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Protocol

A randomized study of consolidation chemo-radiotherapy versus observation after first-line chemotherapy in advanced gall bladder cancers (RACE-GB Study): trial protocol

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ABSTRACT

Background: Chemotherapy (CT) is the standard of care for advanced gall bladder cancer (GBC). However, after completion of 6 cycles of CT, a proportion of patients with good performance status progress within a few months. Retrospective data in locally advanced cases revealed that consolidation chemo-radiotherapy (CTRT) in responders to CT and with good performance status improves overall survival.
Methods: FNA proven advanced GBC with predefined clinical-radiological features will be administered 4 cycles CT (cisplatin-gemcitabine combination). After completion of CT, those in good Karnofsky performance status (KPS) will be randomised to consolidation CTRT versus observation (standard of care). The primary end point of the study is to compare OS between the two arms. The secondary end point is to compare progression free survival (PFS), toxicity, and quality of life between the two study arms. The trial is designed to detect an improvement in 2-year overall survival (OS) from 8% in the control arm to 25% in study arm with 80.0% power at a 0.05 significance level. The resultant sample size to achieve this aim is 140 (70 in each arm) over a duration of 4-5 years with a 10% attrition rate. Accrual has been from January 2019 to October 2022.
Conclusions: This trial aims to assess the incremental gain in outcomes with consolidation CTRT versus observation in responders to first-line CT in advanced GBCs. This is the first randomised study to evaluate role of consolidation chemoradiation.
Trial Registration: The trial is registered with clinical trials registry India (CTRI/2019/04/025204) and clinical trials.gov (NCT05493956).

Keywords: Advanced gallbladder cancer, First line chemotherapy, Responders, Consolidation chemoradiation

INTRODUCTION

Gall bladder cancer (GBC) is common in Northern India and often presents in locally advanced or metastatic stage.[1] Early GBC is an elusive disease. Complete surgical resection is the only treatment modality with curative potential for early GBC. Chemotherapy (cisplatin, gemcitabine combination) is the standard of care for advanced GBC[2]. This results in a median survival of 9-12 months in the west and 8 months in developing countries after which 90% patients progress. However advanced GBC includes a spectrum of patients ranging from locally advanced disease, to frank or overt omental disease and frank liver metastases. Should all these subsets be combined in a same basket or should treatment be individualized according to burden of disease? Locally advanced GBC are those who are un-resectable due to local extension of GBC to liver (more than 2 cm), vessels or CBD in the hepatoduodenal ligament or enlarged lymph-nodes along the coeliac or superior mesenteric vessels. Neoadjuvant chemotherapy

has shown to downstage these tumours and 15-40% of such patients become resectable, but the rest remain unresectable and are administered second-line chemotherapy only on disease progression.[3-4] Should such patients who respond to chemotherapy (CT) and have good performance status be administered consolidation treatment/ maintenance treatment to improve outcomes or offered second-line chemotherapy on disease progression? A small randomized study of GBC in 60 patients investigated maintenance gemcitabine after 6 cycles CT (gemcitabine cisplatin) yielded a median overall survival in gemcitabine arm of 12.4 months as opposed to 9.9 months in observation arm.[5] Retrospective data of consolidation chemo-radiotherapy (CTRT) shows an improvement in OS from 9 months to 15 months and 2 year overall survival of 37.3% vs. 5% in the RT cohort as compared to a no RT cohort.[6-7] This observation informs us that consolidation chemo-radiotherapy (CTRT) improves survival and is hypothesis generating. As far as morbidity of CTRT is concerned, it has been widely practiced in postoperative GBC with node positive disease with less than 10% grade 1-2 morbidity. Our experience with CTRT in postoperative GBC, revealed grade 1-2 morbidity in less than 10% with conformal RT and grade 3 morbidity was rare.[8] GBC presents in endemic proportions in the Indo-gangetic region, and it is mandatory to investigate modalities which could have potential for improvement in outcomes. Hence, we aim to investigate the role of consolidation chemo-radiotherapy (CTRT) in responders to initial CT in fit patients in improving overall survival.

