TULYP-study

Tumours of the gallbladder; a prospective registry of patients and treatment outcomes

The registration and evaluation of current surgical and systemic treatment for gallbladder cancer.

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1. Introduction and rationale

Gallbladder cancer is the most prevalent malignancy of the biliary tract and the fifth most prevalent gastrointestinal malignancy. World-wide incidence of gallbladder cancer (GBC) is estimated to be around 2.3 per 100.000 and demonstrates noteworthy geographic variation. (1, 2) The precise pathogenesis remains unclear, but risk factors appear to include age, gender, ethnicity, gallstones, cholecystitis and other comorbid hepatobiliary diseases. (3) Traditionally, gallbladder cancer is considered to be a very aggressive and highly lethal malignancy. Literature reports overall 5-year survival rates of 10% with a median survival of only 5 – 8 months. (4, 5)

No remarkable changes in treatment strategies or outcomes have been seen the past few decades (6-9); to this date the only curative treatment strategy remains radical excision of the tumour. Unfortunately only 10% of (non-incidental) tumours are amenable for surgical resection at presentation due to a propensity for aggressive local growth and late symptomatology. (4, 10, 11)

Experts have yet to reach a consensus regarding the optimal extent of resection for both small tumours confined to the gallbladder wall as well as locally advanced disease. Available guidelines vary in their recommendations and studies demonstrate considerable inhomogeneity in international practise. (7, 12, 13) Some argue for an aggressive approach and state that lymph node dissection and gallbladder bed resection is required in T1b disease, whilst others state that not enough evidence is available to support this practise. (14) Indications for resection in locally advanced disease are even less clearly defined. Lymph node metastases and jaundice seem to be ominous prognostic factors and are associated with poor outcomes. (15, 16) Some studies demonstrate reasonable survival after extensive hepatic resections. However, the quality of these studies is limited due to small and selective patient samples. (17) Furthermore, morbidity and mortality associated with extensive hepatic resections are high and no randomised evidence is available. (10)

Since radical surgery is frequently unachievable and up to 50% of patients have already developed lymph node metastases at the time of diagnosis (13), there appears to be a dire need for effective adjuvant treatment strategies for early as well as advanced stage GBC.

Regrettably, due to the logistic challenges associated with researching a rare and highly lethal disease, this treatment option remains poorly explored. The ABC-02 trial, researching the value of adjuvant therapy in biliary tract carcinoma, demonstrated a 3-month increase in overall survival when administering gemcitabine plus cisplatin versus gemcitabine alone. (18) Recently, the BILCAP trial (unpublished) showed a significant survival advantage in patients treated with capecitabine compared to observation alone. However, no randomised trials have exclusively studied GBC and evidence remains scarce.

In summary, gallbladder carcinoma remains a malignancy with limited treatment options and a grim prognosis. Long-term survival seems to be dependent on early detection and aggressive surgical management. Management of the disease is largely based on retrospective research and expert opinion, resulting in considerable global practise variation. (19) Randomised research is challenging due to the low incidence of the disease. In this study, we aim to prospectively evaluate the efficacy of current treatment strategies for gallbladder neoplasms in terms of effect on symptom relief as well as disease free- and overall survival. This knowledge will hopefully be used to optimise contemporary treatment strategies and ultimately improve the expediency, homogeneity and efficacy of care for patients with gallbladder cancer.

2. Objectives

2.1 Primary objective

To prospectively analyse the management and outcomes of patients with gallbladder cancer in order to identify the optimal treatment strategy with regard to morbidity and mortality. Treatment outcomes will be analysed in terms of five-year survival rates.

2.2 Secondary objectives

- To identify risk factors for the development of gallbladder cancer.
- To establish guidelines for the pre-operative work-up of patients with gallbladder cancer including laboratory diagnostics, imaging and pre-operative therapy based on diagnostic accuracy of current imaging modalities as estimated during this study.

3. Study design

This study is a prospective multicenter cohort study, coordinated by the department of surgery of the Radboudumc in Nijmegen, the Netherlands. This is an observational study, meaning that participants will not be subjected to randomnisation or an intervention. The study will run over a course of at least five years. Patients with either a confirmed or suspected diagnosis of gallbladder cancer will be included. The first patient will be included in June 2018. Follow-up will continue until at least June 2023.

