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Complete List of Authors:	Engineer, Reena; Tata Memorial Hospital, Radiation Oncology Patkar, Shraddha; Tata Memorial Centre, Department of Surgical Oncology Lewis, Shirley; Tata Memorial Hospital, Radiation Oncology Sharma, Ashutosh; Tata Memorial Centre, radiation oncology; Shetty, Nitin ; Tata Memorial Centre, Department of Radiodiagnosis Ostwal, Vikas; Tata Memorial Centre, Department of Medical Oncology, GastroIntestinal Disease Management Group Ramaswamy, Anant; Tata Memorial Centre, Department of Medical Oncology, Gastrointestinal Disease Management Group Chopra, Supriya; ACTREC,Tata Memorial Centre, Radiation Oncology Agrawal, Archi; Tata Memorial Hospital, Nuclear Medicine Patil, Prachi; Tata Memorial Centre, Department of Digestive Diseases and Clinical Nutrition Mehta, Shaesta; Tata Memorial Centre, Department of Digestive Diseases and Clinical Nutrition Goel, Mahesh; Tata Memorial Centre, Surgical Oncology
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Title page

A Phase III Randomized Clinical trial of Perioperative therapy (Neoadjuvant chemotherapy v/s chemoradiotherapy) in locally advanced gall bladder cancers (POLCAGB).

Reena Engineer[1], Shraddha Patkar[2], Shirley Lewis[1],Ashutosh Das Sharma[1], Nitin Shetty[3], Vikas Ostwal[4], Anant Ramaswamy[4], Supriya Chopra[5], Archi Agrawal[6], Prachi Patil[7], Shaesta Mehta[7], Mahesh Goel[2]

1- Department of Radiation Oncology, Tata Memorial Hospital, Mumbai, India

2- Department of Surgical Oncology, Tata Memorial Hospital, Mumbai, India

3- Department of Radiodiagnosis, Tata Memorial Hospital, Mumbai, India

4- Department of Medical Oncology, Tata Memorial Hospital, Mumbai, India

5- Department of Radiation Oncology, ACTREC, Tata Memorial Centre, Mumbai, India

6- Department of Nuclear Medicine, Tata Memorial Hospital, Mumbai, India

7- Department of Digestive Diseases and Clinical Nutrition, Tata Memorial Hospital, Mumbai, India

Corresponding author Reena Engineer

Room no. 322

Tata Memorial Hospital

Dr.E. Borgese Road

Lower Parel

Mumbai, MH

India

+912224177000(ext-7165)

Email-reena.engineer@gmail.com

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Main Document

A Phase III Randomized Clinical trial of Perioperative therapy (Neoadjuvant chemotherapy v/s chemoradiotherapy) in locally advanced gall bladder cancers (POLCA-GB).

ABSTRACT

Introduction:

Neoadjuvant chemotherapy is considered the current standard for locally advanced gallbladder cancer. There is no consensus on the optimal neoadjuvant approach. A pilot study from our institution has shown improved overall survival and progression free survival with neoadjuvant chemoradiation. The present randomized phase 3 trial is designed to compare neoadjuvant chemoradiation with neoadjuvant chemotherapy alone and will test the superiority of chemoradiation in terms of tumor downstaging and improvement in overall survival.

Methods and analysis:

Patients with locally advanced gallbladder cancer (T3-4) with predefined clinic-radiological features will be randomized to gemcitabine-based chemotherapy alone arm or chemoradiation arm. Patients with resectable disease or with distant metastases will be excluded. The primary end point of the study is to compare overall survival between the two arms. The secondary end points are to compare progression free survival, R0 resection rates, acute and late toxicity, postoperative complications, and quality of life between two study arms. The trial is designed to detect an improvement in median overall survival by 5.5 months in the study arm(11 months in control group; Hazard ratio 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 clinical trial.gov (NCT).

Article summary:

Article focus:

-Does neoadjuvant chemoradiation in locally advanced gallbladder cancer improve overall survival?

-Will neoadjuvant chemoradiation achieve downstaging and facilitate R0 resection?

Key Messages:

-This trial aims to assess the superiority of neoadjuvant chemoradiation over neoadjuvant chemotherapy in locally advanced gallbladder cancers in terms of improvement in overall survival.

-The results of this study will define the optimal neoadjuvant approach in locally advanced gallbladder cancer.

Strengths and limitations of the study:

Strengths of this study are:

1-This is the first randomized study evaluating chemoradiation in the neoadjuvant setting.

2-Treatment of locally advanced GBC is not standardized and this trial will give an opportunity to do so.

The limitations of this study are:

1-Slower recruitment of patients- As majority of patients with GBC in 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.

2-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 drop out and loss of follow up.

3-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.

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 patient 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 are 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, are treated with chemotherapy alone as the current standard of care. In ABC02 trial by Valle et al, neoadjuvant chemotherapy (NACT) with gemcitabine and cisplatin was found to be superior to gemcitabine alone in terms of local tumor response [10]. Some locally advanced non-metastatic GBC do get down-staged to undergo resection following NACT. In a publication from our institute, gemcitabine/cisplatin based NACT alone resulted in R0 resection rate of 46% and median overall survival (OS) and progression free survival (PFS) of 13.4 months 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 3 patients with unresectable tumors, 2 of which were down staged to undergo R0 resection with high dose NACRT [14]. In a

pilot study of 28 patients conducted at our center, treated with NACRT, 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 GBCA. However, most of the treating physicians prefer to use NACT alone followed by surgical resection if down staging is achieved. The present randomized trial is designed to compare NACRT against NACT alone and will test the superiority of one over the other in terms of down staging and prolonging survival.

Methods and analysis

Hypothesis

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

Study aim

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

Study Design

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

Research Setting

The study will be conducted at TMH, Tata Memorial Centre(TMC), and Advanced Centre for Treatment Research and Education(ACTREC), Mumbai, India and other collaborating centers.

