

INDIAN COUNCIL OF MEDICAL RESEARCH



CONSENSUS DOCUMENT FOR MANAGEMENT OF GALLBLADDER CANCER

*Prepared as an outcome of ICMR Subcommittee
on Gallbladder Cancer*



INDIAN COUNCIL OF MEDICAL RESEARCH
Department of Health Research
(Ministry of Health & Family Welfare)
V. Ramalingaswami Bhawan, Post Box 4911,
Ansari Nagar, New Delhi-110029
Phone: 91-11-26588980, 26589794, 26588895
E-mail: icmrhqds@sansad.nic.in
Website: <http://www.icmr.nic.in>

Indian Council of Medical Research
2014

CONSENSUS DOCUMENT FOR MANAGEMENT OF GALLBLADDER CANCER

Prepared as an outcome of ICMR Subcommittee
on Gallbladder Cancer



Coordinated by
Division of Non Communicable Diseases

Indian Council of Medical Research,
Ansari Nagar, New Delhi – 110029
2014

Disclaimer

This consensus document represents the current thinking of experts on the topic based on available evidence. This has been developed by national experts in the field and does not in any way bind a clinician to follow this guideline. One can use an alternate mode of therapy based on discussions with the patient and institution, national or international guidelines. The mention of pharmaceutical drugs for therapy does not constitute endorsement or recommendation for use but will act only as a guidance for clinicians in complex decision –making.

Dr. V.M. Katoch
Secretary,
Department of Health Research
and Director General, ICMR

Published in 2014

Dr. V. K. Srivastava : Head (Publication & Information)

Compiled & Edited by : Dr Tanvir Kaur, Scientist 'E'
: Ms. Sucharita V

Production Controller : JN Mathur, Press Manager

Published by the Division of Publication and Information on behalf of the Secretary, DHR & DG, ICMR, New Delhi.

Designed & Printed at M/s Aravali Printers & Publishers (P) Ltd., W-30, Okhla Industrial Area, Phase-II, New Delhi-110020
Phone: 47173300, 26388830-32

Foreword

I am glad to write this foreword for consensus document for Management of Gallbladder Cancer. The ICMR had constituted sub-committees to prepare this document for management of various cancer sites. This document is the result of the hard work of various experts across the country working in the area of oncology.

This consensus document on Management of Gallbladder cancers summarizes the modalities of treatment including the site-specific anti-cancer therapies, supportive and palliative care and molecular markers and research questions. It also interweaves clinical, biochemical and epidemiological studies.

The various subcommittees constituted under Task Force project on Review of Cancer Management Guidelines worked tirelessly in drafting cancer site-specific guidelines. Each member of the subcommittee's contribution towards drafting of these guidelines deserves appreciation and acknowledgement for their dedicated research, experience and effort for successful completion. We hope that this document would provide guidance to practicing doctors and researchers for the management of Gallbladder cancer patients and also focusing their research efforts in Indian context.

It is understood that this document represents the current thinking of national experts on this topic based on available evidence and will have to be revised as we move. Mention of drugs and clinical tests for therapy do not imply endorsement or recommendation for their use, these are examples to guide clinicians in complex decision making. We are confident that this first edition of these guidelines will serve the desired purpose



(Dr.V.M.Katoch)

Secretary, Department of Health Research &
Director General, ICMR

Message

I take this opportunity to thank Indian Council of Medical Research and all the expert members of the subcommittees for having faith and considering me as Chairperson of ICMR Task Force project on Guidelines for Management of Cancer.



The Task Force on Management of Cancers has been constituted to plan various research projects. Two sub-committees were constituted initially to review the literature on management practices. Subsequently, it was expanded to include more sub-committees to review the literature related to guidelines for management of various sites of cancer. The selected cancer sites are lung, breast, oesophagus, cervix, uterus, stomach, gall bladder, soft tissue sarcoma and osteo-sarcoma, tongue, acute myeloid leukemia, acute lymphoblastic leukemia, CLL, Non Hodgkin's Lymphoma-high grade, Non Hodgkin's Lymphoma-low grade, Hodgkin's Disease, Multiple Myeloma, Myelodysplastic Syndrome and paediatric lymphoma. All aspects related to management were considered including, specific anti-cancer treatment, supportive care, palliative care, molecular markers, epidemiological and clinical aspects. The published literature till December 2012 was reviewed while formulating consensus document and accordingly recommendations are made.

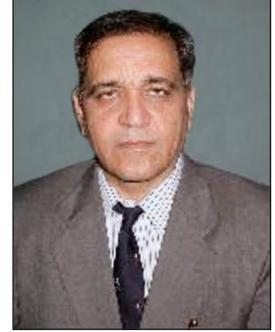
Now, that I have spent over a quarter of a century devoting my career to the fight against cancer, I have witnessed how this disease drastically alters the lives of patients and their families. The theme behind designing of the consensus document for management of cancers associated with various sites of body is to encourage all the eminent scientists and clinicians to actively participate in the diagnosis and treatment of cancers and provide educational information and support services to the patients and researchers. The assessment of the public-health importance of the disease has been hampered by the lack of common methods to investigate the overall; worldwide burden. ICMR's National Cancer Registry Programme (NCRP) routinely collects data on cancer incidence, mortality and morbidity in India through its co-ordinating activities across the country since 1982 by Population Based and Hospital Based Cancer Registries and witnessed the rise in cancer cases. Based upon NCRP's three year report of PBCR's (2009-2011) and Time Trends on Cancer Incidence rates report, the burden of cancer in the country has increased many fold.

In summary, the Consensus Document for management of various cancer sites integrates diagnostic and prognostic criteria with supportive and palliative care that serve our three-part mission of clinical service, education and research. Widespread use of the consensus documents will further help us to improve the document in future and thus overall optimizing the outcome of patients. I, thank all the eminent faculties and scientists for the excellent work and urge all the practicing oncologists to use the document and give us valuable inputs.

(Dr. G.K. Rath)
Chairperson
ICMR Task Force Project

Preface

The Indian Council of Medical Research (ICMR) has taken this welcome lead to bring forth this consensus document on management of Gallbladder Cancer (GBC). One would appreciate the fact that GBC is very common in India particularly in the northern parts of the country where it surpasses, other high incidence areas of the world, due to some yet unknown reasons. Ironically, the guidelines for management of GBC have come before this from such geographical areas where GBC is comparatively uncommon e.g. NCCN, NCI from U.S.A. and ESMO from Europe. Nevertheless, the existence of these guidelines has provided a skeleton on which to build our own Indian consensus document. However, there has been a worrying and constant shortcoming in that the quality evidence for and against a particular management protocol of GBC is not available in Indian and also in the world literature.



Two not so recent developments have helped the clinician to give due attention to GBC and the terrible clinical course it takes. The first of these is a wide spread and qualitatively better application of imaging (Ultrasound/CECT) for gallbladder conditions and secondly, the increasing application of laparoscopic cholecystectomy even in the remote rural settings in India.

GBC is a lethal disease due to various reasons such as insidiously rapid course the diagnosis is often made when the disease is already advanced at a stage where curative procedures are not possible; a general lack of uniformity and decisiveness in appropriate operative procedure for GBC and this is the most worrying feature for successful management of this disease; where GBC is discovered on histopathology of the laparoscopic cholecystectomy specimen often by the pathologist - the situation is often iatrogenically complicated by spillage of bile, no usage of extraction bag and other factors. These are otherwise patients who would benefit from an appropriate operation procedure and/or immediate referrals to higher centers if the requisite expertise for further management is not available at the primary physician level; and there overall, GBC is a relatively chemo-radio resistant tumor. Therefore, the advantages of chemotherapy/radiotherapy in treatment protocols, so effective in some other cancers, seem ineffective in GBC on the basis of our present knowledge. In the foreground of the above, there is need for management of GBC to have a well laid out plan of diagnosis and treatment which this consensus document is expected to provide. The group of experts, from all over India, who have assembled for this task are masters in this field and they have devoted a considerable proportion of their professional activity towards treatment and research of GBC.

The management of GBC is a dynamic process. Therefore, it is expected that as new insights are discovered and developed these will be incorporated from time to time in the future.

H.S. Shukla

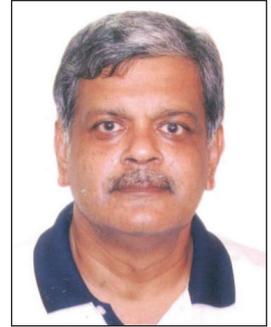
(Dr. Hari S. Shukla)

Chairperson

Sub-committee on Gallbladder Cancer

Preface

Cancer is a leading cause of disease worldwide. Globally cancer of various types effect millions of population and leads to loss of lives. According to the available data through our comprehensive nationwide registries on cancer incidence, prevalence and mortality in India among males; cancers of lung, mouth, oesophagus and stomach are leading sites of cancer and among females cancer of breast, cervix are leading sites. Literature on management and treatment of various cancers in west is widely available but data in Indian context is sparse. Cancer of gallbladder and oesophagus followed by cancer of breast marks as leading site in North-Eastern states. Therefore, cancer research and management practices become one of the crucial tasks of importance for effective management and clinical care for patient in any country. Hence, the need to develop a nationwide consensus for clinical management and treatment for various cancers was felt.



The consensus document is based on review of available evidence about effective management and treatment of cancers in Indian setting by an expert multidisciplinary team of oncologists whose endless efforts, comments, reviews and discussions helped in shaping this document to its current form. This document also represents as first leading step towards development of guidelines for various other cancer specific sites in future ahead. Development of these guidelines will ensure significant contribution in successful management and treatment of cancer and best care made available to patients.

I hope this document would help practicing doctors, clinicians, researchers and patients in complex decision making process in management of the disease. However, constant revision of the document forms another crucial task in future. With this, I would like to acknowledge the valuable contributions of all members of the Expert Committee in formulating, drafting and finalizing these national comprehensive guidelines which would bring uniformity in management and treatment of disease across the length and breadth of our country.

A handwritten signature in blue ink, appearing to read 'D.K. Shukla', written over a horizontal line.

(Dr.D.K.Shukla)
Head, NCD Division

Acknowledgement

The Consensus Document on Management of Cancer is a concerted outcome of effort made by experts of varied disciplines of oncology across the nation. The Indian Council of Medical Research has constituted various sub committees to formulate the document for management of different cancer sites. The Task Force on Management of Cancers has been constituted to formulate the guidelines for management of cancer sites. The sub-committees were constituted to review to review the literature related to management and treatment practices being adopted nationally and internationally of different cancer sites. The selected cancer sites are that of lung, breast, oesophagus, cervix, uterus, stomach, gall bladder, soft tissue sarcoma and osteo-sarcoma, tongue, acute myeloid leukaemia, ALL, CLL, NHL-high grade, NHL-low grade, HD, MM, MDS, and paediatric lymphoma. All aspects related to treatment were considered including, specific anti-cancer treatment, supportive care, palliative care, molecular markers, epidemiological and clinical aspects.



This document represents a joint effort of large effort of large number of individuals and it is my pleasure to acknowledge the dedication and determination of each member who worked tirelessly in completion of the document.

I would like to take this opportunity to thank Dr. GK Rath, chairperson, ICMR Task Force on Guidelines for Management of Cancer for his constant guidance and review in drafting the consensus document especially perseverance behind each subcommittee in formulating these documents. The chairperson of subcommittee is specially acknowledged in getting the members together, organizing the meetings and drafting the document.

I would like to express gratitude to Dr. VM Katoch, Secretary, Department of Health Research and Director General, Indian Council of Medical Research, for taking his special interest and understanding the need of formulating the guidelines which are expected to help cancer patients.

I would like to acknowledge here the initiative undertaken with the able guidance of Dr. Bela Shah. I would like to thank Dr. DK Shukla for his support and coordination in finalizing this document. I would also like to acknowledge the assistance provided by administrative staff. This document is the result of the deliberations by subcommittees constituted for this purpose. The guidelines were further ratified by circulation to extended group of researchers and practitioners drawn from all over the country. It is hoped that these guidelines will help the practicing doctors to treat cancer patients effectively and thus help them to lead a normal and healthy life.

The ICMR appreciatively acknowledges the valuable contribution of the members for extending their support in formulating these guidelines. The data inputs provided by National Cancer Registry Programme are gratefully acknowledged.

A handwritten signature in blue ink that reads "Tanvir Kaur".

(Dr. Tanvir Kaur)
Programme Officer & Coordinator

Members of the Subcommittee

Chairman

Dr. Hari S. Shukla
Professor Emeritus
Department of Surgical Oncology
Institute of Medical Sciences
Banaras Hindu University, Varanasi - 221005 U.P.

Members

Dr. Anu Behari
Associate Professor
Department of GI Surgery
SGPGI, Raebareilly Road
Lucknow

Dr. Jahar Majumdar
Department of Surgical Oncology
Chittaranjan National Cancer Institute
Kolkata

Dr. Mallika Tewari
Associate Professor
Department of Surgical Oncology
Institute of Medical Sciences
Banaras Hindu University
Varanasi

Dr. Sunil Saini
Director, CRI
HIMS, Jolly Grant
Dehradun

Dr. Tomcha Singh
Professor
Department of Radiotherapy
RIMS, Imphal
Manipur

Dr. Atul Sharma
Professor
Department of Medical Oncology
IRCH, AIIMS
New Delhi

Dr. (Brig) Manomoy Ganguly
Commandant
Army Hospital
Rohtak

Dr. Sandeep Kumar
Director
AIIMS, Saket Nagar
Bhopal

Dr. Peush Saini
Professor
Department of GI Surgery
AIIMS
New Delhi

Dr. V.K. Kapoor
Professor
Department of GI Surgery
SGPGI, Raebareilly Road
Lucknow

CONTENTS

| | |
|--|-----|
| Foreword | i |
| Message from Chairperson | ii |
| Preface (Chairperson of Subcommittee) | iii |
| Preface | iv |
| Acknowledgement | v |
| 1. Introduction | 11 |
| 2. Existing Guidelines | 13 |
| 3. Review of Published Data | 14 |
| 4. Diagnostic workup | 37 |
| 5. Treatment | 39 |
| 6. Follow up | 41 |
| 7. Treatment Flow Charts | 42 |
| 8. Research Issues | 44 |
| 9. Appendices | 45 |
| Appendix (i) Radiology reporting template | 46 |
| Appendix (ii) Pathology reporting template | 47 |
| Appendix (iii) AJCC TNM Staging 7th Ed | 48 |
| 10. Bibliography | |
| 11. Abbreviations | |

G allbladder cancer (GBC) is a rare though notoriously lethal malignancy with marked ethnic and geographical variations. It is a common disease in countries such as Chile (16-27/100,000), Japan (7/100,000), India, Central Europe – Poland (14/100,000), Israel (5/100,000) and southern Pakistan (11/100,000); however, it is uncommon in the United States (1.5/100,000). In India, GBC is most prevalent in the northern and northeastern states of Uttar Pradesh, Bihar, Orissa, West Bengal and Assam. It is twice more common in women than in men and is the commonest digestive cancer in women in northern India. The highest frequency of disease is in women over the age of 65. Apart from gallstones, female gender, ethnicity, genetic susceptibility and lifestyle factors are associated risk factors in the development of GBC either as initiators, such as unknown endo- and exobiotic mutagens, or as promoters, including chronic inflammation and infection.

The presenting symptoms are typically vague and are akin to other diseases such as cholelithiasis and cholecystitis. Hence, the diagnosis is commonly made at an advanced stage. The mean survival rate for patients with advanced GBC is 6 months: with a 5-year survival rate of less than 5% in stage IV. GBC should be suspected in patients after 60 years with constant pain in the right hypochondrium and a history of recent weight loss. Patients with advanced GBC may present with anorexia, cachexia, deep icterus, a palpable hard lump in the right hypochondrium, ascites and left supraclavicular lymphadenopathy with poor performance status.

There are no biochemical tests of importance for early diagnosis. A raised bilirubin is a sign of advanced disease. Tumor markers – CEA and CA 19-9 do not have much role in diagnosis as these are not specific for GBC. Various imaging tools available include Ultrasound (USG), Computed Tomographic (CT) scan, and Magnetic Resonance Imaging (MRI) with Magnetic Resonance Cholangiopancreatography (MRCP) and Magnetic Resonance Angiography (MRA). These are used as required to detect structural changes that include intraluminal polyp, focal or diffuse parietal thickening and replacement of the gallbladder lumen by a mass and stage as well as help in assessment of hepatic reserve. MRCP is the investigation that is preferred over ERCP/PTC in patients presenting with jaundice unless a therapeutic intervention is planned.

FNAC is not indicated in resectable GBC because resection should be performed even if FNAC is negative and the tumor has propensity for seeding the biopsy tracts. However, if there is clinical evidence of distant metastatic disease (e.g. left supraclavicular lymph node, umbilical nodule, liver nodule, pelvic deposits or ascites) a tissue diagnosis should be obtained (FNAC, fluid cytology) from the metastasis. Staging laparoscopy should be done in patients with resectable advanced GBC or incidental GBC before re-exploration to rule out distant metastases.

Complete surgical resection (R0) is the only modality that provides hope for long term survival. The optimum treatment for incidental Tis and T1a GBC is simple cholecystectomy (with negative cystic duct

margin) with a 5-year survival of 100% in most studies. Extended cholecystectomy is indicated in lesions T1b and above.

Evidence in support of routine excision of all port-sites during re-resection for incidental GBC is lacking. The extent of liver resection varies ranging from non-anatomical wedge resections, to anatomical parenchyma sparing segment IVb/V resections up to extended right hepatectomy. Extensive liver resections improve the results of advanced GBC at the cost of high morbidity and mortality. An extrahepatic bile duct resection may be indicated in patients with direct infiltration of the cystic duct or the CBD.

Adjuvant therapy is used in all patients with stage II to IVA GBC patients who have undergone extended cholecystectomy, though evidence for improvement in survival is lacking.

Based on the available reports, any of the following protocols may be used for treatment of patients with unresectable/metastatic GBC who have adequate organ functions and ECOG performance status of up to 2: mGEMOX, GEMCIS, GEMCAP.

Pruritus, jaundice, pain, weakness, anorexia, ascites and gastrointestinal obstruction in unresectable/metastatic GBC need adequate non-surgical palliative support.

Special notes from committee members

- All post cholecystectomy gallbladder specimens should be opened and examined carefully by the operating surgeon and be sent for histopathological examination. Any subtle suspicious area/thickening should be marked (with thread/clips) for expert pathological assessment.
- All 'incidental' GBC (GBC picked up on histopathological examination only) should have an expert opinion.
- If there is a high suspicion of GBC preoperatively, prior informed consent for extended cholecystectomy must be obtained.
- If an expertise for extended cholecystectomy is not available, GBC diagnosed per-operatively must never be opened for a biopsy and the patient be referred to a specialist center. A biopsy may however be taken from a node/omentum or perhaps FNAC from the GB mass. A detailed note regarding the pre and per-operative findings should be prepared by the operating surgeon before referral.
- An extensive work up of metastatic GBC may not be mandatory outside a trial setting.
- The members felt that there is an urgent need for multicenter studies/trials from India covering various aspects of epidemiology (viz., identification of population at high-risk, organized follow up), clinical management (viz., bile spill during surgery, excision of all port sites, adjuvant/neoadjuvant therapy) and basic research (viz., what causes GBC) in the field of GBC.

2

EXISTING GUIDELINES

The current document has been prepared taking in to consideration the following published guidelines and relevant quality data published in literature. It is however stated that there are limited randomized controlled trials on the management of GBC and most existing are on biliary tract malignancies that have often enrolled both GBC and other biliary tract malignancies.

- National Comprehensive Cancer Network (NCCN; www.nccn.org)
- National Cancer Institute Physician Data Query (PDQ)
- PDQ® Gallbladder Cancer Treatment. Bethesda, MD: National Cancer Institute (<http://cancer.gov/cancertopics/pdq/treatment/gallbladder/HealthProfessional>)
- European Society of Medical Oncology (ESMO)

Eckel F, Brunner T, Jelic S. On behalf of the ESMO Guidelines Working Group. Clinical practice guidelines: Biliary cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Annals of Oncology 22 (Supplement 6): vi40–vi44, 2011 doi:10.1093/annonc/mdr375

3.1 EPIDEMIOLOGY

National Status

In India, gallbladder cancer (GBC) is most prevalent in northern and northeastern states of Uttar Pradesh, Bihar, Orissa, West Bengal and Assam¹. GBC is two times higher in women than men and is the leading digestive cancer in women in northern India cities². Six cancer registries of the Indian Council of Medical Research (ICMR) (1990-96) show a 10 times lower incidence of GBC per 1 00 000 in South India compared with the North, the age-adjusted incidence rate (AAR) for females being 0.8 in Chennai in the south and 8.9 in Delhi in the north³. GBC ranks amongst the first 10 cancers in the ICMR registries (2006-2008) of Delhi, Dibrugarh, Kolkata, Bhopal and Mumbai⁴. The incidence of GBC increases after the age of 45 years and is maximum at the age of 65 years⁵.

