PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (**http://bmjopen.bmj.com/site/about/resources/checklist.pdf**) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Assessing the safety and feasibility of neoadjuvant hormone and radiation therapy followed by robot-assisted radical prostatectomy for treating locally advanced prostate cancer: protocol for an open-label, dose-escalation, single-centre, phase I clinical trial
AUTHORS	Xiao, Yu-Tian; Zhao, Xianzhi; Chang, Yifan; Lu, Xiaojun; Wang, Ye; Zhang, Huojun; Ren, Shancheng

VERSION 1 – REVIEW

REVIEWER	Pignot Geraldine Institut Paoli-Calmettes, Marseille, France
REVIEW RETURNED	10-May-2020

GENERAL COMMENTS	The authors include patients with locally advanced disease (N1M0 or M1a) but exclude patients with bone metastasis or distant organ metastasis. However, the preoperative evaluation will be carried out by high-resolution MRI of the pelvis, CT scan and bone scan in selected patients. What does “selected patients” mean? Did the authors mean that “all patients included” or only some patients (on what criteria?) will have bone scan? Why didn’t they choose PET-scan for the preoperative evaluation of these patients at high risk of distant metastases? Safety will be assessed through adverse events via CTCAE v5.0, and the perioperative safety profile is a secondary endpoint. The authors should specify how they will evaluate postoperative complications (Clavien-Dindo classification) and when (30 days? 90 days?). Same thing for the functional outcomes (with which questionnaires? When and how often?) The english language must be reviewed: Laparoscopic or robot-assisted approach (rather than « fashion »), first-line curative treatment (rather than “active”), etc.

REVIEWER	Daniel Grass H Lee Moffitt Cancer Center and Research Institute Department of Molecular Oncology
REVIEW RETURNED	12-May-2020

GENERAL COMMENTS	Xiao et al. present there phase I trial idea "Assessing the safety and feasibility of neoadjuvant hormone and radiation therapy followed by robot-assisted radical prostatectomy for treating locally advanced prostate cancer: protocol for an open-label, dose-escalation, single- centre, phase I clinical trial." This is an important trial idea as the authors eluded to in their manuscript. A few concerns should be addressed prior to acceptance:

	1) Can rationale for dose-escalation of the primary prostate tumor be provided as these radiation doses and fractionations are some of the more common regimens used in the pelvis. It is likely the maximum tolerable dose will be any of the dose levels as these have all been shown to be well tolerated when delivered to the prostate, though the difference in toxicity may be in the retroperitoneal fields. This should be clarified. 2) Per point #1, when toxicity is measured, it is unclear if this is toxicity associated with radiation or post-operative toxicity. It would be very helpful to understand what specific toxicity metrics are being analyzed instead of stating grade 3/4. 3) Does prostate cancer diagnosis include all histologies, or just adenocarcinoma. Please clarify. 4) Unclear why prostate biopsy is an exclusion if performed within 2 weeks of enrollment. This is needed for the diagnosis? 5) Why did authors not use conventional radiation nomenclature for planning, GTV -> CTV-> PTV. Some of this nomenclature in the methods is confusing. Does pGTV = CTV + 0.5-1 cm -> PTV? Similar question for nodal volumes. 6) Will testosterone (total) be measured with PSA after RT and surgery? 7) Should include dose/fractionation of 2 trials mentioned in discussion to create context to proposed study. 8) Methods state radiation will start 4 months after ADT, yet Figure 1 states this is 4 weeks. Also, Figure 1 also implies surgery will be within 4-8 weeks of radiation completion, yet methods state at 8 weeks. Need to clarify. Grammar/Minor points: Line 29 - profile needs an 's' Line 69 - statement of surgery as 'the first line' treatment is not accurate. It should be worded as a first-line treatment choice, as radiation is also an efficacious approach for localized disease Line 77- patient need 's'

VERSION 1 – AUTHOR RESPONSE

Reviewer 1:

The authors include patients with locally advanced disease (N1M0 or M1a) but exclude patients with bone metastasis or distant organ metastasis. However, the preoperative evaluation will be carried out by high-resolution MRI of the pelvis, CT scan and bone scan in selected patients. What does “selected patients” mean? Did the authors mean that “all patients included” or only some patients (on what criteria?) will have bone scan? Why didn’t they choose PET-scan for the preoperative evaluation of these patients at high risk of distant metastases?

Response:

We thank Dr. Geraldine for the constructive suggestions. By “selected patients”, we intended to refer to all patients included. We have now modified the expression in the revised manuscript to clarify this. During the development of the first draft of the trial protocol, 68Ga-PSMA PET/CT was not readily available in our institution. Therefore, PET-scan was not previously included as one of the preoperative evaluation measures. In the updated protocol, 68Ga-PSMA PET/CT has now been listed as a preoperative evaluation measure. We have now updated the manuscript as well as the registry website.

Safety will be assessed through adverse events via CTCAE v5.0, and the perioperative safety profile is a secondary endpoint. The authors should specify how they will evaluate postoperative complications (Clavien-Dindo classification) and when (30 days? 90 days?). Same thing for the functional outcomes (with which questionnaires? When and how often?)
Response:
We thank the reviewer for the comments on outcome measurements. Perioperative complications will be evaluated using Clavien-Dindo Classification within 30 days postoperatively.
As for functional outcomes, KPS, FACT-P, and EQ-5D-5L will be used. Timepoints for these measurements are as follows: (1) initiation of ADT, (2) initiation of radiotherapy, (3) completion of radiotherapy, (4) before surgery, (5) discharge after surgery, (6) every 3 months after surgery for the first postoperative year and, (7) every 6 months after surgery for the second postoperative year. Continence will be measured before by pads used per day, at timepoints (4—7) described above. This piece of information has been specified in the revised manuscript.