Patients and Public Involvement

This research was conceived without patient and public involvement. Patient and 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 randomization) using Positron Emission Tomography and contrast enhanced Computed tomography (PET-CECT) scan. Patients found to be non-metastatic will be subjected to staging laparoscopyto rule out peritoneal metastases.

Participants Eligibility:

Inclusion Criteria

Patient older than 18 years of age with histologically proven diagnosis of locally advanced GBCA (adenocarcinoma) T3 or T4 tumors 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 antropyloric region of stomach, duodenum, hepatic flexure of colon or small intestine, but without infiltration of the mucosa on endoscopy.
3. Type I/II invasion –Involvement of bile duct (common hepatic duct or proximal 1/3 of the common bile duct) on percutaneous transhepatic biliary drainage (PTBD)/Magnetic resonance cholangiopancreatography (MRCP) causing obstructive jaundice.
4. Radiological suspicion of regional lymph node involvement along hepatic artery, hepatoduodenal ligament, retropancreatic/retroduodenal: size>1cm 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. Patient who have undergone prior cholecystectomy having residual disease with at least one of the above features.

7. The patients must have good general condition (ECOG 0-2).

8. Normal hematological, 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, port site) are excluded from the study. Patients with involvement of the major part of the liver that restricts delivery of full RT doses and those that have received 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.

Study interventions

NACT alone arm (Standard Arm)

Patients randomized to NACT alone arm will proceed to receive four cycles of gemcitabine (1000 mg/m^2) delivered on day 1 and 8 every 3 weeks along with cisplatin (25 mg/m^2) 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 receive 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 4-5 fractions may be used.

Prior to each cycle of chemotherapy, assessment of hematological, renal and hepatic functions will be done. Patients with creatinine clearance >50 ml/min cisplatin will be administered at a dose of 25 mg/m^2. 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 randomized to NACRT arm will undergo radiation therapy for five 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 would be same as standard arm. The chemotherapy would start 3 weeks after completion of radiation.

Radiotherapy planning and contouring

Simulation

The planning CECT scan will be done in fasting state with patient in supine position with arms over head and a knee rest. Immobilization device such as vacuum bags or thermoplastic masks will be used. Fiducials will be placed at the laser intersection points at the level of xiphisternum. The scan will be taken from the level of carina to L4-5 level with 2.5 mm inter slice thickness in the portal phase of intravenous contrast. Respiratory motion management technique like 4DCT or deep inspiratory breath hold technique may be considered.

Contouring

The gross tumor volume (GTV) 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 pericoledochal, cystic duct, retro-portal, along the common hepatic artery, along the hepatoduodenal ligament, pancreaticoduodenal, hilar, periportal, portacaval, and retro-pancreatic region. 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/m^2).

Organ at risk (OAR) contouring will include liver, esophagus, 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 is 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 < 190cc and for 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 duodenum to minimize radiation induced grade III or higher toxicity.

Radiation plan

All patients will be treated with 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 the kept as low as possible throughout the treatment volume. Patient specific quality assurance of the approved dose plan will be done prior to RT starting.

Treatment Delivery and Monitoring

Treatment will be delivered with daily megavoltage/kilo-voltage CT imaging to ensure adequate PTV coverage. All patients will be prescribed prophylactic antacids and mucosal coating agent from day one of radiation starting as a measure to prevent duodenal toxicity. Hematological, hepatic and renal function 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) Version 4.2 at baseline and weekly during NACRT.

Efficacy and safety Assessments

During week 12-13 of starting the treatment, PET CECT scan will be repeated and compared with the initial scans for response assessment using the Response evaluation criteria in solid

tumors (RECIST) (version 1.1) criteria [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 or 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 of 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 8,12,13) along with sampling of inter aortocaval 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 operating surgeon. Complications following surgery will be recorded as per the Clavien-Dindo grading system [19].

Adjuvant Therapy

All the patients after surgery will receive 3 cycles of adjuvant chemotherapy with gemcitabine (1000mg/m^2) day one and eight and cisplatin (25 mg/m^2) day 1 delivered every three weeks.

Patients with progressive disease and those with CR/PR/SD, not eligible for surgery will be evaluated for second line palliative chemotherapy or best supportive care.

Treatment Evaluation

CTCAE Version 4.2 will be used for reporting all acute and late toxicities. Adverse events (AEs) in both the arms will be graded using the CTCAE Version 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 (QOL): FACT-Hep version 4 will be used to assess QOL scores of all 5 modules of Physical well-being, Social/Family well-being, Emotional well-being, Functional well-being and hepatobiliary functions 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 hemogram and biochemistry along with ultrasound 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

Following outcome measures would be recorded.

OS: Time interval between the date of randomization and death due to any cause.

PFS: Time interval between the date of randomization and loco regional 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 margin status on histopathology report of the specimen would be done.

R1 resection: Microscopic positive margin on histopathology.

R 2 resection: Presence of gross residual disease or tumor spillage during surgery.

The number of patients down-staged 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 the RECIST criteria as mentioned previously.

Primary endpoint

The primary end point of the study is the overall survival (OS). The estimated median OS in 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 a hazard ratio of 0.7 when the control group median OS has a hazard ratio 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).

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, 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, V55 of 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 post-operative 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 version 4 will be used to assess QOL scores of all 5 modules of Physical well-being, Social/Family well-being, Emotional well-being, Functional well-being and hepatobiliary functions 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

Status of the disease will be evaluated with physical examinations and required investigations and recorded at each follow up. A detailed systemic work-up will be performed annually to detect, record and report the locoregional and distant control.

Protocol compliance

Inability to receive the planned treatment as per the protocol (chemotherapy as well as radiation) will be regarded as major violation which will be reported to the institutional review board (IRB). Inability to achieve target or OAR constraints, patient misses 2-3 fractions of RT or 1-2 cycles of concurrent chemotherapy will be considered as minor violation.