A recent study of Unisa S et al 2011⁶, performed ultrasonography (USG) in 5100 with symptoms and 1448 persons without symptoms, respectively in Eastern UP and Bihar. Prevalence of gallstones on USG was found to be 1.99% in males and 5.59% in females; overall the prevalence of gallbladder disease (acute or chronic cholecystitis, gallstones, GBC) was 6.2% and of gallstones 4.15%. Gallbladder disease was more common in 5100 persons with symptoms (7.12%) compared with 1448 without (2.99%) ($p < 0.05$). Prevalence of gallstones was 2.3 times more in both males and females with symptoms than without. Adjusted odds ratio (ORs) [95% confidence interval (CI)] revealed a significantly increased risk of Gallstone Disease (GSD) in females >50 , 1.703 (CI 1.292-2.245); multiparity 1.862 (CI 1.306-2.655) and genetic history 1.564 (CI 1.049 – 2.334). An increased risk noted in males with diabetes was 4.271 (CI 2.130-8.566), chickpea consumption 2.546 (CI 1.563-4.146) and drinking unsafe water 3.835 (CI 2.368 – 6.209). Prevalence of gallstones was more in females than males ($p < 0.05$). Cluster analysis identified a positive correlation of nickel, cadmium and chromium in water with a high prevalence of gallbladder disease.

International status

GBC is a very common disease in countries such as Chile (16-27/100,000), Japan (7/100,000), India, central Europe – Poland (14/100,000), Israel (5/100,000) and south Pakistan (11/100,000); however, it is uncommon in United States (1.5/100,000)⁷⁻⁹. GBC is a leading cause of cancer death in Chilean women surpassing even breast and cervix cancer. Its incidence is increasing in Shanghai, China where it is now the most frequent gastrointestinal malignancy¹⁰.

The highest frequency of the disease is found among females (2-6 times more common) over the age of 65^{5, 11-15}.

There is a marked regional and ethnic variation in the incidence of GBC. The highest mortality rates have been reported among Chilean Mapuche Indians and Hispanics¹⁶⁻¹⁷, Bolivians¹⁸, North American Indians¹⁹ and Mexican Americans²⁰. Incidence rates are much lower in Europe²¹.

3.2 RISK FACTORS

GBC is a notoriously rare though lethal malignancy with marked ethnic and geographical variations. The presenting symptoms are typically vague so that its diagnosis commonly occurs at an advanced stage. The overall 5-year survival of patients with GBC remains low²². There is a clear worldwide association between chronic cholelithiasis and GBC. Aside from gallstones, female gender, ethnicity, genetic susceptibility and lifestyle factors a number of associated risk factors appear to favor the development of GBC either as neoplastic initiators, such as unknown endo- and exobiotic mutagens, or as neoplastic promoters, including chronic inflammation and infection.

The search for risk factors will be greatly helped if population with significantly lower or higher rates of disease could be identified. The association of new risk factors with GBC will explore new challenges for us in this high incidence zone across north India including Pakistan, Nepal and Bangladesh.

3.2.1 Ethnicity, gender and age

This has been discussed above under epidemiology.

3.2.2 Gallstones

A history of gallstones appears to carry the highest risk of GBC, with a relative risk ranging from 3.01 to 23.8^{13-14, 23}. Most (69% to 100%) but not all people with GBC have cholelithiasis. Further these 2 entities are frequently co-factor for this carcinoma²⁴. It has been established that gallstones are associated with GBC. However, there is no evidence of a direct causal relationship between gallstones and GBC²⁴⁻²⁵.

Increasing stone size (>3 cm)²⁶⁻²⁸ carries a Relative Risk (RR) of 9.2 to 10.1, number, volume and weight²⁹, are all associated with an increased risk of cancer. Duration of gallstones more than 20 years is also a risk factor (RR 6.2)³⁰. The risk factors for cholesterol gallstones have been mainly associated with hypersecretion of biliary cholesterol, gallbladder hypomotility, and stasis.

3.2.3 Chronic inflammation

Chronic inflammation of the gallbladder may result from the presence of gallstones, chronic infection or in patients with primary sclerosing cholangitis (PSC). Chronic inflammation from any cause may lead to calcium being deposited in the gallbladder wall, termed the “porcelain gallbladder” because of its bluish color and fragile, brittle consistency³¹. This entity is rare, being identified pathologically in less than 1% of gallbladder specimens. The calcium deposits can be detected on diagnostic imaging- plain abdominal radiographs, ultrasounds or computed tomography images. Controversy exists whether or not the porcelain gallbladder is truly associated with an increased risk of cancer. A high incidence of ~25% has been reported by older series. Stippled or multiple punctate calcifications in the glandular spaces of the mucosa is now thought to be a risk factor rather than broad continuous band of calcification in the muscularis^{10,31-33}.

Chronic bacterial infections also cause irritation and inflammation in the gallbladder. *S. typhi* carriers have a RR of 12.7 to 167 with 6% developing GBC³⁴⁻³⁸. *Helicobacter bilis* is also implicated in GBC with an odds ratio of 6.5 in Japanese patients and 5.86 in Thai patients and has a RR of 2.6 to 6.5³⁹. PSC is typically associated with an increased risk of cholangiocarcinoma. As dysplasia occurs in 37% and adenocarcinoma in 14-18% of gallbladders from patients with PSC, these individuals are at heightened risk for developing GBC⁴⁰.

3.2.4 Genetic factors

Congenital anomalous pancreaticobiliary duct junction (APBDJ) carries a RR of 3% to 18% of GBC. APBDJ without CBD dilatation has increased risk of GBC and those with dilatation have enhanced risk of both GBC and cholangiocarcinoma^{25, 41}.

There are other undoubtedly genetic and environmental factors that coincide to become expressed as GBC. A family history of GBC, though rare, is clearly a risk factor⁴²⁻⁴⁴. The only responsible gene so far identified seems to be that for apolipoprotein B function (the APOB gene), which influences cholesterol handling yet is not associated with gallstones. In fact, the link between cholesterol gallstones and GBC may relate to an interdependent disposal pathway that increases the export of both cholesterol and environmental toxins into bile. As GBC is more common in women, such mutagenic toxins secreted reside longer in the gallbladder due to stasis from impaired contractility associated with the female hormone, progesterone. This protracted exposure allows environmental carcinogens to then cause malignant transformation, helping to reconcile the theory of 'seed versus soil' and incorporate the predilection to the development of gallstones (also requiring some gallbladder stasis) and GBC⁴⁵.

3.2.5 Gall bladder polyps

Polypoidal masses of the gallbladder affect 5% of adults and may be confused with GBC⁴². Over two-thirds of polyps are composed of cholesterol esters; the other lesions are adenomas, leiomyomas or inflammatory polyps. Although occasionally associated with biliary colic, the vast majority of gallbladder polyps are asymptomatic; being found incidentally when abdominal imaging is performed for other purposes. Prophylactic cholecystectomy is warranted in patients with polyps that possess malignant-appearing features (discussed later in the imaging section).

3.2.6 Life Style Factors

The association of gallstones with GBC likely explains why some of the traditional risk factors for gallstones are also risk factors for GBC including obesity, female gender and multiparity. In over 84,000 men and 97,000 women included in the Cancer Prevention Study II Nutrition Cohort, the relative risk of GBC was 1.8 (95% confidence interval [CI], 1.1 to 2.9) in obese men with a Body Mass Index (BMI) of 30.0 to 34.9 compared to men with a normal BMI (18.5 to 24.9). Obese women (BMI, 30.0 to 34.9) had a relative risk of 2.1 (95% CI, 1.6 to 2.9) compared to women with a normal BMI⁴⁶.

Diabetes mellitus⁴⁷, addiction to smoking and alcohol⁴⁸⁻⁴⁹ and dietary contaminants such as exposure to aflatoxins are other risk factors for GBC⁵⁰.

3.3 PREVENTIVE MEASURES

Cholecystectomy as a preventive measure may be indicated in the following situations:²⁵

1. Symptomatic cholelithiasis
2. Gallbladder polyp > 1cm, sessile, and showing increase in the size especially with thick walled gallbladder⁵¹.
3. APBDJ - with CBD dilatation: cholecystectomy + CBD resection may be considered
without CBD dilatation: cholecystectomy is recommended) ± CBD Resection
4. Porcelain GB (insufficient data to support routine cholecystectomy)
5. Selected cases with asymptomatic gallstones:

- A low rate of cancer development in asymptomatic patients with gallstones has been observed (0.01%/year-0.02%/year). Consensus does not favor cholecystectomy for asymptomatic stones^{23,52-55}.
- No Indian evidence is available about natural history of asymptomatic cholelithiasis. Options are nothing, surveillance or cholecystectomy in select cases such as in young patients with asymptomatic large stones (>3cm) or a gallbladder packed with stones in “high incidence zones” though direct evidence to support this is not currently available⁵²⁻⁵³.

Other preventive measures include

Control of obesity and diabetes, a healthy diet – rich in vegetables and fruits and regular exercise⁵⁶⁻⁵⁸.

3.4 DIAGNOSIS, CRITERIA AND INITIAL WORK UP

GBC continues to have sinister reputation since its description by De-stall in 1778 due to poor outcome of treatment⁵⁹. The poor prognosis largely depends on its late diagnosis due to nonspecific nature of the symptoms and signs, that often present only in advanced disease and are akin to other diseases such as cholelithiasis and cholecystitis⁶⁰⁻⁶¹ its ability for invasion of liver and lymph nodes and its propensity to implant peritoneal surface, biopsy trajectories and laparotomy/laparoscopy wounds⁵⁹⁻⁶¹.

However, now due to better diagnosis and surgery⁶¹, the survival has improved⁶²⁻⁶⁶.

3.4.1 History and Examination

The presentation of GBC has three situations*:

1. in advanced, inoperable form⁵⁹⁻⁶⁰ (most common presentation)
2. as a mass lesion in the gallbladder⁶⁴
3. incidental, upon histopathological examination of resected gallbladder⁵⁹⁻⁶⁶.

**Various nomenclature exist for different presentations of GBC-*

Obvious (when diagnosis looks apparent on clinical examination and imaging)

Suspicious (e.g. when focal/diffuse wall thickening/small polypoidal lesions are detected in the gallbladder upon imaging)

Incidental (GBC comes as a surprise finding upon Histopathological Examination (HPE) of the cholecystectomy specimen, the same was unsuspected during preoperative imaging)

Symptoms of GBC are quite similar to GSD and hence an early clinical diagnosis is enigmatic. These patients often present after cholecystectomy with GBC diagnosed upon histopathology. A detailed history of the prior operative intervention and histopathological review at the specialist institution is necessary.

GBC should be suspected in patients after 60 years age with constant pain in right hypochondrium and history of recent weight loss. Patients with advanced GBC may present with anorexia, cachexia, deep icterus, a palpable hard lump in the right hypochondrium, ascites and left supraclavicular lymphadenopathy with poor performance status. Hawkins et al reported that of 34% patients who present with jaundice, only 7% can have curative surgery with 0% 2 year survival⁶⁷. Another study that examined GBC patients with biliary obstruction revealed a resectability rate of 45% with 1- and 3- year survival of 48% and 19% respectively. Interestingly, an R0 resection improved median survival only in the subgroup of N0 patients⁶⁸. Presence of jaundice though does not rule out resectability, often warrants major hepatic resection and confers a poor prognosis; hence referral to experienced centers is mandatory.

3.4.2 Blood investigations

There are no biochemical tests of importance for early diagnosis. Liver function tests revealing raised bilirubin is a sign of advanced disease. Full blood count and renal function tests are indicated. Jaundiced patients may have deranged liver function tests.

Role of tumor markers – CEA and CA 19-9 in diagnosis is uncertain as these markers are not specific for GBC. A CEA >4 mg/ml has sensitivity of 50% and specificity of 93%⁵⁹. CA 19-9 with a cut-off value of >20 IU/ml has sensitivity and specificity of 79%⁵⁹. Its value is further compromised in presence of raised bilirubin. The available data is insufficient to recommend the routine use of the tumor markers in the diagnosis or follow up of patients with GBC.

3.4.3 Imaging

Structural changes in the gallbladder induced by GBC include replacement of gallbladder lumen by mass (40-65%), focal or diffuse parietal thickening (20-30%) and intraluminal polyp (15-25%)²². USG, Computed Tomographic (CT) scan, and Magnetic Resonance Imaging (MRI) with Magnetic Resonance Cholangiopancreatography (MRCP) and Magnetic Resonance Angiography (MRA) are used to detect these structural changes and stage GBC and also help in assessment of the hepatic reserve. In addition, chest imaging should also be performed.

3.4.4 Ultrasound (USG)

Transabdominal USG is often the first investigation ordered in patients presenting with pain in the right hypochondrium⁶⁹. USG is user dependent and hence subtle changes in early GBC are often missed. The best resolution can be obtained at a range of 7.5–10 MHz in a slim patient and of 2.5–5 MHz for an overweight patient.

USG may show a hypo or iso-echogenic mass replacing the gallbladder⁷⁰⁻⁷¹. Gallstones within the gallbladder mass is a useful sign of GBC although it is a known fact that GBC can be present even without gallstones. Thickness of normal gallbladder mucosa is usually less than 3mm. In presence of cancer its thickness increases to more than 1cm and in an irregular/asymmetric way⁷²⁻⁷³. This type of presentation is however mimicked by chronic/acute cholecystitis and hyperplastic cholecystoses. Increased echogenicity (due to fibrosis) and parietal thickness of more than 1 cm is quite confirmatory of GBC⁷². Another less common finding may be an intraluminal mass, at least >10 mm, not displaced by movements, nodular or smooth shape and casting no posterior acoustic shadow⁷⁴ and showing rapid growth⁷⁵. Cholesterol polyp or adenomyomatosis also gives similar USG look⁷⁴⁻⁷⁵ and hence often difficult to differentiate with confidence.

Other useful USG findings are lithiasis in 70-75%, porcelain gallbladder, infiltration of neighboring structures, hepatic metastasis, vascular invasion, biliary dilatation, lymph nodes and ascites⁷¹⁻⁷⁵. In advanced stage, USG sensitivity is 84.6% and global accuracy 90.5%⁷⁵. But the USG detection of early lesion is not as accurate^{69,75-80}.

An early GBC is confined to mucosal layer and up to muscularis propria. Tsuchiya⁸⁰ proposed a microscopic classification for early GBC as a pedunculated polyp, sessile polyp with wide or thin base, thickening of surface elevation of 1.5-3mm and flat lesion at mucosal level. In 71 patients of early GBC, 57% were flat type and others pedunculated or sessile forms. Only 20 were diagnosed preoperatively but none of flat lesions. US showed 75% sensitivity for pedunculated and 53% for sessile forms⁸⁰. Others⁷⁷ have reported accuracy of only 34%. Associated gallstones and flat lesions cause inaccuracy of diagnosis.

3.4.5 Endoscopic ultrasonography (EUS)

Gallbladder wall anomalies can be better visualized with endoscopic ultrasonography (EUS) with accuracy of 80% (using 5-12 MHz, 3600 radial probes)⁸¹. The added advantage of EUS is the possibility of EUS guided FNAC from suspicious areas/lymph nodes. This technique is highly operator dependant and not widely available. On EUS, finding small internal echogenic spots is characteristic of cholesterol polyps, multiple microcysts and posterior comet tail artifact is pathognomonic of adenomyomatosis and absence of these characters indicates a possibility of GBC⁷⁵. The contour of the lesion is granular in benign but smooth or nodular in GBC polyps⁷⁴.

There are four patterns of GBC on EUS⁸¹

Type A – Polypoid with nodular surface but no alteration of wall architecture

Type B – Wide base, parietal irregularities and no change in gallbladder serosa.

Type C and D – Irregularities or rupture respectively of serosa

3.4.6 Color Doppler

Addition of transabdominal Color Doppler differentiates solid lesion from biliary sludge⁸²⁻⁸⁴. Blood flow within the lesion suggests GBC⁸². Benign lesions have low detectable blood flow⁸².

In doubtful cases on Color Doppler, **Ultrasound with contrast** improves diagnosis of T1b lesions but not of those with only mucosal involvement⁸⁵⁻⁸⁶.

USG is a useful first imaging method, wherein it gives preliminary information. If advanced/inoperable GBC is detected on USG further imaging is usually not required. But in resectable patients other imaging techniques are required.

3.4.7 Computed Tomography (CT) Scan

A CT scan is used for assessing gallbladder mass, wall thickening, polyp and staging^{71,87}. Presence of GBC is suggested by hypercaptation of a thick inner layer during both arterial and portal phases with isoattenuation or hyperattenuation in relation to hepatic parenchyma during portal phase³¹. This is in contrast to the finding in chronic cholecystitis wherein the inner layer of gallbladder shows isoattenuation in both phases.

CT reveals depth of infiltration into the liver, bile duct, other adjacent organs, hepatic and peritoneal metastasis and lymphatic dissemination^{22,88} thereby helping in staging the disease more accurately⁸⁹. Infiltrated lymph nodes are > 1cm, ring shaped with heterogeneous uptake after contrast administration⁹⁰⁻⁹¹. Pericholedocal nodes are most frequently involved followed by cystic nodes⁹². The sensitivity of CT is 0.36 to 0.47 for N-staging (PPV: 0.94; NPV: 0.92); 0.65 for hepatic infiltration of <2 cm (PPV: 0.77) and 1.0 for >2 cm (PPV: 1.0); 0.50 for spread to extrahepatic bile duct (PPV: 0.90), 0.57 for digestive tube or pancreas (PPV: 0); 0.71 for detection of hepatic metastases (PPV: 1.0) and 0.21 for interaortic lymph node involvement (PPV: 0.86)⁸⁹.

Spiral CT gives improved information regarding local spread, depth of invasion and resectability⁹³⁻⁹⁵. The diagnostic accuracy of T staging for GBC is 0.83 – 0.86 and is superior to conventional CT⁹⁴. Multidetector CT, a further refined tool, allows a faster examination with lower collimation thickness, reliable volumetric reconstructions and helps in detection of small perivesicular tumor infiltration while minimizing errors⁹⁴⁻⁹⁵.

3.4.8 Magnetic Resonance Imaging (MRI)

It is of particular value in assessing complete penetration of serosa or penetration of liver⁹⁶. GBC appears on MRI as a hypo- or isointense mass or wall thickening in T1 in relation to the liver and is usually hyperintense and poorly defined in T2 sequences⁹⁷. Enhanced sequences in T2 with fat suppression, dynamic postgadolinium T1-weighted images in arterial phase and T1 with fat suppression in equilibrium phase, 2 min after contrast administration helps in the assessment of adjacent structures and lymph nodes⁹⁸. Detection of metastasis is based on size > 1 cm, ring shape or heterogeneous uptake of involved lymph nodes⁹⁷. Sensitivity to demonstrate biliary invasion is low⁹⁹. MRI is poor in detecting peritoneal deposits. MRCP and MRA are of superior diagnostic validity in detection of biliary invasion, vascular invasion, hepatic invasion and lymph node involvement¹⁰⁰. MRCP is especially indicated in patients with jaundice.

3.4.9 Functional Imaging

USG, CT and MRI base their capacity to diagnose GBC on structural alterations produced by GBC. These changes are nonspecific. From this base biochemical method binding widely bioavailable metabolic substrates to positron emitting radionuclides like fluor-18 bound to [18F]-2-deoxy-D-glucose (FDG) has evolved¹⁰¹. There are chances of false negative report in presence of tumors with low metabolic rate and false positive in tubercular granuloma and polyp with adenomyomatosis¹⁰². In GBC the sensitivity is 0.80 and specificity 0.82. There is not enough information on diagnostic validity of FDG-PET in the lymph node staging of GBC.

FDG-PET combined with CT (PET-CT) helps in simultaneous acquisition of structural and functional data of the extent of tumor and facilitates correct T, N and M staging.

This tool may be used in special circumstances such as before re-exploration in incidental GBC or in advanced resectable GBC to screen for an otherwise occult distant metastasis¹⁰³⁻¹⁰⁴. It may also be helpful in differentiating malignant from a benign gallbladder polyp. However, data to support its use in GBC is still lacking.

Differential Diagnosis of GBC on imaging

When gallbladder is replaced by a mass – hepatocarcinoma, cholangiocarcinoma or metastasis makes differential diagnosis. Intra luminal polyps may be adenomatous, hyperplastic and cholesterol polyps, carcinoid or melanoma metastasis. FDG will differentiate between benign and malignant polyps. Parietal thickening of gallbladder wall has many inflammatory and non-inflammatory causes including heart and kidney failure, hepatitis, cholecystitis. Acute cholecystitis with parietal necrosis/abscess or intestinal fistula formation may mimic aggressive GBC²². Xanthogranulomatous cholecystitis is chronic cholecystitis that presents as diffuse thickening of gallbladder wall. There are nodules or bands on gallbladder wall that are hypo-echogenic on USG or hypo-dense on CT¹⁰⁵⁻¹⁰⁷. This can give a false positive result on FGD-PET scan¹⁰⁸. Adenomyomatosis, a non-cancerous lesion, produces focal, segmental or diffuse thickening of gallbladder wall and is often confused with GBC. The presence of Rokitansky-Aschoff sinuses, small outpouchings of mucosa within the thickened muscularis layer as seen on MRCP helps in the diagnosis¹⁰⁹⁻¹¹⁰. On USG, presence of wall thickening with intramural diverticles with or without posterior comet-tail artifact is characteristic of adenomyomatosis. FDG –PET may be false negative and false positive for this condition^{108,111}.

