PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	GETUG-AFU 31: a phase I/II multi-center study evaluating the safety and efficacy of salvage stereotactic radiation in patients with intraprostatic tumor recurrence after external radiation therapy; study protocol
AUTHORS	Pasquier, David; Le Deley, Marie-Cécile; Tresch, Emmanuelle; Cormier, Luc; Duterque, Martine; Nenan, Soazig; Lartigau, eric

VERSION 1 – REVIEW

REVIEWER	Linda Agolli Department of Radiation Oncology, Faculty of Medicine and University Hospital Carl Gustav Carus, Technische Universität Dresden, Dresden 01037, Germany.
REVIEW RETURNED	06-Oct-2018

GENERAL COMMENTS	This is an innovative study protocol by Pasquier et al. regarding the reirradiation using salvage SBRT after EBRT in recurrent prostate cancer. Nowadays, no standard therapy exists for locally recurrent prostate cancer. Patients are often unsuitable to surgery due to previous irradiation of the prostate and also advanced age and comorbidities. Brachytherapy could be and alternative but only a few patients fulfill selection criteria for such a treatment. Theoretically, SBRT seems to be a good alternative in the salvage setting but evidence is needed to confirm the safety and efficacy of such a technique. The current study protocol is interesting and controlled trials in this field are needed. The multicenter setting could help to include more patients with prostate cancer and local relapse, although the enrollment of the candidates could be challenging. - 2-3 years after RT a biopsy could not be useful. It is known that positive tumor cells could be found in the prostate. This could be a bias. Is this factor included in the initial analysis? Please discuss this issue in the introduction. - The rationale and the choice of the radiation dose should be better explained, recurrent prostate cancer is also more radioresistent as the initial tumor. This should be discussed previously. - A pre-treatment staging with choline-PET CT has a certain rate of false positive and false negative compared to the PSMA-PET. Patients with lymph node metastases could be included in the study. These rates should be reported in the inclusion criteria or the risk should be discussed. - The author state that “based on dose-limiting toxicity defined as grade ≥3 gastrointestinal or urinary toxicity or any other grade 4 adverse event observed during the 18 weeks following the

	initiation of salvage-SBRT". Which gastrointestinal or urinary toxicity, please specify. - Are only the severe toxicities a secondary end-point or all kind of toxicity or grade ≥2? - In the phase II part, a table with the selected acute and late toxicity could be useful for the readers in order to know the clinical relevance. - Is biochemical relapse-free survival the only parameter to check treatment response or a new diagnostic imaging would be performed? For example with PET? If the patients develop any kind of macroscopical metastases after phase I or II, are they excluded from the study? How could be determined clinical progression-free survival for example for bone metastases or other distant metastases outside the pelvis? Or other examinations such as PET-CT or CT should be performed in case of increased PSA? - It would be interesting to know the necessary dose-limit parameters for bladder and rectum considered for the plan acceptance. A table could be helpful. - Have the fiducial markers to be delineated? Is an IGRT mandatory? Please add the positioning and verification method. Which MRI sequences are used for the delineation?

REVIEWER	De Meerleer Gert Leuven University Hospitals, Belgium
REVIEW RETURNED	15-Oct-2018

GENERAL COMMENTS	The issue of local relapse after EBRT for prostate cancer is a clinically important question, which the authors will study within a prospective protocol using SBRT. In general, the introduction and description of the different salvage techniques is too long. A table would be better and improve reading. Some minor remarks: - references 2 and 3 are rather old, is it possible to include more recent work on modern radiotherapy outcomes? - Is PSMA PET-CT allowed (p 11)? - A major concern is the lack of surgical nodal staging, as choline PET-CT is not sensitive enough concern nodal staging. Please comment whether salvage nodal therapies are allowed. - Please note and clearly state that a 3-years follow-up is too short to report on GU toxicity. - p13: How do you check whether a positive biopsy is outside the visible MR lesion? - p14: the starting dose is 5 x 6 Gy. 5x5 Gy is not an escalation, no (p15: escalated to the next llevel ...)? Do not fully understand.