Event reporting

All events related to the study will be recorded using CTCAE V.4.2. All serious adverse event (SAE) will be reported. Serious Adverse Events within the test arm will necessitate hospitalization. Toxicity arising out of systemic chemotherapy or patients developing cholangitis will not be considered trial related injury or a related SAE. CTCAE Version 4.2 will be used for

reporting of all SAE to the IRB within 24 hours of the occurrence. Similarly, all deaths will be notified to the IRB.

Trial monitoring

The progress of the trial will be monitored at regular interval by the institutional data and safety monitoring board and the report will be submitted to the ethics committee and IRB.

Data analysis plan

Primary aim

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

Secondary aim A similar Kaplan-Meier analysis will be performed for PFS. Toxicity assessment will be using categorized groups between two the arms and chi square test will be used.R0 surgical resection rates and response rates will be calculated within each treatment arm along with exact 95% confidence intervals based on binomial distributions compared between treatment arms using two-sample Cochran-Mantel-Haenszel test at the 5% level of significance. Rates of Grade III and IV adverse events will be summarized by treatment arm using descriptive statistics.

QOL analysis

Standard recommendations will be used to analyze QOL data of the two study arms and repeated measures ANOVA will be used to compare QOL between two arms.

Implications for research

The current study aims 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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Conflicts of interest-None of the authors have conflicting interests.

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Authors' Contributions

Engineer R. is the Principal Investigator and participated in project concept, design, final approval and manuscript preparation, review and submission.

Patkar S. participated in final approval of protocol, manuscript preparation and manuscript review and submission.

Lewis S. participated in review of protocol, final approval of protocol, manuscript preparation.

Sharma A.D. participated in manuscript preparation, review of manuscript and submission.

Shetty N. participated in final approval of draft, review of manuscript, preparation of manuscript.

Ostwal V. participated in review of manuscript for content, review and preparation of manuscript, submission of final protocol and final approval.

Ramaswamy A. participated in review and preparation of manuscript, preparation of trial protocol and final approval of trial protocol.

Chopra S. participated in drafting final protocol, review of contents of the protocol, manuscript preparation and final approval.

Agrawal A. participated in manuscript preparation, review of final protocol and approval of final protocol draft.

Patil P. participated in concept and design, preparation of manuscript, review of manuscript, final approval of trial protocol.

Mehta S. participated in review of manuscript, manuscript preparation, drafting of final report and final approval.

Goel M. participated in concept and design, review of manuscript, manuscript preparation and drafting of final report and final approval of trial protocol.

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Complete List of Authors:	Engineer, Reena; Tata Memorial Centre Patkar, Shraddha; Tata Memorial Centre, Department of Surgical Oncology Lewis, Shirley; Tata Memorial Hospital, Radiation Oncology Sharma, Ashutosh; Tata Memorial Centre, radiation oncology; Shetty, Nitin ; Tata Memorial Centre, Department of Radiodiagnosis Ostwal, Vikas; Tata Memorial Centre, Department of Medical Oncology, GastroIntestinal Disease Management Group Ramaswamy, Anant; Tata Memorial Centre, Department of Medical Oncology, Gastrointestinal Disease Management Group Chopra, Supriya; Tata Memorial Centre Agrawal, Archi; Tata Memorial Hospital, Nuclear Medicine Patil, Prachi; Tata Memorial Centre, Department of Digestive Diseases and Clinical Nutrition Mehta, Shaesta; Tata Memorial Centre, Department of Digestive Diseases and Clinical Nutrition Goel, Mahesh; Tata Memorial Centre, Surgical Oncology
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Title page

A Phase III Randomized Clinical trial of Perioperative therapy (Neoadjuvant chemotherapy v/s chemoradiotherapy) in locally advanced gall bladder cancers (POLCAGB) - Study Protocol

Reena Engineer[1], Shraddha Patkar[2], Shirley Lewis[1],Ashutosh Das Sharma[1], Nitin Shetty[3], Vikas Ostwal[4], Anant Ramaswamy[4], Supriya Chopra[5], Archi Agrawal[6], Prachi Patil[7], Shaesta Mehta[7], Mahesh Goel[2]

1- Department of Radiation Oncology, Tata Memorial Hospital, Mumbai, India

2- Department of Surgical Oncology, Tata Memorial Hospital, Mumbai, India

3- Department of Radiodiagnosis, Tata Memorial Hospital, Mumbai, India

4- Department of Medical Oncology, Tata Memorial Hospital, Mumbai, India

5- Department of Radiation Oncology, ACTREC, Tata Memorial Centre, Mumbai, India

6- Department of Nuclear Medicine, Tata Memorial Hospital, Mumbai, India

7- Department of Digestive Diseases and Clinical Nutrition, Tata Memorial Hospital, Mumbai, India

Corresponding author- Reena Engineer

Room no. 322

Tata Memorial Hospital

Dr.E. Borgese Road

Parel

Mumbai, MH

India

+912224177000(ext-7165)

Email-reena.engineer@gmail.com

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Main Document

A Phase III Randomized Clinical trial of Perioperative therapy (Neoadjuvant chemotherapy v/s chemoradiotherapy) in locally advanced gall bladder cancers (POLCA-GB).

ABSTRACT

Introduction:

There is no consensus regarding the optimal treatment approach for locally advanced gall bladder cancer. Outcomes following surgery have been modest at its best. Neoadjuvant chemotherapy for downstaging has shown encouraging results in few studies for this group of locally advanced gall bladder cancer (LAGBC) with an inherent aggressive tumor biology. A pilot study from our institution has shown improved overall survival and progression free survival with neoadjuvant chemoradiation. The present randomized phase 3 trial is designed to compare neoadjuvant chemoradiation with neoadjuvant chemotherapy alone and will test the superiority of chemoradiation in terms of tumor downstaging and improvement in overall survival.