P.S Imaging reporting template: Appendix (i)

Pathology reporting template: Appendix (ii)

Endoscopic Retrograde Cholangio Pancreaticography (ERCP) and Percutaneous Transhepatic Cholangiography (PTC)

MRCP is the investigation that is preferred over ERCP/PTC in GBC patients presenting with jaundice unless a therapeutic intervention is planned. ERCP/PTC is usually attempted for stenting the bile duct in advanced and metastatic GBC for relief of jaundice and pruritus and also before planned major liver resection.

Fine Needle Aspiration Cytology (FNAC)

FNAC is not indicated in resectable GBC as the tumor has propensity for seeding the biopsy tracts. However, in presence of clinical evidence of distant metastatic disease (e.g. left supraclavicular lymph node, umbilical nodule, liver nodule, pelvic deposits or ascites) a tissue diagnosis should be obtained (FNAC, fluid cytology) from metastasis. A few centers use EUS-guided FNAC in suspicious gallbladder lesions and has been reported to have sensitivity rate of 80% and specificity of up to 100%¹¹².

Staging Laparoscopy

Staging laparoscopy and biopsy of any metastatic deposits may be indicated in patients with resectable advanced GBC or incidental GBC before re-exploration to rule out distant metastases since chances of peritoneal dissemination are high in this cancer¹¹³. A study from India revealed that staging laparoscopy avoided an unnecessary laparotomy in 22.3% of GBC patients in their series^{113a}. Higher yield is likely in patients with T3 and above GBC, poorly differentiated tumors and those with margin positive cholecystectomy. It may also be indicated in patients with suspicious metastasis that cannot be biopsied percutaneously^{113b}.

Staging

AJCC TNM staging (7th Edition) is the current staging system (Appendix – iii)¹¹⁴

Validation of stage grouping is based on multivariate analysis of outcome and survival data of the National Cancer Database including 10,705 patients nationwide¹¹⁵. Nevins' classification is now obsolete.

Prognostic Criteria:^{22,116-117}

Increasing T-stage, N-stage, liver invasion, lymphovascular invasion, perineural invasion and higher grade are associated with poor outcome. Papillary carcinomas have the most favorable prognosis compared to small cell and undifferentiated GBC. R0 resection has the best prognosis. In addition, a study reported serum level of CA 19-9 >40ng/ml and gallbladder perforation too as prognostic factors.

3.5 SURGICAL MANAGEMENT OF GBC

Amidst very poor prognosis i.e. 5% 5-year survival in GBC¹¹⁸⁻¹¹⁹, complete surgical resection (R0) is the only hope for long term survival¹²⁰.

The approach to surgical management of GBC is influenced by mode of spread of GBC to liver, lymphatic and vascular invasion; direct spread to contiguous organs and intraperitoneal seeding and luminal through the cystic duct (intraductal).

Lymphatic spread – there are 3 lymph node stations involved in order of frequency¹²¹

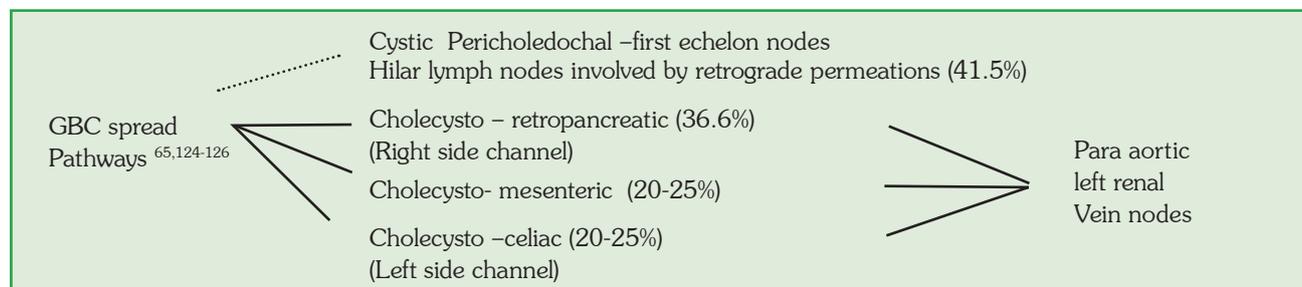
Level I – cystic and peridochal lymph nodes

Level II- pancreaticoduodenal (superior and posterior group) and hepatic artery lymph nodes

Level III - superior mesenteric and celiac axis lymph nodes¹²²⁻¹²³.

These lymph node stations dictate the extent of lymphadenectomy with curative intent.

The Japanese¹²⁴ named these as 3 different pathways namely, cholecysto-retropancreatic pathway, cholecysto- celiac pathway and cholecysto-mesenteric pathway.



It has been shown that lymphatic spread occurs early, before liver involvement and that nodal involvement is a poor prognostic factor^{92,127-130}.

Venous spread

There are 2-20 cholecystic veins that drain directly in the middle hepatic vein radicals¹³¹⁻¹³² forming the basis of enbloc hepatic resection in T1b and above GBC. There is rarely a venous communication to portal vein¹³³. In early mucosal lesion (T1a) venous invasion is very rare.

Intraperitoneal spread

Adjacent organs are affected first and manifests as peritoneal carcinomatosis in advanced cases¹²².

Neural spread occurs in 25-35%^{122,134} and suggests high grade malignancy. Intraductal spread takes place in papillary type of GBC.

With this background, the management of early GBC is discussed below:

There is no clear cut definition of Early and Advanced GBC. For the purpose of this document we have categorized Early GBC as tumors limited to mucosa (pT_{1a}), muscularis (pT_{1b}), perimuscular connective tissue (pT₂), and Advanced GBC when tumor perforates serosa with or without invasion of adjacent viscera/vascular invasion (pT_{3,4}), and Metastatic GBC as those with TNM stage IVB.

Early GBC

1. May be discovered as a surprise finding on cholecystectomy specimen after histopathological examination (Incidental GBC)
2. May be suspected preoperatively on imaging – wall thickening, polypoidal lesion, porcelain gallbladder^{65,127,128, 135-137} or per-operatively.

Incidental GBC

The incidence of incidental GBC is 0.35% - 2%¹³⁶⁻¹⁴⁰. The management of incidental GBC is influenced by TNM stage of GBC. Re-resection is advised in patients with pT1b and above GBC with the aim to resect all possible residual disease.

Pawlik et al reviewed data of 115 patients who underwent re-resection for incidental GBC at 6 major hepatobiliary centers in the USA between 1984 and 2006. 46.4% had evidence of residual cancer. Residual liver disease (p=0.01) was present in 0%, 10.4%, 36.4% and regional lymph nodes (p=0.04)

in 12.5%, 31.3%, 45.5% of patients with pT1, pT2 and pT3 GBC respectively. Further, a cystic duct margin status predicted residual disease in the common bile duct (negative 4.3% versus positive 41.2%; $p=0.01$)¹²⁰.

Further, early GBC found on gallbladder specimen requires further treatment influenced by type of cholecystectomy. Since Laparoscopic Cholecystectomy (LC) is the standard procedure for symptomatic cholelithiasis, an incidental GBC has a special problem of port site recurrence due to tumor cells carried to port site by instruments or chimney effect¹⁴¹⁻¹⁴³. The incidence of port site recurrence after LC is 10-29%¹⁴⁴⁻¹⁴⁶ appearing anytime postoperatively ranging from 2 weeks to 2.5 years (mean 6 months) and any port may be involved¹⁴⁷. Bile spill during LC for unsuspected GBC has been associated with a poor outcome and increased port site recurrence^{137,148-151}. Overall, LC does not seem to adversely impact patients' outcome in unsuspected GBC¹⁵²⁻¹⁵⁴.

Further surgery following detection of incidental GBC should be undertaken as soon as possible. The interval between cholecystectomy and subsequent radical resection are not significant factors influencing survival although it is difficult to interpret due to selection bias^{66,127,155}.

3.5.1 pTis and pT1a GBC

The optimum treatment for pTis and pT1a GBC is simple cholecystectomy with 5-year survival in 100% in most studies. These lesions are almost always diagnosed upon histopathology of the cholecystectomy specimen. But presence of perineural or vascular invasion detected on histopathology or bile spill during cholecystectomy may adversely affect long term survival^{66,150,151,156-162}. What to do in such situations is still unclear and should be a subject of clinical trial.

3.5.2 pT1b GBC

Management of pT1b disease varies from simple cholecystectomy⁴⁴ to extended cholecystectomy (EC).

EC includes cholecystectomy with enbloc limited hepatic resection (2-3cm wedge resection or segment IVb+V) and lymphadenectomy with or without bile duct excision¹⁶³⁻¹⁶⁴. Lymph node dissection should include portal, gastrohepatic and retroduodenal regions. A minimum lymph node count of 6 or more is considered optimum¹⁶⁵. Lymph node ratio (LNR) has also been suggested by some to be a strong predictor of outcome after curative resection of GBC (median DFS 0 <LNR \leq 0.5 vs. LNR > 0.5: 14.00 \pm 2.46 vs. 9.00 \pm 1.55 months; $p<0.001$)¹⁶⁶.

A study reported the outcome of 12 patients after simple cholecystectomy for incidental pT1b GBC. Survival was 71.5 \pm 12.2 months and median survival was 42 months. Five loco-regional failures occurred and all patients treated with simple cholecystectomy died¹⁶⁷. However, Wakai et al¹⁶⁸ found no difference in survival of pT1b patients undergoing simple (13 of 25) versus EC (12 of 25) in a retrospective analysis – the overall 10-year survival was 87%. There is a higher incidence of nodal metastasis (3.8%-25%) in pT1b hence others recommend EC in pT1b disease^{7,169-170b}. There is an observation of recurrence in 60% pT1b patients treated by simple cholecystectomy¹⁶⁹. Thus, pT1b is a locally aggressive disease and EC is treatment of choice¹⁶⁷.

3.5.3 pT2 GBC

pT2 GBC has lymph node metastasis in 20–62%^{66,150,157-161,171,172} mainly to hepatoduodenal ligament. In these patients EC is the treatment of choice, whether done as a re-operation or primary procedure. 5-year survival is 77%. Most published reports^{150,160,172,173} except one⁶⁶ has demonstrated advantage of long survival 61- 100 % in EC as compared to only 17-50% with simple cholecystectomy. SEER database

of early GBC has also shown a survival benefit with extended surgical resection and lymph node dissection in pT2 GBC¹⁷³ that is now considered a standard.

The pT stage of Incidental GBC is important from further surgical point of view:

| pT-Stage | Primary Treatment | Further surgery – Extended Cholecystectomy (EC) |
|----------|--|---|
| T1a | Simple cholecystectomy Cystic duct margin negative: R0 resection | No further Surgery ^{113,151} |
| T1b | Simple cholecystectomy Chances of residual disease in lymph nodes 3.8- 25% ^{170a, b} Possibility of recurrence 60% ¹⁶⁹ | EC is advised ^{151, 166,168-170} |
| T2 | Simple cholecystectomy Chances of residual disease in lymph nodes 20-62% ^{66,150, 157-161,171,172} liver 10.4% ¹²⁰ | EC is advised ¹⁶⁰ |

Laparoscopic Port-Site Excision

Evidence in support of routine excision of all port-sites during re-resection for incidental GBC is lacking¹⁷⁴. Some advise excision of the extraction port¹⁷⁵. The current understanding of the biological behavior of the disease does not support this. In fact it has been shown to increase the chances of wound metastases in an experimental model¹⁷⁶⁻¹⁷⁷. A few studies though advocate routine prophylactic excision of port-sites at re-exploration¹⁷⁸⁻¹⁸¹. Routine port site resection has not been shown to improve outcome^{181a}.

Radical radiotherapy to gallbladder bed and lymphatic drainage area as an alternative to EC in incidental GBC

Only one study by Mondragon-Sanchez et al has been reported¹⁸². However, radical surgery is superior.

| EC 20 patients | | Simple Cholecystectomy + External radiotherapy 25 patients | |
|---------------------------------|---------|---|---------|
| Morbidity | 25% | Mortality | 16% |
| Mortality | 10% | | |
| Nevin stage vs.5-years Survival | | | |
| Stage I | 100% | | 62% |
| Stage II & III | 100% | | 39% |
| Stage IV & V | Similar | | Similar |

Suspected GBC

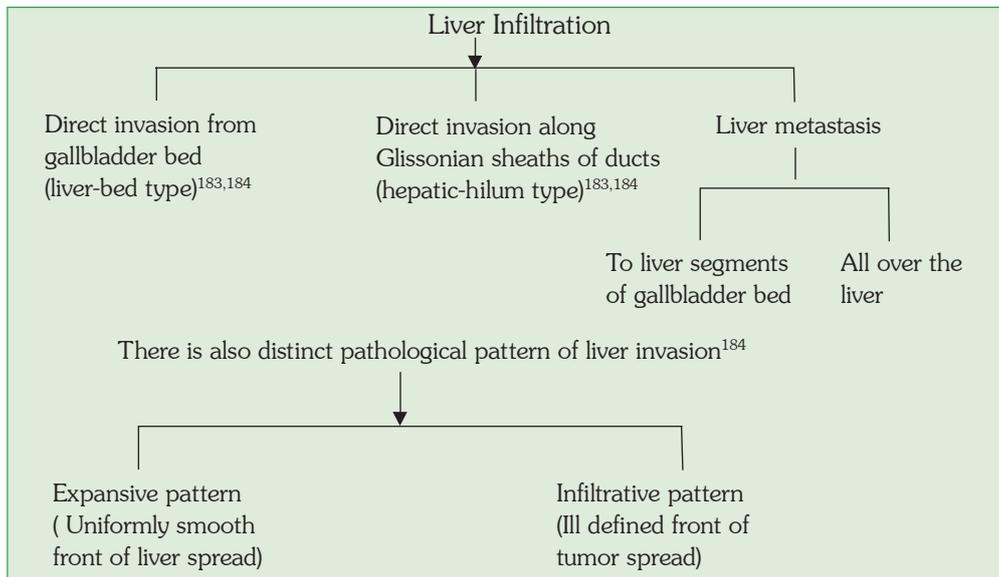
The basic principles of surgical resection remain the same as discussed in the previous section.

A prior informed consent for EC should be taken from the patient with suspected GBC. The task force members strongly recommend surgery for GBC to be undertaken by a surgeon experienced in the procedure. In the event resectable GBC is detected on-table and expertise for EC is not available, no attempt should be made to take an open biopsy from the gallbladder. An omental/lymph node biopsy may however be taken and the patient should be referred to a specialist with a preoperative findings note.

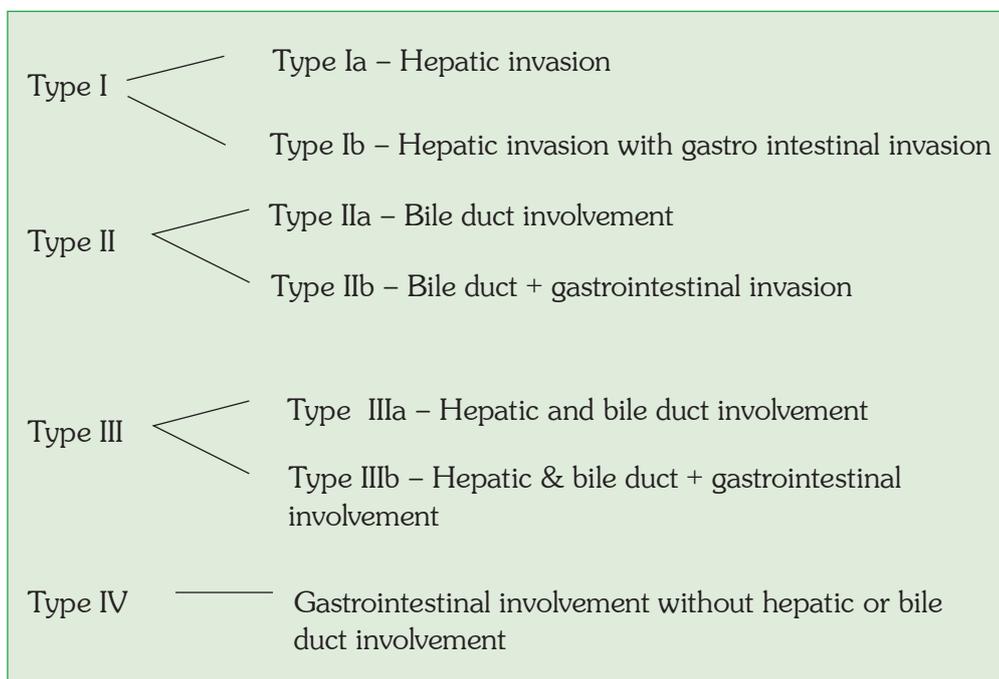
Advanced GBC

The anatomical relationship of gallbladder to surrounding structures weighs heavily in favor of early spread to these structures, on the background of innate aggressiveness of the GBC and pattern of spread.

Liver invasion takes several shapes depending on site of tumor in the gallbladder



There is further classification of local spread of GBC in 4 types¹⁸⁵



Tumors in neck spread early to hepatic hilum¹⁸⁶ as distance from neck to right hepatic duct is only 2 mm and to the bifurcation of the right anterior and posterior duct is only 6 mm. This implies that clean resection margins in tumors localized to neck of the gallbladder may not be achieved by wedge resection of liver.

What should be the extent of liver resection?

Factors influencing extent of liver resection are (1) location of tumor in gallbladder (2) morphological pattern of liver involvement, (3) achievement of R0 resection.

The extent of liver resection varies ranged from non-anatomical wedge resection, to anatomical parenchyma sparing segment IVb/V resection up to extended right hepatectomy. No randomized trials exist on the subject stating a superiority of one over the other and most follow center specific practice.

Ogura et al¹⁸³. measured the distance between the front of the carcinoma invasion and the resection plane in the hepatic parenchyma. The distance ranged between 12–20 mm after wedge resection, 16–35 mm after resections of segments IV+V and 28–58 mm after extended hepatic resections. They mandated a 20mm margin from the tumor front for best outcome.

Examination of 201 patients with GBC invading the subserosa or deeper revealed that resection of segment IVb and segment V of the liver may be beneficial in patients with liver bed type invasion less than 20 mm in depth¹⁸⁷.

Another study¹⁸⁸ analyzed the pathological reports of their liver resection specimen and found that a 3cm distance can also be achieved by 77% of segment IVb/V resections and without the need for blood transfusions.

In a recent retrospective study, a nationwide questionnaire survey from the Japanese Biliary Tract Cancer Registry on 85 patients with pT2, pN0 gallbladder cancer revealed that the 5-year survival rate did not differ significantly between those treated with gallbladder bed resection and with segment 4+5 hepatectomy resection. Recurrence occurred most frequently in both lobes than in segments 4 or 5 of the liver following gallbladder bed resection^{188a}.

The extent of Liver resection may range from:

Wedge resection

Segment IVb/V^{183,187,188a}

Extended right hepatectomy or
central bisegmentectomy
(Couinaud's segments IV,V,VIII)

with caudate lobectomy^{170,184,189,190}

→

with extensive liver invasion (especially hilar type)
± involvement of extrahepatic bile/hepatic duct ±
vascular invasion

Re operative surgery also needs extended hepatic resection at times^{127,173}.

Extensive liver resections improve results of advanced GBC¹⁹¹⁻¹⁹³ at a cost of high morbidity (50%) and mortality (18%)¹⁹¹. Some patients are alive at 5 years in this group. The factors which predict high mortality are male sex, extended right hepatectomy, cholestatic liver and portal vein resection¹²⁵. Preoperative portal vein embolization has been suggested to increase the size of the remnant liver before extended hepatic resections¹⁹⁴.

Lymph node spread

This is the most important prognostic factor. The frequency of lymph node involvement^{66,125,127,154,159,160,170b,191-195} increases with increasing T-stage.

pT₁ = 0-4% (pT_{1a} = 0%; pT_{1b} = 3.8%)

pT₂ = 20-62%

pT₃/T₄ = 60-81%

Lymphadenectomy is an integral component of the radical surgery for GBC. Algorithm for the extent of local resection and lymph node dissection is based on T stage and evaluation of important nodes by frozen section. A positive interaortocaval node upon frozen section at laparotomy indicates metastatic and incurable GBC.

Extent of lymphadenectomy includes

Hepatoduodenal ligament by skeletanization of vessels (hepatic artery and portal vein) and bile duct

Anterior and Posterior to the head pancreas

Hepatic artery is cleared up to its origin from celiac axis

Some units also dissect celiac, superior mesenteric and para aortic¹⁹¹ lymph nodes; involement of which have a very poor prognostic import¹⁹⁶ and is not indicated.

Bile duct involvement

Extra hepatic bile duct may be involved by direct infiltration by GBC or by permeation from lymph nodes of the hepatoduodenal ligament and was reported as 54.2%, 67.7% respectively in one study with only 15% free of invasion in advanced GBC¹⁹⁷.

