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)	Stereotactic body radiotherapy (SBRT) versus androgen deprivation therapy (ADT) for oligometastatic prostate cancer: protocol for a prospective randomized control clinical trial
AUTHORS	Zhao, Xianzhi; Wang, Tao; Ye, Yusheng; Li, Jing; Gao, xu; Zhang, Huojun

VERSION 1 – REVIEW

REVIEWER	Noriyoshi Miura Medical University of Vienna
REVIEW RETURNED	13-May-2021

GENERAL COMMENTS	Comments to the Author This is very interesting trial, which will clarify whether SBRT for the oligometastases of hormone-sensitive PCa can delay the start of ADT and prolong the time from inception of the study to CRPC. The reviewer would like to suggest several points to improve this trial. #1 Is the target only bone or lymph node metastases? If so, indicate in the exclusion criteria that the patients with organ metastases are excluded. #2 The author shows inclusion criteria based solely on the number of metastases. Is the size of the metastasis not taken into account? For example, are 5 mm bone metastases the same as 50 mm bone metastases? I think it is better to limit the minimum and maximum diameters. #3 Please show the definition of CRPC. #4 The authors write that Group A patients will receive luteinizing hormone-releasing hormone agonists only. On the other hand, it also states that the ADT regimen for this study contains bicalutamide. In addition, there is a description of Abiraterone. These explanations confuse us. Please define the treatment for Arm A more clearly.（Page 10 Line18） #5 Please indicate the method of radiation therapy for Arm B. The abstract show that it will use CyberKnife, but it is not shown in the main text.

REVIEWER	Amar Kishan UCLA
REVIEW RETURNED	04-Oct-2021

GENERAL COMMENTS	The authors describe an important randomized trial of SBRT vs.

	ADT for oligorecurrent cancer. This is a very important study to perform and I applaud the effort. I do have some questions about the study design that can be clarified. First, I do not agree that long-term ADT (inclusive of abiraterone) leads to CRPC in most patients after 18-24 months. Though not clearly stated in the abstract or brief summary, it appears that patients would be getting abiraterone here. Can the authors justify this statement from the introduction? Second, I would argue that it is not quite "unknown" whether SBRT to oligometastases or systemic therapy alone is the optimal treatment. We already know that PFS after SBRT alone is quite low, and the randomized trials in the oligorecurrent have compared against surveillance, not ADT. I think it would be better phrased that there are side effect issues with the known "standard of care" options here (ADT indefinitely) so alternate methods are worth pursuing. Third, the authors should clear state if the protocol would only allow M1a lymph node metastases, or if the term metastases is being used here to also include oligorecurrences in pelvic nodes (which would be N1M0) Fourth, I think the sample size section needs to be clarified. It appears the power calculation is based off of the time to use of salvage ADT in the SBRT-only arm, but the other arm has already received advanced ADT, so this doesn't seem to be an endpoint that you can power using the randomization of the study. Is there a consideration of power for the other primary endpoint (which would truly be a comparison between groups) which is time to development of CRPC? Please clarify. Fifth, I would recommend the authors should use the term "oligoprogression" rather than "microprogression", and polyprogression rather than extensive progression. The cutoff of 2 or fewer sites for oligo is odd given the inclusion was for 3 or fewer sites to begin with. Sixth, in the discussion section, the authors should cite STOMP or ORIOLE.

REVIEWER	Holly Hartman Case Western Reserve University, Population and Quantitative Health Sciences
REVIEW RETURNED	06-Dec-2021

GENERAL COMMENTS	This trial is important as patients and practitioners are looking for alternatives to ADT. Comparing SBRT and ADT in this specific patient population is well justified. However, I have some concerns with this protocol. Arm A: there are 2 possible dosing options listed. How will the dosing schedule be determined? Biochemical progression section: Wording makes it sound like only patients who receive SBRT will be examined for biochemical progression, but elsewhere it seems that both treatment arms will be screened. Please clarify.