Methods and analysis:

Patients with biopsy proven LAGBC (T3-4) with predefined clinico-radiological features will be randomized to gemcitabine-based chemotherapy alone arm or chemoradiation arm. Patients with resectable disease or with distant metastases will be excluded. The primary end point of the study is to compare overall survival between the two arms. The secondary end points are to compare progression free survival, 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 the median overall survival by 5.5 months in the study arm (11 months in control group; Hazard ratio 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. The study has been approved by the institutional review board at Tata Memorial Hospital (Project No 1652)

Registration:

The trial is registered with Clinical Trials Registry India (CTRI/2016/08/007199) and ClinicalTrials.gov (NCT02867865)

Strengths and limitations of the study:

Strengths of this study are:

1-This is the first randomized study evaluating chemoradiation in the neoadjuvant setting.

2-Treatment of locally advanced GBC is not standardized and this trial will give an opportunity to do so.

The limitations of this study are:

1-Slower recruitment of patients- As majority of patients with GBC in 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.

2-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 drop out and loss of follow up.

3-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.

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 patient 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 are 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, are treated with chemotherapy alone as the current standard of care. In ABC02 trial by Valle et al, chemotherapy with gemcitabine and cisplatin was found to be superior to gemcitabine alone in terms of local tumor response [10]. Some locally advanced non-metastatic GBC do get down-staged to undergo resection following NACT. In a publication from our institute, gemcitabine/cisplatin based NACT alone resulted in R0 resection rate of 46% and median overall survival (OS) and progression free survival (PFS) of 13.4 months and 8.1 months respectively [11,12].

Few studies have reported the outcomes of neoadjuvant chemoradiation (NACRT) with limited success [13-14]. In an earlier report, we published the outcomes of 3 patients with unresectable tumors, 2 of which were down staged to undergo R0 resection with high dose NACRT [15]. In a pilot study of 28 patients conducted at our center, treated with NACRT, 47% of the patients underwent R0 resections with median OS and PFS being 35 and 20 months respectively [16].

There is no consensus on the optimal neoadjuvant approach in locally advanced GBCA. However, most of the treating physicians prefer to use NACT alone followed by surgical resection if down staging is achieved. The present randomized trial is designed to compare NACRT against NACT alone and will test the superiority of one over the other in terms of down staging and prolonging survival.

Methods and analysis

Hypothesis

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

Study aim

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

Study Design

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

Research Setting

The study will be conducted at TMH, Tata Memorial Centre(TMC), and Advanced Centre for Treatment Research and Education(ACTREC), Mumbai, India and other collaborating centers.

Patients and Public Involvement

This research was conceived without patient and public involvement. Patient and 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 randomization) using Positron Emission Tomography and contrast enhanced Computed tomography (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 T3 or T4 tumors 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 antropyloric region of stomach, duodenum, hepatic flexure of colon or small intestine, but without infiltration of the mucosa on endoscopy.

3. Type I/II invasion –Involvement of bile duct (common hepatic duct or proximal 1/3 of the common bile duct) on percutaneous transhepatic biliary drainage (PTBD)/Magnetic resonance cholangiopancreatography (MRCP) causing obstructive jaundice.

4. Radiological suspicion of regional lymph node involvement along hepatic artery, hepatoduodenal ligament, retropancreatic/retroduodenal: size>1cm 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 -IV disease).

6. Patient who have undergone prior cholecystectomy having residual disease with at least one of the above features.

7. The patients must have good general condition (ECOG 0-2).

8. Normal hematological, renal and hepatic functions done no earlier than 2 weeks prior to treatment initiation.

9. Biopsy confirmation of adenocarcinoma

Exclusion criteria

Those patients with resectable disease or with evidence of distant metastasis (liver, lung, peritoneum, port site) are excluded from the study. Patients with involvement of the major part of the liver that restricts delivery of full RT doses and those that have received 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.

Study interventions

NACT alone arm (Standard Arm)

Patients randomized to NACT alone arm will proceed to receive four cycles of gemcitabine (1000 mg/m^2) delivered on day 1 and 8 every 3 weeks along with cisplatin (25 mg/m^2) 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 receive 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 4-5 fractions may be used.

Prior to each cycle of chemotherapy, assessment of hematological, renal and hepatic functions will be done. Patients with creatinine clearance >50 ml/min cisplatin will be administered at a dose of 25 mg/m^2. 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 randomized to NACRT arm will undergo radiation therapy for five 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 would be same as standard arm. The chemotherapy would start 3 weeks after completion of radiation.

Radiotherapy planning and contouring

Simulation

The planning CECT scan will be done in fasting state with patient in supine position with arms over head and a knee rest. Immobilization device such as vacuum bags or thermoplastic masks will be used. Fiducials will be placed at the laser intersection points at the level of xiphisternum.

The scan will be taken from the level of carina to L4-5 level with 2.5 mm inter slice thickness in the portal phase of intravenous contrast. Respiratory motion management technique like 4DCT or deep inspiratory breath hold technique may be considered.

Contouring

The gross tumor volume (GTV) 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 pericoledochal, cystic duct, retro-portal, along the common hepatic artery, along the hepatoduodenal ligament, pancreaticoduodenal, hilar, periportal, portacaval, and retro-pancreatic region. 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/m^2).

Organ at risk (OAR) contouring will include liver, esophagus, 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 is 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 < 190cc and for duodenum: V55<1 cc, V50< 4 cc [17]. Special focus will be given to restrict dose to normal liver parenchyma and adjacent gastrointestinal structures such as duodenum to minimize radiation induced grade III or higher toxicity.

Radiation plan

All patients will be treated with 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 [18]. 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 the kept as low as possible throughout the treatment volume. Patient specific quality assurance of the approved dose plan will be done prior to RT starting.

Treatment Delivery and Monitoring

Treatment will be delivered with daily megavoltage/kilo-voltage CT imaging to ensure adequate PTV coverage. All patients will be prescribed prophylactic antacids and mucosal coating agent from first day of radiation as a measure to prevent duodenal toxicity. Hematological, hepatic and renal function 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) Version 4.2 at baseline and weekly during NACRT.

