Manuscript

Title - IHPBA - APHPBA – International Delphi Consensus Recommendations for Gallbladder Cancer

Abstract

Background

This 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 the global management of gallbladder cancer (GBC).

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. Opinions from experts who responded via email during the first two rounds were collated. Published evidence on the CQ statements was then shared with the experts through mail. Round 3 involved an open discussion and further refinement of the CQs during a Zoom call. Round 4 was conducted as a hybrid meeting, combining in-person and Zoom interactions, during the APHPBA 2023 conference in Bengaluru, India. The consensus process was guided by previously published evidence and professional judgment. 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 responded in the round 1. 42 , 22, and 33 experts participated in the next 3 rounds respectively. The consensus was achieved in 92.6% (63/68) of the CQs. Consensus covers key aspects such as

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.

Manuscript Main Text

Introduction

GBC is the most common biliary tract cancer and ranks as the 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 lead to it being considered one of the most lethal solid organ cancers.*(2 Jarnagin)* 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 likely 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 or 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. [8] A thorough preparation in identifying the research problem, the format to be used, and the clarity of the Delphi statements is important. (Beidedrbeck D), The Delphi method has been used in developing consensus guidelines in many areas of oncology recently. [9] [10] [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.

Methods

Study design and development.

Despite the variations in using Delphi methods, we largely restricted to the system which followed - identification of the problem area of research and the clinical questions (CQ), selection of panel members, controlled feedback through iterative Delphi rounds, consensus criteria, analysis of feedback, and closing criteria.

Identification of problem areas of research and the clinical questions (CQ)

A Core group of experts was constituted initially. This group identified the problem areas on GBC based on a literature search. A total of 73 CQs were initially identified and put together in different domains including- Epidemiology (16), Clinical Pathology (5), Early and incidental GBC- iGBC (24), advanced GBC (20), and Palliation (8). ***(Table)*** During the initial core group consultations it was opined that CQs involving systemic therapy, radiation therapy, and molecular testing in GBC would be better addressed by another group of experts working specifically in these areas. Therefore, five CQs were removed and finally, the consensus process involved 68 CQs.

Selection of panel members

Forty-seven experts from across the world, representing all continents and 17 countries working actively on GBC participated in the consensus development process. Potential expert panel members were selected based on the possession of theoretical knowledge and extensive practical experience combined with significant scientific contributions in the field of GBC. Experts were predominantly surgeons (75.5%). For a balanced view and opinions a few medical and radiation oncologists were also invited**. (Table)** 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-member team collaborated with an arbitrator to finalize the CQs. The team converted most of the Clinical Questions (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. Comments were analysed to understand the reasons responsible for the lack of consensus. Based on round 1 analysis, a second round of Delphi was conducted with those CQs for which consensus was not developed. 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 (Zoom call) where additional evidence was presented. The voting for the responses was done anonymously. In addition, experts were also asked if they were willing to reconsider their choice if the guideline statement was rephrased. The CQs were modified based on the expert suggestions and group consensus. This was followed by round 4, hybrid in-person and online consensus workshop 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) 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). Out of the sixty experts invited initially to participate in the consensus process 45 responded in the first 2 rounds. A total of 33 experts participated in the Zoom platform meeting. All the 36 questions where consensus was not developed at the end of R2 were discussed. 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 modified based on expert suggestions. This resulted in significant improvement in agreement and consensus could be developed on an additional 27 CQs. In the final in-person round, consensus was reached on 3 more CQs. Overall, consensus was achieved on 63 out of 68 CQs (92.6%). *(Table --)*

Summary Of The Recommendations Of The Consensus Process

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 1,00,000 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 among other possible factors.

The role of smoking was highly debated. 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 less than historical reports. Stippled and incomplete calcification may have a small risk of developing GBC and diffuse calcification is not associated with the risk of GBC. [19] [20] Experts suggested that the risk of GBC with porcelain GB is less than previously reported. ***(CS 12)***

Adenomyomatosis itself is a benign condition. The literature does not suggest a direct association between adenomyomatosis and GBC. There are some reports of occasional coexistence of GBC with adenomyomatosis and particularly focal adenomyomatosis however adenomyomatosis is not a risk factor for GBC. ***(CS 13)*** [21] [22]

Cholecystectomy in both these situations is more often indicated for symptoms and difficulty to differentiate them from malignancy rather than the actual risk of it.

