PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	HypoFocal SRT Trial: Ultra-hypo fractionated focal salvage radiotherapy for isolated prostate bed recurrence after radical prostatectomy - Single-arm phase II Study - Clinical Trial Protocol.
AUTHORS	Mathier, Etienne; Althaus, Alexander; Zwahlen, Daniel; Lustenberger, Jens; Zamboglou, Constantinos; De Bari, Berardino; Aebersold, Daniel M.; Guckenberger, Matthias; Zilli, Thomas; Shelan, Mohamed

VERSION 1 – REVIEW

REVIEWER	Michalet, Morgan Institut régional du Cancer de Montpellier, Radiation Oncology
REVIEW RETURNED	18-Jul-2023

GENERAL COMMENTS	Thi study rises an excellent question for patients with recurrence after RP in the era of metabolic imaging. I think that english writing could be improved (there are also some typos) and I have somme minor suggestions : - abstract, discussion : I do not agree to say that ultrahypofractionated sRT is a valid treatment; it has to be demonstrated - line 67 : comparable oncological results (not a) - background : can you please develop on current PSA level tendencies to consider recurrence and propose sRT ? Can you detailed what is considered as ultra-hypofractionated RT ? - line 71 : RT was assesses for patient with low ... rather than has been utiilized ... - line 72 : demonstrated - line 88 : is to assess rather than explore - line 90 : please rephrase, for example : with delineation based on PSMA PET and MRI - line 111 : with no evidence of N+ or M+ rather than "a lack" - line 114 : patients must have a testosterone level > 50 - line 130 : start rather than commencement - line 137 : allowed rather than permitted - line 163 : outcomes - line 190 : problem with the sentence - line 200 : problem with the sentence - line 204 : ca. ? - line 267 : already explained above, may be need to group paragraph on machines ? - line 275 : precise also for MRI linacs - line 281 : patient will be treated rather than should take

REVIEWER	Chang, Yifan Shanghai Changhai Hospital, Department of Urology

REVIEW RETURNED	17-Sep-2023

GENERAL COMMENTS	In this paper, the authors presented a study protocol of a single-arm phase II clinical trial conducting ultra-hypofractionated focal salvage radiotherapy for hormone-sensitive node-negative prostate cancer patients with radiological recurrence after RP. Overall this study was well conducted with certain significance for future clinical guidance. However I do have some minor concerns that I hope the authors could better address them in the manuscript: 1) Would it be clearer for readers to distinguish if “study protocol” is added to the title? At first glance I thought this study was a phase II trial with study outcomes. 2) Inclusion criteria suggests that pT2a-3b, R0/1, pN0 or cN0 be included. The authors didn’t specify the surgical platform (robotic, laparoscopic or open) or the status or extent of PLND (given pN0 or cN0, presumably both could be included?) would there be any selection bias for this standard? Also would surgical margin status affect time to local recurrence? If possible please explain further or provide evidence support? 3) I fail to locate the manuscript regarding the definition of biochemical relapse-free survival (post-op PSA >0.1ng/ml or >0.2ng/ml? or a different standard for salvage RT?) 4) If cT4/pT4 are excluded from the study, would it be rather challenging for patient recruitment? Since to my knowledge many patients are more prone to bone metastasis or even lymph node metastasis than local recurrence. 5) Timing of post-op RT after radiological local recurrence and how to distinguish between salvage RT and adjuvant RT? 6) Timing and frequency of postoperative radiological assessment? 7) Will 2nd gen antiandrogens (abiraterone/enzalutamide/darolutamide) be adopted for post-op adjuvant ADT? Why or why not? 8) To my knowledge patients typically exhibit Biochemical recurrence before local recurrence (if any). Hypothetically if most patients with local recurrence have recorded biochemical recurrence way ahead of time, How may BFS be adopted as primary outcome under such circumstances?

REVIEWER	Xiao, Yu-Tian Shanghai Changhai Hospital, Department of Urology
REVIEW RETURNED	22-Sep-2023

GENERAL COMMENTS	Mathier et al. their phase II trial protocol 'HypoFocal SRT Trial: Ultra-hypo fractionated focal salvage radiotherapy for isolated prostate bed recurrence after radical prostatectomy - Single-arm phase II trial'. This is an important trial design as the authors explained in the manuscript. A few minor concerns should be addressed. 1. In this trial, recurrence seems to be solely dependent on PSMA PET/CT and mpMRI scans. Judging from the exclusion criterion #1 and the primary outcome of this protocol, I wondered if patients with imaging-confirmed local recurrence plus a rising serum PSA would be excluded from the trial. Might need further clarification on the eligibility criteria. 2. The authors wrote in the sample size calculation section that 'We will therefore test the null hypothesis that the biochemical relapse-free 166 survival at 2 years is lower than 60% against the alternative that it is at least 80%'. Although the process of sample size

	calculation is straightforward, the description on the alternative hypothesis is incorrect. 3. Are there any planned subgroup analysis for this trial?

