Author’s response to reviews

Title: A phase II study of intraoperative radiotherapy using a low-energy x-ray source for resectable pancreatic cancer: a study protocol

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Author’s response to reviews:

Thank you very much for reviewing our study protocol and the thorough review report on the manuscript. We re-examined our work and made revisions in the manuscript with respect to reviewers’ comments. We tried to respond to reviewers’ comments as thoroughly as possible. Thank you for the opportunity for this revision and we look forward to receiving a positive decision.

1. Trial Registration Date

Can you please include the date the trial was registered as part of the TRN details in the abstract. Please also state here whether the trial was prospectively or retrospectively registered.

Response:

We added the date of prospective trial registration in the abstract as follows:

Trial registration: The trial was prospectively registered at Clinicaltrials.gov NCT03273374 on September 6, 2017.

2. Funding and peer-review
Regarding the independent funding body (National Research Foundation of Korea), can you please provide further details of their peer-review process.

- Do you know how many referees were involved

- Were major/minor/any revisions requested

Response:

The National Research Foundation of Korea (NRF) review process includes online blind review and debate evaluation. Research proposals with a total research period of 1 to 5 years only undergo online blind review and those with research period of 6 to 10 years undergo online review and debate evaluation. Our project requires the total research period of 3 years and underwent online blind review only. Online review includes initial screening process followed by a blind review by a panel of expert referees. The number of referees that formed the review panel was not informed. There was no revision requested by NRF upon reviewing our proposal. There was only a minor revision requested by our institutional Office of Industry-university Research Cooperation regarding the details of funding information such as the overhead cost.

3. In the NRF documentation, the Korean version suggests that the manuscript is going to be submitted to BMC Gastroenterology. Can you confirm why this journal is listed in this document, and if the funding body are aware that you are submitted to BMC Surgery – will this affect the funding outcome?

Response:

Our research project was approved by NRF and funding began in June 1, 2017. The confirmation letter of conducting research was issued by NRF on October 18, 2018 upon our request. Issuing of the confirmation letter required the purpose of the confirmation letter and the potential body to whom the confirmation letter was to be submitted. BMC Gastroenterology was one of the journals we were considering submission of our study protocol. Since the funding had been already approved, the identity of the journal that publishes our study protocol will not affect the funding outcome.

4. SPIRIT checklist

For the purposes of transparency, can you please provide a completed SPIRIT checklist (http://www.spirit-statement.org/) that demonstrates adherence to these guidelines. We would prefer the author to copy the text directly form the manuscript into the checklist to show exactly how each point has been addressed.

Response:

The SPIRIT checklist is completed as below and submitted as a supplementary file.
A phase II study of intraoperative radiotherapy using a low-energy x-ray source for resectable pancreatic cancer: a study protocol (page 1).

The trial was prospectively registered at Clinicaltrials.gov NCT03273374 on September 6, 2017 (page 3).

The study protocol was approved by the institutional review board at Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul, Korea (3-2017-0171) on June 12, 2017 (page 14).

This work was supported by the Faculty Research Grant from Yonsei University College of Medicine (6-2016-0094) and the Basic Science Research Program through the National Research Foundation of Korea (NRF), funded by the Ministry of Education, Republic of Korea (2017R1D1A1B03035047) (page 14).
JK participated in the trial designing, conducted IORT, and prepared the manuscript. YC prepared the study protocol, and conducted IORT. HK assisted in preparing the study protocol and conducted the surgical procedures. WC assisted in preparing the study protocol and conducted the medical physics procedures. JP designed the trial, conducted surgical procedures, and conducted the correspondence. IL designed the trial, prepared the study protocol, and conducted the correspondence. All authors read and approved the final manuscript.

5b. Name and contact information for the trial sponsor

Check)

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5c. Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities

Check)

These funding sources had no role in the design of this study and will not have any role during its execution, analyses, interpretation of the data, or decision to submit results.

5d. Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)

Check) n/a
6a. Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention

Check)

Background

Even after successful surgical resection, long-term survival is rare, and the five-year survival rate of patients with resected pancreatic adenocarcinoma is approximately 10% – (page 4)

6b. Explanation for choice of comparators

Check)

Previous trials involving external beam radiation therapy (EBRT) have shown improved local control in combination with surgical resection [6, 8]. However, the efficacy of EBRT in pancreatic cancer is limited by the difficulty of delivering an adequate dose of radiation due to the limited tolerance of critical organs, including the stomach, small bowel, kidney, liver, and spinal cord. Furthermore, adjuvant EBRT concurrently administered with gemcitabine is excluded from reimbursement by the Korean National Health Insurance (page 4).