METHODS

Hypothesis

On the basis of encouraging outcomes with consolidation CTRT in responders to first-line CT with good performance status, we hypothesize that Consolidation CTRT after first-line CT will improve outcomes as compared to first line CT alone in advanced gall-bladder cancers.

Research setting

The study will be conducted at Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, India. Accrual has been from January 2019 to October 2022.

Patients and public involvement

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

Study design

This will be a phase III randomized trial of advanced gall bladder cancers. 140 patients will be randomized. Randomisation will be on a 1:1 ratio between the experimental arm and the control arm. In the experimental arm, 4-6 cycles of first-line CT (Gemcitabine and Cisplatin) will be followed by consolidation CTRT with concurrent capecitabine (@1250mg/m2, five days a week) while in observation arm patients on first-line CT will be followed by observation until disease progression (Figure 1).

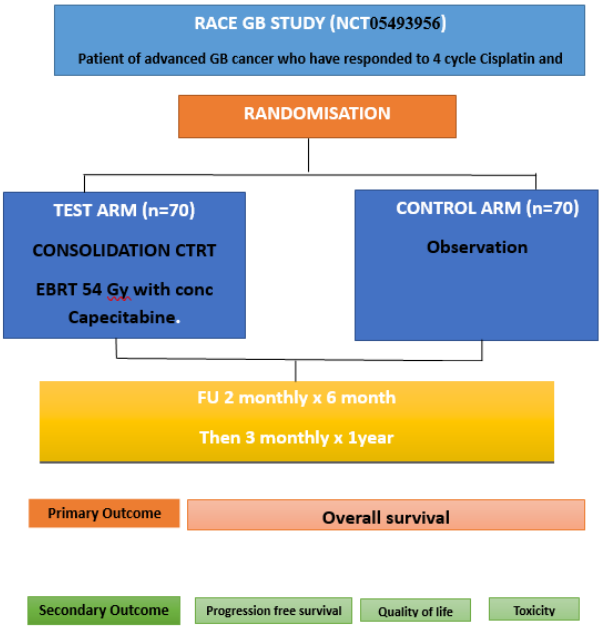

Figure 1: Consort diagram.

Inclusion criteria

Inclusion criteria for current study were; patients who are advanced GBC (T3, T4, N1), Rt hepatic artery involvement, Rt Branch of portal vein and main PV involvement, CBD/CHD/primary biliary confluence involvement, Duodenum involvement, Pancreas involvement, Colon involvement, Nodes in the hepato-duodenal, peripancreatic, common hepatic artery region, Para or preaortic region, Omental metastases on CT scan without ascites, Liver metastases limited to segment IV and V, Good performance status, BMI >15, Have normal organ and marrow function and Weight loss not exceeding 10% in the preceding 3 months.

Exclusion criteria

Exclusion criteria for current study were; multiple liver metastasis, presence of ascites, manifest omental disease and evidence of significant clinical disorder or laboratory finding that makes it undesirable for the patient to participate in the trial

Discontinuation of patients

Patients were discontinued if patient has evidence of progressive disease despite treatment and patient is noncompliant with study procedures.

Treatment

After a confirmation of diagnosis by an FNAC, patients will be taken up for chemotherapy. After completion of 4 cycles chemotherapy they will be evaluated for response. If resectable they will be taken up for surgery. If unresectable without progression they will be randomized to the following arms.

DISCUSSION

Consolidation chemo-radiotherapy

Patients in experimental arm will be administered 4 cycles of gemcitabine 1000 mg/m^2 d 1+8 and cisplatin 25 mg/m^2 d 1+8 repeated 3 weekly followed by abdominal radiotherapy using a standardized 3 dimensional conformal radiotherapy (3DCRT) technique on a linear accelerator operating at beam energy of ≥ 6MV.The total target dose of RT will be 45Gy in 25 fractions of 1.8 Gy to GBC and lymphatics (GBC, liver infiltration, periportal coeliac, superior mesenteric and paraortic lymph-nodes till L2) followed by a boost of 9 Gy to the GBC. Concurrent capeciatbine@1250 mg/m2 (Monday-Friday) would be administered along-with RT. Observation: After completion of 4 cycles of CT, patients will be observed until disease progression.