A classification of hepatoduodenal involvement¹⁹⁸ includes

Type I - direct spread

Type II - continuous intra mural spread

Type III - Non-continuous metastatic spread separate from primary

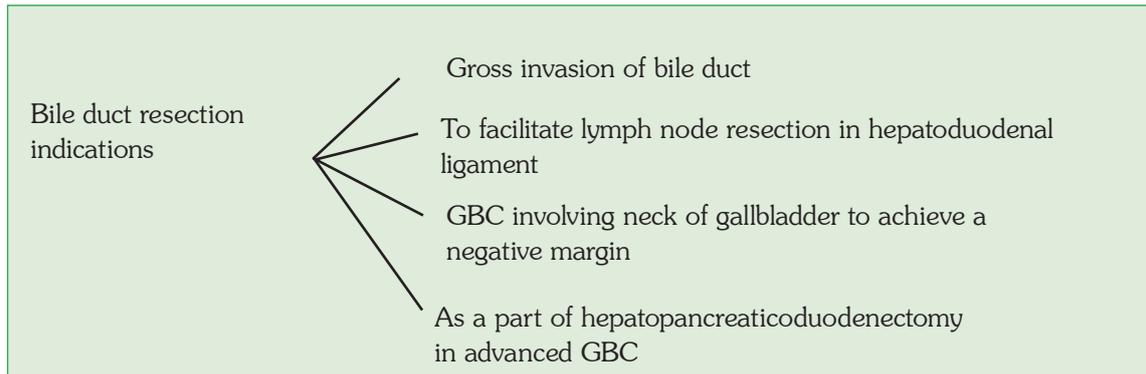
Type IV - Permeation from metastatic lymph node in hepatoduodenal ligament.

Bile duct involvement also indicates incurability. Only 5% jaundiced patients may have a curative R0 resection as compared to 39% non jaundiced patients⁶⁸. Further, the authors found that jaundiced patients did not survive long term but 21% non jaundice patients survived for 2 years. Curative resection is possible in 75% patients without bile duct infiltration but in only <30% with bile duct infiltration¹⁹⁸. Perineural invasion around hepatoduodenal ligament often results in non curative resection. Over all 3 year survival with bile duct involvement was 6 % as compared to non involvement in 64%¹⁹⁸.

An extrahepatic bile duct resection may be indicated in only those with direct infiltration of hepatoduodenal ligament or the cystic duct¹⁹⁹.

Another prospective study in 104 patients revealed significantly increased morbidity with major hepatectomy and CBD resection without having any independent effect on survival²⁰⁰.

Thus routine bile duct resection does not give much survival advantage⁶⁵.



Vascular involvement

Portal vein and hepatic artery and its branches are often involved in advanced GBC of the gallbladder neck. In most of these cases the disease is not resectable. However, a few surgeons have tried aggressive resections in selected patients and have reported a better survival than the patients with unresectable GBC^{93,201}.

Right vascular pedicle involvement may need an extended right hepatectomy. However, any involvement of the hepatic or left hepatic artery is a contraindication to surgery²⁰².

Portal vein involvement dealt with segmental or wedge resection and repair has been reported²⁰³. There is increased postoperative mortality¹²⁵. Portal vein excision/repair may only be used for R0 resection.

There is insufficient evidence in literature to suggest any significant survival benefit in GBC patients subjected to such aggressive resections.

Duodenal and pancreatic involvement

The pancreas may be involved by –

1. Direct invasion from gallbladder
2. Spread along the bile duct
3. Bulky peripancreatic lymph nodes

Procedures done include –

1. Hepato-pancreaticoduodenectomy (HPD)¹⁷⁰
2. Local (sleeve) excision of duodenum wall in localized involvement^{201,203a}
3. Pancreaticoduodenectomy for local and peri pancreatic lymph spread²⁰⁴⁻²⁰⁵

Involvement of other surrounding organs

Omentum

Hepatic flexure

Parietal abdominal wall

Antrum of stomach

HPD¹⁷⁰ in 150 patients produced a major complication rate in 54%. In another study, 7 patients

underwent HPD. Morbidity was in 100% and mortality 28.5% and only one patient was alive at 22 months. All others died of recurrence²⁰⁶. Other reports²⁰⁷ have shown morbidity of 91%, mortality of 12.5 % in 24 patients with a median survival of 12 months and 20% 2-year survival.

Again, the real benefit if at all after such resections is yet to be proved.

3.6 ADJUVANT TREATMENT FOR GBC

Definite recommendations for adjuvant treatment in GBC cannot be made because of lack of RCT. Similar to cholangiocarcinoma studies on adjuvant treatment in GBC are heterogeneous and retrospective and therefore are not comparable. External Beam Radiotherapy (EBRT), Intraoperative Radiotherapy (IORT) and brachytherapy in various combinations with or without chemotherapy has been used for adjuvant treatment of GBC²⁰⁸⁻²¹³. A recent meta analysis and systematic review reported that there is non significant improvement in the overall survival with any adjuvant therapy compared to surgery alone (OR=0.76, p=0.06)²¹⁴.

Adjuvant therapy is used in all patients with stage II to IVA GBC patients who have undergone extended cholecystectomy, even in the absence of robust evidences. Patients with stage IA who have tumor confined to lamina propria that is diagnosed incidentally on cholecystectomy specimens, do not need adjuvant treatment as their survival approaches 100% with simple cholecystectomy alone^{113, 215}.

3.6.1 Adjuvant Chemotherapy

Data on adjuvant therapy in GBC is very limited. Most of the recommendations represent extrapolation of studies on patients with advanced GBC and biliary tract cancer.

Two large retrospective studies have shown no benefit of adjuvant chemotherapy²¹⁶⁻²¹⁷. However, the number of patients who received adjuvant therapy in these studies was small and markedly heterogeneous clinical and treatment details precluding any definitive conclusions.

A phase III RCT from Japan by Takada et al²¹⁸ evaluated the role of adjuvant chemotherapy in pancreatobiliary cancers. In this study the number of patients with cholangiocarcinoma, GBC and ampullary cancer was 118, 112 and 48 respectively. The patients were randomized in to two groups, one group received adjuvant 5-FU and mitomycin-C (MF), and the other group was kept under observation after surgery. The 5-year OS rate in GBC patients was significantly better in the MF group (26.0%) compared with the control group (14.4%) (p = 0.0367). Similarly, the 5-year disease free survival (DFS) rate of patients with GBC was 20.3% in the MF group, which was significantly higher than the 11.6% DFS rate reported in the control group (p = 0.0210). However, statistically significant survival benefit was observed in patients who underwent non-curative resection (8.9% vs. 0%; p=0.0226) but not in patients with completely resected GBC.

3.6.2 Adjuvant Chemoradiotherapy (CRT)

In a retrospective study of 2325 patients by Mojica P, et al²¹⁹, adjuvant chemoradiation has shown a better median survival (14 months vs. 8 months; p<0.0001) in the chemoradiation group and this benefit was even more in node positive patients.

A multivariate Cox proportional hazards model on SEER database of 4180 patients also showed better survival in patients with node positive and pT2 or higher GBC²⁰⁸. Many other studies also support CRT as the adjuvant treatment option^{208a,b,c}.

A small study from Mayo clinic reported a higher 5-year survival (64%) in patients with completely resected (R0) GBC with postoperative chemoradiation with 5-FU compared to historical surgical controls (33%)²⁰⁹. In another study of 22 resected GBC patients, 18 received postoperative chemoradiotherapy

with 5 FU. The authors suggested the use of CRT in resectable and advanced GBC may improve survival²²⁰.

These findings suggest benefit with adjuvant chemoradiation in patients with resected pT2 and higher or node positive GBC.

In the absence of any robust data for adjuvant therapy (radiation or chemo-radiation) the practice at some tertiary care centers in India is to treat these patients with adjuvant chemo-radiation.

MANAGEMENT OF UNRESECTABLE/METASTATIC GBC

With various chemotherapeutic agents (with or without 5FU) response rates reported are 0-36% of cases²²¹⁻²²⁶. Median survival for patients presenting with unresectable disease is 2-4 months, with less than 5% patients surviving one year²²⁷.

The three main drawbacks of the published literature in this field are: small number of patients, inclusion of bile duct and ampulla of Vater cancers in the studies and lack of RCTs.

Several phase II trials have shown benefit with gemcitabine, cisplatin, oxaliplatin, capecitabine and 5-FU based chemotherapy in biliary tract cancer^{224-225,228-235}.

Pooled analysis of 104 trials involving 1368 patients revealed that gemcitabine combined with platinum based chemotherapy shows maximum benefit in advanced biliary tract cancer. Subgroup analysis showed higher response rate but poor overall survival in patients with GBC compared to cholangiocarcinoma patients²³⁶.

There were only 2 RCTs comparing Best Supportive Care (BSC) and chemotherapy in biliary tract cancer (not limited to GBC only) using 5FU based chemotherapy. In a study reported by Glimelius²³⁷ 37 patients were randomized to 5FU based chemotherapy or BSC. Median OS was 6.5 months in chemotherapy group and 2.5 months in BSC group ($p=0.1$). It was possible that because of small sample size statistical significance could not be achieved. In another study reported by Takada, et al²²⁶ chemotherapy was compared to BSC. Patients' population was heterogeneous including pancreatic, GBC, and biliary tract cancers. There was no improvement in survival.

Gemcitabine and Oxaliplatin as single agents or in combinations with other drugs have shown activity in adenocarcinoma of pancreas, gall bladder, and biliary tracts^{222-224,238-240}. Hence, it is natural that combinations of gemcitabine and platinum (oxaliplatin or cisplatin) is explored in this condition.

The two RCTs that tried to address the issue of chemotherapy in biliary tract malignancy/GBC were reported recently²⁴¹⁻²⁴².

Most important has been a phase III RCT ABC-02 which enrolled 410 patients with locally advanced or metastatic GBC, cholangiocarcinoma or ampullary carcinoma. There were 149 GBC patients. An improved overall survival (11.7 vs. 8.1 months; $p<0.001$) and median progression-free survival (8 vs. 5 months; $p<0.001$) was observed in combination chemotherapy with gemcitabine and cisplatin compared to gemcitabine alone²⁴¹. It is now considered the standard of care in this group of patients.

A B22 Japanese phase II trial involving 83 patients conducted with the use of the same treatment regimens as those used in the ABC-02 trial²⁴³. They showed a median overall survival of 11.2 months in the cisplatin-gemcitabine group and 7.7 months in the gemcitabine-only group.

Oxaliplatin is a third generation platinum compound with much less emetic and renal toxicity compared to high dose cisplatin. Combination of gemcitabine and oxaliplatin may be suitable alternative to gemcitabine and cisplatin and was compared with best supportive care and 5FU and Folinic acid

(FUFA) in a 3 arm randomized study. The dose and schedule of gemcitabine and oxaliplatin used in this study was different from that used by Andre et al²²⁵ and this new combination was labeled as modified GEMOX (mGEMOX)²⁴². This study also suggested that mGEMOX is superior not only to best supportive care but also with 5FU and FA combination. Median survival was 9.5 months in mGEMOX compared to 4.5 and 4.6 months in BSC and FUFA arms respectively (p=0.039).

Another chemotherapy protocol which was explored was that of using gemcitabine and capecitabine. Knox et al²³⁰ in a phase II study reported the median survival of 14 months and progression free survival of 7 months in advanced biliary tract cancer.

The French Biliary Cancers: EGFR Inhibitor, Gemcitabine and Oxaliplatin (BINGO) trial²³² (ClinicalTrials.gov number, NCT00552149) randomly assigned 101 patients to receive gemcitabine plus oxaliplatin with or without cetuximab. In the BINGO trial, investigators reported 4-month progression-free survival rates of 50% in the gemcitabine–oxaliplatin group and 61% in the gemcitabine–oxaliplatin plus cetuximab group. These findings compare with a 4-month progression-free survival rate of approximately 70% in the cisplatin–gemcitabine group in the ABC-02 trial.

Currently, there is no evidence of efficacy of targeted agents like cetuximab, bevacizumab, small TKIs, or multi kinase inhibitors in GBC.

Based on the available reports any of the protocols may be used for the treatment of unresectable GBC patients with adequate organ functions and ECOG performance status of up to 2:

mGEMOX

Inj Oxaliplatin 80 mg/m² 2 hours infusion in Dextrose 5% Day 1 and 8

Inj Gemcitabine 900 mg/m² IV 30 minutes infusion day1 and 8

Cycles to be repeated every 3 weeks for maximum of 6 cycles

GEMCIS

Inj Cisplatin 25 mg/m² PO Days 1 and 8

Inj Gemcitabine 1000 mg/m² IV 30 minutes infusion day1 and 8

Cycles to be repeated every 3 weeks for maximum of 8 cycles

GemCap

Inj Gemcitabine 1000 mg/m² IV 30 minutes infusion day1 and 8

Capecitabine 650mg/m² twice a day PO Days 1-14

Cycles to be repeated every 3 weeks.

Treatment should be continued until progression, unacceptable toxicity, or withdrawal of patient consent.

3.7 RADIATION THERAPY 243a,b

Palliative radiation therapy after biliary drainage may be beneficial, and it helps to relieve pain and other symptoms by shrinking tumors causing biliary obstruction or nerve/plexus compression. These patients may be candidates for inclusion in clinical trials.

3.8 NEOADJUVANT THERAPY

Preoperative chemoradiotherapy reduce implantability of exfoliated cells during surgery, non-responders may be spared surgery as such patients will not benefit by surgical procedures, and radiation

in pre-operative setting is more effective in well oxygenated cells. With this approach 9 apparently inoperable extrahepatic cholangiocarcinoma patients became operable as reported by one study²⁴⁴.

A recently published study on 3 locally advanced GBC with a PET-CT negative for any distant metastasis showed complete metabolic and radiological response in 2 and partial response in one patient with gemcitabine-based neoadjuvant CRT. Two underwent radical resection and one had pathological complete response. This study though reports on only 3 patients but the outcome is encouraging in this otherwise fatal disease²⁴⁵.

In a retrospective study involving 157 patients who underwent resection for primary GBC (n=63) and Cholangio Carcinoma (CC) (n=94), 17.8% received neoadjuvant chemotherapy, 48.7% received adjuvant chemotherapy, while 15.8% received adjuvant chemoradiotherapy. The authors found that neoadjuvant therapy delayed surgical resection on average for 6.8 months ($p < 0.0001$) and immediate resection increased median survival from 42.3 to 53.5 months ($p = 0.01$). They came to the conclusion that early surgical resection of biliary tract malignancies with 1 cm tumor-free margins provides the best probability for long-term survival and the currently available neoadjuvant or adjuvant therapy does not improve survival^{245a}.

One report on hepatic artery infusion (HAI) with cisplatin and 5-FU exists with 5 patients showing a partial response²⁴⁶.

In summary, the role of adjuvant chemotherapy, radiotherapy, and chemoradiotherapy in biliary tract cancers is not well defined. Adjuvant therapy should be considered for patients who have good performance status. Combined radiotherapy techniques may provide better survival and chemo-radiotherapy may be better than radiotherapy alone. There is an urgent need to start RCT to address the issue of adjuvant therapy in biliary cancers by active collaboration of various Indian and international centers.

3.9 PALLIATIVE CARE

In GBC patients, the symptoms may be caused by primary malignancy, as well as by treatment (surgery, radiotherapy or chemotherapy), debility conditions (anemia, COPD etc) and concurrent second disorders. A patient with advanced cancer may suffer from a plethora of symptoms involving multiple function systems.

3.9.1 Jaundice

Biliary obstruction leading to jaundice and pruritus should be relieved by non-operative interventions such as biliary stenting (plastic or metallic) as far as possible^{246a}. Stents may get blocked or displaced needing replacements every few months. Stents are placed by percutaneous or endoscopic routes. In only very select cases a segment III biliary bypass should be undertaken.

3.9.2 Duodenal/Intestinal Obstruction

A number of patients with advanced GBC may experience gastric outlet obstruction due to direct tumor infiltration or compression from surrounding lymph nodes. This may need a gastrojejunostomy if the patient can withstand surgery.

3.9.3 Pain

Patients with advanced disease often experience severe upper abdominal pain. This is treated in a step wise manner (as detailed below) with escalating dose of non-opioid and opioid drugs and celiac

plexus block under imaging in unrelenting cases.

3.9.4 Ascites

Ascites in a cancer patient is very distressing. Pathogenesis of ascites includes peritoneal metastasis, subphrenic lymphatic obstruction due to tumor infiltration, or electrolyte imbalance. Treatment options include systemic and intraperitoneal chemotherapy, diuretics like spironolactone and frusemide, paracentesis and peritoneovenous shunt. Permanent percutaneous drains may prevent the need for repeated paracentesis, although there is potential for infection.

Besides the ones listed above, the other most prevalent symptoms are easy fatigue, weakness, anorexia, lack of energy, dry mouth, constipation, early satiety, dyspnea, and greater than 10% weight loss²⁴⁷.

(A) General Symptoms

1) Pain

The sources of pain in terminal cancer patients may be classified as

- (i) Directly related to tumor: bony metastases, soft-tissue infiltration, nerve infiltration
- (ii) Indirectly related to malignancy: infection, intestinal obstruction, massive edema, ascites, nerve-compression
- (iii) Due to therapeutic interventions: post-surgical pain, radiotherapy-induced, painful peripheral neuropathy due to chemotherapy (e.g. vinca alkaloids), peptic ulceration, opiate induced constipation. The patient may suffer from acute or chronic pain; which may be mild, moderate or severe. The prevalence of chronic pain is about 30-50% among patients with cancer who are undergoing active treatment and 70-90% among those with advanced disease²⁴⁸. The pain may be somatic, visceral or neuropathic in origin. In the cancer population, neuropathic pain is often related to compression, direct neoplastic invasion of the peripheral nerves or spinal cord, or to a neuropathy caused by chemotherapy. Various assessment tools to evaluate the severity of cancer pain include a 10-point visual analogue scale (VAS), Brief Pain Inventory (BPI), the satisfaction questionnaire and visual analogue scale quality of life (VASQOL)²⁴⁹.

WHO provides a treatment algorithm using a step-ladder approach: Non-opioids like NSAIDs, paracetamol etc in the first step; weak opioids like codeine, dextropropoxyphene in the second step; and strong opioids like morphine, methadone, levorphanol, buprenorphine etc in the third step. Each step in the ladder may be associated with adjuvant treatment with antiemetics, antidepressants and anticonvulsants as needed.

2) Hiccup

The causes of hiccup in a cancer patient are gastric distension, diaphragmatic irritation, phrenic nerve irritation, brain tumor, infection and rarely iatrogenic ie chemotherapy-induced. The treatment includes reducing gastric distension by antifatulents, metoclopramide, domperidone and nasogastric intubation; pharyngeal stimulation; elevation of PCO₂ by breath holding and rebreathing; central suppression of hiccup reflex by chlorpromazine; and suppression of central irritation from intracranial tension by phenytoin and sodium valproate²⁵⁰.

3) Gastrointestinal Symptoms

Nearly one-half of the most frequently reported and most distressing symptoms in patients with advanced cancer are gastrointestinal in nature. In one study, Komurcu et al reported dry mouth (84 %), weight loss (76%), early satiety (71%), taste change (60%), constipation(58 %), anorexia (56%), bloating (50 %), nausea (48 %), abdominal pain (42 %), and vomiting (34 %) as the 10 most common gastrointestinal symptoms²⁵¹.

- i) Vomiting:* Nausea and vomiting is a common symptom in patients with advanced cancer, occurring in approximately 21% to 68% of these patients. Nausea and vomiting in a terminally ill cancer patient may result from a variety of causes including gastrointestinal obstruction, infiltration of the wall of the gastrointestinal tract, liver metastases, brain or meningeal metastases, azotemia, hypercalcemia, electrolyte problems, or from treatment including radiation, chemotherapy, hormonal or biological therapy²⁵². Clinical consequences of chemotherapy induced emesis include serious metabolic derangements, nutritional depletion and anorexia, risk of aspiration pneumonia, deterioration of patients' physical and mental status, esophageal tears, fractures, wound dehiscence, withdrawal from potentially useful and curative antineoplastic treatment, and degeneration of self care and functional ability²⁵³.

Management centers on identifying the underlying causes, addressing these when possible, and controlling the symptoms. Multiple antiemetic regimens have been proposed for the management of chronic nausea in the setting of advanced cancer. Metoclopramide or domperidone are generally recommended as first-line agents because they improve gastrointestinal motility and act on the chemoreceptor trigger zone (as a result of their antidopaminergic properties). A continuous parenteral infusion of metoclopramide, at doses of 60 to 120 mg/day, may be helpful for patients with intractable chronic nausea²⁵⁴. In contrast to radiation therapy or chemotherapy-induced nausea, the role of 5-HT₃ receptor antagonists (such as ondansetron) is not clear in the setting of chronic nausea in advanced cancer. Non-drug measures like reassurance, small frequent feeds and avoidance of nauseating food; correction of reversible causes like hypocalcaemia, increased intracranial tension and constipation, avoidance of gastric irritant drugs and control of hyperacidity by H₂ receptor blockers.

