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)	Safety and efficacy of stereotactic body radiation therapy combined with S-1 simultaneously followed by sequential S-1 as an initial treatment for locally advanced pancreatic cancer (SILAPANC trial): Study design and rationale of a phase II clinical trial
AUTHORS	Zhu, Xiaofei; Ju, Xiaoping; Cao, Fei; Fang, Fang; Qing, Shuiwang; Shen, Yuxin; Jia, Zhen; Cao, Yangsen; Zhang, Huojun

VERSION 1 - REVIEW

REVIEWER	Wang,Yanming Dpt. of radiation oncology, Jinan military general hospital, China
REVIEW RETURNED	23-Jul-2016

GENERAL COMMENTS	Less research on the treatment of SBRT combined with S-1 in the treatment of pancreatic cancer, the research design is reasonable, the statistics are appropriate, the results are credible. Recommendations continue to follow up, and further summarize the complications of long-term treatment.

REVIEWER	Joseph Herman Johns Hopkins University Consulting with Merrimack and BTG not related to this manuscript.
REVIEW RETURNED	13-Aug-2016

GENERAL COMMENTS	1. It is not clear to me why CyberKnife needs to be included in the title. Since it is a commercial entity, I propose that it be replaced by stereotactic body radiation therapy or SBRT. Has this study been opened yet? How is it being funded? There are some areas where grammar could be improved. 2. What is the primary objective of the study based on? If it is overall survival is it being compared to historical controls? Is the 20% increased based on which historical study? 3. Which type of fiducials are being used? 4. Is more aggressive chemotherapy allowed after SBRT? 5. If patients undergo surgery, how will that influence the final statistical analysis? 6. Why are you waiting 1-3 weeks between fiducial placement and simulation. In most cases there is minimal migration after placement. 7. Line 16 page 20. You stated dose to CTV, did you mean PTV? 8. Is there a “target” radiation dose you are trying to achieve? Is there a BED goal? 9. How do you contour your “normal structures”? 10. I would recommend adding more recent studies to the references and perhaps include a table of published studies in order

	to demonstrate why you selected your 1 year OS expectation. These include the following: Herman JM, Chang DT, Goodman KA, et al. Phase 2 multi-institutional trial evaluating gemcitabine and stereotactic body radiotherapy for patients with locally advanced unresectable pancreatic adenocarcinoma.Cancer. 2015;121:1128-1137. Mahadevan A, Jain S, Goldstein M, et al. Stereotactic body radiotherapy and gemcitabine for locally advanced pancreatic cancer. Int J Radiat Oncol Biol Phys. 2010;78:735-742. Chuong MD, Springett GM, Freilich JM, et al. Stereotactic body radiation therapy for locally advanced and borderline resectable pancreatic cancer is effective and well tolerated. Int J Radiat Oncol Biol Phys. 2013;86:516-522.

VERSION 1 – AUTHOR RESPONSE

Reviewer 2:

1. It is not clear to me why CyberKnife needs to be included in the title. Since it is a commercial entity, I propose that it be replaced by stereotactic body radiation therapy or SBRT. Has this study been opened yet? How is it being funded? There are some areas where grammar could be improved.
Response: Thanks for the comment. “Cyberknife” has been replaced by stereotactic body radiation therapy. Enrolment of patients began just after approval of the independent Ethic Committee of our hospital and registration in the clinicaltrials.gov database. It will be opened to the public after results are available. This study was sponsored by our department. The grammar has been improved by a native speaker.

2. What is the primary objective of the study based on? If it is overall survival is it being compared to historical controls? Is the 20% increased based on which historical study?
Response: The ideal treatment of locally advanced pancreatic cancer still remains controversial. Surgery alone is not the standard treatment. Additionally, radiation therapy has been placed more emphasis in different guidelines. Stereotactic body radiation therapy and S-1 were proved to effectively improve prognosis in previous studies but few studies have focused on combination of stereotactic body radiation therapy and S-1. Also, due to lack of level I evidence, stereotactic body radiation therapy or S-1 has not been strongly recommended in guidelines. Therefore it is necessary to evaluate the efficacy of the treatment modality. As a result, the overall survival is predominant in our study. Besides, the overall survival in the study would be compared to historical controls, namely prognosis of patients treated with upfront surgeries, chemotherapy, conventional radiotherapy or other combination therapies in our center. Therefore, the 20% increase was based on our previous case control studies.

3. Which type of fiducials are being used?
Response: Soft tissue gold markers, 0.9×3mm, CIVCO, Orange City, Iowa 51041 USA.

4. Is more aggressive chemotherapy allowed after SBRT?
Response: Patients would receive follow-up examinations according to our protocol. Those with complete response, partial response or stable disease would not be treated with other modality. Patients with progression would be required to receive other chemotherapy. According to guidelines, FOFIRINOX or gemcitabine + albumin-bounded paclitaxel are preferred. However, more aggressive chemotherapy is not proper for patients with bad performance status. Those patients should receive other supportive or palliative treatment.

5. If patients undergo surgery, how will that influence the final statistical analysis?
Response: If patients were appropriate for surgical resection after combination of SBRT and S-1, which was proved by our multidisciplinary team, sub-group analysis would be conducted. The prognosis of patients undergoing surgery after combination of SBRT and S-1 would be compared with that of patients treated with combination of SBRT and S-1 alone, in order to evaluate the necessity efficacy of follow-up surgery after combination of SBRT and S-1.

6. Why are you waiting 1-3 weeks between fiducial placement and simulation. In most cases there is minimal migration after placement.
Response: Actually, the planning CT scan was performed 1 week after fiducials implantation in our center, which was similar to other previous studies. However, migration of fiducials may tend to occur when the tumor and fiducials are closely adjacent to major vessels, which appeared in our center and other studies, but rare. Therefore, the interval was replaced by “7-10 days”.

7. Line 16 page 20. You stated dose to CTV, did you mean PTV?
Response: We are grateful for the reviewer precise comment. We actually meant dose to PTV. Only when the tumor was adjacent to critical organs, the expansion of CTV to PTV was avoided and the CTV, other than PTV, were covered by prescription doses.

8. Is there a “target” radiation dose you are trying to achieve? Is there a BED goal?
Response: The dose-response relationship in pancreatic cancer remains unclear, or may be even weaker than that in lung cancer. The single doses were determined by our previous dose escalation studies, case series and other studies. It was found that more radiation-induce toxicities may occur when the single dose was above 9Gy in our center. Therefore, the upper limit of the total dose of SBRT was no more than 45Gy. Besides, the total dose of conventional radiotherapy in our center and previous studies for pancreatic cancer was proved to be no less than 40-45Gy, which means the lower limit of the total dose of SBRT was at least 32.5Gy (6.5Gy/f).

9. How do you contour your “normal structures”?
Response: The contouring of “normal structures” were based on the RTOG’s consensus (https://www.rtog.org/CoreLab/ContouringAtlases.aspx).

10. I would recommend adding more recent studies to the references and perhaps include a table of published studies in order to demonstrate why you selected your 1 year OS expectation.
Response: In our study, the primary outcome was OS, and 1-, 2-, 3-, 4- and 5-year OS rates were also included as primary endpoints in order to demonstrate the efficacy of combination of SBRT and S-1 in locally advanced pancreatic cancer. Additionally, 1 year OS rate was used in determination of sample size. Therefore, based on limited literature and previous small sample size studies on patients treated with SBRT and S-1 in our center, increase of 1 year OS rate was assumed in the determination of sample size.

The table about recent studies evaluating SBRT in pancreatic cancer has been uploaded in the file.