Radiation planning

Contouring: GBC mass along-with liver infiltration would be gross target volume (GTV), and a 5 mm margin around it would be clinical target volume (CTV). Nodal CTV would be delineated after drawing combining combining portal vein (PV), coeliac artery (CA), superior mesenteric artery (SMA) and aortic nodes as per the guidelines for postoperative pancreatic cancers.[10] A Boolean of CTV and Nodal CTV would be designated Final CTV. PTV margin would be 1 cm around Final CTV. DVH constraints would be: mean liver dose <30 Gy (liver would be delineated after subtracting GTV), mean kidney dose <18 Gy (combining both kidneys) (Table 1). Other OAR to be delineated: stomach, duodenum, bowel and their doses to be noted.

Table 1: Target volume and organs at risk dose-volume constraints.

Target	Dose/volume constraint
PTV (Primary/node)	95% volume to be covered by 95% dose
Duodenum	1 CC <55 Gy
	4 CC <50 Gy
Liver	Mean dose <30 Gy
Spinal cord	D max <45 Gy
Kidneys (b/l)	Mean <18 Gy

Treatment planning

After the generation of ICRU target volumes GTV, CTV and PTV and organs at risk the medical physicist places the classical plan template of three fields (one anterior and two laterals). Plans are created using in-homogeity calculation algorithms (AAA or CCC) and optimized choosing mixed energies 6 MV and 15MV along with enhanced dynamic wedges (mostly wedge angles between 15 degree and 45 degree are used) and target conformation done with multi-leaf collimator (Millennium 120 or Agility 160). 15 MV beam is mostly preferred to avoid lateral edge effect when the lateral separation is more about 35 cm). To improve dose homogeneity in the intersection area of beams in and around the target the field in field approach (FIF) is considered. Quantitative and qualitative analysis are considered for plan acceptance (the minimum and maximum dose to the target coverage as per ICRU 50 and 62 recommendations ie 95% isodose coverage to PTV and 107% dose envelope volume should not be more than 1.5cm diameter). When 107% dose area is more than 1.5 cm diameter, FIF is employed for reducing high dose volume. Once plan is finalised electronic chart is prepared for treatment execution through record and verify (R&V) module at the treatment console with first day verification protocol (orthogonal setup fields of field size 20 x 20 cm^2 for setup verification).

Treatment delivery and monitoring

All patients will be prescribed prophylactic antacids and mucosal coating agent from day 1 of radiation starting as a measure to prevent duodenal toxicity. Haematological, hepatic and renal functions, as well as tolerance to the treatment, will be assessed weekly. Toxicities documented during treatment will be recorded using the CTCAE version 3.0 (NCI 2006 scale).

Toxicities arising more than 90 days since the completion of radiation therapy and attributed to radiation will be assessed according to CTCAE criteria and counted as late radiation toxicities (RILD, gastric and duodenal toxicity). Toxicity profile for thrombocytopenia, neutropenia, vomiting, gastritis, hepatic dysfunction, hand-foot syndrome 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 capecitabine dose will be withheld for a week or until recovery. Observation: enrolled patients will be administered 4 cycles of standard gemcitabine and cisplatin combination (as in experimental arm) and then kept on observation until disease progression. On evidence of disease progression in either arm, patients will be treated with CAPIRI (irinotecan @180 mg/m^2 and capecitabine @1650 mg/m^2×14 days q 3 weekly) or single agent capecitabine (@1650 mg/m^2×14 days q 3weekly) depending on the performance status of patient.