- ii) Anorexia:* The loss of appetite may result from fear of vomiting, unappetizing food, dysphagia, uremia, radiotherapy, chemotherapy, or psychogenic in origin. The patient should be informed about the probable mechanism of anorexia and offered psychological support. Small and frequent installments of palatable and easily digestible food should be recommended. Appetite stimulants may be tried. In advanced cases, hyperalimentation may be offered²⁵⁵.
- iii) Diarrhoea:* The treatment options include identification and elimination of underlying cause like discontinuation of chemotherapy or suspected medication, obtaining stool-assay for *Clostridium difficile* and starting appropriate antibiotics. Bismuth subsalicylate and simethicone help in infectious diarrhoea. Salicylate and indomethacin are helpful in PG-mediated secretory diarrhoea. The supportive measures include intensive oral rehydration with fluids/ORS, avoiding high fat, high fiber food and taking frequent small meals rich in carbohydrates & proteins. Serious cases may be managed by giving opioid congeners, loperamide, diphenoxylate and octreotide²⁵⁶.
- iv) Constipation:* The causes of constipation in a cancer patient include mass in anorectal region, neurologic and mechanical changes from surgery, decreased oral intake, decreased mobility and supine positioning, medications like opioids and tricyclic antidepressants, and chemotherapeutic

agents like vinca alkaloids. The different treatment options for constipation in cancer patients include encouraging movement and ambulation, maintaining bowel awareness, ensuring adequate hydration and bulk-forming diet, use of laxatives like senna, lactulose and sorbitol, glycerine and bisacodyl suppositories, isotonic saline enemas, small-volume phosphate enemas and manual evacuation in extreme cases²⁵⁷.

4) Respiratory Symptoms

- i) **Dyspnoea:** The causes of dyspnoea in cancer patients include: pleuropericardial effusions, obstruction of a main bronchus, atelectasis, replacement of lung by cancer, superior vena caval compression, abdominal distension, pulmonary embolism, lung fibrosis due to radiotherapy and bleomycin, and concurrent ailments like COPD, pneumonia, anaemia etc. The treatment options include antibiotics and physiotherapy for infection, bronchodilators to relieve bronchospasm, diuretics and digoxin for cardiac failure, blood transfusion for anaemia, tapping of fluids for effusions, corticosteroids and radiotherapy for obstructed bronchus, breathing exercises and hypnotic relaxation, diazepam to reduce anxiety, morphine to reduce respiratory rate, nebulized bupivacaine to suppress the J- receptors, and oxygen administration for acute severe dyspnoea²⁵⁸.
- ii) **Cough:** The incidence of cough is 50% of all terminal cancer patients. The main causes of cough in a cancer patient include mechanical irritation of tracheobronchial tree, chest infection, pleural effusion, chronic obstructive airways disease, replacement of lung by cancer, cigarette smoking, and radiation-induced fibrosis. The treatment options of cough include antihistaminics for postnasal drip, bronchodilators for bronchospasm, diuretics for heart failure, antibiotics for infection, radiotherapy or chemotherapy for malignant lesion, resection of respectable lesions, postural drainage and physiotherapy, cessation of smoking, mucolytics and antitussives as indicated.

5) Oral Cavity Symptoms

- i) **Xerostomia:** The underlying pathophysiology of dry mouth is diminished secretion of saliva or diseased buccal mucosa. The causes include anxiety, depression, hypercalcemia, invasion of salivary glands by cancer, erosion of buccal mucosa, local radiation, local radical surgery, anticholinergic drugs etc. For treatment, meticulous mouth-care every two hours is indicated by effervescent mouthwash tablets containing peppermint oil, clove oil, spearmint, menthol etc. 0.1% hexidine has got antibacterial activity. Chewing gums, flavored candy and pineapple chunks maybe tried. Artificial salivas, plenty of fluid-intake and frequent moistening of lips is also helpful.
- ii) **Oral candidiasis:** Oral candidiasis may be a distressing problem in a terminal cancer patient. Dry mouth, corticosteroids and bacterial antibiotics are the common factors implicated²⁵⁹. Antifungal agents like nystatin, ketoconazole, fluconazole etc provide good symptomatic relief.
- iii) **Metallic taste:** It may be due to decreased sensitivity of taste buds, decreased number of taste buds, toxic dysfunction of taste buds, nutritional deficiencies or poor dental hygiene. Patient should be advised to reduce urea content of diet; to eat white meats, eggs, dairy products; to drink more liquids; to eat cold food; and to have fresh fruits and vegetables²⁶⁰.
- iv) **Halitosis:** Many cancer patients develop halitosis i.e. feeling of unpleasant or foul smelling breath. Causes may be any infection, gastric outlet obstruction, smoking, or ingestion of substances like garlic, onion, alcohol. Treatment possibilities include attention to orodental hygiene, adequate fluid intake, treatment of oral candidiasis, use of mouthwashes.

6) Psychiatric Symptoms:

Any physical ailment must be ruled out before labeling any symptom as psychiatric. The prevalence of anxiety and depression is about 77% in those with advanced disease²⁶¹. These patients should be treated with supportive therapy, hypnosis, relaxation therapy, and pharmacological drugs. Lorazepam, alprazolam and diazepam are the common anxiolytic drugs. Amitriptyline, imipramine and fluoxetine are the commonly used antidepressants. The evaluation tools to assess psychological distress in cancer patients and their relatives include Hospital Anxiety and Depression Scale (HADS), Cognitive Behavioral Assessment 2.0, the Family Strain Questionnaire and the Satisfaction with Life Scale²⁶².

Overall about 70% of patients in developing and underdeveloped countries present in advanced stages of disease, where adequate symptom control and comfort of the remaining life should be the aim of treatment. Palliative care should be provided by a dedicated team consisting of doctor, nurse and ancillary staff. Recent developments that are important to oncology practice are: the role of artificial nutrition; management of malignant small bowel obstruction; communication tasks, recognition of patient preferences, advanced-care planning and bereavement care. In India, the standard of palliative care is still disappointing as far as facilities are concerned. Newer centers for palliative care of cancer patients need to be made available and the public should be made aware in this regard as a form of treatment option.

FOLLOW UP

There is no robust data to support aggressive surveillance post resection. Patients may be followed up every 6 months for 2 years by imaging. Re-staging according to initial work-up should be considered in the event of disease relapse or progression²⁶³.

4

DIAGNOSTIC WORKUP

4.1 SUSPECTED GBC

Essential

- a) History and Physical Examination
- b) Liver Function Tests, Blood counts
- c) Ultrasound of the abdomen (*to rule out obvious distant metastasis*)
- d) Chest X-ray
- e) Contrast Enhanced Computed Tomography scan (CECT)/Magnetic Resonance Imaging of the abdomen (MRI)
 - In a Jaundiced patient:
 - a) Coagulation profile (*prothrombin time, etc.*)
 - b) Magnetic Resonance Cholangio Pancreaticography (MRCP)
 - c) Endoscopic Retrograde Cholangio Pancreaticography (ERCP)/Percutaneous Transhepatic Cholangiography (PTC) if a therapeutic intervention (biliary stenting) is planned
 - d) Informed Consent for Extended Cholecystectomy (EC)

Ideal

- CECT thorax
- Staging Laparoscopy
- Intraoperative frozen section of the gallbladder following cholecystectomy if diagnosis of GBC is doubtful, followed by definitive resection in the same setting

Optional

- Positron Emission Tomography (PET) scan
 - Serum Ca 19-9*, CEA
- * Preferably after biliary decompression in a jaundiced patient*

4.2 INCIDENTAL GBC (DISCOVERED UPON HPE OF THE CHOLECYSTECTOMY SPECIMEN)

Essential

- Same as in the above section
- Institutional Block/Slide Review, if possible

- Review primary surgeon’s operative notes, if available
- Informed consent for relaparotomy (*explaining the possibility that re-excision specimen may not show evidence of malignancy*)

Ideal

- CECT Thorax
- Staging Laparoscopy
- Frozen Section of the cystic duct stump

Optional

- PET scan
- Serum Ca 19-9, CEA

4.3 METASTATIC/UNRESECTABLE GBC*

- Fine Needle Aspiration Cytology (FNAC) of the primary GBC or the metastatic deposit to confirm the diagnosis before administering palliative chemotherapy or chemoradiotherapy
- Further investigations to assess the extent of disease to be planned on individual basis. Enrollment of patients in clinical trials is encouraged.

**Extensive investigations are discouraged in patients presenting with features suggestive of metastatic GBC such as*

- Poor performance status (ECOG 3 or 4)
- Ascitis
- Left supraclavicular lymph node
- Multiple liver metastasis, etc

A. RESECTABLE GBC [pT1-3 (Selected T4), N0-1, M0]

(Medically fit patients)

5.1 Surgery

- pT1a* - Simple Cholecystectomy (with negative cystic duct margin)
- pT1b, pT2† - Extended Cholecystectomy (enbloc *wedge resection/segment IVb+V resection of the liver + LND#*) ± CBD resection
- pT3, pT4**#† - Enbloc hepatic resection + cholecystectomy

**It is very difficult to diagnose pT1, pT2 GBC preoperatively. It is usually diagnosed upon HPE of the cholecystectomy specimen. Relaparotomy and hepatic resection+ LND ±CBD resection is indicated in pT1b and above incidental GBC.*

It is advisable to open every cholecystectomy gallbladder specimen to look for any suspicious mass lesion/thickening and intraoperative frozen section if facilities and the necessary expertise are available.

***Wedge resection/segment IVb+V resection of the liver/major hepatic resection (Extended right hepatectomy/central hepatectomy ± caudate lobectomy), CBD resection, duodenum/colon/omentum resection may be needed in advanced GBC and need to be assessed on an individual basis.*

LND; Lymph Node Dissection should include dissection of the hepatoduodenal ligament by skeletonization of vessels (hepatic artery and portal vein) and bile duct, anterior and posterior to the head pancreas clearing the hepatic artery up to its origin from celiac axis.

†Most recent studies indicate that there is no benefit of excision of port sites in a case of incidental GBC. However, no data from any randomized control trial exists on the subject.

Such complex procedures should only be carried out by those who have expertise in the field. If the requisite expertise is not available, the patient should be referred to a higher centre.

5.2 Adjuvant Therapy

pT2 and above (following R0 resection) → Adjuvant chemotherapy/chemoradiotherapy*

**At present no data from phase III trials is available on the best adjuvant therapy after R0 resection of GBC. Institutional policies vary from adjuvant Gemcitabine/fluoropyrimidine based chemotherapy to fluoropyrimidine chemoradiotherapy.*

B. METASTATIC/UNRESECTABLE GBC

Palliative Chemotherapy

(Medically fit patients- ECOG status up to 2)

mGEMOX

Inj Oxaliplatin 80 mg/m² 2 hours infusion in Dextrose 5% Day 1 and 8

Inj Gemcitabine 900 mg/m² IV 30 minutes infusion day1 and 8

Cycles to be repeated every 3 weeks for maximum of 6 cycles

GEMCIS

Inj Cisplatin 25 mg/m² PO Days 1 and 8

Inj Gemcitabine 1000 mg/m² IV 30 minutes infusion day1 and 8

Cycles to be repeated every 3 weeks for maximum of 8 cycles

GemCap

Inj Gemcitabine 1000 mg/m² IV 30 minutes infusion day1 and 8

Capecitabine 650mg/m² twice a day PO Days 1-14

Cycles to be repeated every 3 weeks.

Palliative Radiotherapy

May be used for relief of pain (after biliary decompression in patients with jaundice) in selected patients

Other Palliative procedures

- for relief of jaundice and pruritus – ERCP and stenting (*metallic/plastic stent*)
- for pain relief - Medicines as per the WHO step-ladder or celiac plexus block in refractory cases
- for relief of gastric outlet obstruction - Gastrojejunostomy in patients with good performance status

Neoadjuvant Chemotherapy/Chemoradiotherapy

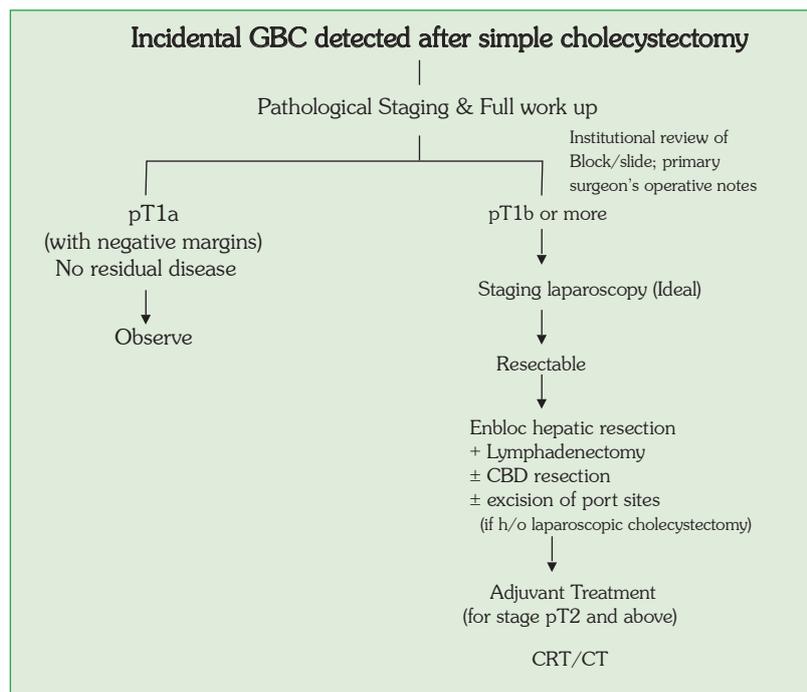
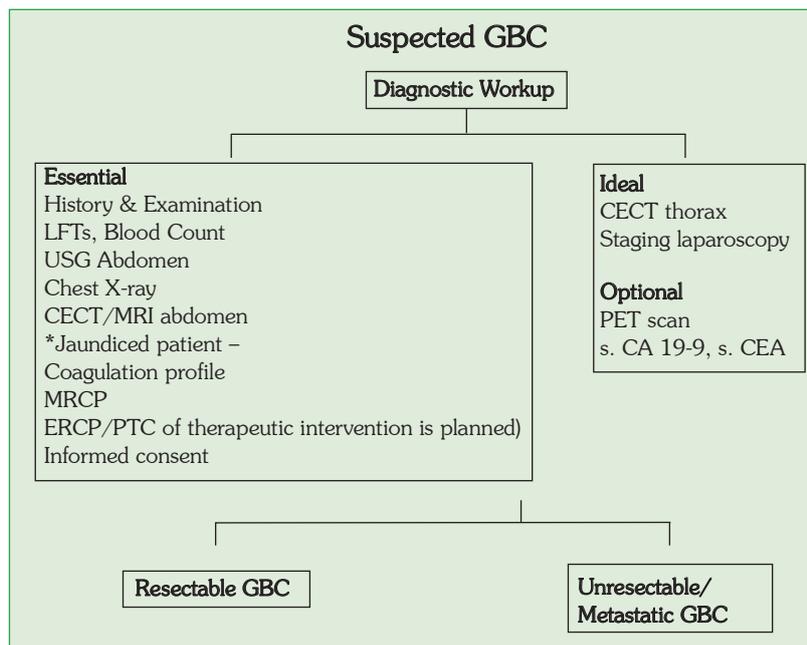
Only in context of a clinical trial

6 FOLLOW UP*

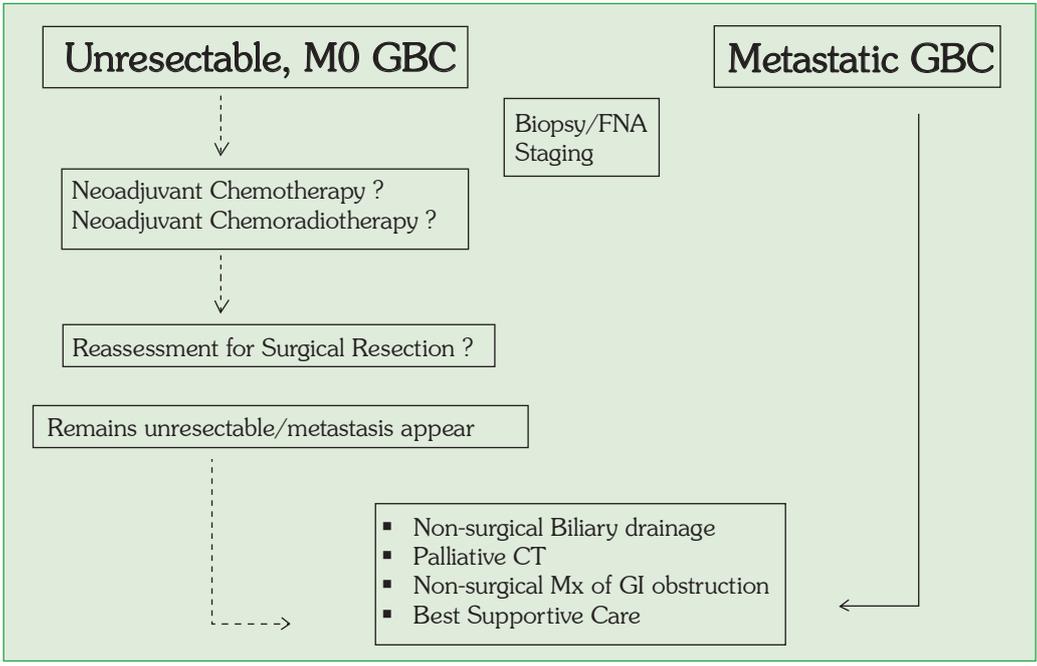
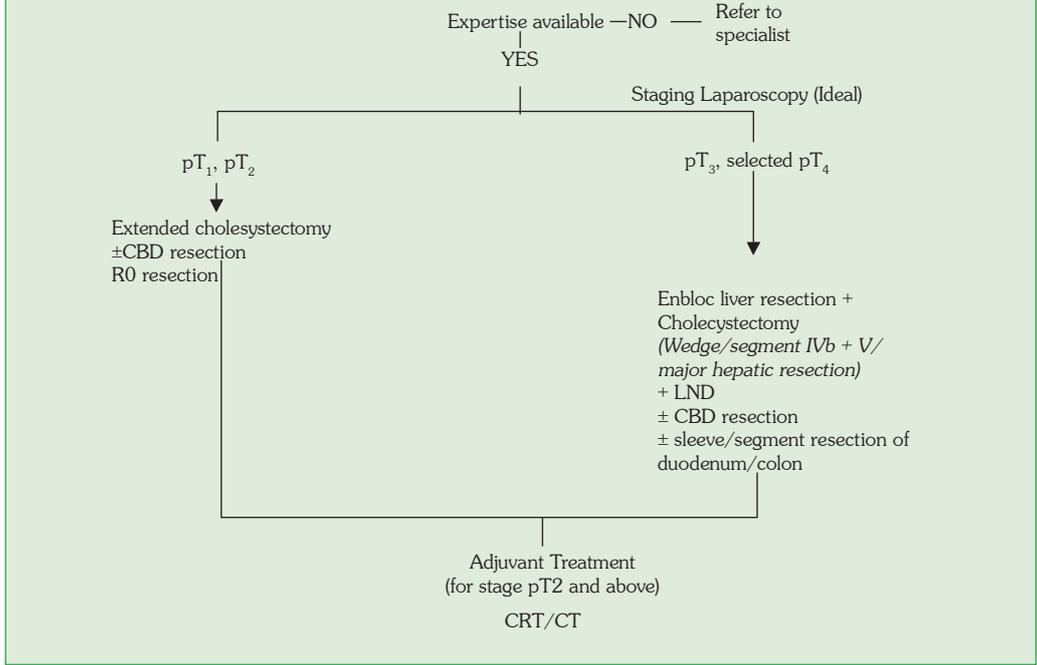
Every 6 months for 2 years

**There is no robust data to support aggressive surveillance post resection. Patients may be followed up by imaging. Re-staging according to initial workup should be considered in the event of disease relapse or progression.*

Please see the preceding sections for detailed information



Preoperatively diagnosed: Early GBC and Advanced GBC



There is a tremendous scope for research and multi institutional trials in GBC as we have very limited data on the subject. Enumerated below are some of the important research issues:

1. Indications for staging laparoscopy
2. Wedge resection versus segment IVb+V resection of liver in the surgical management of GBC
3. Re-resect or not to re-resect pT1b incidental GBC
4. Impact of bile spill during laparoscopic cholecystectomy for unsuspected GBC
5. Adjuvant therapy – chemotherapy or chemoradiotherapy or observation after R0 resection of GBC
6. Best follow up protocol
7. Role of neoadjuvant therapy in downstaging GBC and how best to treat responders and non responders
8. Role of tumor markers for early diagnosis and follow up – s. CA 19-9, CEA and finding new biomarkers
9. Epidemiological population based studies on the incidence and prevalence of GBC and gallstone disease
10. Etiopathogenesis of GBC – analysis of environment, soil, water, role of gallbladder motility, molecular and genetic studies (including genome sequencing and proteomics)
11. Creation of biobanks storing bile, serum and tissue from GBC and gallstone disease patients
12. Establishment of GBC cell lines and research on GBC stem cells
13. Centralization of treatment policies in GBC so as to develop a nation wide standard data base
14. To develop consensus regarding preventive cholecystectomy for asymptomatic gallstone carriers in areas with high incidence of GBC in our country.