REVIEWER	Qing Liu Amgen Inc. USA
REVIEW RETURNED	20-Jan-2019

GENERAL COMMENTS	This is a well-written manuscript describing a phase I/II study protocol to evaluate the safety and efficacy of salvage stereotactic radiation in prostate cancer patients. Below, I have some additional comments and suggestions, which hopefully can help the authors improve the paper. Major comments: 1. In the simulation study to evaluation the operating characteristics of TITE-CRM model, the authors performed the simulations based on 47 subjects. If the final recommended dose will be confirmed after all study patients enrolled, then this simulation study provides values. However, when run TITE-CRM model to guide dose-escalation decision making in phase I, there will not have such many subjects. To evaluate the model performance in small sample size that also represents the real practice situation, please add additional simulations based on the approximate sample size that will be enrolled in phase I part to re-evaluate the model performance. Minor comments: 1. This is a phase I/II study, the objective of the phase I is to find the MTD, suggest to adding evaluation of safety into study title and overall study objective. 2. In “Sample size calculation” section, suggest to adding the approximate sample size for phase I and phase II respectively in this section as well. 3. The study requires 44 subjects evaluable at 3 years follow-up, please clarify, if some of the subjects lost follow-up, will the study re-open enrollment? 4. In “Statistical considerations” section, under “phase I”, please add cohort size for each dose level, and DLT analysis frequency. It is only mentioned that the first DLT analysis will be occurred after the first 3 subjects have been completed the 18 weeks follow-up, then when to perform the next DLT analysis? 5. In Appendix Table 1, to improve understanding, please add proportion of DLT in addition to mean n. of DLT.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name: Linda Agolli
Institution and Country: Department of Radiation Oncology, Faculty of Medicine and University Hospital Carl Gustav Carus, Technische Universität Dresden, Germany.
Please state any competing interests or state 'None declared': None declared.

Please leave your comments for the authors below
This is an innovative study protocol by Pasquier et al. regarding the reirradiation using salvage SBRT after EBRT in recurrent prostate cancer. Nowadays, no standard therapy exists for locally recurrent prostate cancer. Patients are often unsuitable to surgery due to previous irradiation of the prostate and also advanced age and comorbidities. Brachytherapy could be and alternative but only a few patients fulfill selection criteria for such a treatment. Theoretically, SBRT seems to be a good alternative in the salvage setting but evidence is needed to confirm the safety and efficacy of such a technique.
The current study protocol is interesting and controlled trials in this field are needed. The multicenter setting could help to include more patients with prostate cancer and local relapse, although the enrollment of the candidates could be challenging.

1. 2-3 years after RT a biopsy could not be useful. It is known that positive tumor cells could be found in the prostate. This could be a bias. Is this factor included in the initial analysis? Please discuss this issue in the introduction.

Reply R1-Q1. We agree with the reviewer. In the literature and guidelines a minimum time of two years is recommended between radiotherapy and prostate biopsies to minimize the risk of false positive and this two-year interval has been selected in our study. This risk decreases over time. Nevertheless the guidelines recommend to perform prostate biopsies before any salvage treatment, and the diagnosis is based on imaging too in our study.

2. The rationale and the choice of the radiation dose should be better explained, recurrent prostate cancer is also more radioresistent as the initial tumor. This should be discussed previously.

Reply R1-Q2. The higher radioresistance of recurrence is likely, but this is a hypothesis. As we stated in introduction SBRT delivers highly conformal, high-dose radiation in a few fractions (hypofractionation), typically 5 to 7 fractions for prostate cancer. It is reported that prostate canceris more sensitive to large doses of radiation per fraction. The choice of the dose was discussed in Discussion section.
The dose levels selected in our study are close to those used in de novo patients, and the same as those described in retrospective salvage treatment series. These schemes seem to provide a good compromise between efficacy and toxicity but have not been evaluated prospectively.
We stated this assertion in introduction section too.

3. A pre-treatment staging with choline-PET CT has a certain rate of false positive and false negative compared to the PSMA-PET. Patients with lymph node metastases could be included in the study. These rates should be reported in the inclusion criteria or the risk should be discussed.

Reply R1Q3, R2Q2, R2Q3. We agree with reviewers 1 and 2. The sensitivity of PSMA PET is higher than that of choline PET for the detection of lymph node disease. To have a high sensitivity, a lymph node staging must be extensive, which can have side effects.
Nevertheless clinical and biological selection criteria (no high risk cancer before first treatment, PSA level, PSA doubling time,...) are designed to select the patients to have most likely intra-prostatic recurrence only.
Unfortunately PSMA PET is not routinely available in France. A modification of the inclusion criteria is being drafted to allow PSMA PET if this review becomes available during the study period. This is

now specified in Discussion section. A new article is quoted: Lecouvet FE, Oprea-Lager DE, Liu Y, Ost P, Bidaut L, Collette L, et al. Use of modern imaging methods to facilitate trials of metastasis-directed therapy for oligometastatic disease in prostate cancer: a consensus recommendation from the EORTC Imaging Group. Lancet Oncol. 2018 Oct;19(10):e534–45.