	Table 1 is unclear. Some lines are misaligned. What does it mean "selected items?" Are these only going to be measured under certain conditions? Please expand. Sample size calculation don't state the expected difference in endpoints which is required to estimate the sample size. Thus the calculations can not be reproduced. Additionally, the authors mention recruiting 7, 18, and 50 patients but it is unclear if this is total or per arm. Since there is missing information, it is also not possible to reproduce these numbers. Please provide additional information to make these calculations reproducible. Data analysis does not mention toxicity data although it is mentioned as being of interest in the outcomes and measurements section. Please describe how this information will be analyzed or if it will just be summarized. Since this is a randomized trial, you do not need to compare baseline variables between groups. Any differences are truly random. Please do not test for difference between baseline variables. Are there any interim analyses planned to examine if the SBRT treatment arm for evidence of efficacy? For example, if you reach a certain point in the trial and all SBRT patients experience progression, then the trial should likely be concluded. Are there any measures of quality of life being considered? One major reason to identify a new therapy highlighted in the introduction is that ADT decreases quality of life. As such, quality of life measures should be included. EPIC would be one potential option as it has a specific sexual domain component. https://medicine.umich.edu/dept/urology/research/epic Some formatting errors and typos (citation style differing in text, missing paranthesis, repeated sentences, etc).

VERSION 1 – AUTHOR RESPONSE

Reviewer 1#:

1) Is the target only bone or lymph node metastases? If so, indicate in the exclusion criteria that the patients with organ metastases are excluded.
Response: Thank you for your suggestion. Yes, targets only includ bone or lymph node metastases. Patients with organ metastases are excluded. We have added the related content in the exclusion criteria.

2) The author shows inclusion criteria based solely on the number of metastases. Is the size of the metastasis not taken into account? For example, are 5 mm bone metastases the same as 50 mm bone metastases? I think it is better to limit the minimum and maximum diameters.
Response: Thank you for your advice. Indeed the size of the metastasis was taken into account. The diameter of the target was not exceeding 5cm or not less than 1.0cm. We have added the related content in the inclusion criteria.

3) Please show the definition of CRPC.

Response: Thank you for your suggestion. The definition of CRPC are as follows:

Castrate serum testosterone < 50 ng/dL or 1.7 nmol/L plus either:

• Biochemical progression: Three consecutive rises in PSA one week apart resulting in two 50% increases over the nadir, and a PSA > 2 ng/mL or,

• Radiological progression: The appearance of new lesions: either two or more new bone lesions on bone scan or a soft tissue lesion using RECIST(Response Evaluation Criteria in Solid Tumours)

Reference:

Howard I Scher, Susan Halabi, Ian Tannock, et al. Design and end points of clinical trials for patients with progressive prostate cancer and castrate levels of testosterone: recommendations of the Prostate Cancer Clinical Trials Working Group. J Clin Oncol. 2008;26(7):1148-59.

4) The authors write that Group A patients will receive luteinizing hormone-releasing hormone agonists only. On the other hand, it also states that the ADT regimen for this study contains bicalutamide. In addition, there is a description of Abiraterone. These explanations confuse us. Please define the treatment for Arm A more clearly.（Page 10 Line18）.

Response: Thank you for your correction. We have corrected it as follows. The ADT regimen for patients in arm A includes bicalutamide 50mg PO once daily for 2 weeks and goserelin acetate, a gonadotropin-releasing hormone agonist. The latter will be administered subcutaneously either at a dose of 3.6mg every 4 weeks or at a dose of 10.8mg every 12 weeks. Abiraterone with prednisone should be given with concurrent steroid.

5) Please indicate the method of radiation therapy for Arm B. The abstract show that it will use CyberKnife, but it is not shown in the main text.

Response: Thank you for your comment. We have added it in the main text of interventions section. SBRT will be administered, which would be performed with CyberKnife.

Reviewer 2#:

1) I do not agree that long-term ADT (inclusive of abiraterone) leads to CRPC in most patients after 18-24 months. Though not clearly stated in the abstract or brief summary, it appears that patients would be getting abiraterone here. Can the authors justify this statement from the introduction?

Response: Thank you for your suggestion. Long-term ADT (inclusive of abiraterone) leads to CRPC in most patients after 33-36 months. We have corrected it in the manuscript.

References

2. Fizazi K, Tran N P, Fein L, et al. Abiraterone plus prednisone in metastatic, castration-sensitive prostate cancer[J]. New England Journal of Medicine, 2017, 377: 352-360.

3. Barata P C, Sartor A O. Metastatic castration-sensitive prostate cancer: Abiraterone, docetaxel, or…[J]. Cancer, 2019, 125: 1777-1788.

