Response to Reviewers of Manuscript ID 567738

LhARA: The Laser-hybrid Accelerator for Radiobiological Applications

The authors would like to thank the reviewer for the insightful, constructive comments. In the preparation of this response, the Reviewer's comments have been numbered as indicated in the appended annotated copies of the Reviewer's evaluations and supporting files.

Reviewer 1

Evaluation

1. **The major limitation is a dichotomy between excessive simplicity and verbosity in describing well-known concept (e.g. RBE) on one side and an excessive detail on technicalities regarding the design of the beam line.**
   There is indeed a dichotomy, arising partly from the fact that this paper is of interest (primarily) to two groups of scientists, those with expertise in radiobiology and those with expertise in accelerator science. While concepts like RBE will indeed be well-known to the former, the latter may not be familiar with them. The interdisciplinary nature of the paper therefore necessitates a little more description of "elementary" concepts than may normally be required. Having said this, the authors agree with both reviewers in regard to the style and content of the introductory sections of the paper and Section 2 has been redrafted and compacted in the light of these comments.
   The principal goal of the paper is to demonstrate the feasibility of the technologies required to deliver the novel laser-hybrid accelerator system, LhARA. The authors believe that the present level of description of the laser-driven source, the novel capture system, and the accelerator system is required to allow the results presented to be independently verified.

2. **. . . there appears to be a vagueness about the actual implementation of such an ambitious and clearly extremely well-thought out programme: no time frame, no cost-effectiveness evaluation, no mention on the actual overall cost.**
   The paper was written to document the concepts and technologies that underpin the laser-hybrid accelerator concept. The consortium has prepared a "pre-CDR" document [1] which contains an initial evaluation of both the cost and the schedule. Our analysis indicates that, assuming sufficient resources are made available, LhARA stage 1 could be executed over a 5-year period.
   The pre-CDR is cited in the paper. The authors believe that it is not appropriate to publish here either the cost or the schedule for the facility. Such information is subject to revision in the light of funding pressures and competing priorities among the funders, consortium, and other stakeholders.

3. **Although I checked that the reference list is adequate, there is a disagreement on two of those, which I strongly believe must be replaced as illustrated in the attached detailed report.**
   The authors thank the reviewer for the comment and have revised the bibliography accordingly.

Review supporting file – 48618

1. **. . . it seems extremely simplistic in some basic aspects particle radiobiology as is the case for the explanation of the difference of biological effectiveness and DNA damage between photons and high-LET particles.**

As noted under point 1 above, the authors agree with both the reviewers in regard to the style and content of the introductory sections of the paper, and Section 2 has been redrafted and compacted in the light of these comments.

2. **I understand that this information was used in simulations, but is such a degree of detail necessary? The essential table is arguably the last one, Table 5, where the true relevant information for radiobiological experiments is reported, i.e. the dose per pulse, as the instantaneous and average dose rates achievable with the two types of particles chosen for the simulation, the low- and high-energy protons and C ions.**
   The authors believe that the information provided in the text and the various tables is essential to justify the performance of the facility presented in figures 5, 8, 10, and 11, and in table 5. The novel combination of a laser-driven source, with a strong-focusing plasma lens, and fixed-field alternating-gradient acceleration has enormous potential but its performance has not been demonstrated. Therefore, it is important that the reader be provided with details sufficient for the claimed performance of the facility to be validated.

3. **. . . what is the time scale of the project? Can the authors say a date by which stage 1 and/or stage 2 will be initiated/completed? What is actually the funding status? It is understood this is part of a well-structured Consortium but has LhARA, as described, been already granted funding for its complete implementation? Also, only towards the very end of the manuscript (line 758) the reader learns that "It is envisaged that LhARA will be built at an STFC National Laboratory or equivalent research institute which has an established safety-management system and culture in place". So, hasn't even the building site been decided yet? This may also help to corroborate a rather important statement at line 273 " At present, a dedicated ion beam for radiobiology, based on a laser-driven source, is not available anywhere in the world. Therefore, LhARA will be a unique, state-of-the-art system, able to explore the radiobiological benefits of a laser-accelerated ion source". Yes, true, that depends on the time scale and the implementation feasibility.**
   Resources to allow the present concept for LhARA to be developed have been provided by the UK Science and Technology Facilities Council (STFC) and by members of the consortium. The consortium is now actively engaged with the STFC, other UK funding agencies, and stakeholders with the goal of securing the resources necessary to take the programme forward. The focus at the moment is on delivering the R&D required to demonstrate that the principal technical risks (the laser-driven target, plasma-lens capture system, and the instrumentation and dosimetry) are properly under control.
   The site for the facility has not been decided. Discussion of the possibility that the LhARA initiative could be developed by the consortium in collaboration with the STFC Laboratories has been initiated. In the UK, the Daresbury or Rutherford Appleton Laboratories seem to offer the most natural potential sites for the eventual implementation of LhARA.
   The foci of the present paper are the LhARA concept, the underlying science, and the technical feasibility of the various systems that will be required. The authors are aware of the importance of the issues raised by the reviewer and are trying to address each of them. However, we do not believe it appropriate to include discussion of such political issues in this paper.