4. Study population

4.1 Study population (base)

All patients with (suspected) gallbladder cancer will be included in this study. Yearly, about 150-200 patients are diagnosed with gallbladder cancer in the Netherlands. The number of patients with suspected gallbladder cancer is unknown. Patients will be recruited in the

Netherlands through a collaborative network of all academic hospitals as well as a network of community hospitals participating in the SECURE (NTR4022) and FANCY trials.

4.2 Inclusion criteria

- Individuals of >18 years of age with a (suspected) diagnosis of primary gallbladder carcinoma.
- Written informed consent.

4.3 Exclusion criteria

- Inability to provide informed consent

4.4 Sample size calculation

A previously conducted national cohort study reported that >150 patients are diagnosed with gallbladder cancer in the Netherlands every year. Since recruitment will run through a very large network (+-50 out of 83 Dutch community hospitals as well as all 8 academic hospitals in the Netherlands) it is expected that a minimum inclusion rate of 100 patients per year should be feasible. The aim is to include a total of at least 500 patients. Assuming a loss to follow-up of 15% in the first year, 10% in the second year and 5% in the years thereafter this sample size should be sufficient to provide over 1000 patient years in follow-up. It is estimated that this will provide sufficient data to provide an accurate estimation of survival differences in varying treatment strategies.

For example, in the case of re-resections in the treatment of T1-T2 gallbladder cancer, literature reports a relative survival advantage of around 50%. Assuming 20% of patients receive a re-resection, 102 events would provide 80% power to demonstrate a significant difference at a 95% confidence level. (10, 14)

5. Treatment of subjects

5.1 Diagnostic procedures and treatment strategies

Diagnostic and treatment strategies will be left up to the discretion of the treating physician. All physicians will be advised to adhere to both recommendations provided by the consensus statement from the 2015 American Hepato-Pancreato-Biliary Association expert meeting as well as pre-existing national guidelines. (10, 20) A full outline of recommendations for diagnosis and treatment strategies based on the aforementioned consensus statement and guidelines is provided in the appendix (Figure 1 + 2, Table 4).

5.2 Data collection

All data will be gathered on-site by the coordinating investigator in collaboration with the treating physician. At inclusion the coordinating investigator will fill out an online case-report form involving items on baseline characteristics, diagnosis (incidental versus pre-operatively diagnosed gallbladder cancer) and choice and outcome of imaging modalities. During follow-up any gallbladder-cancer related event will be recorded (including, but not limited to; choice of and motivation for imaging and therapeutic strategy, treatment outcomes (in terms of symptom relief, morbidity and mortality), imaging and histopathological results and survival data). A summary of the variables that will be registered is provided in the appendix (Table

3). Deviations in management strategy from the guidelines provided in the appendix will be noted and motivated. Data collection will continue until March 2023.

6. Methods

6.1 Study endpoints

6.1.1 Primary study endpoint

- Overall- and disease-free five-year survival of patients with gallbladder carcinoma.

6.1.2 Secondary study endpoints

- Overall- and disease-free one– year survival of patients with gallbladder carcinoma.
- Treatment outcomes of patients with gallbladder carcinoma in terms of treatment-related morbidity and mortality, quality of life measures and recurrence rates.

6.1.3 Other study endpoints

- The epidemiological and clinical characteristics of patients with gallbladder cancer.
- Tumour- and patient related factors correlated with prognosis.
- Adequacy of current imaging strategies for the staging of gallbladder cancer in terms of sensitivity, specificity and diagnostic accuracy.

6.2 Study procedures

6.2.1 General study procedures

All eligible patients will receive a leaflet containing information on the background, procedures, demands and risks of the study before participation. Patients will be required to sign an informed consent form before being enrolled into the study. After informed consent is obtained, baseline characteristics will be entered into an electronic CRF (eCRF) by the coordinating investigator.

All treatment and follow-up will take place at the hospital of origin. Treatment plans and procedures are left up to the discretion of the treating physician. Although guidelines for diagnostic and treatment strategies are provided by the study protocol (see paragraph 5.1-5.3), physicians are free to deviate from said recommendations when deemed necessary or beneficial.

6.2.2 Handling and analysis of tissues

All tissue specimens will be analysed and stored at the hospital of origin. Tissues will be preserved as either formalin-fixed tissue, fresh-frozen tissue or paraffin-embedded tissue, depending on local practise.