2) I would argue that it is not quite “unknown” whether SBRT to oligometastases or systemic therapy alone is the optimal treatment. We already know that PFS after SBRT alone is quite low, and the randomized trials in the oligorecurrent have compared against surveillance, not ADT. I think it would be better phrased that there are side effect issues with the known “standard of care” options here (ADT indefinitely) so alternate methods are worth pursuing.
Response: Thank you for your comment. Firstly, I agree the reviewer’s opinion that PFS after SBRT alone is quite low and not all oligometastatic patients were suitable for SBRT alone. Howerver, there is a subgroup that bPFS is high after radiotherapy alone according to Shankar Siva’s study. In those not on androgen deprivation therapy (ADT; n = 22), the 2-yr freedom from ADT was 48%. The character of this subgroup is unclear. So, our clinical trial aims to explore it. Secondly, ADT ± chemotherapy is the system therapy while SBRT belongs to local therapy. Some studies recommend system therapy for oligometastatic patients others think local therapy for oligometastases is feasible. So, our study aims to answer this question. Third, we think surveillance for oligometastatic patients is a negative treatment. So, the control group in our clinical trial will receive ADT.

References:

(14). Siva S, Bressel M, Murphy DG, et al. Stereotactic Abative Body Radiotherapy (SABR) for Oligometastatic Prostate Cancer: A Prospective Clinical Trial. Eur Urol 2018;74:455-62.

3) The authors should clear state if the protocol would only allow M1a lymph node metastases, or if the term metastases is being used here to also include oligorecurrences in pelvic nodes (which would be N1M0).
Response: Thank you for your constructive comment. We have added the related content in the manuscript. The protocol would not only allow M1a lymph node metastases, but also include oligorecurrences in pelvic nodes (which would be N1M0).

4) I think the sample size section needs to be clarified. It appears the power calculation is based off of the time to use of salvage ADT in the SBRT-only arm, but the other arm has already received advanced ADT, so this doesn’t seem to be an endpoint that you can power using the randomization of the study. Is there a consideration of power for the other primary endpoint (which would truly be a comparison between groups) which is time to development of CRPC? Please clarify.
Response: Thank you for your comments. We have added the related information in the manuscript. The time from randomization to CRPC is the primary objective. It is estimated that long-term ADT inclusive of abiraterone leads to CRPC in most patients after 33-36 months. There will be a 1:1 randomization between arm A and arm B. In order to detect a 36-month difference in the studied endpoint from 33 to 69 months, each group needs at least 45 samples while α is 0.05 and the test efficiency is 80%. Assuming a 10% rate of loss to follow-up, 50 patients of each group will be recruited considering the time from randomization to CRPC.

5) I would recommend the authors should use the term “oligoprogression” rather than “microprogression”, and polyprogression rather than extensive progression. The cutoff of 2 or fewer sites for oligo is odd given the inclusion was for 3 or fewer sites to begin with.
Response: Thank you for your suggestion. We have corrected "microprogression " to "oligoprogression "," extensive progression " to " polyprogression ". We have corrected the cutoff of "2 or fewer sites" for oligometastases to "3 or fewer sites".

6) In the discussion section, the authors should cite STOMP or ORIOLE.
Response: Thank you for your comments. We have cited STOMP or ORIOLE in the discussion section as follows. Some clinical trials are exploring alternate methods to postpone ADT. STOMP trial is a randomized phase II trial comparing surveillance with metastasis-directed surgery or SBRT for oligometastatic prostate cancer recurrence. Another phase II randomized trial is ORIOLE comparing observation with stereotactic ablative radiation for oligometastatic prostate cancer. However, we think surveillance for oligometastatic patients is a negative treatment attitude. So, the control group in our clinical trial will receive ADT, while experimental group will receive SBRT.

References:

(19) Radwan N, Phillips R, Ross A, et al. A phase II randomized trial of Observation versus stereotactic ablative RadiatIon for OLigometastatic prostate CancEr (ORIOLE).BMC Cancer.2017;17:453.

(20) Decaestecker K, De Meerleer G, Ameye F, et al.Surveillance or metastasis-directed Therapy for OligoMetastatic Prostate cancer recurrence (STOMP): study protocol for a randomized phase II trial. BMC Cancer.2014;14:671.

Reviewer 3#:

1) Arm A: there are 2 possible dosing options listed. How will the dosing schedule be determined?
Response: Thank you for your comments. Actually, the ADT regimen for patients in arm A includes bicalutamide 50mg PO once daily for 2 weeks and goserelin acetate, a gonadotropin-releasing hormone agonist. The latter will be administered subcutaneously either at a dose of 3.6mg every 4 weeks or at a dose of 10.8mg every 12 weeks. Abiraterone with prednisone should be given with concurrent steroid. There are 2 possible dosing options listed for goserelin acetate. However, there is no difference between two dosing regimens. So, both regimens are OK.

