its branches was suggested to be classified as locally advanced unresectable GBC. ***(CS 56)***

However there was significant overlap in experts interpretation of need for upfront systemic therapy and technical resectability of these situations and consensus could not be achieved for a few statements.

PET-CT evaluation in LA-GBC may upstage a significant proportion of patients. It helps define intent, prognosticate and change management plans as necessary early in the course of disease management.[43,44] PET-CT was recommended to stage locally advanced disease. PET was also suggested as an investigation which may aid response assessment after neoadjuvant therapy. ***(CS 66, 72)***

In view of high mortality and morbidity and limited survival gain, there was a clear consensus that current evidence does not support extended resections like hepatopancreaticoduodenectomy (HPD) or major vascular resection with major hepatectomy for GBC. ***(CS 67, 68)*** These procedures are practiced at very few centres across the world and most of these centres would offer such resections to a select few patients after initial systemic chemotherapy. Resectability in these situations would depend on the practice at a particular centre.[45–47]

Metastatic GBC and palliation

Palliative chemotherapy should be administered in metastatic and locally advanced unresectable GBC. ***(CS 75)*** Surgical palliation in GBC patients with compromised performance status carries substantial morbidity and mortality. Surgical options should be considered only when absolutely indicated or when endoscopic or percutaneous alternatives have failed or are unavailable. Obstructive jaundice can be effectively addressed by endoscopic or percutaneous approaches. ***(CS 76,77)*** Even for situations involving colonic or gastroduodenal obstruction, endoscopic stent placement can prevent a morbid laparotomy in advanced GBC patients.[48] Palliative surgery (biliary bypass, gastric bypass) has very limited clinical benefit in the era of endoscopic stenting. ***(CS 74)***[49] Palliative cholecystectomy has no benefit in metastatic GBC. ***(CS 73)***

Discussion

This is the first international effort under the auspices of IHPBA and APHPBA, which adopted a modified Delphi process to develop consensus recommendations on GBC. Consensus could be achieved on more than 90% of clinical questions. Recommendations cover most aspects of GBC management and

contemporary contentious issues. Definitions for radical and extended cholecystectomy, the extent of liver resection and LN dissection, and definitions of BR and LA-GBC are some of the important aspects covered by this consensus process.

Major issues lacking consensus

Smoking as a risk factor for GBC

The lack of consensus on smoking as an independent risk factor for GBC was an important finding of this study. The role of smoking was highly debated among the experts. A few studies do suggest smoking as a risk factor for GBC. Dose–response relationship and synergistic effects with other risk factors (such as diabetes mellitus and alcohol intake) have been reported.[50,51] However, there are a few important negative studies.[52–54]

Experts discussed that the prospective evidence needs to be stronger to associate smoking as an independent risk factor for GBC. Other well-established risk factors currently overshadow any direct link between smoking and GBC. Geographical factors may further complicate the relationship. While smoking is accepted as a general risk factor for solid organ cancers, consensus was not achieved to associate smoking as a specific independent risk factor for GBC.

Extent of liver resection in T3 GBC

The extent of liver resection in GBC surgery has always remained an important debate. Some studies suggest avoidance of liver resection for T2a (peritoneal) GBC.[55] Others recommend a formal segment IVB-V resection for any T2-T3 GBC and a few argue for margin negative wedge resection for the same extent of liver involvement.[56,57] Formal segment IVB-V resection may not necessarily provide survival benefit, can be technically demanding and is associated with slightly higher morbidity as compared to wedge resection.[58,59]

This divide did affect the consensus process. Though consensus was achieved for T2 GBC where most experts agreed to the adequacy of margin negative wedge resection, opinions on the approach to T3 GBC were divided. With a nearly equal number of supporters for wedge and formal segment IVB-V resection, experts suggested that both need to be considered acceptable for T3 GBC. Surgeon discretion will guide the extent of surgery. The aim of surgery should be R0 resection.

Experts also discussed that recommendations about 2 or 3 cm margins in wedge resection are arbitrary. Larger margins are aimed to achieve pathologically negative margins. Resection should include the wedge wide enough to achieve pathologically negative margins.

Role of 16b1 LN sampling during surgery for GBC

Few studies have suggested the benefit of radical surgery in patients with a limited 16b1 disease burden and/or good response to chemotherapy. Some of these patients experience improved survival than those who receive only palliative chemotherapy if an R0 resection can be performed.[60–62] However, outcome in majority of the patients with 16b1 LN metastasis is similar to those with distant metastasis. Patient selection, extent of resection and overall benefit over standard systemic chemotherapy remain debatable.[63,64] Experts uniformly suggested that 16b1 station should be considered metastatic disease and surgery cannot be recommended as a standard practice.

Station 16b1 sampling is performed during surgery for GBC at some centres and has been reported to prevent non therapeutic radical resection in up to 20% of the cases.[37] A proportion of experts did support this practice. However, there was no consensus for routine 16b1 sampling and frozen section analysis during surgery. The consensus was not achieved even for selective use of this practice for T2 GBC and beyond. Experts pointed towards recently improved preoperative evaluation and increased use of PET scan in metastatic work up and suggested a low threshold for biopsy in suspicious cases. Lack of availability of frozen section facilities at many centres also influenced against making this a standard recommendation.