4. **"The research project is time limited such that, should it not prove possible to produce a suitable Gabor lens, there will remain time sufficient to procure conventional solenoids in their place". Well, then one may wonder: a) what about all the work presented after this line, based on the use of Gabor lenses, completely useless? For instance, all the work described in lines 419-426, and**

the whole design, really seems heavily Gabor lens-dependent; b) if there is really an alternative in conventional solenoids, why propose Gabor lenses in the first place? Or is there something I cannot grasp?

The authors thank the reviewer for the question and agree that the discussion of the use of a solenoid as an alternative to the Gabor lens was not clear in the original draft of the paper.

The reviewer is correct; the solenoids are an option that is being considered to mitigate the risk that the Gabor lens is not able to deliver the performance required for LhARA. The discussion of the alternative option has been revised to make it clear that the use of solenoids has been considered to demonstrate that the LhARA project is viable even in the event that the Gabor lens solution fails to meet specification.

5. **. . . facilities such as LhARA, or at least based on the hybrid acceleration system proposed for LhARA, will help in the direction of making PBT accessible also to those vast part of the world population that are now excluded. Am I right in understanding this statement in this sense? If so, it should be probably better argued exactly how: the whole design for LhARA does not come cheap and does require R&D investments that do not look trivial to me. Or are the authors saying that LhARA could serve as a prototype for similar facility for delivering PBT?**

   The authors thank the reviewer for the observation. Indeed, the consortium continues to work to articulate both concisely and with precision its vision for the the route to reducing the cost and complexity of a clinical system using the laser-hybrid technique. The consortium believes that it is the combination of the triggerable, laser-hybrid acceleration coupled with a sophisticated fast feedback-and-control system that incorporates real-time dose-deposition imaging that has the potential to reduce the need for a large gantry, thereby making the whole clinical system more compact. The authors have revised the relevant statements to make the case more clearly.

6. **. . . nowhere it is cited for instance that hypothesis such as the oxygen depletion or other radiochemical phenomena will be investigated with an array of energies and ion species which will be truly unique . . .**

   The authors thank the reviewer for the comment and agree that oxygen depletion and the ability to investigate a range of energies and species is a unique capability of the proposed facility. The text of section 2 (Motivation) has been revised to make this point more clearly.

7. **I am specifically referring to the sentence at line 205 "In addition, LhARA will enable exhaustive evaluations of RBE using more complex end-points (e.g. angiogenesis and inflammation) in addition to routine survival measurements", and this concept is repeated elsewhere as well.**

   The authors' intention was to highlight the broad range of radiobiological end-points that can be measured with LhARA but that are not easily addressed at other clinical facilities due to the lack of an appropriate laboratory and associated equipment. The repetition has been removed.

8. **There is indeed a tendency on repeating over and over the same concept, i.e. that LhARA is going to be a novel facility allowing unprecedented research, and sometimes the same exact sentence. For example, "The laser-driven source allows protons and ions to be captured at energies significantly above those that pertain in conventional facilities, thus evading the current space-charge limit on the instantaneous dose rate that can be delivered" in the Abstract (line 10 and subsequent), in the Introduction (lines 72 and subsequent) and later on line 227, page 13. The same repetition occurs for the concepts of the exciting finding related to FLASH and micro-beams from line 63 and from line 193.**

The authors appreciate the reviewer's comment and have removed inappropriate repetition from the manuscript.

9. **Reducing the length of the manuscript (28 pages without references), considering the above-mentioned unbalance, should be corrected maybe moving part of the more technical information to an appendix or supplemental material.**
   The length manuscript has been reduced by revising sections 1, 2, and 3. The paper documents the authors' study of a novel, perhaps paradigm-changing, technique for the delivery of proton and ion beams for biomedical applications. In contrast to other comparable proposals, the authors seek to exploit the plateau region in the laser-driven proton and ion spectrum to provide a beam that is stable shot-to-shot. Acceleration to high energy is provided by means of a novel fixed-field alternating-gradient accelerator (FFA) that has the advantage that the rapid acceleration is flexible and can accelerate protons and ions from helium to carbon. The authors therefore feel that the technical detail is necessary both to justify the performance quoted in section 4 and to provide a scholarly work that allows the findings to be validated by an interested reader.

10. **Paragraph 2 Motivation is unnecessarily long.**
    The authors have accepted this comment which was made by both reviewers and the text has been revised accordingly.