Efficacy and safety Assessments

At week 12-13 from day 1 of RT, PET CECT scan will be repeated and compared with the initial scans for response assessment using the Response evaluation criteria in solid tumors (RECIST) (version 1.1) criteria [19]. 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 or 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 of 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 8,12,13) along with sampling of inter aortocaval 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 operating surgeon. Complications following surgery will be recorded as per the Clavien-Dindo grading system [20].

Adjuvant Therapy

All the patients after surgery will receive 3 cycles of adjuvant chemotherapy with gemcitabine (1000mg/m^2) day one and eight and cisplatin (25 mg/m^2) day 1 delivered every three weeks. Patients with progressive disease and those with CR/PR/SD, not eligible for surgery, will be evaluated for second line palliative chemotherapy or best supportive care.

Treatment Evaluation

CTCAE Version 4.2 will be used for reporting all acute and late toxicities. Adverse events (AEs) in both the arms will be graded using the CTCAE Version 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 (QOL): FACT-Hep version 4 will be used to assess QOL scores of all 5 modules of Physical well-being, Social/Family well-being, Emotional well-being, Functional well-being and hepatobiliary functions 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 hemogram and biochemistry along with ultrasound 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

Following outcome measures would be recorded.

OS: Time interval between the date of randomization and death due to any cause.

PFS: Time interval between the date of randomization and loco regional 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 margin status on histopathology report of the specimen would be done.

R1 resection: Microscopic positive margin on histopathology.

R 2 resection: Presence of gross residual disease or tumor spillage during surgery.

The number of patients down-staged 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 the RECIST criteria as mentioned previously. Pathological response rate in both arms would also be assessed.

Primary endpoint

The primary end point of the study is the overall survival (OS). The estimated median OS in 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 a hazard ratio of 0.7 when the control group median OS has a hazard ratio 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).

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, 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, V55 of 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 post-operative 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 version 4 will be used to assess QOL scores of all 5 modules of Physical well-being, Social/Family well-being, Emotional well-being, Functional well-being and hepatobiliary functions 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

Status of the disease will be evaluated with physical examinations and required investigations and recorded at each follow up. A detailed systemic work-up will be performed annually to detect, record and report the locoregional and distant control.

Protocol compliance

Inability to receive the planned treatment as per the protocol (chemotherapy as well as radiation) will be regarded as major violation which will be reported to the institutional review board (IRB). Inability to achieve target or OAR constraints, patient misses 2-3 fractions of RT or 1-2 cycles of concurrent chemotherapy will be considered as minor violation.

Event reporting

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

Trial monitoring

The progress of the trial will be monitored at regular interval by the institutional data and safety monitoring board and the report will be submitted to the ethics committee and IRB.

Data analysis plan – Intention to treat analysis will be performed along with survival for patients who undergo surgery in both the groups.

Primary aim

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

Secondary aim A similar Kaplan-Meier analysis will be performed for PFS. Toxicity assessment will be using categorized groups between two the arms and chi square test will be used. R0 surgical resection rates and response rates will be calculated within each treatment arm along with exact 95% confidence intervals based on binomial distributions compared between treatment arms using two-sample Cochran-Mantel-Haenszel test at the 5% level of significance. Rates of Grade III and IV adverse events will be summarized by treatment arm using descriptive statistics.

Ethics and Dissemination:

The institutional ethics committee of Tata Memorial Hospital 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 analyze QOL data of the two study arms and repeated measures ANOVA will be used to compare QOL between two arms.

Implications for research

The current study aims 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.

Funding: The study is funded by intramural grant supported by the institution where it is being conducted.

Conflicts of Interest-None of the authors have conflicting interests.

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Authors' Contributions

Engineer R. is the Principal Investigator and participated in project concept, design, final approval and manuscript preparation, review and submission.

Patkar S. participated in final approval of protocol, manuscript preparation and manuscript review and submission.

Lewis S. participated in review of protocol, final approval of protocol, manuscript preparation.

Sharma A.D. participated in manuscript preparation, review of manuscript and submission.

Shetty N. participated in final approval of draft, review of manuscript, preparation of manuscript.

Ostwal V. participated in review of manuscript for content, review and preparation of manuscript, submission of final protocol and final approval.

Ramaswamy A. participated in review and preparation of manuscript, preparation of trial protocol and final approval of trial protocol.

Chopra S. participated in drafting final protocol, review of contents of the protocol, manuscript preparation and final approval.

Agrawal A. participated in manuscript preparation, review of final protocol and approval of final protocol draft.

Patil P. participated in concept and design, preparation of manuscript, review of manuscript, final approval of trial protocol.

Mehta S. participated in review of manuscript, manuscript preparation, drafting of final report and final approval.

Goel M. (Co-PI of the study) participated in concept and design, review of manuscript, manuscript preparation and drafting of final report and final approval of trial protocol.

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description
Administrative information		
Title	1	A Phase III Randomized Clinical trial of Perioperative therapy (Neoadjuvant chemotherapy v/s chemoradiotherapy) in locally advanced gall bladder cancers (POLCAGB) - Study Protocol
Trial registration	2a	ClinicalTrials.gov (NCT02867865)
	2b	Not applicable
Protocol version	3	Date - 18th March 2016, version 2
Funding	4	Intramural grant from host institution – Tata Memorial centre
Roles and responsibilities	5a	Written on page 16 & 17
	5b	Dr R A Badwe, Director Tata Memorial Hospital
	5c	Not Applicable
	5d	The Tata Memorial centre would be responsible for the overall conduct of the trial. The results would be presented to the Instituitional ethics committee (IEC) and IRB (Institutional review board) and data and safety monitoring committee
Introduction		
Background and rationale	6a	Written on page 4 & 5
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Methods: Participants, interventions, and outcomes		
Study setting	9	Page 5 - Tata Memorial centre and other centres in Northern India
Eligibility criteria	10	Page 6 & 7
Interventions	11a	Page 7 & 8
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Outcomes	12	Page 11
Participant timeline	13	Page 9
Sample size	14	Page 12
Recruitment	15	To improve the accrual rate the study has been made muticentric and is open to any centres interested in participation
Methods: Assignment of interventions (for controlled trials)		
Allocation:		
Sequence generation	16a	Page 5
Allocation concealment mechanism	16b	Not applicable
Implementation	16c	Page 5
Blinding (masking)	17a	Not applicable
	17b	Not applicable
Methods: Data collection, management, and analysis		
Data collection methods	18a	Page 12 & 13
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Data management	19	Page 13
Statistical methods	20a	Page 14
	20b	Page 14