APPENDIX (i)

Imaging Reporting Template

- Screening the entire gallbladder – fundus/body/neck/cystic duct
- Gallbladder wall–focal or diffuse thickening/asymmetry; mass lesion; adenomyomatosis; xanthogranulomatosis
- Cholelithiasis
- Invasion of adjacent structures: 1) interface of gallbladder with liver; depth of liver invasion – segments involved; metastasis ; IHBR 2) invasion of common hepatic duct, CBD, confluence of hepatic ducts; their size; presence of APBDJ 3) Vascular invasion – portal vein/hepatic artery
- Nodes - peri-choledochal, portahepatis, celiac, peripancreatic, interaorto-caval; para aortic , paracaval, others
- Ascites, metastases to distant organs

APPENDIX (ii)

Pathology Reporting Template: ²⁶⁴

Macroscopic

Specimen submitted

Gall Bladder/Cystic Duct/Common Hepatic Duct/Common Bile Duct/Liver/Lymph nodes

Tumor Site

Fundus/Body/Neck/Cystic duct/Common Hepatic Duct/Common bile duct

Macroscopic appearance: Papillary/Tubular/Nodular

Tumor Size

Greatest dimension (cm)

Microscopic

Histologic type

Carcinoma in situ/Adenocarcinoma/Mucinous Adenocarcinoma/adenosquamous carcinoma/small cell carcinoma

Histologic Grade

Well differentiated/Moderately Differentiated/Poorly Differentiated/Undifferentiated/Cannot be assessed.

Angiolymphatic Invasion

Present (Positive)/Not identified (Negative)/Cannot be assessed

Perineural invasion:

Present (Positive)/Absent (Negative)/Indeterminate/Cannot be assessed/other

Margins

Margin(s) are involved - If margin positive, specify which margin involved

If negative, specify distance from tumor of closest margin

Margins cannot be assessed

Tumor Extent

Tumor confined within gallbladder/Tumor invades adjacent liver

Lymph Nodes

Number of nodes examined/Number of nodes positive

Additional findings

None identified, Dysplasia/adenoma, Acute cholecystitis, cholelithiasis

Pathological stage: pTNM

Comments:

APPENDIX (iii)

AJCC TNM staging of gallbladder cancer (7th Ed; 2010)¹¹⁴

| Primary tumor (T) | |
|--------------------------|--|
| TX | Primary tumor cannot be assessed |
| T0 | No evidence of primary tumor |
| Tis | Carcinoma in situ |
| T1 | Tumor invades lamina propria or muscular layer |
| T1a | Tumor invades lamina propria |
| T1b | Tumor invades muscular layer |
| T2 | Tumor invades perimuscular connective tissue; no extension beyond serosa or into liver |
| T3 | Tumor perforates the serosa (visceral peritoneum) and/or directly invades the liver and/or one other adjacent organ or structure, such as the stomach, duodenum, colon, pancreas, omentum or extrahepatic bile ducts |
| T4 | Tumor invades main portal vein or hepatic artery or invades two or more extrahepatic organs or structures |
| Regional lymph nodes (N) | |
| NX | Regional lymph nodes cannot be assessed |
| N0 | No regional lymph node metastasis |
| N1 | Metastases to nodes along the cystic duct, common bile duct, hepatic artery and/or portal vein |
| N2 | Metastases to periaortic, pericaval, superior mesenteric artery and/or celiac artery lymph nodes |
| Distant metastasis (M) | |
| M0 | No distant metastasis |
| M1 | Distant metastasis |
| Stage grouping | |
| Stage 0 | Tis N0 M0 |
| Stage I | T1 N0 M0 |
| Stage II | T2 N0 M0 |
| Stage IIIA | T3 N0 M0 |
| Stage IIIB | T1–3 N1 M0 |
| Stage IVA | T4 N0–1 M0 |
| Stage IVB | Any T N2 M0 Any T Any N M1 |
| Histological Grade (G) | |
| GX | Grade cannot be assessed |
| G1 | Well differentiated |
| G2 | Moderately differentiated |
| G3 | Poorly differentiated |
| G4 | Undifferentiated |

1. Nandakumar A, Gupta PC, Gangadharn P, Visweswara RN, Parkin DM. Geographic pathology revisited: development of an atlas of cancer in India. *Int J Cancer* 2005; 116:740-754.
2. Dhir V, Mohandas KM. Epidemiology of digestive tract cancers in India IV. Gall bladder and pancreas. *Indian J Gastroenterol* 1999; 18:24-28.
3. National Cancer Registry Programme. Consolidated report of the Population Based Cancer Registries 1990-96. New Delhi: Indian Council of Medical Research 2001.
4. National Cancer Registry Programme. Three year report of the Population Based Cancer Registries 2006-2008. New Delhi: Indian Council of Medical Research 2010.
5. Murthy NS, Rajaram D, Gautham MS et al. Trends in incidence of gallbladder cancer – Indian scenario. In: *Gastrointestinal cancer: Targets and therapy* 2011;1:1-9.
6. Unisa S, Jagananth P, Dhir V, Khandelwal C, Sarangi L and Roy TK. Population-based study to estimate prevalence and determine risk factors of gallbladder diseases in the rural Gangetic basin or North India. *HPB* 2011; 13:117-125.
7. de Aretxabala X, Roa I, Burgos L, et al. Gallbladder Cancer in Chile. A report on 54 potentially resectable tumors. *Cancer* 1992; 69:60-65.
8. Wistuba I, Gazdar AF. Gallbladder Cancer; Lessons from a rare tumor. *Nat Rev J Cancer* 2004;4:695-705.
9. Ito H, Matros E, Brooks DC, et al. Treatment outcomes associated with surgery for gallbladder cancer. *J Gastrointest Surg* 2004;8:183-190.
10. Stintom LM, Shaffer EA. Epidemiology of Gallbladder Disease: Cholelithiasis and Cancer. *Gut and Liver* 2012;6(2):172-187.
11. Eslick GD. Epidemiology of gallbladder cancer. *Gastroenterol Clin North Am.* 2010;39(2):307-30.
12. Scott TE, Carroll M, Cogliano FD, Smith BF, Lamorte WW. A case-control assessment of risk factors for gallbladder carcinoma. *Dig Dis Sci.* 1999;44(8):1619-25.
13. Ishiguro S, Inoue M, Kurahashi N, Iwasaki M, Sasazuki S, Tsugane S. Risk factors of biliary tract cancer in a large-scale population-based cohort study in Japan (JPHC study); with special focus on cholelithiasis, body mass index, and their effect modification. *Cancer Causes Control.* 2008;19(1): 33-41.
14. Hsing AW, Gao YT, Han TQ, et al. Gallstones and the risk of biliary tract cancer: a population-based study in China. *Br J Cancer* 2007;97:1577-1582.
15. Alvi AR, Siddiqui NA, Zafar H. Risk factors of gallbladder cancer in Karachi-a case-control study. *World J Surg Oncol.* 2011 Dec 9;9:164. doi: 10.1186/1477-7819-9-164.

16. Nervi F, Duarte I, Gomez G, Rodriguez G, et al. Frequency of gallbladder cancer in Chile, a high risk area. *Int J Cancer* 1988;41:657-660.
17. Ferreccio C, Chianale J, Gonzalez C, Nervi F. *Epidemiologia Descriptiva del Cancer Diagestico en Chile (1982-1991): Una Aproximacion desde la Mortalidad. Monography. Alfa Beta, Santiago, Chile. 1995.*
18. Strom B, Soloway R, Rios-Dalenz J, Rodriguez-Martinez H, et al. Risk factors for gallbladder cancer. An international collaborative case control study. *Cancer* 1995; 76:1747-1756.
19. Black W, Key C, Carmassy T, Hermass D. Carcinoma of gallbladder in a population of southwestern American Indians. *Cancer* 1977; 39:1267-1279.
20. Deihl A. Epidemiology of gallbladder cancer: A synthesis of recent data. *J Natl Cancer Int* 1980; 65:1209-1214.
21. Zatonski W, La Vecchia C, Levi F, Negri E, Lucchii F. Descriptive epidemiology of gallbladder cancer in Europe. *J Cancer Res Clin Oncol* 1993; 119(3):165-171.
22. Pilgrim CH, Groeschl RT, Turaga KK, Gamblin TC. Key Factors Influencing Prognosis in Relation to Gallbladder Cancer. *Dig Dis Sci.* 2013 May 22. [Epub ahead of print]
23. Randi G, Franceschi S, La Vecchia C. Gallbladder cancer worldwide: geographical distribution and risk factors. *Int J Cancer.* 2006;118:1591–1602.
24. Shrikhande SV, Barreto SG, Singh S, Udwardia TE, Agarwal AK. Cholelithiasis in gallbladder cancer: coincidence, cofactor, or cause. *Eur J Surg Oncol.* 2010;36:514–519.
25. Miyazaki M, Takada T, Miyakawa S, Tsukada K, Nagino M, Kondo S, et al; Japanese Association of Biliary Surgery; Japanese Society of Hepato-Pancreatic Surgery; Japan Society of Clinical Oncology. *J Hepatobiliary Pancreat Surg.* 2008;15(1):15-24. Epub 2008 Feb 16.
26. Diehl AK. Gallstone size and the risk of gallbladder cancer. *JAMA.* 1983;250:2323–2326.
27. Csendes A, Becerra M, Rojas J, Medina E. Number and size of stones in patients with asymptomatic and symptomatic gallstones and gallbladder carcinoma: a prospective study of 592 cases. *J Gastrointest Surg.* 2000;4:481–485.
28. Lowenfels AB, Walker AM, Althaus DP, Townsend G, Domellöf L. Gallstone growth, size, and risk of gallbladder cancer: an interracial study. *Int J Epidemiol.* 1989 Mar;18(1):50-4.
29. Roa I, Ibacache G, Roa J, Araya J, et al. Gallstones and gallbladder cancer- volume and weight are associated with gallbladder cancer: a case-control study. *J Surg Oncol* 2006;93:624-628.
30. Zatonski WA, Lowenfels AB, Boyle P, Maisonneuve P, Bueno de Mesquita HB, et al. Epidemiologic aspects of gallbladder cancer: a case-control study of the SEARCH Program of the International Agency for Research on Cancer. *J Natl Cancer Inst.* 1997 Aug 6;89(15):1132-8.
31. Berk RN, Armbuster TG, Saltzstein SL. Carcinoma in the porcelain gallbladder. *Radiology.*1973;106: 29–31.
32. Stephen AE, Berger DL. Carcinoma in the porcelain gallbladder: a relationship revisited. *Surgery.* 2001 Jun;129(6):699-703.
33. Kim JH, Kim WH, Yoo BM, Kim JH, Kim MW. Should we perform surgical management in all patients with suspected porcelain gallbladder? *Hepatogastroenterology.* 2009 Jul-Aug;56(93):943-5.

34. Caygill CP, Hill MJ, Braddick M, Sharp JC. Cancer mortality in chronic typhoid and paratyphoid carriers. *Lancet*. 1994 Jan 8;343(8889):83-4.
35. Storm BL, Soloway RD, Rios-Dalenz JL, et al. Risk factors for gallbladder cancer. An international collaborative case-control study. *Cancer* 1995;76:1747-1756.
36. Kumar S, Kumar S, Kumar S. Infection as a risk factor for gallbladder cancer. *J Surg Oncol*.2006;93:633-639.
37. Dutta U, Garg PK, Kumar R, Tandon RK. Typhoid carriers among patients with gallstones are at increased risk for carcinoma of the gallbladder. *Am J Gastroenterol*. 2000;95:784-787.
38. Tewari M, Mishra RR, Shukla HS. Salmonella typhi and gallbladder cancer: report from an endemic region. *Hepatobiliary Pancreat Dis Int*. 2010;9:524-530.
39. Matsukura N, Yokomuro S, Yamada S, et al. Association between *Helicobacter bilis* in bile and biliary tract malignancies: H. bilis in bile from Japanese and Thai patients with benign and malignant diseases in the biliary tract. *Jpn J Cancer Res*. 2002;93:842-847.
40. Lewis JT, Talwalkar JA, Rosen CB, Smyrk TC, Abraham SC. Prevalence and risk factors for gallbladder neoplasia in patients with primary sclerosing cholangitis: evidence for a metaplasia-dysplasia-carcinoma sequence. *Am J Surg Pathol*. 2007;31:907-913.
41. Kang CM, Kim KS, Choi JS, Lee WJ, Kim BR. Gallbladder carcinoma associated with anomalous pancreaticobiliary duct junction. *Can J Gastroenterol*. 2007 Jun;21(6):383-7.
42. Myers RP, Shaffer EA, Beck P, et al. Gallbladder polyps: epidemiology, natural history and management. *Can J Gastroenterol* 2002; 16:187-194.
43. Goldgar DE, Easton DF, Cannon-Albright LA, Skolnick MH. Systematic population-based assessment of cancer risk in first-degree relatives of cancer probands. *J Natl Cancer Inst*. 1994;86:1600-1608.
44. Hemminki K, Li X. Familial liver and gall bladder cancer: a nationwide epidemiological study from Sweden. *Gut*. 2003;52:592-596.
45. Venniyoor A. Cholesterol gallstones and cancer of gallbladder (CAGB): molecular links. *Med Hypotheses*. 2008;70:646-653.
46. Larsson SC, Wolk A. Obesity and the risk of gallbladder cancer: a meta-analysis. *Br J Cancer*. 2007 May 7;96(9):1457-61.
47. Ren HB, Yu T, Liu C, Li YQ. Diabetes mellitus and increased risk of biliary tract cancer: systematic review and meta-analysis. *Cancer Causes Control*. 2011 Jun;22(6):837-47. doi: 10.1007/s10552-011-9754-3.
48. Schlesinger S, Aleksandrova K, Pischon T, Fedirko V, Jenab M. Abdominal obesity, weight gain during adulthood and risk of liver and biliary tract cancer in a European cohort. *Int J Cancer*. 2012 May 23. doi: 10.1002/ijc.27645.
49. Andreotti G, Liu E, Gao YT, Safaeian M, Rashid A, Shen MC, et al. Medical history and the risk of biliary tract cancers in Shanghai, China: implications for a role of inflammation. *Cancer Causes Control*. 2011 Sep;22(9):1289-96.
50. Tsuchiya Y, Terao M, Okano K, Nakamura K, Oyama M, Ikegami K, et al. Mutagenicity and mutagens of the red chili pepper as gallbladder cancer risk factor in Chilean women. *Asian Pac J Cancer Prev*. 2011;12(2):471-6.

51. Choi SY, Kim TS, Kim HJ, Park JH, Park DI, Cho YK, et al. Is it necessary to perform prophylactic cholecystectomy for asymptomatic subjects with gallbladder polyps and gallstones? *J Gastroenterol Hepatol*. 2010 Jun;25(6):1099-104.
52. Sheth S, Bedford A, Chopra S. Primary gallbladder cancer: recognition of risk factors and the role of prophylactic cholecystectomy. *Am J Gastroenterol*. 2000 Jun;95(6):1402-10.
53. Kapoor VK. Cholecystectomy in patients with asymptomatic gallstones to prevent gall bladder cancer—the case against. *Indian J Gastroenterol*. 2006;25(3):152-4.
54. Attili AF, De Santis A, Capri R, Repice AM, Maselli S. The natural history of gallstones: the GREPCO experience. The GREPCO Group. *Hepatology*. 1995 Mar;21(3):655-60.
55. Tewari M. Contribution of silent gallstones in gallbladder cancer. *J Surg Oncol*. 2006 Jun 15;93(8):629-32.
56. Wang F, Wang B, Qiao L. Association between obesity and gallbladder cancer. *Front Biosci*. 2012 Jun 1;17:2550-8.
57. Rai A, Mohapatra SC, Shukla HS. Correlates between vegetable consumption and gallbladder cancer. *Eur J Cancer Prev*. 2006 Apr;15(2):134-7.
58. Rai A, Mohapatra SC, Shukla HS. Role of fruit consumption in gall bladder cancer. *Indian J Gastroenterol*. 2005 Jan-Feb;24(1):32-3.
59. Bartlett DL, Fong Y. Tumors of the gallbladder. In: Blumgart LH, Fong Y, editors: *Surgery of the liver and biliary tract*. 3rd edition. London: WB Saunders; 2000. 993-1015.
60. Blalock AA. A statistical study of 888 cases of biliary tract disease. *Johns Hopkins Hosp Bull* 1924;35:391-409.
61. Fung Y, Jarnagin W, Blumgart LH. Gallbladder cancer: Comparison of patients presenting initially for definitive operation with those presenting after prior noncurative intervention. *Ann Surg* 2000;232:557-569.
62. Roa I, de Aretxabala X, Roa J. et al. Is gallbladder cancer a disease with bad prognosis? *Rev Med Chi* 2002;130:1295-1320.
63. Tiner CB, Nagomey OM, Donohue JH. Surgical Treatment of gallbladder cancer. *J V Gastrointest Surg* 2004;8:83-89.
64. Kokudo N, Makuuchi M, Natori T, et al. Strategies for surgical treatment of gallbladder carcinoma based on information available before resection. *Arch Surg* 2003; 138:741-750.
65. Toyonaga T, Chijiwa K, Nakano K, et al. Completion radical surgery after cholecystectomy for accidentally undiagnosed gallbladder carcinoma. *World J Surg* 2003;27:266-271.
66. Atsusaka S, Yamasaki H, Kitayama Y, et al. Occult gallbladder carcinoma diagnosed by a laparoscopic cholecystectomy. *Surg Today* 2003;33:740-742.
67. Hawkins WG, De Matteo RP, Jarnagin WR, et al. Jaundice predicts advanced disease and early mortality in patients with gallbladder cancer. *Ann Surg Oncol* 2004;11:310-315.
68. Regimbeau JM, Fucks D, Bachellier P, et al. Prognostic value of jaundice in patients with gallbladder cancer by the AFC-GBC-2009 study group. *Eur J Surg Oncol* 2011 Jun;37(6):505-12.

69. Gandolfi L, Torresan F, Solmi L, et al. The role of ultrasound in biliary and pancreatic diseases. *Eur J Ultrasound* 2003;16:141–159.
70. Yum HY, Fink AH. Sonographic findings in primary carcinoma of the gallbladder. *Radiology* 1980;134:693–696.
71. Franquet T, Montes M, Ruiz de Azua Y, et al. Primary gallbladder carcinoma: Imaging findings in 50 patients with pathologic correlation. *Gastrointest Radio1* 1991;16:143–148.
72. Dalla Palma L, Rizzato G, Pozzi-Mucelli RS, et al. Grey scale ultrasonography in the evaluation of carcinoma of the gallbladder. *Br J Radiol* 1980;53:662–667.
73. Soiva M, Aro K, Parnilo M, et al. Ultrasonography in carcinoma of the gallbladder. *Acta Radiol* 1987;28:711–714.
74. Sugiyama M, Atomi Y, Yamato T. Endoscopic ultrasonography for differential diagnosis of polypoid gall bladder lesions: Analysis in surgical and follow up series. *Gut* 2000;46:250–254.
75. Kimura K, Fujita N, Noda Y, et al.: Differential diagnosis of largesize pedunculated polypoid lesion of the gallbladder by endoscopic ultrasonography: A prospective study. *J Gastroenterol* 2001;36:619–622.
76. Grigorov N, Glavincheva I, Damianov D, Stoianov G, Et rska M. Diagnostic value and the criteria for abdominal echography in cancer of the gallbladder and bile ducts. *Vutr Boles.* 1985;24(2):53-60.
77. Bach AM, Loring LA, Hann LE, et al. Gallbladder cancer: Can ultrasonography evaluate extent of disease? *J Ultrasound Med* 1998;17:303–309.
78. Hendrestrom E, Fossberg L. Ultrasonography in carcinoma of the gallbladder. Diagnostic difficulties and pitfalls. *Acta Radiologica* 1987;28:715–718.
79. Onoyama H, Yamamoto M, Takada M, et al. Diagnostjc imaging of early gallbladder cancer: Retrospective study of 53 cases. *World J Surg* 1999;23:708–712.
80. Tsuchiya Y. Early carcinoma of the gallbladder: Macroscopic features and US findings. *Radiology* 1991;179:171–175.
81. Roseau G. The application of digestive endoscopic ultrasonography in the gallbladder pathology. *Presse Med* 2004;28:33;954–960.
82. Komatsuda T, Ishida H, Konno K, et al. Gallbladder carcinoma: Color Doppler sonography. *Abdom Imaging* 2000;25:194–197.
83. Wilbur AC, Sagireddy PB, Aizenstein RI. Carcinoma of the gallbladder: Color Doppler ultrasound and CT findings. *Abdom Imaging* 1997;22:187–189.
84. Li D, Dong BW, Wu YL, et al. Image-directed and color Doppler studies of gallbladder tumors. *J Clin Ultrasound* 1994;22:551–555.
85. Hayakawa S, Goto H, Hirooka Y, et al. Colour Doppler- guided spectral analysis of gall-bladder wall flow. *J Gastroenterol Hepatol* 1998;13:181–185.
86. Sato M, Ishida H, Konno K, et al. Localized gallbladder carcinoma: Sonographic findings. *Abdom Imaging* 2001;26:619–622.
87. Kumar A, Aggarwal S. Carcinoma of the gallbladder: CT findings in 50 cases. *Abdom Imaging* 1994;19:304–308.

