

BMJ Open A phase III randomised clinical trial of perioperative therapy (neoadjuvant chemotherapy versus chemoradiotherapy) in locally advanced gallbladder cancers (POLCAGB): study protocol

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ABSTRACT

Introduction Neoadjuvant chemotherapy (NACT) is considered the current standard for locally advanced gallbladder cancer (GBC). There is no consensus on the optimal neoadjuvant approach. A pilot study from our institution has shown improved overall survival (OS) and progression-free survival (PFS) with neoadjuvant chemoradiation (NACRT). The present randomised phase III trial is designed to compare NACRT with NACT alone and will test the superiority of chemoradiation in terms of tumour downstaging and improvement in OS.

Methods and analysis Patients with biopsy-proven locally advanced GBC (T3–4) with predefined clinical–radiological features will be randomised to the gemcitabine-based chemotherapy-alone arm or the chemoradiation arm. Patients with resectable disease or with distant metastases will be excluded. The primary end point of the study is to compare OS between the two arms. The secondary end point was to compare PFS, R0 resection rates, acute and late toxicity, postoperative complications and quality of life between the two study arms. The trial is designed to detect an improvement in median OS by 5.5 months in the study arm (11 months in the control group, HR of 0.7) with 80.0% power at a 0.05 significance level. The resultant sample size to achieve this aim is 314 (157 in each arm) over a duration of 5 years with a 10% attrition rate.

Ethics and dissemination The institutional ethics committee has approved this trial and will be routinely monitoring the trial at frequent intervals. The results of the study will be disseminated via peer-reviewed scientific journals, conference presentations and submission to regulatory authorities.

Registration The trial is registered with Clinical Trials Registry India (CTRI/2016/08/007199) and ClinicalTrials.gov (NCT02867865). This trial aims to assess the superiority of NACRT over NACT in locally advanced GBCs in terms of improvement in OS. The results of this study will define the optimal neoadjuvant approach in locally advanced GBC.

Strengths and limitations of this study

- This is the first randomised study evaluating chemoradiation in the neoadjuvant setting.
- Treatment of locally advanced gallbladder cancer (GBC) is not standardised, and this trial will give an opportunity to do so.
- Slower recruitment of patients: as majority of patients with GBC in the population present late in the course of the disease, a large fraction of the screened patients turn out to be metastatic or with advanced disease that do not meet the stringent inclusion criteria for the trial. This has resulted in low enrolment into the study.
- Compliance of patients: the long treatment time (>6 months), combined with the socioeconomic restrictions of the majority of the population, makes it challenging for the patients to stick to the advised care, resulting in financial burden and subsequently increased susceptibility of dropout and loss of follow-up.
- As the treatment is decided and delivered by a large team of physicians that consists of radiologists, gastroenterologist, oncosurgeons, medical oncologists and radiation oncologists, the coordination of the team becomes challenging.

Trial registration number NCT02867865; Pre-results.

INTRODUCTION

Gallbladder cancer (GBC) is the most common malignancy of the biliary tract.¹ Its incidence is alarmingly high in Chile, Japan and northern India.² Complete surgical excision is the standard of care for early-stage GBC. Unfortunately, majority of the cases are diagnosed at an advanced or metastatic stage,

and only 10%–30% of the patients present with resectable disease.²

GBC with liver infiltration, with or without visceral/vascular infiltration, or having large local lymph node metastases in the absence of distant metastases is generally considered as locally advanced. Prognosis for locally advanced disease in terms of resectability and survival remains dismal in most of the reports.³ Even with aggressive surgery like extrahepatic bile duct resection or pancreaticoduodenectomy, the 5-year survival rate for stage III disease at best ranges from 30% to 42%. These results are often not reproducible in routine clinical practice.^{4–9}

Locally advanced GBC, where surgery is not possible, is treated with chemotherapy alone as the current standard of care. In the advanced biliary cancer (ABC-02) trial by Valle *et al*, neoadjuvant chemotherapy (NACT) with gemcitabine and cisplatin was found to be superior to gemcitabine alone in terms of local tumour response.¹⁰ Some locally advanced non-metastatic GBCs do get downstaged to undergo resection following NACT. In a publication from our institute, gemcitabine/cisplatin-based NACT alone resulted in an R0 resection rate of 46% and a median overall survival (OS) and progression-free survival (PFS) of 13.4 and 8.1 months, respectively.¹¹

Few studies have reported the outcomes of neoadjuvant chemoradiation (NACRT) with limited success.^{12 13} In an earlier report, we published the outcomes of three patients with unresectable tumours, two of which were downstaged to undergo R0 resection with high-dose NACRT.¹⁴ In a pilot study of 28 patients treated with NACRT conducted at our centre, 47% of the patients underwent R0 resections with median OS and PFS being 35 and 20 months, respectively.¹⁵

There is no consensus on the optimal neoadjuvant approach in locally advanced gallbladder carcinoma (GBC). However, most of the treating physicians prefer to use NACT alone followed by surgical resection if downstaging is achieved. The present randomised trial is designed to compare NACRT with NACT alone and will test the superiority of one over the other in terms of downstaging and prolonging survival.