4. The author state that “based on dose-limiting toxicity defined as grade ≥3 gastrointestinal or urinary toxicity or any other grade 4 adverse event observed during the 18 weeks following the initiation of salvage-SBRT”. Which gastrointestinal or urinary toxicity, please specify.

R1Q4: All types of toxicity

5. Are only the severe toxicities a secondary end-point or all kind of toxicity or grade ≥2?

R1Q5: All types of toxicity, whatever the grade

6. In the phase II part, a table with the selected acute and late toxicity could be useful for the readers in order to know the clinical relevance.

R1Q6. All types of toxicity are taken into account

7. Is biochemical relapse-free survival the only parameter to check treatment response or a new diagnostic imaging would be performed? For example with PET? If the patients develop any kind of macroscopical metastases after phase I or II, are they excluded from the study? How could be determined clinical progression-free survival for example for bone metastases or other distant metastases outside the pelvis? Or other examinations such as PET-CT or CT should be performed in case of increased PSA?

R1Q7. Choline PET and pelvic mpMRI are requested in case of biochemical recurrence after salvage SBRT. This is now stated in the Fig 2 legend. Patients with second biochemical recurrence will not be excluded in order to assess late toxicity. This is now stated in the text.

8. It would be interesting to know the necessary dose-limit parameters for bladder and rectum considered for the plan acceptance. A table could be helpful.

R1Q8 OAR constraints are specified in a table.

Rectum	Bladder	Urethra + 3 mm
V27 Gy <2 cc V12 Gy <20%	V27 Gy <5 cc V12 Gy <15%	V24 Gy <30% Dmax (35 mm3) <39 Gy V36 Gy <1 cc

9. Have the fiducial markers to be delineated? Is an IGRT mandatory? Please add the positioning and verification method. Which MRI sequences are used for the delineation?

R1Q9. Delineation of the fiducials is not mandatory. Daily IGRT is mandatory, intra fraction tracking is recommended. This is now stated in the text. All mpMRI sequences will be used (T2, perfusion, diffusion). Perfusion and diffusion are the most useful.

Reviewer: 2
Reviewer Name: De Meerleer Gert
Institution and Country: Leuven University Hospitals, Belgium Please state any competing interests or state ‘None declared’: None declared

Please leave your comments for the authors below The issue of local relapse after EBRT for prostate cancer is a clinically important question, which the authors will study within a prospective protocol using SBRT. In general, the introduction and description of the different salvage techniques is too long. A table would be better and improve reading.

We agree with the reviewer and we removed some details of the salvage treatments in the introduction. As we have mentioned, this is a description of the main results of these various treatments. In our opinion, the presentation in the form of a table would require an extensive review of the literature, which is beyond the scope of this study. A new article is quoted to which the reader can refer for more information.

Philippou Y, Parker RA, Volanis D, Gnanapragasam VJ. Comparative Oncologic and Toxicity Outcomes of Salvage Radical Prostatectomy Versus Nonsurgical Therapies for Radiorecurrent Prostate Cancer: A Meta-Regression Analysis. Eur Urol Focus. 2016 Jun;2(2):158–71

Some minor remarks:

1. references 2 and 3 are rather old, is it possible to include more recent work on modern radiotherapy outcomes?

R3Q1. Ref 3 (Zapatero) was replaced. In this series (MRC RT01), a positive biopsy 2 years after radiotherapy was prognostic of worse bPFS, going forward, compared with negative and suspicious biopsies, hazard ratio (HR)=4.81 (95% confidence interval [CI]: 2.50-9.26, p<0.001). The estimate for survival was HR=1.58 (95% CI: 0.52-4.78, p=0.42).

2. Is PSMA PET-CT allowed (p 11)?

Please cf R1 Q3

3. A major concern is the lack of surgical nodal staging, as choline PET-CT is not sensitive enough concern nodal staging. Please comment whether salvage nodal therapies are allowed.

Please cf R1 Q3

4. Please note and clearly state that a 3-years follow-up is too short to report on GU toxicity.

R3Q4. We agree that a 3 years follow up is too short to assess on late GU (and perhaps GI toxicity). Secondary objective is 3 years toxicity but patients will be followed 5 years after SBRT to report late toxicity (cf flow chart). This is now stated in the text. This objective was written at 3 years because the French National Cancer Institute does not fund trials with a duration of more than 5 years, which is not suitable for radiotherapy trials.

5. p13: How do you check whether a positive biopsy is outside the visible MR lesion?