	20c	Page 13
Methods: Monitoring		
Data monitoring	21a	The hospital data and safety monitoring committee (DSMC); is independent from the sponsor and competing interests. The details of can be found on our website www.tmc.gov.in It monitors all serious adverse events and overall conduct of the trial as per the GCP guidelines.
	21b	No interim analysis has been planned for this study
Harms	22	Page 13
Auditing	23	A thorough monitoring of all the accrued cases is done annually by its members independent from investigators to the study.
Ethics and dissemination		
Research ethics approval	24	The study was submitted for the Human ethics committee and institutional review board (IRB) and the approval was obtained on 10/05/2016
Protocol amendments	25	No amendments to the protocol have been done. In future if there is any amendment it will be informed to the relevant parties (eg, investigators, IRB, trial participants, trial registries, journals, regulators)
Consent or assent	26a	Page 5 An informed consent would be obtained from the patients by any of the investigators in this study.
	26b	Not applicable
Confidentiality	27	All measures would be taken to protect the confidentiality of the patients, before, during, and after the trial
Declaration of interests	28	All investigators declare that they have no financial and other competing interests for the overall trial and each study site
Access to data	29	The principal investigator and the IRB will have access to the final trial dataset, and there is no disclosure of contractual agreements that limit such access for investigators
Ancillary and post-trial care	30	Provisions for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation have been accounted for in the budget sheet of this study.
Dissemination policy	31a	Investigators do plan to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements).

	31b	Authorship to the final manuscript will be as per the ICMJE criteria. We do not intend to use professional writers
	31c	Not applicable

Appendices

Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates (Attached)
Biological specimens	33	Not applicable

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

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A Phase III Randomized Clinical trial of Perioperative therapy (Neoadjuvant chemotherapy v/s chemoradiotherapy) in locally advanced gall bladder cancers(POLCAGB) - Study Protocol

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Complete List of Authors:	Engineer, Reena; Tata Memorial Centre Patkar, Shraddha; Tata Memorial Centre, Department of Surgical Oncology Lewis, Shirley; Tata Memorial Hospital, Radiation Oncology Sharma, Ashutosh; Tata Memorial Centre, radiation oncology; Shetty, Nitin ; Tata Memorial Centre, Department of Radiodiagnosis Ostwal, Vikas; Tata Memorial Centre, Department of Medical Oncology, GastroIntestinal Disease Management Group Ramaswamy, Anant; Tata Memorial Centre, Department of Medical Oncology, Gastrointestinal Disease Management Group Chopra, Supriya; Tata Memorial Centre Agrawal, Archi; Tata Memorial Hospital, Nuclear Medicine Patil, Prachi; Tata Memorial Centre, Department of Digestive Diseases and Clinical Nutrition Mehta, Shaesta; Tata Memorial Centre, Department of Digestive Diseases and Clinical Nutrition Goel, Mahesh; Tata Memorial Centre, Surgical Oncology
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Title page

A Phase III Randomized Clinical trial of Perioperative therapy (Neoadjuvant chemotherapy v/s chemoradiotherapy) in locally advanced gall bladder cancers (POLCAGB) - Study Protocol

Reena Engineer[1], Shraddha Patkar[2], Shirley Lewis[1],Ashutosh Das Sharma[1], Nitin Shetty[3], Vikas Ostwal[4], Anant Ramaswamy[4], Supriya Chopra[5], Archi Agrawal[6], Prachi Patil[7], Shaesta Mehta[7], Mahesh Goel[2]

1- Department of Radiation Oncology, Tata Memorial Hospital, Mumbai, India

2- Department of Surgical Oncology, Tata Memorial Hospital, Mumbai, India

3- Department of Radiodiagnosis, Tata Memorial Hospital, Mumbai, India

4- Department of Medical Oncology, Tata Memorial Hospital, Mumbai, India

5- Department of Radiation Oncology, ACTREC, Tata Memorial Centre, Mumbai, India

6- Department of Nuclear Medicine, Tata Memorial Hospital, Mumbai, India

7- Department of Digestive Diseases and Clinical Nutrition, Tata Memorial Hospital, Mumbai, India

Corresponding author Reena Engineer

Room no. 322

Tata Memorial Hospital

Dr.E. Borgese Road

Lower Parel

Mumbai, MH

India

+912224177000(ext-7165)

Email-reena.engineer@gmail.com

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Word Count: 3157

Main Document

A Phase III Randomized Clinical trial of Perioperative therapy (Neoadjuvant chemotherapy v/s chemoradiotherapy) in locally advanced gall bladder cancers (POLCAGB) - Study Protocol

ABSTRACT

Introduction:

Neoadjuvant chemotherapy is considered the current standard for locally advanced gallbladder cancer. There is no consensus on the optimal neoadjuvant approach. A pilot study from our institution has shown improved overall survival and progression free survival with neoadjuvant chemoradiation. The present randomized phase 3 trial is designed to compare neoadjuvant chemoradiation with neoadjuvant chemotherapy alone and will test the superiority of chemoradiation in terms of tumor downstaging and improvement in overall survival.

Methods and analysis:

Patients with biopsy proven locally advanced gallbladder cancer (T3-4) with predefined clinic-radiological features will be randomized to gemcitabine-based chemotherapy alone arm or chemoradiation arm. Patients with resectable disease or with distant metastases will be excluded. The primary end point of the study is to compare overall survival between the two arms. The secondary end points are to compare progression free survival, R0 resection rates, acute and late toxicity, postoperative complications, and quality of life between two study arms. The trial is designed to detect an improvement in median overall survival by 5.5 months in the study arm(11 months in control group; Hazard ratio 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 neoadjuvant chemoradiation over neoadjuvant chemotherapy in locally advanced gallbladder cancers in terms of improvement in overall survival.