METHODS AND ANALYSIS

Hypothesis

On the basis of encouraging results obtained with NACRT, we hypothesise that NACRT and additional chemotherapy will improve OS compared with NACT alone in locally advanced GBC.

Study aim

The primary aim of the study is to compare the OS between the patients treated with NACT alone with NACRT. The secondary aim is to compare the R0 surgical resection rate, PFS, acute and late toxicities, postoperative complications and quality of life (QOL) between two study arms.

Study design

This study is a phase III randomised control trial designed to compare the OS between the two neoadjuvant treatment arms. All patients with diagnosis of non-metastatic locally advanced GBC who fulfil the study eligibility criteria will be evaluated for participation in the study. Patients will undergo upfront randomisation into one of the study arms (NACT or chemoradiation) using permuted block stratified randomisation. Stratification will be done according to the T stage (T1–4). All randomisations will be done through the clinical research secretariat at Tata Memorial Hospital (TMH).

Research setting

The study will be conducted at TMH, Tata Memorial Centre, and Advanced Centre for Treatment Research and Education, Mumbai, India, and other collaborating centres.

Patients and public involvement

This research was conceived without patient and public involvement. The patients and the public were not invited at any stage of the study design or initiation.

Screening

All patients will be screened for distant metastases at baseline (prior to randomisation) using positron emission tomography–contrast-enhanced CT (PET-CECT) scan. Patients found to be non-metastatic will be subjected to staging laparoscopy to rule out peritoneal metastases. A tissue diagnosis from the primary would be done by either biopsy or fine needle aspiration cytology.

Participants eligibility

Inclusion criteria

Patient older than 18 years of age with histologically proven diagnosis of locally advanced GBC (adenocarcinoma) T3 or T4 tumours with one or more of the following criteria will be included in the trial:

1. Liver invasion: more than 2 cm but less than 5 cm.
2. Radiological involvement of the antropyloric region of the stomach, duodenum, hepatic flexure of the colon or small intestine, but without infiltration of the mucosa on endoscopy.
3. Type I/II invasion: involvement of the bile duct (common hepatic duct or proximal one-third of the common bile duct) on percutaneous transhepatic biliary drainage/magnetic resonance cholangiopancreatography causing obstructive jaundice.
4. Radiological suspicion of regional lymph node involvement along the hepatic artery, hepatoduodenal ligament, retropancreatic/retroduodenal: size >1 cm in short axis, round in shape and heterogeneous enhancement on PET scan.
5. Vascular involvement: impingement/involvement (<180 degree angle) of one or more of the following blood vessels: common hepatic artery/right hepatic artery/main portal vein/right portal vein (stage III disease).

6. Patients who have undergone prior cholecystectomy, having residual disease with at least one of the above features.
7. The patients must have good general condition Eastern Co-operative Oncology Group (ECOG 0–2).
8. Normal haematological, renal and hepatic functions done no earlier than 2 weeks prior to treatment initiation.

Exclusion criteria

Those patients with resectable disease or with evidence of distant metastasis (liver, lung, peritoneum and port site) are excluded from the study. Patients with involvement of the major part of the liver that restricts delivery of full radiotherapy (RT) doses and those who have undergone prior radiation or chemotherapy are deemed ineligible to participate in the trial. Patients with evidence of active cholangitis or unresolved biliary obstruction will be excluded.

Informed consent

Any of the investigators or coinvestigators or a research officer/nurse of this trial can obtain informed consent or assent from potential trial participants or authorised surrogates. The consent form will be given at least 2 days prior to randomisation. All efforts would be taken to keep their confidentiality.

Study interventions

NACT-alone arm (standard arm)

Patients randomised to NACT-alone arm will proceed to receive four cycles of gemcitabine (1000 mg/m²) delivered on days 1 and 8 every 3 weeks, along with cisplatin (25 mg/m²) on day 1. Patients will be assessed for response and evaluated for surgical resection using PET-CECT scan after four cycles of chemotherapy. If the scans show stable but unresectable disease, then patients will continue to undergo the same chemotherapy. Patients showing locally progressive/systemic disease may be considered for either second-line palliative chemotherapy or best supportive care. The use of radical-dose chemoradiation is not allowed on disease progression in this arm. However, palliative radiation of 20–25 Gy in four to five fractions may be used.