88. Yun EJ, Cho SG, Park S, et al. Gallbladder carcinoma and chronic cholecystitis: Differentiation with two-phase spiral CT. *Abdom Imaging* 2004;29:102–108.
89. Ohtani T, Shirai Y, Tsukada K, et al. Spread of gallbladder carcinoma: CT evaluation with pathologic correlation. *Abdom Imaging* 1996;21:195–220.
90. Ohtani T, Shirai Y, Tsukada K, et al. Carcinoma of the gallbladder: CT evaluation of lymphatic spread. *Radiology* 1993;189:875–880.
91. Efremidis SC, Vougiouklis N, Zafiriadou E, et al. Pathways of lymph node involvement in upper abdominal malignancies: Evaluation with high-resolution CT. *Eur Radiol* 1999;9:868–874.
92. Tsukada K, Kurosaki I, Uchida K, et al. Lymph node spread from carcinoma of the gallbladder. *Cancer* 1997;80:661–667.
93. Kumaran V, Gulati S, Paul B, Pande K, Sahni P, Chattopadhyay K. The role of dual-phase helical CT in assessing resectability of carcinoma of the gallbladder. *Eur Radiol.* 2002 Aug;12(8):1993-9.
94. Yoshimitsu K, Honda H, Shinozaki K, et al. Helical CT of the local spread of carcinoma of the gallbladder: Evaluation according to the TNM system in patients who underwent surgical resection. *AJR Am J Roentgenol* 2002;179:423–428.
95. Kim BS, Ha HK, Lee JJ, Kim JH, Eun HW, Bae IY, et al. Accuracy of CT in local staging of gallbladder carcinoma. *Acta Radiol.* 2002 Jan;43(1):71-6.
96. Demachi H, Matsui O, Hoshihara K, et al. Dynamic MRI using a surface coil in chronic cholecystitis and gallbladder carcinoma: Radiologic and histopathologic correlation. *J Comput Assist Tomogr* 1997;21:643–651.
97. Sagoh T, Itoh K, Togashi K, et al. Gallbladder carcinoma: Evaluation with MR imaging. *Radiology* 1990;174:131–136.
98. Till RB, Semelka RC, Reinhold C: Gallbladder and biliary system. In: Semelka RC, editor. *Abdominal-pelvic MRI*. New York: Wiley-Liss; 2002. pp319-371.
99. Schwartz LH, Black J, Fong Y, et al.: Gallbladder carcinoma: Findings at MR imaging with MR cholangiopancreatography. *J Comput Assist Tomogr* 2002;26:405–410.
100. Kim JH, Kim TK, Eun HW, et al. Preoperative evaluation of gallbladder carcinoma: Efficacy of combined use of MR imaging, MR cholangiography, and contrast-enhanced dual-phase threedimensional MR angiography. *J Magn Reson Imaging* 2002;16:676–684.
101. Rota Kops E, Krause HJ: Partial volume effects/corrections. In: Wieler HJ, Coleman RE, editors. *PET in clinical oncology*. Darmstadt: Springer; 2000. pp 33–42.
102. Rodriguez-Fernandez A, Gomez-Rio M, Llamas-Elvira JM, et al. Positron-emission tomography with fluorine 8-2-deoxy-d-glucose for gallbladder cancer diagnosis. *Am J Surg* 2004;188:171-175.
103. Petrowsky H, Wildbrett P, Husarik DB, et al. Impact of integrated positron emission tomography and computed tomography on staging and management of gallbladder cancer and cholangiocarcinoma. *J Hepatol* 2006;45:43-50
104. Corvera CU, Blumgart LH, Akhurst T, et al. 18F-fluorodeoxyglucose positron emission tomography influences management decisions in patients with biliary cancer. *J Am Coll Surg* 2008;206:57-65.

105. Parra JA, Acinas O, Bueno J, et al.: Xantogranulomatous cholecystitis: Clinical, sonographics and CT finding in 26 patients. *AJR Am J Roentgenol* 2000;174:979–983.
106. Kim PN, Lee SH, Gong GY, et al.: Xantogranulomatous cholecystitis: Radiologic findings with histologic correlation that focuses on intramural nodules. *AJR Am J Roentgenol* 1999;172:949–953.
107. Hatakenaka M, Adachi T, Matsuyama A, et al.: Xantogranulomatous cholecystitis: Importance of chemical-shift gradient-echo MR imaging. *Eur Radiol* 2003;13:2233–2235.
108. Miles KA, Connelly LB: Cost-effectiveness studies of PET in oncology. In: Oehr P, Biersack HJ, Coleman RE, editors. *PET and PET-CT in oncology*. Berlin: Springer-Verlag; 2004. pp 321–329.
109. Haradome H, Ichikawa T, Sou H, et al. The pearl necklace sign: An imaging sign of adenomyomatosis of the gallbladder at MR cholangiopancreatography. *Radiology* 2003;227:80–88.
110. Wycherley A. Hepatobiliary function: Biliary kinetics. In: Ell PI, Gambhir SS, editors. *Nuclear medicine in clinical diagnosis and treatment*, 3th edition. Edinburgh: Churchill Livingstone; 2004. pp 837–846.
111. Gore RM, Yagmai V, Newmark G, et al. Imaging benign and malignant disease of the gallbladder. *Radiol Clin North Am* 2002;40:1307–1323.
112. Meera RS, Jhala D, Eloubeidi MA, Eltoun I, Chhieng DC, Crowe DR, et al. Endoscopic ultrasound-guided FNA biopsy of the bile duct and gallbladder: analysis of 53 cases. *Cytopathology* 2006;17(1):42-49.
113. Hueman MT, Vollmer CM, Pawlik TM. Evolving treatment strategies for gallbladder cancer. *Ann Surg Oncol* 2009;16:2101-2115.
- 113a. Agarwal AK, Kalayarasan R, Javed A, Gupta N, Nag HH. The role of staging laparoscopy in gallbladder cancer: an analysis of 409 patients: a prospective study to evaluate the role of staging laparoscopy in the management of gallbladder cancer. *Ann Surg* 2013 Aug;258(2):318-23.
- 113b. Butte JM, Gonan M, Allen PJ, et al. The role of laparoscopic staging in patients with incidental gallbladder cancer. *HPB* 2011;13:463-472.
114. Gallbladder. In: Edge SB, Byrd DR, Compton CC, et al., eds.: *AJCC Cancer Staging Manual*. 7th ed. New York, NY: Springer, 2010, pp 211-7.
115. Fong Y, Wagman L, Gonen M, et al. Evidence-based gallbladder cancer staging: changing cancer staging by analysis of data from National cancer Database. *Ann Surg* 2006;243(6):767-71; discussion771-4.
116. Pais-Costa SR, Farah JF, Artigiani-Neto R, Franco MI, Martins SJ, Goldenberg A. Gallbladder adenocarcinoma: evaluation of the prognostic factors in 100 resectable cases in Brazil. *Arq Bras Cir Dig*. 2012 Mar;25(1):13-9.
117. Kayahara M, Nagakawa T, Nakagawara H, Kitagawa H, Ohta T. Prognostic factors for gallbladder cancer in Japan. *Ann Surg*. 2008 Nov;248(5):807-14.
118. Bengmark S, Jeppsson B: Tumours of the gallbladder In: Yakamada T, editor. *Textbook of Gastroenterology*, 2nd edition. Philadelphia: JB Lippincott; 1955. pp 2739-2744.
119. Klammer TW, Max MH: Cancer of the gallbladder. *Surg Gynecol Obstet* 1983;156:641-645.
120. Pawlik TM, Gleisner AL, Viganò L, et al. Incidence of finding residual disease for incidental gallbladder carcinoma: implications for re-resection. *J Gastrointest Surg* 2007;11:1478-1486.
121. Nevin JE, Moran TJ, Kay S, et al.: Carcinoma of the gallbladder: Staging, treatment, and prognosis. *Cancer* 1976;37:141-148.

122. Fahim RB, McDonald JR, Richards JC et al.: Carcinoma of the gallbladder: A study of its modes of spread. *Ann Surg* 1962;156:114-124.
123. Clermont D: Lymphatiques des voie biliaire: Cancer de la vesicule (anatomie pathologique et traitement chirurgical). *Toulouse* 1909;814-114.
124. Ito M, Mishima Y, Sato T: An anatomical study of the lymphatic drainage of the gallbladder. *Surg Radiol Anot* 1991;13:89-104.
125. Kondo S, Nimura Y, Kamiya J, et al.: Factors influencing postoperative hospital mortality and long-term survival after radical resection for stage IV gallbladder carcinoma. *World J Surg* 2003;27:272-277.
126. Shimada H, Endo I, Togo S, et al.: The role of lymph node dissection in the treatment of gallbladder carcinoma. *Cancer* 1997;79:892-899.
127. Fong Y, Jarnagin W, Blumgart LH: Gallbladder cancer: comparison of patients presenting initially for definitive operation with those presenting after prior noncurative intervention. *Ann Surg* 2000, 232:557-569.
128. de Arextabala XA, Roa IS, Burgos LA, Araya JC, Villaseca MA, Silva JA: Curative resection in potentially resectable tumors of the gallbladder. *Eur J Surg* 1997, 163:419-426.
129. Chijiwa K, Noshiro H, Nakano K, Okido M, Atsushi S, Ymaguchi K, Tanaka M: Role of surgery for gallbladder carcinoma with special reference to lymph node metastasis and stage using Western and Japanese classification systems. *World J Surg* 2000, 23:1271-1277.
130. Paolucci V, Neckell M, Götze T: Unsuspected gallbladder carcinoma – The CAE-S/CAMIC registry. *Zentralbl Chir* 2003,128:309-312.
131. Petren T: Die extrahepatischen gallenwegsvenen und ihre pathogissch-anatomische bedeutug. *Verhandl. Anotomische Gesellsch* 1932;41:139.
132. Onoyama H, Yamamoto M, Tseng A, et al.: Extended cholecystectomy for carcinoma of the gallbladder. *World J Surg* 1995;19:758-763.
133. Karlmark E: Die lokalisationstendenz bei metasatasierung durch die venen in die leber. *Acta Pathol Microbiol Scand* 1932;13:203.
134. Kuwayti K, Baggenstoss AH, Stauffer MH, et al: Carcinoma of the major intrahepatic and extrahepatic bile ducts exclusive of the papilla of vater. *Surg Gynoeocol Obstet* 1957;104:357-366.
135. Silk YN, Douglas HO, Nava HR, et al.: Carcinoma of the gallbladder: The Roswell park experience. *Ann Surg* 1989;210:751-757.
136. Frauenschuh D, Greim R, Kraas E: How to proceed in patients with carcinoma detected after Laparoscopic cholecystectomy. *Langenbeck Arch Surg* 2000;385:495-500.
137. Wibbenmeyer LA, Wade TP, Chen RC, et al.: Laparoscopic cholecystectomy can disseminate in situ carcinoma of the gallbladder. *J Am Coll Surg* 1995;181:504-510.
138. Braghetto I, Bastias J, Csendes A, et al.: Gallbladder carcinoma during laparoscopic cholecystectomy: Is it associated with bad prognosis? *Int Surg* 1999;84:344-349.
139. Kimura TW, Nagai H, Kuroda A, et al.: Clinicopathologic study of asymptomatic gallbladder found at autopsy. *Cancer* 1989;64:98-103.

140. Paolucci V, Schaeff B, Schneider M, et al.: Tumour seeding following laparoscopy: International surgery. *World J Surg* 1999;23:989-997.
141. Bouvy ND, Marquet RL, Jeekel J, et al.: Impact of gas (less) laparoscopy and laparotomy on peritoneal growth and abdominal wall metastasis. *Ann Surg* 1996;224:694-701.
142. Aoki Y, Shimura H, Li H, et al.: A model of port-site metastases of gallbladder cancer: The influence of peritoneal injury and its repair on abdominal wall metastases. *Surgery* 1999;125:553-559.
143. Steinert R, Lippert H, Reymond MA: Tumor cell dissemination during laparoscopy: Prevention and therapeutic opportunities. *Dig Surg* 2002;19:464-472.
144. Lundberg O, Kristoffersson A: Port site metastases from gallbladder cancer after laparoscopic cholecystectomy. Results of a Swedish surgery and review of published reports. *Eur J Surg* 1999;165:215-222.
145. Darabos N, Stare R: Gallbladder cancer: laparoscopic and classic cholecystectomy. *Surg Endosc* 2004;18:144-147.
146. Lundberg O, Kristoffersson A: Open versus laparoscopic cholecystectomy for gallbladder carcinoma. *J hepatobiliary Pancreat Surg* 2001;8:525-529.
147. Schaeff B, Paolucci V, Thomopoulos J: Port site recurrences after laparoscopic surgery. A review. *Dig Surg* 1998;15:124-134.
148. Wullstein C, Woeste G, Barkhausen S, et al.: Do complications related to laparoscopic cholecystectomy influence the prognosis of gallbladder cancer? *Surg Endosc* 2002;16:828-832.
149. Weiland ST, Mahvi DM, Niederhuber JE, et al.: Should suspected early gallbladder cancer be treated laparoscopically? *J Gastro-intest Surg* 2002;6:50-56.
150. Wakai T, Shirai Y, Hatakeyama K: Radical second resection provides survival benefit for patients with T2 gallbladder carcinoma first discovered after laparoscopic cholecystectomy. *World J Surg* 2002;26:867-871.
151. Ouchi K, Sugawara T, Ono H, et al. Diagnostic capability and rational resectional surgery for early gallbladder cancer. *Hepato-gastroenterology* 1999; 46:1557-1560.
152. de Aretxabala XA, Roa IS, Mora JP, et al.: Laparoscopic cholecystectomy: Its effect on the prognosis of patients with gallbladder cancer. *World J Surg* 2004;28:544-547.
153. Yoshida T, Matsumoto T, Sasaki A, et al.: Laparoscopic cholecystectomy in the treatment of patients with gall bladder cancer. *J Am Coll Surg* 2000;191:158-163.
154. Ouchi K, Mikuni J, Kakugawa Y: Organizing Committee, the 30th Annual Congress of the Japanese Society of Biliary Surgery. Laparoscopic for gallbladder carcinoma: Results of a Japanese survey of 498 patients. *J Hepatobiliary Pancreat Surg* 2002;9:256-260.
155. Shih SP, Schulick RD, Cameron JL, et al. Gallbladder cancer: the role of laparoscopy and radical resection. *Ann Surg* 2007;245:893-901.
156. Shirai Y, Yoshida K, Tsukuda K, et al.: Early carcinoma of the gallbladder. *Eur J Surg* 1992;158:545-548.
157. Suzuki S, Yokoi Y, Kurachi K, et al.: Appraisal of surgical treatment for pT2 gallbladder carcinomas. *World J Surg* 2004;28:160-165.

158. Muratore A, Polastri R, Bouzari H, et al.: Radical surgery for gallbladder cancer : A worthwhile operation? *Eur j Surg Oncol* 2000;26:160-163.
159. Wakai T, Shirai Y, Yokoyama N, et al.: Depth of subserosal invasion predicts long-term survival after resection in patients with T2 gallbladder carcinoma. *Ann Surg Oncol* 2003;10:447-454.
160. Shirai Y, Yoshida K, Tsukuda K, et al.: Inapparent carcinoma of the gallbladder. *Ann Surg* 1992;215:326-331.
161. Yamaguchi K, Tsuneyoshi M: Subclinical gallbladder carcinoma. *Am J Surg* 1992;163:382-386.
162. Benoist S, Panis Y, Fazniez P-L, The French University Association for Surgical Research. Long term results after curative resection for carcinoma of the gallbladder. *Am J Surg* 1998;175:118-122.
163. Bartlett DL, Ramanathan RK, E. B-J. Cancers of the biliary tree. In: De Vita VT, Lawrence TS, Rosenberg SA, eds. *Cancer: Principles and Practice of Oncology* (ed 8): Wolters Kluwer; Lippincott Williams & Wilkins; 2008:1156-1186.
164. Reid KM, Ramos-De la Medina A, Donohue JH. Diagnosis and surgical management of gallbladder cancer: a review. *J Gastrointest Surg* 2007;11:671-681.
165. Ito H, Ito K, D'Angelica M, Gonen M, Klimstra D, Allen P, DeMatteo RP, Fong Y, Blumgart LH, Jarnagin WR. Accurate staging for gallbladder cancer: implications for surgical therapy and pathological assessment. *Ann Surg*. 2011 Aug;254(2):320-5.
166. Negi SS, Singh A, Chaudhary A. Lymph node involvement as prognostic factor in gallbladder cancer: location, count or ratio? *J Gastrointest Surg*. 2011 Jun;15(6):1017-25.
167. Waghlikar GD, Behari A, Krishnani N, et al.: Early gallbladder cancer *J Am Coll Surg* 2002;194:137-141.
168. Wakai T, Shirai Y, Yokoyama N, et al.: Early gallbladder carcinoma does not warrant radical resection. *Br J Surg* 2001;88:675-678.
169. Ouchi K, Owada Y, Matsuno XX, et al.: Prognostic factors in the surgical treatment of gallbladder carcinoma. *Surgery* 1987;101:731-737.
170. Ogura Y, Mizumoto R, Isaji S, et al.: Radical operations for carcinoma of the gallbladder. *World J Surg* 1991;15:337-343.
- 170a. Barreto SG, Pawar S, Shah S, Talole S, Goel M, Shrikhande SV. Patterns of Failure and Determinants of Outcomes Following Radical Re-resection for Incidental Gallbladder Cancer. *World J Surg*. 2013 Oct 2. [Epub ahead of print].
- 170b. You DD, Lee HG, Paik KY, et al. What is an adequate extent of resection for T1 Gallbladder cancers? *Ann Surg* 2008 May;247(5):835-8.
171. Kousuge T, Sano K, Shimada K, et al.: Should the bile duct be preserved or removed or removed in radical surgery for gallbladder cancer? *Hepatogastroenterology* 1999;46:2133-2137.
172. Chijiwa K, Nakano K, Ueda J, et al.: Surgical treatment of patients with T2 gallbladder carcinoma invading the subserosal layer. *J Am Coll Surg* 2001;192:600-607.
173. Downing SR, Cadogan KA, Ortega G, Oyetunji TA, Siram SM, Chang DC, Ahuja N, Leffall LD Jr, Frederick WA. Early-stage gallbladder cancer in the Surveillance, Epidemiology, and End Results database: effect of extended surgical resection. *Arch Surg*. 2011 Jun;146(6):734-8.

174. Fuks D, Regimbeau JM, Pessaux P, et al. Is port-site resection necessary in the surgical management of gallbladder cancer? *J Visc Surg*. 2013 May 9. pii: S1878-7886(13)00032-5. doi: 10.1016/j.jvisc Surg.2013.03.006. [Epub ahead of print]
175. Guidelines of the German Surgical Society and of the German Cancer Society. In: Junigiger T, Hossfeld DK, Muller RP, editors. *Leitlinien zur Diagnostik und Therapie von Tumoren des Gastrointestinaltrakts und der Schilddrüse*. Demeter: Stuttgart;1999.
176. Pearlstone BD, Gurley SA, Feig BW, et al.: The management of gallbladder cancer: Before, during and after laparoscopic cholecystectomy. *Semin Laparosc Surg* 1998;5:121-128.
177. Watson DJ, Ellis T, Leeder P, et al.: Excision of laparoscopic port sites increases the likelihood of wound metastases in an experimental model. *Surg Endosc* 2002;16:S194.
178. Fong Y, Brennan MF, Turnball A, et al.: Gallbladder cancer discovered during laparoscopic surgery. Potential for iatrogenic tumour dissemination. *Arch Surg* 1993;128:1054-1056.
179. Winston CB, Chen JW, Fong Y, et al.: Recurrent gallbladder carcinoma along laparoscopic cholecystectomy port tracks. CT demonstration. *Radiology* 1999;212:439.
180. Drouard F, Delamarre J, Capron J: Cutaneous seeding of gallbladder cancer after laparoscopic cholecystectomy. *N Eng J Med* 1991;325:1316.
181. Clair DJ, Lautz DB, Brooks DC: Rapid development of umbilical metastases after laparoscopy cholecystectomy for unsuspected gallbladder carcinoma. *Surgery* 1993;114:355.
- 181a. Maker AV, Butte JM, Oxenberg J, et al. Is port site resection necessary in the surgical management of gallbladder cancer? *Ann Surg Oncol* 2012;19: 409-417.
182. Mondragon – Sanchez R, Gonzalez-Geroniz M, Onate-Ocana LF, et al.: A retrospective analysis of patients with gallbladder cancer treated with radical resection versus cholecystectomy plus external radiotherapy. *Hepatogastroenterology* 2003;50:1806-1810.
183. Ogura Y, Tabata M, Kawarada Y, et al.: Effect of hepatic invasion on the choice of hepatic resection for advanced carcinoma of the gallbladder: Histologic analysis of 32 surgical cases. *World J Surg* 1998;22:262-267.
184. Nagai H, Kuroda A, Morioka Y, et al.: Modes of spread of gallbladder carcinoma: A study of autopsied cases (in Japanese). *Tan to Sui (J Bill Pancr)* 1983;4:1227.
185. Miyazaki M, Ito H, Ambiru S, et al.: Radical surgery for advanced gallbladder carcinoma. *Br J Surg* 1996;83:478-481.
186. Yamaguchi K, Chijiwa K, Shimizu S, et al.: Anatomical limit of extended cholecystectomy for gallbladder carcinoma involving the neck of the gallbladder. *Int Surg* 1998;83:21-23.
187. Yoshikawa T, Araida T, Azuma T, Takasaki K. Bisubsegmental liver resection for gallbladder cancer. *Hepato-Gastroenterology* 1998; 45: 14–9.
188. Scheingraber S, Justinger C, Stremovskaia T, et al. The standardized surgical approach improves outcome of gallbladder cancer. *World Journal of Surgical Oncology* 2007, 5:55 doi:10.1186/1477-7819-5-55.
- 188a. Horiguchi A, Miyakawa S, Ishihara S, Miyazaki M, Ohtsuka M, Shimizu H, et al. Gallbladder bed resection or hepatectomy of segments 4a and 5 for pT2 gallbladder carcinoma: analysis of Japanese registration cases by the study group for biliary surgery of the Japanese Society of Hepato-Biliary-Pancreatic Surgery. *J Hepatobiliary Pancreat Sci*. 2013 Jun;20(5):518-24. doi: 10.1007/s00534-012-0584-9.