The English language must be reviewed: Laparoscopic or robot-assisted approach (rather than « fashion »), first-line curative treatment (rather than “active”), etc.
Response:
We thank the reviewer for the suggestion on English language. The revised manuscript has been thoroughly reviewed and edited for clarity and grammatical errors.

Reviewer 2:

Xiao et al. present their phase I trial idea "Assessing the safety and feasibility of neoadjuvant hormone and radiation therapy followed by robot-assisted radical prostatectomy for treating locally advanced prostate cancer: protocol for an open-label, dose-escalation, single- centre, phase I clinical trial."

This is an important trial idea as the authors eluded to in their manuscript. A few concerns should be addressed prior to acceptance:

1) Can rationale for dose-escalation of the primary prostate tumor be provided as these radiation doses and fractionations are some of the more common regimens used in the pelvis. It is likely the maximum tolerable dose will be any of the dose levels as these have all been shown to be well tolerated when delivered to the prostate, though the difference in toxicity may be in the retroperitoneal fields. This should be clarified.
Response:
We thank the Dr. Grass for the interest in this trial design and the thoughtful comments.
We agree with the reviewer that these radiation doses and fractionations are commonly used in the pelvis and we do expect that the radiation delivered to the prostate will likely be well tolerated. However, currently there is no modern-era clinical trial on radiation therapy for N1/ M1a prostate cancer in a preoperative setting. In addition to the uncertain toxicity in retroperitoneal fields, perioperative safety profile is another important issue to consider. The intention of the dose-escalation design of this trial is to determine the optimal dose/fractionation which is not only maximally tolerable in terms of radiation therapy, but also does not significantly increase the difficulty of prostatectomy or increase perioperative complication rate.

2) Per point #1, when toxicity is measured, it is unclear if this is toxicity associated with radiation or post-operative toxicity. It would be very helpful to understand what specific toxicity metrics are being analyzed instead of stating grade 3/4.
Response:

We thank the reviewer for the comment on toxicity measurement. For this trial, we focus on the following toxicity metrics: (1) any grade 4+ toxicity, (2) any grade 3 toxicity except urinary incontinence, erectile dysfunction, and responsive diarrhea, (3) grade 2+ fistula, or (4) any grade colonic or rectal perforation, or (5) intraoperative rectal injury. We have specified these in the revised manuscript.

3) Does prostate cancer diagnosis include all histologies, or just adenocarcinoma. Please clarify.
Response:
Only prostate adenocarcinoma is included. We have added clarifications on this in the revised manuscript. We thank the reviewer for pointing this out.

4) Unclear why prostate biopsy is an exclusion if performed within 2 weeks of enrollment. This is needed for the diagnosis?
Response:
We thank the reviewer for the comment. We intended to imply that any surgery or re-biopsy should be performed at least 2 weeks away from a recent prostate biopsy. We think that the expression is indeed confusing in this context and have decided to remove this exclusion criterion in the revised manuscript.

5) Why did authors not use conventional radiation nomenclature for planning, GTV -> CTV-> PTV. Some of this nomenclature in the methods is confusing. Does pGTV = CTV + 0.5-1 cm -> PTV? Similar question for nodal volumes.
Response:
We thank the reviewer for the comment. In order to elaborate clearly, we did not use conventional radiation nomenclature for planning. Radiation therapy was dose-escalated with dose levels of 39.6, 45, 50.4, and 54 Gy. The pelvic lymph nodes were treated up to 45 Gy with any additional dose given to the prostate and seminal vesicles. pGTV is 5–10mm outwards for GTV in any direction, but only 5 mm in the posterior to reduce rectal irradiation. pGTVnd for GTVnd shall be delineated with an additional 5mm margin. pCTV for CTV shall be delineated with an additional 5mm margin.

6) Will testosterone (total) be measured with PSA after RT and surgery?
Response:
Yes, testosterone is also measured throughout the trial. We have added this piece of information in the revised manuscript.

7) Should include dose/fractionation of 2 trials mentioned in discussion to create context to proposed study.
Response:
We thank the reviewer for the nice suggestion and agree that the dose/fractionation information should be included in the Discussion section. We have updated the discussion section in the revised manuscript.

8) Methods state radiation will start 4 months after ADT, yet Figure 1 states this is 4 weeks. Also, Figure 1 also implies surgery will be within 4-8 weeks of radiation completion, yet methods state at 8 weeks. Need to clarify.
Response:
We thank the reviewer for these observations. We apologize for these mistakes in the manuscript. These discrepancies have been resolved in the revised manuscript.

Grammar/Minor points:
Line 29 - profile needs an 's'

Line 69 - statement of surgery as 'the first line' treatment is not accurate. It should be worded as a first-line treatment choice, as radiation is also an efficacious approach for localized disease
Line 77- patient need 's'
Response:
We thank the reviewer for these observations. We have revised the expressions and grammar points as suggested.

VERSION 2 – REVIEW

REVIEWER	Daniel Grass H. Lee Moffitt Cancer Center and Research Institute
REVIEW RETURNED	09-Jul-2020

GENERAL COMMENTS	The authors have adequately addressed the concerns of this reviewer and the manuscript is more clear in its presentation. Interested to see the results of this trial in the near future.