Prior to each cycle of chemotherapy, assessment of haematological, renal and hepatic functions will be done. Patients with creatinine clearance >50 mL/min cisplatin will be administered at a dose of 25 mg/m². In case of creatinine clearance between 40 and 50 mL/min, either substitution with oxaliplatin or 20%–25% dose reduction may be applied. Gemcitabine+cisplatin or gemcitabine+oxaliplatin is used and dose modification is done as decided by the medical oncologist's decision as per standard oncological guidelines.

NACRT arm (experimental arm)

Patients randomised to the NACRT arm will undergo radiation therapy for 5 weeks with concurrent gemcitabine-based chemotherapy (300 mg/m² weekly) followed

by two cycles of gemcitabine+cisplatin systemic chemotherapy. The dose and schedule for gemcitabine+cisplatin chemotherapy will be same as the standard arm. The chemotherapy will start 3 weeks after completion of radiation.

RADIOTHERAPY PLANNING AND CONTOURING

Simulation

The planning contrast-enhanced CT (CECT) scan will be done in fasting state with the patient in supine position with arms over the head and a knee rest. An immobilisation device such as a vacuum bag or a thermoplastic mask will be used. Fiducials will be placed at the laser intersection points at the level of the xiphisternum. The scan will be taken from the level of the carina to L4–5 levels with 2.5 mm interslice thickness in the portal phase of intravenous contrast. Respiratory motion management technique, such as Four-dimensional computed tomography (4DCT) or deep inspiratory breath hold technique, may be considered.

Contouring

The gross tumour volume will be delineated using the information from all available imaging, such as the diagnostic triphasic CECT and PET scan, and it will be fused with planning scan. It will include the primary and involved locoregional lymph nodes. The clinical target volume (CTV) consists of the adjacent areas of suspected microscopic disease in the surrounding liver parenchyma and the draining locoregional lymph nodes at the pericoledochal, cystic duct, retroportal, along the common hepatic artery, along the hepatoduodenal ligament, pancreaticoduodenal, hilar, periportal, portacaval and retropancreatic regions. The planning target volume (PTV) will be generated by adding a safety margin of 5–7 mm around the CTV to counter motion and set-up variations. The aim will be to deliver 52–57 Gy/25 fractions to the gross disease and 45 Gy/25 fractions to the suspected microscopic disease, along with weekly gemcitabine (300 mg/m²).

Organ at risk (OAR) contouring will include the liver, oesophagus, stomach, duodenum, kidneys, heart, lungs, bowel and spinal cord. All care will be taken to restrict OAR doses as per standard guidelines. The dose constraints for the OAR are as follows: 70% of the liver <30 Gy, mean liver dose <25 Gy, 70% of each kidney to receive <20 Gy, mean dose <18 Gy for each kidney, V15 of the small bowel <190 cc and for the duodenum: V55 <1 cc, V50 <4 cc.¹⁶ Special focus will be given to restrict dose to normal liver parenchyma and adjacent gastrointestinal structures, such as the duodenum, to minimise radiation-induced grade 3 or higher toxicity.

Radiation plan

All patients will be treated with intensity-modulated radiotherapy (IMRT) (RapidArc or tomotherapy). Dose-volume histograms will be evaluated for target volume

coverage and normal tissue-sparing according to standard IMRT plan evaluation indices.¹⁷ It will be ensured that 95% of the target volume receives at least 95% of the prescribed dose. Volumes of hotspots (>107% of the prescription dose) will be kept as low as possible throughout the treatment volume. Patient-specific quality assurance of the approved dose plan will be done prior to starting RT.

Treatment delivery and monitoring

Treatment will be delivered with daily megavoltage/kilovoltage CT imaging to ensure adequate PTV coverage. All patients will be prescribed prophylactic antacids and mucosal coating agent from day 1 of radiation starting as a measure to prevent duodenal toxicity. Haematological, hepatic and renal functions, as well as tolerance to the treatment, will be assessed weekly during NACRT. Toxicity will be recorded as per National Cancer Institute Common Terminology Criteria (CTCAE) V.4.2 at baseline and weekly during NACRT.

Efficacy and safety assessments

During weeks 12–13 of starting the treatment, PET-CECT scan will be repeated and compared with the initial scans for response assessment using Response Evaluation Criteria in Solid Tumours (RECIST) V.1.1.¹⁸ The response of the therapy will be assessed in terms of

Complete response (CR): disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.