2) Biochemical progression section: Wording makes it sound like only patients who receive SBRT will be examined for biochemical progression, but elsewhere it seems that both treatment arms will be screened. Please clarify.
Response: Thank you for your comments. Both arms may develp CRPC. However, treatment is different after biochemical progression for two arms. In arm A, once biochemical progression

becomes, the primary endpoint CRPC occurs. In arm B, after biochemical progression the associated treatment is shown in Figure 1.

3) Table 1 is unclear. Some lines are misaligned. What does it mean “selected items?” Are these only going to be measured under certain conditions? Please expand.
Response: Thank you for your advice. We have aligned all the lines. “Selected items” means not a must. There are some test items only going to be measured under certain conditions. For example, ECT in follow-up is going to be measured once patient treated with bone metastases.

4) Sample size calculation don’t state the expected difference in endpoints which is required to estimate the sample size. Thus the calculations can not be reproduced. Additionally, the authors mention recruiting 7, 18, and 50 patients but it is unclear if this is total or per arm. Since there is missing information, it is also not possible to reproduce these numbers. Please provide additional information to make these calculations reproducible.
Response: Thank you for your advice. We have added the related information in the manuscript. The time from randomization to CRPC is the primary objective. It is estimated that long-term ADT inclusive of abiraterone leads to CRPC in most patients after 33-36 months. There will be a 1:1 randomization between arm A and arm B. In order to detect a 36-month difference in the studied endpoint from 33 to 69 months, each group needs at least 45 samples while α is 0.05 and the test efficiency is 80%. Assuming a 10% rate of loss to follow-up, 50 patients of each group will be recruited considering the time from randomization to CRPC.
5) Data analysis does not mention toxicity data although it is mentioned as being of interest in the outcomes and measurements section. Please describe how this information will be analyzed or if it will just be summarized.
Response: Thank you for your advice. We have added the related information in the manuscript. Toxicity data of both arms will be summarized.
6) Since this is a randomized trial, you do not need to compare baseline variables between groups. Any differences are truly random. Please do not test for difference between baseline variables.
Response: Thank you for your advice. We have deleted the related information in the manuscript. As follows:“For comparisons between the baseline variables, the χ2 test and Fisher’s exact test will be performed.”
7) Are there any interim analyses planned to examine if the SBRT treatment arm for evidence of efficacy? For example, if you reach a certain point in the trial and all SBRT patients experience progression, then the trial should likely be concluded.
Response: Thank you for your advice. If there is no defference between the time from randomization to CRPC of two arms, the trial should likely be concluded.
8) Are there any measures of quality of life being considered? One major reason to identify a new therapy highlighted in the introduction is that ADT decreases quality of life. As such, quality of life measures should be included. EPIC would be one potential option as it has a specific sexual domain component. https://medicine.umich.edu/dept/urology/research/epic

Response: Thank you for your advice. Quality of life of two arms is very inmportant in the study. Quality of life will be measured using Karnofsky Performance Status Scale, the Expanded Prostate Cancer Index Composite (EPIC) and the 5-level EQ-5D (EQ-5D-5L) instrument. We have added it in the manuscript.

References:

(16) Péus D, Newcomb N, Hofer S. Appraisal of the Karnofsky performance status and proposal of a simple algorithmic system for its evaluation. BMC Med Inform Decis Mak 2013;13:72.

(17) https://medicine.umich.edu/dept/urology/research/epic

(18) Luo N, Li M, Liu GG, et al. Developing the Chinese version of the new 5-level EQ-5D descriptive system: the response scaling approach. Qual Life Res 2013;22:885–90.

9) Some formatting errors and typos (citation style differing in text, missing paranthesis, repeated sentences, etc).

Response: Thank you for your comments. This manuscript has been revised by a native speaker. Some formatting errors and typos have been corrected. Please see the marked manuscript. Thank you.

VERSION 2 – REVIEW

REVIEWER	Holly Hartman Case Western Reserve University, Population and Quantitative Health Sciences
REVIEW RETURNED	11-Feb-2022

GENERAL COMMENTS	My comments were sufficiently addressed. I look forward to reading the results of this study.