189. Ogura Y, Matsuda S, Sakurai H, et al.: Central Bisegmentectomy of the liver plus caudate lobectomy for carcinoma of the gallbladder. *Dig Surg* 1998;15:218-223.
190. Ouchi K, Suzuki M, Saijo S, et al.: Do recent advances in the diagnosis and operative management improve outcome of gallbladder carcinoma? *Surgery* 1993;113:324-329.
191. Kondo S, Nimura Y, Hayakawa N, et al.: Regional and para-aortic lymphadenectomy in radical surgery for advanced gallbladder carcinoma. *Br J Surg* 2000;87:418-422.
192. Behari A, Sikora SS, Waghlikar GD, et al.: Long term survival after extended resection in patients with gallbladder cancer, *J Am Coll Surg* 2003;196:82-88.
193. Todoroki T, Kawamoto T, Takahashi H, et al.: Treatment of gallbladder cancer by radical resection. *Br J Surg* 1990;86:622-627.
194. Nagino M, Nimura Y, Kamiya J, et al.: Precoperative transhepatic portal vein embolization for impaired residual hepatic function in patients with obstructive jaundice. *J Hepatobiliary Pancreat Surg* 1997;4:373-376.
195. You DD, Lee HG, Paik KY, et al. What is an adequate extent of resection for T1 gallbladder cancers? *Ann Surg* 2008 May;247(5):835-8.
196. Barlett DL, Fong Y, Fortner JG, et al.: Long-term results after resection for gallbladder cancer. Implications for staging and management. *Ann Surg* 1996;224:639-646.
197. Kaneoka Y, Yamaguchi A, Isogai M, et al.: Hepatoduodenal ligament invasion by gallbladder carcinoma: Histologic patterns and surgical recommendation. *World J Surg* 2003;27:260-265.
198. Shimizu Y, Ohtsuka M, Ito H, et al.: Should the extrahepatic bile duct be resected for locally advanced gallbladder cancer? *Surgery* 2004;136:1012-1017.
199. Araida T, Higuchi R, Hamano M, Kodera Y, Takeshita N, Ota T, Yoshikawa T, Yamamoto M, Takasaki K. Should the extrahepatic bile duct be resected or preserved in R0 radical surgery for advanced gallbladder carcinoma? Results of a Japanese Society of Biliary Surgery Survey: a multicenter study. *Surg Today*. 2009;39(9):770-9.
200. D'Angelica M, Dalal KM, DeMatteo RP, Fong Y, Blumgart LH, Jarnagin WR. Analysis of the extent of resection for adenocarcinoma of the gallbladder. *Ann Surg Oncol*. 2009 Apr;16(4):806-16.
201. Kondo S, Nimura Y, Hayakawa N, et al.: Extensive surgery for gallbladder cancer. *Br J Surg* 2002;89:179-184.
202. Gall FP, Kockerling F, Scheele J, et al.: Radical operations for carcinoma of the gallbladder: Present status in Germany. *World J Surg* 1991;15:328-336.
203. Nimura Y, Hayakawa N, Kamiya J, et al.: Combined portal vein and liver resection for carcinoma of the biliary tract. *Br J Surg* 1991;78:727-731.
- 203a. Agarwal AK, Mandal S, Singh S, Sakhuja P, Puri S. Gallbladder cancer with duodenal infiltration: is it still resectable? *J Gastrointest Surg*. 2007 Dec;11(12):1722-7.
204. Todoroki T, Takahashi H, Koike N, et al.: Outcomes of aggressive treatment of stage IV gallbladder cancer and predictors of survival. *Hepatogastroenterology* 1999;46:2114-2121.
205. Nakamura S, Nishiyama R, Yoki Y, et al.: Hepatopancreatoduodenectomy for advanced gallbladder carcinoma. *Arch Surg* 1994;129:625-629.

206. Tsukada K, Yoshida K, Aono T, et al.: Major hepatectomy and pancreaticoduodenectomy for advanced carcinoma of the biliary tract. *Br J Surg* 1994;81:108-110.
207. Nimura Y, Hayakawa N, Kamiya J, et al.: Hepatopancreatoduodenectomy for advanced carcinoma of the biliary tract. *Hepatogastroenterology* 1991;38:170-175.
208. Wang SJ, Fuller CD, Kim JS, et al. Prediction model for estimating the survival benefit of adjuvant radiotherapy for gallbladder cancer. *J Clin Oncol* 2008;26(13):2112-7.
- 208a. Gold DG, Miller RC, Haddock MG, et al. Adjuvant therapy for gallbladder carcinoma: the Mayo Clinic Experience. *Int J Radiat Oncol Biol Phys.* 2009 Sep 1;75(1):150-5.
- 208b. Cho SY, Kim SH, Park S-J, et al. Adjuvant chemoradiation therapy in gallbladder cancer. *J Surg Oncol.* 2010 Jul 1;102(1):87-93.
- 208c. Kim K, Chie EK, Jang JY, et al. Postoperative chemoradiotherapy for gallbladder cancer. *Strahlenther Onkol.* 2012 May;188(5):388-92. Epub 2012 Mar 10.
209. Kresl JJ, Schild SE, Henning GT, et al. Adjuvant external beam radiation therapy with concurrent chemotherapy in the management of gallbladder carcinoma. *Int J Radiat Oncol Biol Phys* 2002;52:167-75.
210. Czito BG, Hurwitz HI, Clough RW, et al. Adjuvant external-beam radiotherapy with concurrent chemotherapy after resection of primary gallbladder carcinoma: a 23-year experience. *Int J Radiat Oncol Biol Phys* 2005;62:1030-4.
211. Balachandran P, Agarwal S, Krishnani N, et al. Predictors of long-term survival in patients with gallbladder cancer. *J Gastrointest Surg* 2006;10:848-54.
212. Duffy A, Capanu M, Abou-Alfa GK, et al. Gallbladder cancer (GBC): 10-year experience at Memorial Sloan-Kettering Cancer Centre (MSKCC). *J Surg Oncol* 2008;98(7):485-9.
213. Gold DG, Miller RC, Haddock MG, et al. Adjuvant therapy for gallbladder carcinoma: the Mayo Clinic experience. *Int J Radiat Oncol Biol Phys* 2009;75(1):150-5.
214. Horgan AM, Amir E, Walter T, et al. Adjuvant therapy in the treatment of biliary tract cancer: A systematic review and meta-analysis. *J Clin Oncol* 2012; 30: 1934-1940.
215. Bartlett DL, Di Bisceglie AM, Dawson LA *Cancer of the Liver In: Principles and Practice of Oncology*, 9th edition. Eds. Devita, Hellman, Rosenberg. Lippencott, Williams & Wilkins, Philadelphia.2011.
216. Duffy A, Capanu M, Abou-Alfa GK, et al. Gallbladder cancer (GBC): 10 year experience at memorial Sloan-Kettering cancer centre (MSKCC). *J Surg Oncol* 2008;98:485-489.
217. Kayahara M, Nagakawa T. Recent trends of gallbladder cancer in Japan: an analysis of 4,770 patients. *Cancer.* 2007 Aug 1;110(3):572-80.
218. Takada T, Amano H, Yasuda H, Nimura Y, Matsushiro T, Kato H, Nagakawa T, Nakayama T; Study Group of Surgical Adjuvant Therapy for Carcinomas of the Pancreas and Biliary Tract. Is postoperative adjuvant chemotherapy useful for gallbladder carcinoma? A phase III multicenter prospective randomized controlled trial in patients with resected pancreaticobiliary carcinoma. *Cancer.* 2002 Oct 15;95(8):1685-95.
219. Mojica P, Smith D, Ellenhorn J. Adjuvant radiation therapy is associated with improved survival for gallbladder carcinoma with regional metastatic disease. *J Surg Oncol.* 2007 Jul 1;96(1):8-13

220. Takada T, Kato H, Matsushiro T, Nimura Y, Nagakawa T, Nakayama T. Comparison of 5-fluorouracil, doxorubicin, and mitomycin with 5-fluorouracil alone in the treatment of pancreatic-biliary carcinomas. *Oncology* 1994; 51: 396-400.
221. Okusaka T, Ishii H, Funakoshi A, et al. Phase II study of single agent gemcitabine in patients with advanced biliary tract cancer. *Cancer Chemother Pharmacol* 2006; 57: 647-653.
222. Sharma A, Bedi R, Shukla NK, et al. Does Chemotherapy Improves Survival in Gall Bladder Cancer ? *Proc Am Soc Clin Oncol* 2004;362, no 4202
223. C Hsu, Y-C Shen, C-H Yang, et al. Weekly gemcitabine plus 24 hour infusion of 5-fluorouracil/leucovorin for locally advanced or metastatic carcinoma of biliary tract. *Br J Cancer* 2004; 90: 1715-1719.
224. Doval DC, Shekhon JS, Gupta SK, et al. A phase II study of gemcitabine and cisplatin in chemotherapy naïve, unresectable gall bladder cancer. *Br J Cancer* 2004; 90: 1516-1520.
225. André T, Tournigand C, Rosmorduc O, et al; GERCOR Group. Gemcitabine combined with oxaliplatin (GEMOX) in advanced biliary tract adenocarcinoma: a GERCOR study. *Ann Oncol* 2004; 15: 1339-1343.
226. Takada T, Nimura Y, Katoh H, et al. Prospective randomized trial of 5 Fluorouracil, doxorubicin, and mitomycin C for non respectable pancreatic and biliary carcinoma: multicenter randomized trial. *Hepatogastroenterology* 1998; 45: 2020-2026.
227. Perpetuo MO, Valdivieso M, Heilbrun LK, et al. Natural history study of gallbladder cancer: a review of 36 years experience at M.D. Anderson Cancer Center. *Cancer* 1978; 42: 330.
228. Valle JW, Wasan H, Johnson P, et al. Gemcitabine alone or in combination with cisplatin in patients with advanced or metastatic cholangiocarcinomas or other biliary tract tumours: a multicentre randomized phase II study – The UK ABC-01 Study. *Br J Cancer* 2009;101:621-627.
229. Thongprasert S, Napapan S, Charoentum C, Moonprakan S. Phase II study of gemcitabine and cisplatin as first-line chemotherapy in inoperable biliary tract carcinoma. *Ann Oncol* 2005;16:279-281.
230. Knox JJ, Hedley D, Oza A, et al. Combining gemcitabine and capecitabine in patients with advanced biliary cancer: a phase II trial. *J Clin Oncol* 2005;23:2332-2338.
231. Koeberle D, Saletti P, Borner M, et al. Patient-reported outcomes of patients with advanced biliary tract cancers receiving gemcitabine plus capecitabine: a multicenter. Phase II trial of the Swiss Group for Clinical Cancer Research. *J Clin Oncol* 2008;26:3702-3708.
232. Malka D, Trarbach T, Fartoux L, et al. A multicenter, randomized phase II trial of gemcitabine and oxaliplatin (GEMOX) alone or in combination with biweekly cetuximab in the first-line treatment of advanced biliary cancer: Interim analysis of the BINGO trial [abstract]. *J Clin Oncol* 2009;27 (15_suppl):Abstract 4520.
233. Nehls O, Oettle H, Hartmann JT, et al. Capecitabine plus oxaliplatin as first-line treatment in patients with advanced biliary system adenocarcinoma: a prospective multicentre phase II trial. *Br J Cancer* 2008;98:309-315.
234. Kim TW, Chang HM, Kang HJ, et al. Phase II study of capecitabine plus cisplatin as first-line chemotherapy in advanced biliary cancer. *Ann Oncol* 2003;14:1115-1120.
235. Kobayashi K, Tsuji A, Morita S, et al. A phase II study of LFP therapy (5-FU (5-fluorouracil) continuous infusin (CVI) and Low-dose consecutive (Cisplatin) CDDP) in advanced biliary tract carcinoma. *BMC Cancer* 2006;6:121-121.

236. Eckel F, Schimid RM, Chemotherapy in advanced biliary tract carcinoma: a pooled analysis of clinical trials. *Br J Cancer* 2007;96:896-902.
237. Glimelius B, Hoffman K, Sjöden PO, Jacobsson et al. Chemotherapy improves survival and quality of life in pancreatic and biliary tract cancer. *Ann Oncol* 1996; 7: 593-600.
238. Sharma A, Mohanti B, Raina V, et al. A Phase II Study of Gemcitabine and Oxaliplatin (OXIGEM) in Unresectable Gall Bladder Cancer. *Cancer Chemotherapy and Pharmacology*. 10.1007/s00280-009-1055-0 Published online: 3 July 2009. Volume 65, Issue 3 (2010), Page 497-502
239. Castro MP. Efficacy of Gemcitabine in the treatment of patients with gallbladder: a case report. *Cancer*; 82: 639-641
240. Gallardo JO, Rubio B, Fodor M, et al. A phase II study of gemcitabine in gall bladder carcinoma. *Ann Oncol* 2001; 12: 1403-1406
241. Valle J, Wasan H, Palmer DH, et al. Cisplatin plus gemcitabine versus gemcitabine for biliary tract cancer. *N Engl J Med* 2010;362:1273-1281.
242. Sharma A, Dwary A D, Mohanti B K, et al. Best supportive care compared with chemotherapy for unresectable gall bladder cancer: A randomized controlled study. *J Clin Oncol* 2010; 28: 4581-4586.
243. Furuse J, Miyazaki M, Taniai H, Nimura Y. A randomized study of gemcitabine/cisplatin versus single-agent gemcitabine in patients with biliary tract cancer. *J Clin Oncol* 2009;27:Suppl:15s. abstract.
- 243a. National Cancer Institute. Physician Data Query (PDQ). Gallbladder Cancer Treatment. Last modified: 05/24/2013. Accessed at: <http://www.cancer.gov/cancertopics/pdq/treatment/gallbladder/HealthProfessional/page5/AllPages/Print>
- 243b. American Cancer Society. Gallbladder Cancer. Last revised 06/12/2013. Accessed at: <http://www.cancer.org/acs/groups/cid/documents/webcontent/003101-pdf.pdf>
244. Mac Masters KM, Tuttle TM, Leach SD: neoadjuvant chemotherapy for extrahepatic cholangiocarcinoma. *Am J Surg* 1997;174:605-609.
245. Engineer R, et al. Chemoradiation for unresectable gallbladder cancer: time to review historic nihilism? *J Gastrointest Cancer*. 2011;42(4):222-7.
- 245a. Glazer ES, Liu P, Abdalla EK, et al. Neither neoadjuvant nor adjuvant therapy increases survival after biliary tract cancer resection with wide negative margins. *J Gastrointest Surg*. 2012 Sep;16(9):1666-71. Epub 2012 Jul 10.
246. Fukuda S, Okuda K, Kinoshita H, Nakayama T, Tanaka M, Yoshida T, et al. Study of hepatic arterial chemoinfusion with continuous CDDP, 5-FU low dose administration for advanced gallbladder cancer. *Gan To Kagaku Ryoho* 1996;23(11):1610-3.
- 246a. Baron TH. Expandable metal stents for the treatment of cancerous obstruction of the gastrointestinal tract. *N Engl J Med* 344 (22): 1681-7, 2001.
247. Walsh D, Donnelly S, Rybicki L. The symptoms of advanced cancer: relationship to age, gender, and performance status in 1,000 patients. *Support Care Cancer* 2000; 8(3): 175-79.
248. Morita T, Tsunoda J, Inoue S, Chihara S. Contributing factors to physical symptoms in terminally-ill cancer patients. *J Pain Symptom Manage*, 1999; 18(5): 338-46.

249. Hwang SS, Chang VT, Kasimis B. Dynamic cancer pain management outcomes: the relationship between pain severity, pain relief, functional interference, satisfaction and global quality of life over time. *J Pain Symptom Manage* 2002; 23(3): 190-200.
250. Takiguchi Y, Watanabe R, Nagao K, Kuriyama T. Hiccups as an adverse reaction to cancer chemotherapy. *J Natl Cancer Inst* 2002; 94(10): 772-73.
251. Komurcu S, Nelson KA, Walsh D, Ford RB, Rybicki LA. Gastrointestinal symptoms among inpatients with advanced cancer. *Am J Hosp Palliat Care* 2002; 19(5): 351-5.
252. Ballatori E, Roila F. Impact of Nausea and Vomiting on Quality of Life in Cancer Patients during Chemotherapy. *Health Qual Life Outcomes* 2003; 1(1): 46.
253. Buijt I, Wait S, Groot AU. Economics and health-related quality of life in antiemetic therapy: recommendations for trial design. *Euro J Cancer* 2000; 36(12): 1522-35.
254. Gralla RJ, Osoba D, Kris MG. Recommendations for the use of antiemetics: evidence-based, clinical practice guidelines: American Society of Clinical Oncology. *J Clin Oncol* 1999; 17: 2971-94.
255. Weitzman S. Alternative nutritional cancer therapies. *Int J Cancer* 1998;11: 69-72.
256. Schultz M, Scholmerich J, Kullmann F. Management of chemotherapy induced diarrhea. *Z Gastro* 2004; 42(6): 527-38.
257. Tsuji Y, Sagawa T, Takayanagi N, Hirayama Y, Sakamaki S. Management of cancer treatment-related diarrhea and constipation. *Nippon Rinsho* 2003; 61(6): 966-72.
258. Oh EG. Symptom experience in Korean adults with lung cancer. *J Pain Symptom Manage* 2004; 28(2): 133-39.
259. Vissink A, Burlage FR, Spijkervet FK, Jansma J, Coppes RP. Prevention and treatment of the consequences of head and neck radiotherapy. *Crit Rev Oral Biol Med* 2003; 14(3): 213-25.
260. Wickham RS, Rehwaldt M, Kefer C, Shott S, Abbas K, Glynn-Tucker E et al. Taste changes experienced by patients receiving chemotherapy. *Oncol Nurs Forum* 1999; 26(4): 697-706.
261. Kugaya A, Akechi T, Okuyama T, Nakano T, Mikami I, Okamura H et al. Prevalence, predictive factors, and screening for psychological distress in patients with newly diagnosed head and neck cancer. *Cancer* 2000; 88(12): 2817-23.
262. Rossi Ferrario S, Zotti AM, Massara G, Nuvolone G. A comparative assessment of psychological and psychosocial characteristics of cancer patients and their caregivers. *Psychooncology* 2003; 12(1): 1-7.
263. NCCN Clinical Practice Guidelines in Oncology. Hepatobiliary Cancers (version 2.2012). Available at nccn.org
264. University of Rochester Tumor reporting system – Web based tool for pathology tumor reporting since 2003.

ABBREVIATIONS

| | |
|-------|--|
| AAR | Age Adjusted Rate |
| AJCC | American Joint Committee on Cancer |
| APBDJ | Anomalous Pancreaticobiliary Duct Junction |
| BMI | Body Mass Index |
| BSC | Best Supportive Care |
| CBD | Common Bile Duct |
| CI | Confidence Interval |
| CRT | Chemoradiotherapy |
| CT | Computed Tomographic scan |
| DFS | Disease Free Survival |
| EBRT | External Beam Radiotherapy |
| ECOG | Eastern Cooperative Oncology Group |
| EC | Extended Cholecystectomy |
| ERCP | Endoscopic Retrograde Cholangiopancreatography |
| EUS | Endoscopic Ultrasonography |
| FDG | [18F]-2-deoxy-D-glucose |
| FNAC | Fine Needle Aspiration Cytology |
| GBC | Gallbladder Cancer |
| GSD | Gallstone Disease |
| HAI | Hepatic Artery Infusion |
| H&P | History & Physical Examination |
| HPD | Hepato-pancreaticoduodenectomy |
| ICMR | Indian Council of Medical Research |
| IORT | Intraoperative Radiotherapy |
| LC | Laparoscopic Cholecystectomy |
| LFT | Liver Function Tests |
| MRI | Magnetic Resonance Imaging |
| MRCP | Magnetic Resonance Cholangiopancreatography |
| MRA | Magnetic Resonance Angiography |
| OS | Overall Survival |
| PET | Positron Emission Tomography |
| PSC | Primary Sclerosing Cholangitis |
| PTC | Percutaneous Transhepatic Cholangiography |
| RCT | Randomized Controlled Trial |
| RR | Relative Risk |
| TNM | Tumor, Node, Metastasis |
| USG | Ultrasound |

| | |
|------------------|---|
| *Desirable/Ideal | : Tests and treatment that may not be available at all centres but the centres should aspire to have them in near future. |
| Essential | : Rare minimum that should be offered to all the patients by all centres treating patients with cancer. |