Partial response (PR): at least a 30% decrease in the sum of diameters of target lesions.

Progressive disease (PD): at least a 20% increase in the sum of diameters of target lesions or appearance of one or more lesions. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm.

Stable disease (SD): neither sufficient shrinkage to qualify for PR/CR nor sufficient increase to qualify for PD.

Surgery

All patients with a CR, PR or SD will be re-evaluated for feasibility of surgery after at least 3 weeks of completion of all neoadjuvant therapy in both arms. Surgical resection, if considered feasible, will be done between weeks 14 and 15 after starting the neoadjuvant therapy. The decision regarding surgery will be taken by a hepatobiliary surgical oncology consultant. Surgical resection will entail en bloc resection of the gallbladder with a wedge excision of liver/segment IVb/V excision with an aim to achieve negative margin and complete periportal lymphadenectomy (stations 8, 12 and 13), along with a sampling of interaortocaval nodes to detect occult metastasis. Additional organ resection may be performed if necessitated to achieve R0 status as guided by intraoperative frozen section. Performance of extended resections like pancreatoduodenectomy or major hepatectomy to achieve

negative margins will be left to the discretion of the operating surgeon. Complications following surgery will be recorded as per the Clavien–Dindo grading system.¹⁹

Adjuvant therapy

All the patients after surgery will undergo three cycles of adjuvant chemotherapy with gemcitabine (1000 mg/m²) on days 1 and 8 and cisplatin (25 mg/m²) on day 1 delivered every 3 weeks. Patients with PD and those with CR/PR/SD and are not eligible for surgery will be evaluated for second-line palliative chemotherapy or best supportive care.

Treatment evaluation

CTCAE V.4.2 will be used for reporting all acute and late toxicities. Adverse events (AEs) in both arms will be graded using the CTCAE V.4.2. Toxicity profile for thrombocytopenia, neutropenia, fatigue, neuropathy, vomiting, flu-like syndrome, hepatic dysfunction, gemcitabine-induced rash and febrile neutropenia will be recorded. Grade 3 or more thrombocytopenia and vomiting is dose-limiting toxicity and warrants a dose reduction of 25%. If grade 3 or more toxicities are observed during radiotherapy, concurrent gemcitabine dose will be withheld for a week.

Quality of life

FACT-Hep V.4 will be used to assess QOL scores of all five modules of physical well-being, social/family well-being, emotional well-being, functional well-being and hepatobiliary function-related specific questions. It will be done at baseline, at completion of all neoadjuvant treatment (prior to surgery), at treatment completion and at all follow-up time points.

Follow-up

Patients will be evaluated every 3 months for a period of 2 years with routine complete haemogram and biochemistry, along with ultrasound of the abdomen and pelvis on each follow-up and thereafter every 6 months. QOL with FACT-Hep will be filled on every follow-up.

STATISTICAL CONSIDERATIONS

Outcome measures

The following outcome measures will be recorded.

OS: time interval between the date of the first neoadjuvant treatment and death due to any cause.

PFS: time interval between the date of randomisation and locoregional or distant disease progression or death from any cause.

R0 surgical resection rate: negative surgical margin (R0) rate as determined by intraoperative frozen section. However, final confirmation of the margin status on the histopathology report of the specimen would be done.

R1 resection: microscopic positive margin on histopathology.

R2 resection: presence of gross residual disease or tumour spillage during surgery.

The number of patients downstaged by neoadjuvant treatment in either arm enabling a margin-negative surgical resection will be documented.

Response rate: response to treatment will be assessed with PET-CECT scan using RECIST as mentioned previously. The pathological response rate in both arms would also be assessed.

Primary endpoint

The primary end point of the study is the OS. The estimated median OS in the control group is 11 months with an expected increase of median OS of 16.5 months in the study arm. The sample size is 286 subjects (143 in each arm) with 80.0% power at a 0.05 two-sided significance level to detect an HR of 0.7 when the control group median OS has an HR of 1. With 10% expected lost to follow-up in both groups, we will accrue 314 patients (157 in each arm) for the whole study. The study duration is 60 months, of which subject accrual will be done in the first 36 months. The accrual pattern across time periods is uniform (all periods equal). To improve accrual, other centres will be encouraged to participate in this study.

Data collection

All the data related to the study will be collected and maintained by the principal investigator at the TMH, Mumbai.

Treatment planning data

The volume, mean, median and maximum radiation dose to PTV, the duodenum, liver, stomach, both the kidneys and the bowel will be recorded for each patient. In addition, V30 liver, V20 kidney, V15 small bowel and V45, V50 and V55 of the duodenum will be recorded.