Gallbladder cancer has a strong association with gallstones. ***(CS 14)*** [23] [24] However, experts suggested that current evidence does not support prophylactic cholecystectomy for patient with asymptomatic gallstones to reduce the risk of GBC***.*** ***(CS 20)*** *Cancer* risk reduction achieved does not justify the risk of surgery in general population. Even in high risk populations studies suggest that multiple factors contribute to GBC risk reduction and cholecystectomy rates in

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 1cm 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/metastatic workup if the size of the polyp is >2cm or if the USG shows suspicious features. ***(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 2cm. [26] [27] Experts suggested the selective use of cross-sectional imaging in GB polyps for these clinical situations.

With the increasing use of minimally invasive surgery at least in early GBC, debate about the use of the laparoscopic approach for GB polyp surgery has probably turned redundant. Experts 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 thickening/mass. ***(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 to 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 standard radical operation for GBC or iGBC.

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

1) Liver resection beyond routine radical cholecystectomy – 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 per-primum 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 case 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 %. 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 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 (46%) of experts considered margin-negative wedge excision an 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 lymph node) if sampled during the cholecystectomy should be evaluated. However, lymph node dissection is not mandatory for pT1a iGBC. ***(CS 43)***

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

There was no consensus on routine intraoperative frozen section analysis of 16b1 lymph node 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 suspected 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] [40] [41] [42]Experts recommended that 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 OJ (Type I/II Block) was also classified as BR/LA potentially resectable cancer***.(CS 59)*** However there was significant overlap in experts interpretation of need for upfront systemic therapy, 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 benefit gain , there was a clear consensus that current evidence does not support extended resections like hepatopancreaticoduodenectomy 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] [46] [47]

Metastatic GBC and palliation

Palliative chemotherapy should be administered in metastatic and locally advanced unresectable GBC.**(CS 75)** Surgical palliation is associated with significant morbidity and mortality particularly in patients where performance status is already affected. Generally , surgical options should be offered only when absolutely indicated or when endoscopic or percutaneous options either fail or are not available. 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 and they should be assessed for feasibility of this intervention. [48] Palliative surgery (biliary bypass, gastric bypass) has very limited clinical benefit in the era of 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 lymph node 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. This association has been reported to have regional variation , dose response relationship and synergistic effect with other risk factors like diabetes mellitus and alcohol intake. [50] [51] However, there are a few important negative studies. [52] [53] [54]

Experts suggested that specific prospective evidence needs to be stronger to associate smoking as an independent risk factor for GBC. Presently, the influence of other well-established risk factors appears to overshadow any direct link between smoking and GBC. Moreover, geographical factors may further complicate the relationship between cigarette smoking and

GBC risk. It is accepted as a general risk factor for solid organ cancers. However, 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 lymph node 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] [61] [62] However , outcome in majority of the patients with 16b1 lymph node 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. *(36 Agarwal AK)* 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] [66] [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 to 8 weeks and even 10-14 weeks and some suggest the outcome may be independent of the time of surgery. [69] [70] [71] [72] Essentially there was 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 lymph node ratio are important predictors of prognosis in GBC. Lymph node dissection during surgery should include all the primary drainage sites. For proper staging, it is recommended that a minimum of 4 to 6 lymph nodes should be dissected. [73] [74] This ensures quality of resection and proper staging , allows for better prognostication and may contribute to improvement in disease specific survival. [75] [76] [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 lymph node stations 8 , 12c, 12b, 12a, 12p, and 13a. Any lymph node dissection beyond this template should be labelled as 'extended' resection.

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] [79] [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 2cm 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). [32Amin] 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 and LA GBC and indications for neoadjuvant therapy remains a work in progress and needs to be discussed 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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