6.2.3 Patient questionnaires

In order to assess physical and mental symptoms during follow-up, patients will be requested to fill out questionnaires at inclusion as well as during follow-up. The questionnaires will be administered via e-mail. Participation in the questionnaires is optional; in case patients do not wish to provide their e-mail address for this purpose they may still partake in the study. The questionnaires will be sent upon inclusion as well as after six months and yearly thereafter as well as before and after resection, the start of chemotherapy or other palliative treatment strategies. The items covered in the questionnaires include questions on symptomatology

and quality of life. In order to assess general symptoms and quality of life, the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire- C30 (EORTC-QLQ30) will be administered. The EORTC-QLQ30-questionnaire has been extensively validated and is frequently used to assess symptoms and quality of life of cancer patients. (21) Additionally, the 36-Item Short Form Survey (SF-36) will be administered. (22) The SF-36 is a general tool for the assessment of emotional and physical quality of life as well as the influence of symptoms on daily-, social- and work-related activities. The filling out of the questionnaire will take approximately 10-15 minutes.

6.3 Withdrawal of individual subjects

Individuals may withdraw from the study at any time without providing a reason. No consequences will follow and subjects will continue to receive care as usual from their treating physician.

6.4 Replacement of individual subjects after withdrawal

Not applicable.

6.5 Follow-up of subjects withdrawn from treatment

All subjects withdrawn from the study will continue to receive routine care from their treating physician.

6.6 Premature termination of the study

Not applicable.

7. Statistical analyses

All analyses and reporting will be done according to the STROBE-statement. SPSS 24.0 (SPSS Inc., Chicago, IL), SAS and R 3.2.0 statistical package will be used to conduct all statistical analyses. The first planned analyses will take place after 2 years and concern preliminary data regarding the study endpoints as described in 6.1. The second, final analyses will be conducted upon completion of the study. All statistical analyses will be conducted using SPSS Statistical Package for Social Sciences (SPSS Inc, Chicago, IL.) version 22.0, SAS and R statistical package 3.2.0. A p-level of <0.05 will be considered statistically significant.

7.1 Descriptive statistics

Baseline patient and tumour characteristics will be described using means for continuous variables and counts and percentages for categorical variables. Differences in baseline characteristics between subgroups will be assessed using the Student’s t-test, median test, chi-square test (with Yates’ correction when necessary) or Fisher exact test where appropriate. Descriptives of the secondary end points will be given for the total cohort as well as the following subgroups: 1) incidental versus pre-operatively diagnosed gallbladder cancer 2) T1, T2, T3 and T4 gallbladder cancer 3) surgically versus conservatively treated patients with locally advanced gallbladder cancer 4) node- positive and node-negative disease. If the sample size is sufficient, additional exploratory subgroup analyses will be conducted.

7.2 Diagnostic accuracy

The diagnostic accuracy of all used imaging modalities (MDCT, MRI, PET-CT and ERCP) in the staging of gallbladder carcinoma will be assessed by comparing the pre-operative imaging results to the final results on histopathological analysis. Clinical TNM-stage will be compared to histopathological TNM stage. 2x2 contingency tables will be generated to display true positives, true negatives, false positives and false negatives. Sensitivity, specificity and diagnostic accuracy will be calculated alongside with corresponding 95% confidence intervals. Diagnostic accuracy for T-stage (T1+T2 vs. T3+T4), liver invasion, bile duct invasion, organ invasion, distant metastases and nodal status will be assessed.

7.3 Survival analyses

Survival curves (concerning study endpoints as described in 6.1) will be constructed using Kaplan-Meier methods and displayed using cumulative survival curves. Overall survival is defined as the number of days between diagnosis and death or end of follow-up. Postoperative survival is defined as number of days between the initial surgery and death of any cause or end of follow-up. Patients alive at the last date of follow-up will be censored. Survival differences between pre-defined subgroups will be analysed using log-rank testing. The following subgroup analyses will be conducted: 1) survival stratified according to tumour stage 2) node-positive versus node-negative disease 3) incidental versus pre-operatively diagnosed gallbladder cancer 4) common bile duct involvement 5) adjacent organ involvement 6) R0 versus R1 or R2 resection 6) adjuvant versus no adjuvant therapy 7) simple versus extended cholecystectomy in T1b GBC. If a sufficient sample size is achieved, additional exploratory subgroup analyses may be conducted.

Cox-regression analysis will be used to identify possible prognostic factors associated with prolonged or decreased survival. An overview of possible prognostic factors is provided in Table 1.

7.4 Treatment outcomes

Treatment outcomes as described in 6.1 will be summarised. Univariate analyses will be conducted in order to identify possible risk factors for treatment-related morbidity, mortality and recurrence. An overview of potential prognostic factors is provided in Table 1. All risk factors with a p-value of <0.1 in univariate analysis will be entered into a multivariate model.