-The results of this study will define the optimal neoadjuvant approach in locally advanced gallbladder cancer

Strengths and limitations of the study:

Strengths of this study are:

1-This is the first randomized study evaluating chemoradiation in the neoadjuvant setting.

2-Treatment of locally advanced GBC is not standardized and this trial will give an opportunity to do so.

The limitations of this study are:

1-Slower recruitment of patients- As majority of patients with GBC in 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.

2-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 drop out and loss of follow up.

3-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.

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 patient 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 are 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, are treated with chemotherapy alone as the current standard of care. In ABC02 trial by Valle et al, neoadjuvant chemotherapy (NACT) with gemcitabine and cisplatin was found to be superior to gemcitabine alone in terms of local tumor response [10]. Some locally advanced non-metastatic GBC do get down-staged to undergo resection following NACT. In a publication from our institute, gemcitabine/cisplatin based NACT alone resulted in R0 resection rate of 46% and median overall survival (OS) and progression free survival (PFS) of 13.4 months 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 3 patients with unresectable tumors, 2 of which were down staged to undergo R0 resection with high dose NACRT [14]. In a pilot study of 28 patients conducted at our center, treated with NACRT, 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 GBCA. However, most of the treating physicians prefer to use NACT alone followed by surgical resection if down staging is achieved. The present randomized trial is designed to compare NACRT against NACT alone and will test the superiority of one over the other in terms of down staging and prolonging survival.

Methods and analysis

Hypothesis

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

Study aim

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

Study Design

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

Research Setting

The study will be conducted at TMH, Tata Memorial Centre(TMC), and Advanced Centre for Treatment Research and Education(ACTREC), Mumbai, India and other collaborating centers.

Patients and Public Involvement

This research was conceived without patient and public involvement. Patient and 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 randomization) using Positron Emission Tomography and contrast enhanced Computed tomography (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 GBCA (adenocarcinoma) T3 or T4 tumors 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 antropyloric region of stomach, duodenum, hepatic flexure of colon or small intestine, but without infiltration of the mucosa on endoscopy.
3. Type I/II invasion –Involvement of bile duct (common hepatic duct or proximal 1/3 of the common bile duct) on percutaneous transhepatic biliary drainage (PTBD)/Magnetic resonance cholangiopancreatography (MRCP) causing obstructive jaundice.
4. Radiological suspicion of regional lymph node involvement along hepatic artery, hepatoduodenal ligament, retropancreatic/retroduodenal: size>1cm 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. Patient who have undergone prior cholecystectomy having residual disease with at least one of the above features.
7. The patients must have good general condition (ECOG 0-2).
8. Normal hematological, 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, port site) are excluded from the study. Patients with involvement of the major part of the liver that restricts delivery of full RT doses and those that have received 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 randomization. All efforts would be taken to keep their confidentiality.

Study interventions

NACT alone arm (Standard Arm)

Patients randomized to NACT alone arm will proceed to receive four cycles of gemcitabine (1000 mg/m^2) delivered on day 1 and 8 every 3 weeks along with cisplatin (25 mg/m^2) 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 receive 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 4-5 fractions may be used.

Prior to each cycle of chemotherapy, assessment of hematological, renal and hepatic functions will be done. Patients with creatinine clearance >50 ml/min cisplatin will be administered at a dose of 25 mg/m^2. 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 randomized to NACRT arm will undergo radiation therapy for five 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 would be same as standard arm. The chemotherapy would start 3 weeks after completion of radiation.

Radiotherapy planning and contouring

Simulation

The planning CECT scan will be done in fasting state with patient in supine position with arms over head and a knee rest. Immobilization device such as vacuum bags or thermoplastic masks will be used. Fiducials will be placed at the laser intersection points at the level of xiphisternum. The scan will be taken from the level of carina to L4-5 level with 2.5 mm inter slice thickness in the portal phase of intravenous contrast. Respiratory motion management technique like 4DCT or deep inspiratory breath hold technique may be considered.

Contouring

The gross tumor volume (GTV) 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 pericoledochal, cystic duct, retro-portal, along the common hepatic artery, along the hepatoduodenal ligament, pancreaticoduodenal, hilar, periportal, portacaval, and retro-pancreatic region. 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/m^2).

Organ at risk (OAR) contouring will include liver, esophagus, 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 is 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 < 190cc and for 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 duodenum to minimize radiation induced grade III or higher toxicity.

Radiation plan

All patients will be treated with 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 the kept as low as possible throughout the treatment volume. Patient specific quality assurance of the approved dose plan will be done prior to RT starting.

Treatment Delivery and Monitoring

Treatment will be delivered with daily megavoltage/kilo-voltage CT imaging to ensure adequate PTV coverage. All patients will be prescribed prophylactic antacids and mucosal coating agent from day one of radiation starting as a measure to prevent duodenal toxicity. Hematological, hepatic and renal function 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) Version 4.2 at baseline and weekly during NACRT.

Efficacy and safety Assessments

During week 12-13 of starting the treatment, PET CECT scan will be repeated and compared with the initial scans for response assessment using the Response evaluation criteria in solid tumors (RECIST) (version 1.1) criteria [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 or 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 of 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 8,12,13) along with sampling of inter aortocaval 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 operating surgeon. Complications following surgery will be recorded as per the Clavien-Dindo grading system [19].

Adjuvant Therapy

All the patients after surgery will receive 3 cycles of adjuvant chemotherapy with gemcitabine (1000mg/m^2) day one and eight and cisplatin (25 mg/m^2) day 1 delivered every three weeks. Patients with progressive disease and those with CR/PR/SD, not eligible for surgery will be evaluated for second line palliative chemotherapy or best supportive care.