R3Q5. We agree with reviewer this is a difficult topic. There is no standard for target delineation in the salvage context and MRI may underestimate prostatic recurrence. The location of biopsies is given according to the ESUR guidelines, such as MRI. An example was added in the text.

6. p14: the starting dose is 5 x 6 Gy. 5x5 Gy is not an escalation, no (p15: escalated to the next llevel ...)? Do not fully understand.

Reply R2-Q6: We understand this needed to be clarified. It is actually stated in the full protocol: "The lower dose level, 5 x 5 Gy, will be considered if excessive toxicity is reported at the first dose-level (5 x 6 Gy)." This sentence has been added in the manuscript (page 15, line 378-379).

Reviewer: 3
Reviewer Name: Qing Liu
Institution and Country: Amgen Inc. USA
Please state any competing interests or state 'None declared': None declared

Please leave your comments for the authors below This is a well-written manuscript describing a phase I/II study protocol to evaluate the safety and efficacy of salvage stereotactic radiation in prostate cancer patients. Below, I have some additional comments and suggestions, which hopefully can help the authors improve the paper.

Major comments:

1. In the simulation study to evaluation the operating characteristics of TITE-CRM model, the authors performed the simulations based on 47 subjects. If the final recommended dose will be confirmed after all study patients enrolled, then this simulation study provides values. However, when run TITE-CRM model to guide dose-escalation decision making in phase I, there will not have such many subjects. To evaluate the model performance in small sample size that also represents the real practice situation, please add additional simulations based on the approximate sample size that will be enrolled in phase I part to re-evaluate the model performance.

Reply R3-Q1: We thank the reviewer for his very good suggestion. It is true that we will not recruit 47 patients in the escalation phase of the design. We have added in the appendix a scenario based on the accrual of 13 patients. However, we still think that the simulations based on 47 patients are relevant as we will re-estimate the probability of DLT and the recommended dose, even during the second stage of the trial, allowing dose modification in the expansion phase (Phase II part). This is one of the advantages of the CRM method.

Minor comments:

2. This is a phase I/II study, the objective of the phase I is to find the MTD, suggest to adding evaluation of safety into study title and overall study objective.

Reply R3-Q2: We completely agree with your suggestion. The title has been revised accordingly.

3. In "Sample size calculation" section, suggest to adding the approximate sample size for phase I and phase II respectively in this section as well.

Reply R3-Q3: As the reassessment will be continued from the first patients (escalation phase) until the end of the study, we cannot formally distinguish both phases. However we have written that: "The dose-escalation part of the study will terminate once 10 patients have been treated and evaluated at a dose currently identified as the recommended dose." This means that at least 13 patients will be recruited before we consider that the expansion phase (Phase II part) is open. This has been added in the subsection Sample Size.

4. The study requires 44 subjects evaluable at 3 years follow-up, please clarify, if some of the subjects lost follow-up, will the study re-open enrollment?

Reply R3-Q4: The sample size calculation for the Phase II part is based on a binomial distribution, assuming that all patients will be evaluable. However, we have anticipated the issue of subjects lost to follow-up. If this happens, the estimate of the bRFS will be based on Kaplan-Meier estimate. This is stated in the statistical considerations. For practical reasons, although it would be meaningful for power considerations, we do not plan to re-open enrollment.

5. In “Statistical considerations” section, under “phase I”, please add cohort size for each dose level, and DLT analysis frequency. It is only mentioned that the first DLT analysis will be occurred after the first 3 subjects have been completed the 18 weeks follow-up, then when to perform the next DLT analysis?

Reply R3-Q5: Recruitment may be staggered, and patients will not be recruited considering cohort of fixed sample size. However, accrual at the dose level 6x6 will start only after evaluation of at least 3 patients at the dose level 5 x 6.

6. In Appendix Table 1, to improve understanding, please add proportion of DLT in addition to mean n. of DLT.

Reply R3-Q5: This has been added into the tables in appendix.

VERSION 2 – REVIEW

REVIEWER	Linda Agolli Department of Radiation Oncology, Faculty of Medicine and University Hospital Carl Gustav Carus, Technische Universität Dresden, Germany
REVIEW RETURNED	16-Apr-2019

GENERAL COMMENTS	Improvements were made.

REVIEWER	Gert De Meerleer, MD, PhD Department of Radiation Oncology Leuven University Hospitals Belgium
REVIEW RETURNED	05-Apr-2019

GENERAL COMMENTS	The authors answered all questions in a satisfactory way.

REVIEWER	Qing Liu Amgen Inc. USA
REVIEW RETURNED	13-Apr-2019

GENERAL COMMENTS	The authors well addressed my comments.