7. Specific objectives or hypotheses

Check)

Hypothesis

This trial tests the hypothesis that IORT in addition to the current standard of care will improve local control compared with that observed so far in patients with resectable pancreatic adenocarcinoma.

Study objectives and endpoints

The primary endpoint is to evaluate the local recurrence rate after one year. The secondary endpoints include disease-free survival (DFS) and overall survival (OS) rates as well as acute and late toxicities, perioperative morbidity and mortality, and quality of life (page 6).
8. Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)

Check)

The purpose of the study is to investigate the role of IORT in patients with primarily resectable pancreatic cancer. The trial will be conducted as a single-center, one-armed phase II study (page 6).

9. Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained

Check)

The trial will be conducted as a single-center, one-armed phase II study. The trial has been registered at www.clinicaltrials.gov (NCT03273374). Patients will be recruited at the Pancreatobiliary Cancer Center, Gangnam Severance Hospital, Yonsei University College of Medicine (page 6).

10. Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)

Check)

Inclusion criteria

• 20 years of age or older ~

Exclusion criteria

• Prior EBRT in the abdominal area ~

(page 7)

11a. Interventions for each group with sufficient detail to allow replication, including how and when they will be administered

Check)
The mobile 50-kV x-ray source (Intrabeam) will be attached to the robotic arm, which maintains the stability of the source throughout the procedure (Fig. 2). The isotropy and output of the IORT unit are verified and the pre-IORT calibration process required by the system is performed prior to each treatment. The target volume of IORT includes the tumor bed, the celiac and superior mesenteric origins, the mesenteric root, and the portal vein or any areas deemed risky by the surgeon and the radiation oncologist. An applicator with an appropriate diameter (3.0, 3.5, or 4.0 cm) will be selected according to the size of the target volume, and the applicator attached over the probe of the x-ray source. ~ (page 9)

11b. Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)

Check)

Study participation will be terminated, if the patient suffers from a grade 4 toxicity related to treatment, if a different treatment is required that is not approved in this trial, or if the patient withdraws consent for further participation (page 10).

11c. Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)

Check) n/a

11d. Relevant concomitant care and interventions that are permitted or prohibited during the trial

Check)

Pretreatment evaluation

Percutaneous or endoscopic biliary drainage will be recommended for patients with obstructive jaundice before or during treatment.

Treatment

All patients who fulfill the inclusion criteria and provide written informed consent will be assigned to the treatment regimen shown in Figure 1. An explorative laparotomy will be performed and the indication to continue with a resection will be based upon the absence of peritoneal or distant metastasis and the loco-regional extension of the disease, particularly major vascular involvement. A curative resection either as pancreatoduodenectomy or distal pancreatectomy will be performed (page 9).
12. Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended.

Check)

Study objectives and endpoints

The primary endpoint is to evaluate the local recurrence rate after one year. The secondary endpoints include disease-free survival (DFS) and overall survival (OS) rates as well as acute and late toxicities, perioperative morbidity and mortality, and quality of life.

Follow-up and assessment of efficacy

The local recurrence rate after one year is the primary endpoint of the trial. It will be assessed by repeated CT, MRI, or PET-CT during regular follow-up. In case of suspected local recurrence, histological confirmation will be attempted. New lesions with typical radiological signs of a local recurrence in combination with or without increase in the levels of tumor markers will be considered a local recurrence. DFS and OS are the secondary endpoints of the study. DFS will be counted from the day of surgery until the date of the first local or distant event or death due to any cause (page 6, page 10).

13. Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure).

Check)

Study design and period

The expected total duration of patient enrollment is two years and the follow-up period is three years.

Follow-up and assessment of efficacy

Regular follow-up visits will take place every three months after surgery for the first two years and every six months thereafter (page 6, page 10).
14. Estimated number of participants needed to achieve study objectives and how it was
determined, including clinical and statistical assumptions supporting any sample size
calculations

Check)

Sample size calculation

The local recurrence rate one year after resection in our institution was 36%; the local recurrence
rates after one year in comparable patient populations treated with IORT and resection ranged
between 21–41.6%. The sample size calculation was designed on the assumption that addition of
IORT will decrease the local recurrence rate after one year by 14% (from 36% to 22%) with a
power of 80%. Using the two-sided binomial test with a level of significance of $\alpha = 5\%$, the
study requires 33 patients. Assuming a drop-out rate of 20%, a total of 42 patients will be
required for this trial (page 8).

