PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	A Phase III Randomized Clinical trial of Perioperative therapy (Neoadjuvant chemotherapy v/s chemoradiotherapy) in locally advanced gall bladder cancers(POLCAGB) - Study Protocol
AUTHORS	Engineer, Reena; Patkar, Shraddha; Lewis, Shirley; Sharma, Ashutosh; Shetty, Nitin; Ostwal, Vikas; Ramaswamy, Anant; Chopra, Supriya; Agrawal, Archi; Patil, Prachi; Mehta, Shaesta; Goel, Mahesh

VERSION 1 - REVIEW

REVIEWER	Passot lyon sud france
REVIEW RETURNED	20-Dec-2018

GENERAL COMMENTS	This study protocol address an important point, however, few comments could be adressed: - Do the authors considere pathological diagnosis prior to neoadjuvant chemotherapy? It is mandatory most of the time. If so, it has to be reported and the way of biospy is also important (through liver parentchyma, endoscopically...) - For patients who will undergo surgery, pathological response to preoperative chemotherapy should analysed -A major goal is the resectability. The authors should compared final resectability in both group, complete resection. Intent to treat analysis should be perfomed along with survival for patients who underg surgery -It is not clear why the authors evaluate survival since the date of randomization, this time does not correspond to disease evolution. They should either choose date of diagnosis (on pathology), or date of first neoadj treatement.

REVIEWER	Fuyuhiko Motoi Tohoku University, Japan
REVIEW RETURNED	11-Jan-2019

GENERAL COMMENTS	My major concern of this protocol is whether the standard treatment of the targets is neoadjuvant treatment. Based on the reference the authors cited, the median survival of upfront surgery was ranging 17 months (ref 4) or 18 months (ref 5). However the authors described the median survival time of control arm

	(neoadjuvant chemotherapy) and test arm (neoadjuvant chemoradiotherapy) were estimated for 11 months and 16.5 months respectively. Although neoadjuvant therapy might be promising for advanced gallbladder cancer, it has not been established as standard strategy. In that situation, I recommend the protocol would be better to set randomized phase II study to evaluate R0 resection rate of both arm (selection design) before comparison to upfront surgery. Overall survival should be measured as secondary endopoint.

REVIEWER	Lillian Kao McGovern Medical School at University of Texas Health Science Center at Houston United States
REVIEW RETURNED	24-Feb-2019

GENERAL COMMENTS	Engineer et al report the study protocol for a randomized trial of neoadjuvant chemoradiation versus chemotherapy for locally advanced gallbladder cancer. The authors should be commended for studying this important question using a randomized trial and for recording both clinical and patient-reported outcomes (such as quality of life). Major comment: 1. The biggest question is that of feasibility of answering the question as posed. a) The authors do not provide any details regarding how many patients they see with locally advanced gallbladder cancer per year. Furthermore, it would be helpful to know what proportion of those patients would meet study enrollment criteria. b) According to clinicaltrials.gov, the trial has been ongoing since August 2016. In the protocol, the authors state that they expected enrollment to occur over the first 3 years of the trial, which will be up in just a few months. The authors allude to a slow recruitment of patients, but do not describe how many patients have been enrolled up until this point and how this affects the timeline and likelihood of completion for the trial. c) Slow recruitment is a fact of life in the world of clinical trials. Given that, what do the authors plan to do? Do they have any criteria for declaring futility in being able to answer the question? Do they have any plans to enlist other centers to enroll patients? Do they plan to do alternative analyses such as Bayesian analyses that may more easily accommodate small sample sizes? What is their plan? Minor comments: 2) The reporting seems reasonable, but explicitly alluding to the CONSORT criteria and checklist would be helpful. 3) The study design states that stratification will be by T stage, and it lists T1-T4 -- should this really just be T3 or T4 given the inclusion criteria? 4) In adjudicating the outcome of completeness of resection, how will non-surgical candidates be accounted for? 5) The authors state that the study will redefine the current standard of care for locally advanced gallbladder disease. Since this is a one-center trial being conducted in India, can the authors describe how their patient population and their treatment

	algorithms compare to those worldwide? Do the authors expect their results to be widely generalizable? 6) Unless I missed them, I did not see the NCT number (although I found it online) or the dates of the planned study in the manuscript (as required by the editors for protocols).