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Dr. Morgan Michalet, Institut régional du Cancer de Montpellier

This study rises an excellent question for patients with recurrence after RP in the era of metabolic imaging.

We thank reviewer 1 for the positive feedback on the study conception.

I think that english writing could be improved (there are also some typos) and I have somme minor suggestions :

- abstract, discussion : I do not agree to say that ultrahypofractionated sRT is a valid treatment; it has to be demonstrated

Due to word count matters, we had to remove this discussion section in the abstract.

- line 67 : comparable oncological results (not a)

Corrected

- background : can you please develop on current PSA level tendencies to consider recurrence and propose sRT ? Can you detailed what is considered as ultra-hypofractionated RT?

We thank the reviewer for this comments. Due to the word count matters, we explained what ultra-hypofractionated RT in the background is. For the PSA Level tendencies and propose sRT, we refer to main protocol Section 2.2

- line 71 : RT was assesses for patient with low ... rather than has been utiilized ...

Corrected

- line 72 : demonstrated
Corrected

- line 88 : is to assess rather than explore

Corrected

- line 90 : please rephrase, for example : with delineation based on PSMA PET and MRI

Corrected

- line 111 : with no evidence of N+ or M+ rather than "a lack"

Corrected

- line 114 : patients must have a testosterone level > 50

Corrected

- line 130 : start rather than commencement

Corrected

- line 137 : allowed rather than permitted

Corrected

- line 163 : outcomes

Corrected

- line 190 : problem with the sentence

Corrected

- line 200 : problem with the sentence

Corrected

- line 204 : ca. ?

removed

- line 267 : already explained above, may be need to group paragraph on machines ?

Due to word count limit, we removed the dose computation. Details are mentioned in the main study protocol.

- line 275 : precise also for MRI linacs

Stated under treatment techniques section. Due to word count limit, we removed equipment and tool section. Details are mentioned in the main study protocol.

- line 281 : patient will be treated rather than should take

Corrected

Reviewer: 2
Mr. Yifan Chang, Shanghai Changhai Hospital

In this paper, the authors presented a study protocol of a single-arm phase II clinical trial conducting ultra-hypofractionated focal salvage radiotherapy for hormone-sensitive node-negative prostate cancer patients with radiological recurrence after RP. Overall this study was well conducted with certain significance for future clinical guidance. However I do have some minor concerns that I hope the authors could better address them in the manuscript:

1) Would it be clearer for readers to distinguish if “study protocol” is added to the title? At first glance I thought this study was a phase II trial with study outcomes.

We thank the reviewer 2 for this comment. We adapted the title and stated it is a clinical trial protocol.

2) Inclusion criteria suggests that pT2a-3b, R0/1, pN0 or cN0 be included. The authors didn’t specify the surgical platform (robotic, laparoscopic or open) or the status or extent of PLND (given pN0 or cN0, presumably both could be included?) would there be any selection bias for this standard? Also would surgical margin status affect time to local recurrence? If possible please explain further or provide evidence support?

We thank reviewer 2 for this comment. We totally agree with this comment. The clinical practice in Switzerland are treated usually with robotic assisted radical prostatectomy and PLND. Additionally, isolated recurrence within the prostate bed is a local problem which we aim to target with customized approach offering ultra-hypofractionated radiotherapy in combination with ADT. The integration of PSMA PET Scan in the postoperative setting changed the landscape of the management in this setting and should be assisting in detecting regional lymph node recurrences or distant metastasis.

3) I fail to locate the manuscript regarding the definition of biochemical relapse-free survival (post-op PSA >0.1ng/ml or >0.2ng/ml? or a different standard for salvage RT?)

We thank reviewer 2 for this comment. Due to word count limitation, we didn’t mention the definition of the endpoints in the manuscript. However, in the main protocol provided as supplementary material, all definitions for endpoints are described (Section 5.2).

A biochemical recurrence is defined by any confirmed PSA rise above 0.20 ng/mL with a confirmatory rise at least 2 weeks later. For those patients whose PSA does not drop below 0.20 ng/mL at time of first response assessment at 3 months are considered as non-responders to treatment and are considered to have a biochemical recurrence in case a second measurement at least 2 weeks later confirms a rising PSA above this level.

4) If cT4/pT4 are excluded from the study, would it be rather challenging for patient recruitment? Since to my knowledge many patients are more prone to bone metastasis or even lymph node metastasis than local recurrence.

We thank reviewer 2 for this comment. Due to regular screening programs offered, most of prostate cancer cases are detected early and do not present in cT4 stage and they are usually treated primarily with curative radiation in combination with hormonal treatment after discussion in the multidisciplinary tumorboard. For example, in our center we have less than 5% of the patients with pT4 situation. We decided to exclude cT4/pT4 as we believe this group of patients profit from radiation to whole prostate bed. Additionally, the incidence of local recurrence after RP was described as a common problem (PMID:17538167).

5) Timing of post-op RT after radiological local recurrence and how to distinguish between salvage RT and adjuvant RT?