Treatment Evaluation

CTCAE Version 4.2 will be used for reporting all acute and late toxicities. Adverse events (AEs) in both the arms will be graded using the CTCAE Version 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 (QOL): FACT-Hep version 4 will be used to assess QOL scores of all 5 modules of Physical well-being, Social/Family well-being, Emotional well-being, Functional well-being and hepatobiliary functions 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 hemogram and biochemistry along with ultrasound 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

Following outcome measures would be recorded.

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

PFS: Time interval between the date of randomization and loco regional 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 margin status on histopathology report of the specimen would be done.

R1 resection: Microscopic positive margin on histopathology.

R 2 resection: Presence of gross residual disease or tumor spillage during surgery.

The number of patients down-staged 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 the RECIST criteria as mentioned previously. Pathological response rate in both arms would also be assessed.

Primary endpoint

The primary end point of the study is the overall survival (OS). The estimated median OS in 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 a hazard ratio of 0.7 when the control group median OS has a hazard ratio 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 centers 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, 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, V55 of 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 post-operative 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 version 4 will be used to assess QOL scores of all 5 modules of Physical well-being, Social/Family well-being, Emotional well-being, Functional well-being and hepatobiliary functions 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

Status of the disease will be evaluated with physical examinations and required investigations and recorded at each follow up. A detailed systemic work-up will be performed annually to detect, record and report the locoregional and distant control.

Protocol compliance

Inability to receive the planned treatment as per the protocol (chemotherapy as well as radiation) will be regarded as major violation which will be reported to the institutional review board (IRB). Inability to achieve target or OAR constraints, patient misses 2-3 fractions of RT or 1-2 cycles of concurrent chemotherapy will be considered as minor violation.

Event reporting

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

Trial monitoring

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

Data analysis plan – No interim analyses has 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 perfomed along with survival for patients who undergo surgery in both the groups.

Primary aim

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

Secondary aim A similar Kaplan-Meier analysis will be performed for PFS. Toxicity assessment will be using categorized groups between two the arms and chi square test will be used.R0 surgical resection rates and response rates will be calculated within each treatment arm along with exact 95% confidence intervals based on binomial distributions compared between treatment arms using two-sample Cochran-Mantel-Haenszel test at the 5% level of significance. Rates of Grade III and IV adverse events will be summarized by treatment arm using descriptive statistics.

Ethics and Dissemination:

The institutional ethics committee of Tata Memorial Hospital 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 analyze QOL data of the two study arms and repeated measures ANOVA will be used to compare QOL between two arms.

Implications for research

The current study aims 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.

Funding: The study is funded by intramural grant supported by the institution where it is being conducted.

Conflicts of interest-None of the authors have conflicting interests.

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Authors' Contributions

Engineer R. is the Principal Investigator and participated in project concept, design, final approval and manuscript preparation, review and submission.

Patkar S. participated in final approval of protocol, manuscript preparation and manuscript review and submission.

Lewis S. participated in review of protocol, final approval of protocol, manuscript preparation.

Sharma A.D. participated in manuscript preparation, review of manuscript and submission.

Shetty N. participated in final approval of draft, review of manuscript, preparation of manuscript.

Ostwal V. participated in review of manuscript for content, review and preparation of manuscript, submission of final protocol and final approval.

Ramaswamy A. participated in review and preparation of manuscript, preparation of trial protocol and final approval of trial protocol.

Chopra S. participated in drafting final protocol, review of contents of the protocol, manuscript preparation and final approval.

Agrawal A. participated in manuscript preparation, review of final protocol and approval of final protocol draft.

Patil P. participated in concept and design, preparation of manuscript, review of manuscript, final approval of trial protocol.

Mehta S. participated in review of manuscript, manuscript preparation, drafting of final report and final approval.

Goel M (Co-PI). participated in concept and design, review of manuscript, manuscript preparation and drafting of final report and final approval of trial protocol.

Trial sponsor - Dr R A Badwe, Director Tata Memorial Hospital

Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial

We having Institutional ethics committee kindly follow the link below

https://tmc.gov.in/TMH/index.php/institutional-ethics-committees

Composition of data monitoring committee (DMC); Follow the following link
https://tmc.gov.in/TMH/index.php/education-and-research/research/dsm-sub-committee

Any protocol modifications will be submitted and taken permission from the IEC and IRB of the hospital

Declaration of interests

We declare no financial and other competing interests for principal investigators or co-investigators for the overall trial and each study site

Access to data – The principal investigator and the study team members will have access to all the clinical data of patients. After completion of study the raw data will be submitted to TMC Research Administration Council

Ancillary and post-trial care –

Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation has been budgeted for and mentioned in the informed consent form

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Changes by author
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	Page 1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	Page 3 Line 2
	2b	All items from the World Health Organization Trial Registration Data Set	NA - Not applicable
Protocol version	3	Date and version identifier	Page 3
Funding	4	Sources and types of financial, material, and other support	Page 15
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	Page 17
	5b	Name and contact information for the trial sponsor	Page 17
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	NA
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	Page 17
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	Page 2 & 4

	6b	Explanation for choice of comparators	Page 5
Objectives	7	Specific objectives or hypotheses	Page 5
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	Page 5
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	Page 5
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	Page 6 &7
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	Page 7
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	Page 7
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	Page 7
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	Page 9
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	Page 11
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Page 9

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	Page 11
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	Page 12
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	Page 5
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	Page 5
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	Page 5
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	NA
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	NA
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	Page 12

	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	Page 13
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	Page 12
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	Page 13
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	NA
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	Page 13
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	Page 13
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	Page 13
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	Page 13
Ethics and dissemination			

Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	Page 14
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	Page 17
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	Page 7
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NA
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	Page 7
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	Page 18
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	Page 18
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	Page 18
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	Page 14
	31b	Authorship eligibility guidelines and any intended use of professional writers	NA
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	NA
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Attached

Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	NA

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.