15. Strategies for achieving adequate participant enrolment to reach target sample size

Check) n/a

16a. Method of generating the allocation sequence (eg, computer-generated random numbers),
and list of any factors for stratification. To reduce predictability of a random sequence, details of
any planned restriction (eg, blocking) should be provided in a separate document that is
unavailable to those who enrol participants or assign interventions

Check) n/a

16b. Mechanism of implementing the allocation sequence (eg, central telephone; sequentially
numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until
interventions are assigned

Check) n/a

16c. Who will generate the allocation sequence, who will enrol participants, and who will assign
participants to interventions

Check) n/a

17a. Who will be blinded after assignment to interventions (eg, trial participants, care providers,
outcome assessors, data analysts), and how
17b. If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant’s allocated intervention during the trial

Check) n/a

18a. Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol

Check)

The local recurrence rate after one year is the primary endpoint of the trial. It will be assessed by repeated CT, MRI, or PET-CT during regular follow-up. In case of suspected local recurrence, histological confirmation will be attempted. New lesions with typical radiological signs of a local recurrence in combination with or without increase in the levels of tumor markers will be considered a local recurrence.

Toxicity will be assessed according to Common Terminology Criteria for Adverse Events Version 3.0. Any toxicity occurring within three months after surgery will be considered acute toxicity. Late toxicity will be assessed during the regular follow-up visits (page 10).

18b. Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols

Check) n/a

19. Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol

Check) n/a

20a. Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol

Check)
DFS and OS are the secondary endpoints of the study. DFS will be counted from the day of surgery until the date of the first local or distant event or death due to any cause. Patients alive without recurrent disease at the time of data analysis will be censored at the time of the most recent follow-up. The OS will be determined from the day of surgery until death due to any cause. Patients alive or lost to follow-up will be censored at the date of the last follow-up visit. For timed endpoints including DFS and OS, the Kaplan-Meier survival analysis followed by multivariable Cox proportional hazards model for adjusting for baseline variables will be used. P-values < 0.05 will be considered significant (page 10).

20b. Methods for any additional analyses (eg, subgroup and adjusted analyses)
Check) n/a

20c. Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)
Check) n/a

21a. Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed
Check) n/a

21b. Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial
Check) n/a

22. Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct
Check)

Safe evaluation and reporting of adverse effects

Adverse and serious adverse events must be reported in order to protect participants. Study participation will be terminated, if the patient suffers from a grade 4 toxicity related to treatment, if a different treatment is required that is not approved in this trial, or if the patient withdraws
consent for further participation. Serious adverse events will be reported within seven days of detection by the investigators (page 11).

23. Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor

Check) n/a

24. Plans for seeking research ethics committee/institutional review board (REC/IRB) approval

Check)

Ethics approval and consent to participate

The study protocol was approved by the institutional review board at Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul, Korea (3-2017-0171) on June 12, 2017. The study complies with the Declaration of Helsinki and the principles of Good Clinical Practice. All patients who fulfill the inclusion criteria will provide written informed consent (page 14).

25. Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)

Check) n/a

26a. Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)

Check) n/a

26b. Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable

Check) n/a

27. How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial
Check) n/a

28. Financial and other competing interests for principal investigators for the overall trial and each study site

Check)

Competing interests

The authors declare that they have no competing interests (page 14).

29. Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators

Check) n/a

30. Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation

Check) n/a

31a. Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions

Check) n/a

31b. Authorship eligibility guidelines and any intended use of professional writers

Check) n/a

31c. Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code

Check)

Availability of data and material:
The trial is ongoing and collecting data. The clinical datasets will be available via the corresponding author (page 14).

32. Model consent form and other related documentation given to participants and authorised surrogates

Check) n/a

33. Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable

Check) n/a

The following changes are made in the manuscript in order to fulfill the SPIRIT checklist requirements.

Page 14: the date of protocol approval was added

The study protocol was approved by the institutional review board at Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul, Korea (3-2017-0171) on June 12, 2017.

Phage 14: the roles of funders were added

This work was supported by the Faculty Research Grant from Yonsei University College of Medicine (6-2016-0094) and the Basic Science Research Program through the National Research Foundation of Korea (NRF), funded by the Ministry of Education, Republic of Korea (2017R1D1A1B03035047). These funding sources had no role in the design of this study and will not have any role during its execution, analyses, interpretation of the data, or decision to submit results.

Page 10: the method of statistical analysis was added

For timed endpoints including DFS and OS, the Kaplan-Meier survival analysis followed by multivariable Cox proportional hazards model for adjusting for baseline variables will be used. P-values < 0.05 will be considered significant.