Efficacy and safety assessments

During weeks 12-13 of starting the treatment, CECT scan will be repeated and compared with the initial scans for response assessment using response evaluation criteria in solid tumours (RECIST) V.1.1.18 The response of the therapy will be assessed in terms of complete response (CR): disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm. Partial response (PR): at least a 30% decrease in the sum of diameters of target lesions. Progressive disease (PD): at least a 20% increase in the sum of diameters of target lesions or appearance 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. If patient shows evidence of resectability after 4-6 cycles of CT/CTRT, a PET-CT will be done to rule out distant disease. Prior to consolidation CTRT, all patients who can afford PET-CT will be encouraged for the same to rule out distant metastases.

Follow-up

After completion of treatment, patients will be followed up and assessed clinically every month until disease progression. Patients who develop symptoms of disease progression would be advised CECT scan to confirm disease progression before administering second-line chemotherapy (CAPIRI). Patients who develop obstructive jaundice would be stented.

Statistical considerations

Assuming 2-year survival probability of the patients were 0.25 and 0.08 in the treatment (group 1) and control (group 2), at minimum two-sided 95% confidence interval and 80% power of the study, overall sample size came out to be 132 subjects (66 in the group1 and 66 in the group 2) using a two-sided log rank test. The proportion dropping out in each of the treatment and control group was 0.10 (i.e., 10%). The proportion of switching from the treatment to control or control to treatment is assumed to be Nil. The number of events required to achieve a power of 0.8 with an assumed hazard ratio of 2 was estimated as 67. At a recruitment rate of 60 subjects a year, and recruitment duration of 2 years and subsequent follow up of 3 years (total study period of five years), the estimated number of total events was calculated as eighty. Assuming a lost to follow up of ten percent, a sample size of 140 would result in more than 67 events sufficient to achieve 80% power at 0.05 alpha.

Quality of life

FACT-Hep V.4 will be used to assess QOL scores of all five modules of physical well-being, social/family wellbeing, emotional well-being, functional well-being and hepatobiliary function-related specific questions. It will be done at baseline (at time of randomisation), at week 2 of CTRT and one month after completion of CTRT. In the observation arm it will be done at time of randomisation and at one, two month follow-up.

Endpoints

Primary endpoint would be to compare the overall survival of patients in both arms. Secondary: To estimate the disease-free survival and incidence of adverse events in experimental arm.

Data collection

All the data related to the study will be collected and maintained by the principal investigator at the department of Radiotherapy, SGPGI, Lucknow.

Treatment planning data

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

Treatment data

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

Toxicity evaluation

Treatment-related toxicity will be reported using CTCAE V 3. 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.

Clinical outcome data

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

Protocol compliance

Inability to receive the planned treatment as per the protocol (chemotherapy as well as radiation) will be recorded and considered major violation and included in intent to treat analysis. The inability to achieve target or OAR constraints or the patient missing two to three

fractions of RT or one to two cycles of concurrent chemotherapy will be considered as a minor violation. All serious adverse events (SAEs) will be reported. SAEs necessitating hospitalisation will be recorded. Toxicity arising out of systemic chemotherapy or patients developing cholangitis, or biliary obstruction will not be considered a trial-related injury or a related SAE.

Data analysis plan

No interim analyses have been planned for this study; intention-to-treat as well as per protocol analysis will be performed along with survival analysis.

Primary and secondary aim

Primarily Kaplan-Meier curves for OS will be generated for both arms, and OS will be compared using log-rank test. A p value of <0.05 will be considered statistically significant and will be used to reject the null hypothesis. Secondarily a similar Kaplan-Meier analysis will be performed for PFS. Toxicity assessment will be done using categorised groups between the two arms and $\chi 2$ test will be used. Rates of grades 3 and 4 AEs will be summarised by treatment arm using descriptive statistics.

CONCLUSION

This trial aims to assess the incremental gain in outcomes with consolidation CTRT versus observation in responders to first-line CT in advanced GBCs. This is the first randomised study to evaluate role of consolidation chemoradiation.

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Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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