Optimal time for re-operation for iGBC

More than 80% patients iGBC are pT2 or T3 and they benefit with completion radical cholecystectomy. pT and N stage, R0 resection and the presence of residual disease are the main determinants of prognosis.[65–67] Majority of experts did believe that the timing of surgery is also an important prognostic factor. Median time for reoperation in many countries is nearly 8 weeks or more.[68] There is wide variation in the recommended timing of completion surgery in the literature. Studies have recommended early surgery within 4 weeks, 4–8 weeks and even 10–14 weeks and some suggest the outcome may be independent of the time of surgery.[69–72] Essentially there was no consensus on the ideal time for completion radical cholecystectomy for iGBC.

Major achievements of the consensus process

Definitions of oncologic operations for GBC

Definitions of oncologic operations for GBC in different clinical situations and surgical extent needed clarity. Literature previously has used varied terminologies such as radical, completion, extended, revision etc to describe radical operation for GBC or iGBC. The word ‘radical’ suggests resection for oncologic safety. Whereas the word ‘extended’ intends to describe the extent of resection. It was suggested that the term ‘extended’ should be used to mean resection beyond the usual routine and should not be used to describe standard radical operation for GBC. Standardisation of definitions and terms as suggested in this consensus can bring uniformity in future reporting of literature on GBC.

Definition of standard lymphadenectomy for GBC

Prognostic analysis studies have suggested that the number of dissected nodes and LN ratio are important predictors of prognosis in GBC. LN dissection during surgery should include all the primary drainage sites. A minimum of 4–6 lymph nodes should be dissected for proper staging.[73,74] This ensures quality

of resection, allows for better prognostication and may contribute to improvement in disease specific survival.[75–77]

It was recommended that, standard lymphadenectomy (D2) for radical cholecystectomy includes dissection of the conventional level 1 (nodes along cystic duct or the common bile duct) and level 2 (nodes located posterosuperior to the head of the pancreas and around the portal vein/hepatic arteries) lymph nodes. This includes stations 8, 12c, 12b, 12a, 12p, and 13a. Any LN dissection beyond this template should be labelled as 'extended' resection (Fig. 1).

BR/LA-GBC

The majority of the experts agreed to the concept of BR/LA-GBC. One of the important aspects of this consensus was to understand global practice on LA-GBC and understand what experts believe constitutes BR/LA-GBC. Few centres have previously attempted to define these terms. However, global consensus on these terms and approach to management is lacking. GBCs with a presumed high risk of recurrence and the possibility of margin-positive resection or non-resectability may be categorised as BR/LA-GBC. There was consensus that these patients may benefit from neoadjuvant therapy. It has a potential to downsize a significant proportion of locally advanced GBCs and improve resectability and margin negative resections and has shown to benefit node positive patients.[78–80]

There was notable variation in the interpretation of each scenario among the experts. What some considered 'borderline resectable' others labelled it 'resectable'. Similarly, situations which few experts considered BR/LA resectable others classified them as unresectable. However consensus could be achieved in the majority clinical questions of this subject.

GBC with more than 2 cm contiguous liver involvement and single extrahepatic organ (stomach, duodenum, colon) involvement which are technically resectable, were the two main clinical scenarios where expert opinion was divided. These are essentially T3 GBCs as per AJCC TNM classification (8th edition).[32] Stratified by T stage, GBC survival drops significantly for stage T3 (8–28%) when compared to T1/T2 (100–50%). T3 GBC patients have higher chances of margin positive resections and most of these patients also have node positive disease.[81] Higher T stage, nodal involvement and positive margins are associated with reduced survival in GBC.[82] Though the majority of experts considered this as a technically resectable GBC others did point to a relatively advanced nature and potentially poorer survival outcome among these patients. There was no consensus to define these situations as BR-GBC. Defining BR/LA-GBC and indications for neoadjuvant therapy remains a work in progress and needs to be studied further.

Strengths and limitations

The systematic application of the modified Delphi process, and the participation of experts across the world representing various continents and countries with different incidence and management strategies on GBC are important strengths of this study. As most participants were surgeons, the study has predominantly focussed on addressing clinicopathologic and surgical management of GBC. Issues about systemic therapy in advanced cancers, adjuvant therapy, newer immunotherapeutic drugs, the role of radiotherapy etc are being addressed by a separate expert group of medical oncologists.

Expert participation for the online round and in-person round during APHPBA-2023 in Bengaluru was less than in the first two rounds. A few experts were not able to attend the online meeting because of differences in time zones and busy schedules. Facility for online participation was provided even during in-person meetings in Bengaluru as few experts could not travel to India for the meeting. Approval of these experts regarding the results of the consensus was sought by mail later.

Conclusion

This is the first international Delphi consensus on GBC. These recommendations provide uniform terminology and practical clinical guidelines on the current management of GBC. Unresolved contentious issues like borderline resectable/locally advanced GBC need to be addressed by future clinical studies.

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Conflict of interest

All authors declare no conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.hpb.2024.07.411.