8. Ethical considerations

8.1 Regulation statement

This study will be conducted according to the principles of the Declaration of Helsinki (sixth version, 2008) and in accordance with the Medical Research Involving Human Subjects Act (WMO), the Dutch privacy law (Wet op Bescherming Persoonsgegevens) and the Medical Treatment Contract Act (Wet op de Geneeskundige Behandelingsovereenkomst).

8.2 Recruitment and consent

Eligible patients will be informed about the study by the treating physician. Additionally outpatient clinic patient personnel in all participating hospitals will be informed about this study. In case an eligible patient visits the outpatient clinic, the coordinating investigator will be notified. The coordinating investigator will then contact the treating physician with the

request to notify the patient about the possibility of participation in this study. In case a diagnosis of gallbladder polyp or gallbladder cancer is made intra- or postoperatively on histopathological analysis, patients will be approached by their treating physician and provided with study information after the operation has taken place. Potential participants will also be provided with a patient information brochure containing a description of the background, aims, methods and potential benefits and risks of the study. Patients will be required to provide written informed consent before being enrolled into the study. In case a participant is not willing to partake in the questionnaires or to make their tissue specimens available for further analysis, an opt-out option is provided on the informed consent form for these parts of the study.

8.3 Benefits and risk assessments

Participation in this study does not pose any risk for patients since the study is observational in nature. Treatment and surveillance strategies recommended by the protocol do not vary from current practise. No randomisation will take place and no experimental or additional interventions will be administered. Subjects might benefit from the contemporary guideline-based management approach encouraged in this study.

8.4 Compensation for injury

Not applicable.

8.5 Incentives

Not applicable.

9. Administrative aspects

9.1 Handling and storage of data and documents

All data will be gathered on-site and recorded in an eCRF. The coordinating investigator is responsible for data collection and storage. When entered into the eCRF each subject will be provided with a unique study ID. The subject identification log will be stored separately from the dataset and will only be accessible by authorised study personnel. Data collection and storage will be coordinated by the Radboudumc. All data will be stored in an online, secure database.

9.2 Privacy rules

This study will be conducted in accordance with the Dutch privacy law (Wet Bescherming Persoonsgegevens) Data will be managed using CastorEDC, an online database and data management tool. Castor is protected against unauthorised access according to the Good Clinical Practise Guidelines.

9.3 Archiving of data

All study data including subject identification log, source documents, informed consent forms and clinical databases will be kept until 15 years after completion of the study. The coordinating investigator is tasked with record keeping and will nominate someone in writing to be responsible for record keeping in case he/she will no longer be involved in the study due to any reason.

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11. Appendix

Table 1. Potential prognostic factors for treatment related morbidity & mortality, recurrence and overall survival

Patient-related	Tumour-related	Treatment-related
Age	ACJJ stage	*Operative treatment*
ASA-class	Grade	Extent of liver resection
Sex (M/F)	Location	Extent of lymphadenectomy
History of gallbladder disease	Nodal status	Vascular reconstruction
History of malignancy	Histopathological profile	Bile duct resection
History of previous abdominal surgery	Presence of CBD invasion	Pre-operative biliary drainage
Family history of gallbladder disease	Presence of liver invasion	*Systemic treatment*
Presence of jaundice	Presence of invasion of abdominal organs	Type of cytostatic administered
Smoking	Presence of neurovascular invasion	Frequency & dose
Alcohol abuse	Presence of lymph node invasion	Timing of systemic therapy (adjuvant, neo-adjuvant or palliative)
		Radiotherapy
		Frequency & dose
		Timing of radiotherapy (adjuvant, neo-adjuvant or palliative)

Table 2. Case-report form for histopathological analysis

Characteristic	Description
Histological type	
Histological grade	
Depth of invasion (T stage)	
Resection margin (in mm)	
Completeness of resection (R0, R1, R2)	
Number of excised lymph nodes	
Number and location of metastatic lymph nodes (N stage)	
Invasion	
Perineural	
Lymphatic	
Vascular	
Tumour size	
Tumour location	
Macroscopic description of tumour	
Other findings (dysplasia, BIN, ICTPN, cholecystolithiasis, chronic inflammation)	

Figure 1. Pre-operative work-up of GBC according to the national guidelines and 2015 consensus statement. (10, 20)