VERSION 1 – AUTHOR RESPONSE

Response from Authors

Reviewer 1

1	Do the authors consider pathological diagnosis prior to neoadjuvant chemotherapy? It is mandatory most of the time. If so, it has to be reported and the way of biospy is also important (through liver parentchyma, endoscopically...)	Yes an additional sentence about the biopsy has been added on page 6 para 2
2	For patients who will undergo surgery, pathological response to preoperative chemotherapy should analysed	A sentence has been added on Page 12 para 1 "Pathological response rate in both arms would also be assessed"
3	A major goal is the resectability. The authors should compare final resectability in both group, complete resection. Intent to treat analysis should be performed along with survival for patients who undergo surgery	This has been mentioned on page 12 para 1 A sentence has been added on page 13 last para Intent to treat analysis will be performed along with survival for patients who undergo surgery
4	It is not clear why the authors evaluate survival since the date of randomization, this time does not correspond to disease evolution. They should either choose date of diagnosis (on pathology), or date of first neoadj treatment	Date of randomization would be close to the first neoadjuvant treatment hence would not be any much different than the date of diagnosis

Reviewer 2

5	whether the standard treatment of the targets is neoadjuvant treatment	Given the aggressive biology and poor outcomes of these patients the standard treatment at our hospital is neoadjuvant chemotherapy followed by assessment for surgery.
6	Based on the reference the authors cited, the median survival of upfront surgery was ranging 17 months (ref 4) or 18 months (ref 5). However the authors described the median survival time of control arm (neoadjuvant chemotherapy) and test arm (neoadjuvant chemoradiotherapy) were estimated for 11 months and 16.5 months respectively. Although neoadjuvant therapy might be promising for advanced gallbladder cancer, it has not been established as standard strategy.	This estimation was based on ABC 02 study the median survival for these patients were 11 months The study published from our centre (having a short follow up) where neoadjuvant chemotherapy followed by surgery had MOS of 13 months (Sirohi et al 2015). Whereas the MOS of 16.5 months is estimated on the basis of a prospective study (Engineer et al 2016 Ann of surg. Oncol) using neoadjuvant chemoradiation where we observed a MOS of 20 months

	In that situation, I recommend the protocol would be better to set randomized phase II study to evaluate R0 resection rate of both arm (selection design) before comparison to upfront surgery. Overall survival should be measured as secondary end point.	

Reviewer 3

7	a) The authors do not provide any details regarding how many patients they see with locally advanced gallbladder cancer per year. Furthermore, it would be helpful to know what proportion of those patients would meet study enrollment criteria.	We see approximately 1000 case of Gall bladder cancer per year. Of these approximately 150 cases are locally advanced and meet the enrollment criteria.
8	b) According to clinicaltrials.gov, the trial has been ongoing since August 2016. In the protocol, the authors state that they expected enrollment to occur over the first 3 years of the trial, which will be up in just a few months. The authors allude to a slow recruitment of patients, but do not describe how many patients have been enrolled up until this point and how this affects the timeline and likelihood of completion for the trial.	Though the study was approved in August 2016, we accrued our first patient in November 2016. We have accrued only 67 patients till now.
9	c) Slow recruitment is a fact of life in the world of clinical trials. Given that, what do the authors plan to do? Do they have any criteria for declaring futility in being able to answer the question? Do they have any plans to enlist other centers to enroll patients? Do they plan to do alternative analyses such as Bayesian analyses that may more easily accommodate small sample sizes? What is their plan?	Due to this slow recruitment the study has been made multicentric and other centers in India (at least 3) where this disease is endemic are in the process of obtaining ethical approval from their respective institutions.
10	2) The reporting seems reasonable, but explicitly alluding to the CONSORT criteria and checklist would be helpful.	The checklist as per CONSORT can be made if the editors suggest. Will it increase the word limit ?
11	3) The study design states that stratification will be by T stage, and it lists T1-T4 -- should this really just be T3 or T4 given the inclusion criteria?	T1-T2 tumors having node positive disease will be included
12	4) In adjudicating the outcome of completeness of resection, how will non-surgical candidates be accounted for?	Patients not undergoing surgery will be separately analyzed since the primary outcome is overall survival.
13	5) The authors state that the study will redefine the current standard of care for locally advanced gallbladder disease. Since this is a one-center trial being	Since the study is being made multicentric, hopefully it will be applicable to the patients where this disease is common.

	conducted in India, can the authors describe how their patient population and their treatment algorithms compare to those worldwide? Do the authors expect their results to be widely generalizable?	
14	6) Unless I missed them, I did not see the NCT number (although I found it online) or the dates of the planned study in the manuscript (as required by the editors for protocols).	ClinicalTrials.gov (NCT02867865) has been added at the end of abstract

VERSION 2 – REVIEW

REVIEWER	Fuyuhiko Motoi Tohoku University (Japan)
REVIEW RETURNED	03-Apr-2019

GENERAL COMMENTS	The manuscript is adequately revised according to the reviewer's comment.

REVIEWER	Lillian Kao McGovern Medical School at the University of Texas Health Science Center at Houston
REVIEW RETURNED	06-Apr-2019

GENERAL COMMENTS	The clarifications have improved the manuscript. The authors should be congratulated for conducting a randomized trial in locally advanced gallbladder cancer. The authors may want to give additional thought to strategies for increasing patient enrollment if the addition of 3 more centers is not sufficient to ensure adequate sample size and power for their primary outcome.