Treatment data

Data of all the treatment received will be compiled to report the dose of radiation to target and OAR, overall time of treatment, treatment gaps, if any, chemotherapy dose, dose reductions, surgical outcomes and postoperative complications.

Toxicity evaluation

Treatment-related toxicity will be reported using CTCAE V.4.2. CTCAE forms will be filled at baseline before starting radiation, weekly during treatment and on each scheduled follow-up. If any toxicity occurs at another time point, additional forms will be filled to record the toxicity.

Quality of life

FACT-Hep V.4 will be used to assess QOL scores of all five modules of physical well-being, social/family well-being, emotional well-being, functional well-being and hepatobiliary function-related specific questions. It will be done at baseline, during treatment (at completion of neoadjuvant treatment), at treatment completion and at subsequent follow-ups.

Clinical outcome data

The status of the disease will be evaluated with physical examinations and required investigations and will be

recorded at each follow-up. A detailed systemic work-up will be performed annually to detect, record and report the locoregional and distant controls.

Protocol compliance

Inability to receive the planned treatment as per the protocol (chemotherapy as well as radiation) will be regarded as a major violation that will be reported to the institutional review board (IRB). The inability to achieve target or OAR constraints or the patient missing two to three fractions of RT or one to two cycles of concurrent chemotherapy will be considered as a minor violation.

Event reporting

All events related to the study will be recorded using CTCAE V.4.2. All serious adverse events (SAEs) will be reported. SAEs within the test arm will necessitate hospitalisation. Toxicity arising out of systemic chemotherapy or patients developing cholangitis will not be considered a trial-related injury or a related SAE. CTCAE V.4.2 will be used for reporting of all SAEs to the IRB within 24 hours of the occurrence. Similarly, all deaths will be reported to the IRB.

Trial monitoring

The progress of the trial will be monitored at regular intervals (annually) by the institutional data and safety monitoring board, and the report will be submitted to the ethics committee and the IRB. The process will be independent of investigators and the sponsor.

Data analysis plan

No interim analyses have been planned for this study; however, the data monitoring committee has full authority to stop the trial if it perceives harm to any of the arm of patients. Intention-to-treat analysis will be performed along with survival for patients who undergo surgery in both groups.

Primary aim

Kaplan-Meier curves for OS will be generated for both arms, and OS will be compared using log-rank test stratified for the stratification factors that were used during randomisation (T stage). A p value of <0.05 will be considered statistically significant and will be used to reject the null hypothesis.

Secondary aim

A similar Kaplan-Meier analysis will be performed for PFS. Toxicity assessment will be using categorised groups between the two arms and χ^2 test will be used. R0 surgical resection rates and response rates will be calculated within each treatment arm, along with exact 95% CIs based on binomial distributions compared between treatment arms using two-sample Cochran-Mantel-Haenszel test at the 5% level of significance. Rates of grades 3 and 4 AEs will be summarised by treatment arm using descriptive statistics.

Ethics and dissemination

The institutional ethics committee of TMH, Mumbai, has approved this trial and will be routinely monitoring the trial at frequent intervals. The results of the study will be disseminated via peer-reviewed scientific journals, conference presentations and submission to regulatory authorities.

QOL ANALYSIS

Standard recommendations will be used to analyse QOL data of the two study arms and repeated measures analysis of variance will be used to compare QOL between the two arms.

Implications for research

The current study aimed to assess the benefit of NACRT over chemotherapy alone in terms of OS in locally advanced GBC. If proven to be effective, it would redefine the current standard of care for these patients.

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Contributors RE is the principal investigator and participated in the project concept, design, final approval, and manuscript preparation, review and submission. SP participated in the final approval of the protocol and manuscript preparation, review and submission. SCL participated in the review and final approval of the protocol, and manuscript preparation. ADS participated in the manuscript preparation, review and submission. NS participated in the final approval of the draft, and the review and preparation of the manuscript. VO participated in the review of the manuscript for content, review and preparation of manuscript, submission of the final protocol and final approval. AR participated in the review and preparation of manuscript, and preparation and final approval of the trial protocol. SC participated in the drafting of the final protocol, review of the contents of the protocol, manuscript preparation and final approval. AA participated in the manuscript preparation, review of the final protocol and approval of the final protocol draft. PP participated in the concept and design, preparation and review of the manuscript, and the final approval of the trial protocol. SM participated in the review and preparation of the manuscript, drafting of the final report and final approval. MG (co-principal investigator) participated in the concept and design, review and preparation of the manuscript, drafting of the final report and final approval of the trial protocol.

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