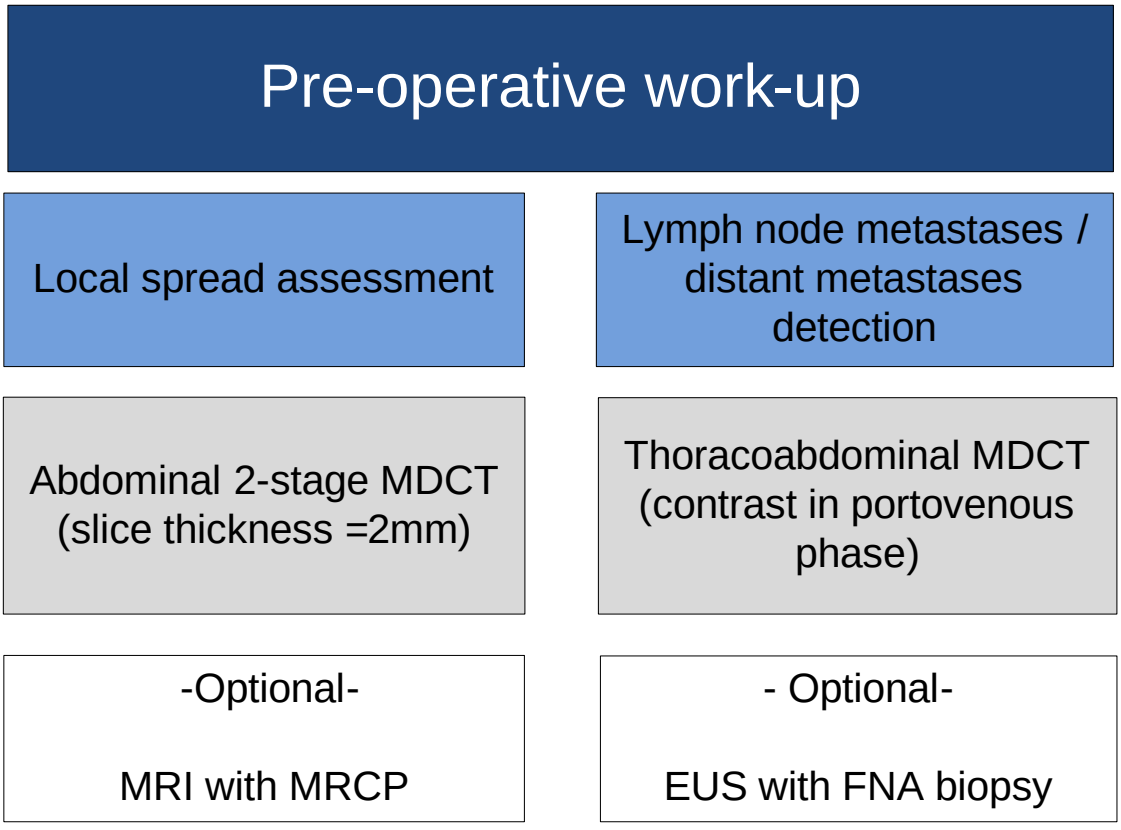

Figure 2. Surgical strategies & recommendations

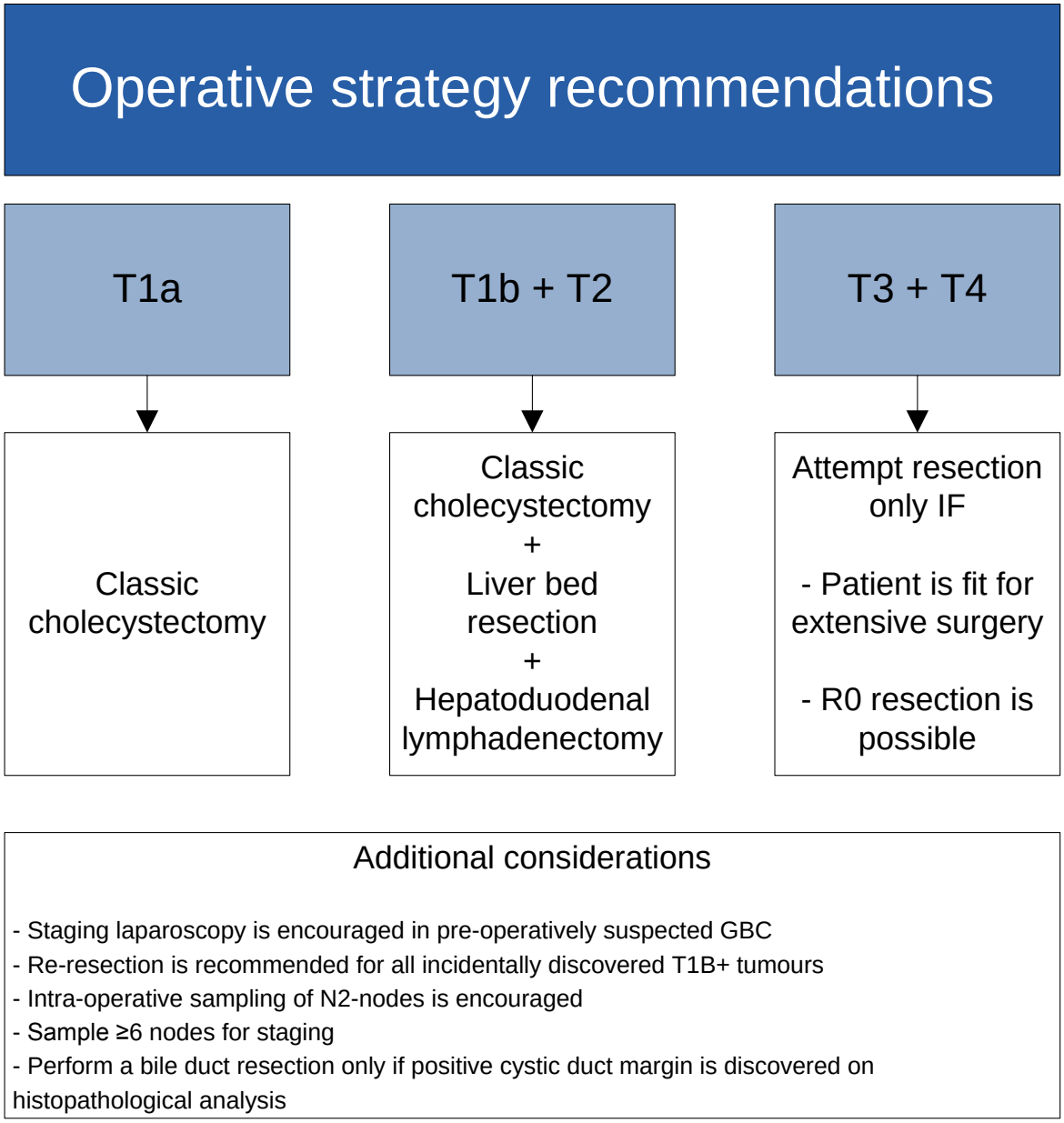

Table 3: Summary of case-report form for data collection

Baseline characteristics			
Age Gender ASA class	Presence of risk factors for GBC Previous medical and surgical history	Hospital type (community vs. academic)	Presenting symptoms and complaints
Diagnostic evaluation/imaging			
Imaging		*Laboratory values*	
Type of imaging modality used Imaging reports		Hepatic function Tumour marker levels	
Operative therapy			
Pre-operative therapy (ERCP, stent)	Type of resection Operative notes	Re-resection yes/no Operative notes re-resection	Complications Clavien-Dindo grade
Systemic therapy			
Type of systemic therapy ((neo) adjuvant or palliative)	Chemotherapeutic drug type, dose and dosing schedule	Adverse reactions CTC-grade	Tumour response (complete response, partial response, stable disease, tumour progression)
Radiotherapy			
Type of radiotherapy ((neo)adjuvant or palliative)	Dose (GY) Dosing schedule	Adverse reactions	Tumour response (complete response, partial response, stable disease, tumour progression)
Other/palliative therapy			
Therapy type (ERCP, PTC, stent)	Indication		Adverse reactions/events
Histopathological analysis results			
TNM-stage Organ invasion Neurovascular invasion Lymph node metastases Common bile duct invasion Distant metastases Resection margin	Macroscopic growth pattern Microscopic growth pattern Histopathological grade Tumour morphology Lesion size Lesion location		Microsatellite instability BIN ICTPN Immunohistochemistry
Follow-up/survival			
Recurrence (local/distant)	Follow-up duration (days)		Vital status Cause of death

Table 4: Recommendations and considerations for systemic therapy

Chemotherapy	Radiotherapy
- Adjuvant chemotherapy is not considered standard of care - Consider adjuvant therapy in T2+ node-positive disease - Palliative chemotherapy should be considered for patients with unresectable and/or metastatic GBC - Gemcitabine and capecitabine are commonly used agents in palliative therapy	- Adjuvant radiotherapy is not considered standard of care - Palliative radiotherapy (8GY, single dose) can be considered for symptom relief