We thank reviewer 2 for his comment. Based on the inclusion criteria patients included in the trial are treated with RP at least 6 months before trial registration with biochemical recurrence after reaching postoperative Nadir. Those are usually the patients where salvage radiotherapy is offered.

6) Timing and frequency of postoperative radiological assessment?

We thank reviewer 2 for his comment. The timing and frequency of postoperative radiological assessment is usually lead by surgeons. In the current practice PSMA Scans are offered for patients with biochemical recurrence with a value of 0.2 n/ml or higher

7) Will 2nd gen antiandrogens (abiraterone/enzalutamide/darolutamide) be adopted for post-op adjuvant ADT? Why or why not?

We thank reviewer 2 for this comment. The 2nd generation antiandrogens are covered by the insurance in Switzerland only in the metastatic setting and not yet apart of the guidelines in the salvage setting.

8) To my knowledge patients typically exhibit Biochemical recurrence before local recurrence (if any). Hypothetically if most patients with local recurrence have recorded biochemical recurrence way ahead of time, How may BFS be adopted as primary outcome under such circumstances?

We thank reviewer 2 for this comment. We don't understand the question appropriately but we will try to answer it. Every isolated macroscopic local recurrence within the prostate bed is preceded by biochemical failure. However in some circumstances, the urologists wait for a positive PSMA PET imaging even if the patients have biochemical failure. This is not yet a standard but sometimes it's what we see in our clinic

Reviewer: 3
Mr. Yu-Tian Xiao, Shanghai Changhai Hospital

Mathier et al. their phase II trial protocol 'HypoFocal SRT Trial: Ultra-hypo fractionated focal salvage radiotherapy for isolated prostate bed recurrence after radical prostatectomy - Single-arm phase II trial'. This is an important trial design as the authors explained in the manuscript. A few minor concerns should be addressed.

We thank reviewer 3 for his positive comment on the trial design.

1. In this trial, recurrence seems to be solely dependent on PSMA PET/CT and mpMRI scans. Judging from the exclusion criterion #1 and the primary outcome of this protocol, I wondered if patients with imaging-confirmed local recurrence plus a rising serum PSA would be excluded from the trial. Might need further clarification on the eligibility criteria.

We thank reviewer 3 for his comment. Exclusion criterion #1 is for patients who do not reach PSA nadir after RP. Those patients who develop PSA persistence have worse outcome. We believe those patients might needed treatment intensification not a customized treatment as offered within the trial.

2. The authors wrote in the sample size calculation section that 'We will therefore test the null hypothesis that the biochemical relapse-free 166 survival at 2 years is lower than 60% against the alternative that it is at least 80%'. Although the process of sample size calculation is straightforward, the description on the alternative hypothesis is incorrect.

We thank reviewer 3 for his comment. We adapted the description in the text.

3. Are there any planned subgroup analysis for this trial?

We thank reviewer 3 for his comment. Further subgroup analysis will follow after finalizing the accrual (R0 vs. R1), (pN0 vs. cN0) and based the location of the recurrence.

VERSION 2 – REVIEW

REVIEWER	Chang, Yifan Shanghai Changhai Hospital, Department of Urology
REVIEW RETURNED	04-Dec-2023

GENERAL COMMENTS	The authors have addressed all relevant issues raised by the reviewers.

REVIEWER	Xiao, Yu-Tian Shanghai Changhai Hospital, Department of Urology
REVIEW RETURNED	16-Dec-2023

GENERAL COMMENTS	The authors have addressed nearly all my previous concerns. I look forward to the results of this important clinical trial. However, I would like to kindly bring the authors' attention to the following issues before publication: 1. It seems that the attached SPIRIT checklist is based on a SPIRIT Checklist template for another journal, namely Trials. Moreover, the authors should update the information provided in the 'Page and Line Number' column since most of them are now incorrect. 2. The authors are encouraged to present their pre-specified subgroup analysis scheme in the trial protocol. This is methodologically important and contributes to Reporting Item #20b of the SPIRIT reporting guidelines.

VERSION 2 – AUTHOR RESPONSE

Reviewer: 2
Mr. Yifan Chang, Shanghai Changhai Hospital

The authors have addressed all relevant issues raised by the reviewers.

We are thanking Reviewer 2 for the opportunity to improve our manuscript with these insightful comments

Reviewer: 3
Mr. Yu-Tian Xiao, Shanghai Changhai Hospital

1. It seems that the attached SPIRIT checklist is based on a SPIRIT Checklist template for another journal, namely Trials. Moreover, the authors should update the information provided in the 'Page and Line Number' column since most of them are now incorrect.

We thank reviewer 3 for his comment. We adapted the SPIRIT Checklist and corrected the 'Page and Line Number' column.

2. The authors are encouraged to present their pre-specified subgroup analysis scheme in the trial protocol. This is methodologically important and contributes to Reporting Item #20b of the SPIRIT reporting guidelines

We thank reviewer 3 for his comment. We included the subgroup analysis into the manuscript.