11. **Line 117: maybe adding a reference?**
    The statement has been removed in the revision of section 2, so a reference is no longer required.

12. **Line 153: Is this statement really necessary, concerning the observed increase of RBE at distal position along proton SOBPs "Some of this variation may be due to the positioning of the cells during irradiation relative to the Bragg peak". Here the authors are broadly illustrating theoretical basis for uncertainties affecting particle radiobiology; implying that some published results may be due to banal positioning errors, that may be true, but it reads out of context here.**
    The reviewer's comment has been accommodated in the revision of section 2.

13. **From line 156: as said before, most concepts can be summarized and also poised in a slightly more rigorous manner. RT does not just induced cell death by DNA damage, there is Therapy-Induced Senescence (TIS) affecting cancer cells' microenvironment with its related Senescence-Associated Secretory Phenotype (SASP), but it's just an example.**
    The authors' thank the reviewer for the comment and have taken it into account in the revision of section 2.

14. **Line 184: apart from being a repetition of what already said in the introduction, the sentence saying that RT is administered in daily fractions of 2 Gy, here it is said at dose rates of 5 Gy/min or less, in the Intro of 10 Gy/min less. If this sentence really must be repeated, may it be done so consistently?**
    This statement has now been removed from this section.

15. **Lines 190 and subsequent, on the dose rate at which the FLASH effect is observed: I would strongly suggest the authors to change the references Systems (200) and IBA (2019). One actually points to a press release concerning the first patient treated with FLASH-RT. Please use a scientific paper,**

which was published exactly on that: Bourhis J, Sozzi WJ, Jorge PG, Gaide O, Bailat C, Duclos F, Patin D, Ozsahin M, Bochud F, Germond JF, Moeckli R, Vozenin MC. Radiother Oncol. 2019 Oct;139:18-22. doi: 10.1016/j.radonc.2019.06.019. Epub 2019 Jul 11.

The authors' thank the reviewer for the comment and have added the requested reference relating to the first patient treated with FLASH RT.

16. **From line 306 to 312 it reads as a repetition of a concept said abundantly before.**

    The authors accept the reviewer's comment and have removed the paragraph.

17. **Caption of Fig.3: has really the figure relative to the length of the beam line to be given with this accuracy, 17.225 m?**

    The authors accept the reviewer's comment and have reduced the precision with which the length of the beam line is reported.

18. **Line 474: is the aberration issue observed in the simulations as in fig. 4 going to be solved/mitigated by using Gabor lenses? Because that is what seems to me the authors are stating when saying they will replace the solenoids used with a full electromagnetic simulation of these lenses. Again, what if the use of Gabor lenses will be not feasible? Is a risk mitigation plan in place?**

    The aberration shown in figure 5 is indeed a concern as it demonstrates that the optics is not linear. This effect is currently being investigated. Despite the non-linearity observed in the simulations, the lattice presented in the paper is able to deliver a uniform dose distribution at the end station. It is expected that the Gabor-lens focusing will behave in a similar way. However, the focusing of off-momentum particles in the Gabor lens will differ from that of the equivalent solenoid. This will change the form of the aberrations to some extent. The current results show that we can achieve the beam quality required if it becomes necessary to use the equivalent solenoids.

    The authors hope that these comments clarify the situation. We propose not to alter the text as we feel it describes accurately the properties of the beam delivered to the end station.

19. **Fig. 6: Are the numbers on both y-axes intended to be followed by a full stop, i.e. 50. 100. and -3. -2. and so forth?**

    The decimal points indicate that the values on the axes are not integers. The figure will be revised in line with the journal's editorial practice at proof stage.

20. **Line 722: the sentence "will enable multiple groups of researchers to perform productive and high-quality biological research" referred to the state-of the-art lab..well, isnt' high-quality, productive research what we all strive to do? That is helped by having a good, fully equipped lab. I would omit that, please, it sounds appropriate in a Grant application, probably not here.**

    The authors accept the reviewer's comment. This sentence has been deleted.

21. **Line 757: the acronym STFC suddenly appears. It should be explicated, not all readers will be from the UK.**

    The authors accept the reviewer's comment. Reference to STFC has been removed.

22. **Line 787: the 30-micron cell thickness was of course need to put a number to use in the simulations but I am confident the authors know that unless each single time they place a monoayer under the**

beam, they will not expect its thickness to be measured, right? And generally single monolayers are a bit thinner than that in normal cell culture conditions.
The authors accept the reviewer's comment. The dimensions were introduced to define the configuration used to simulate the dose delivered to the end stations. In operation the experimenters will need to assess the degree of variation in the thicknesses of the various materials in the path of the beam. The development of the techniques necessary to ensure that the dose deposited in the cell layer is accurate will be the focus of work in the R&D phase.

23. **Line 793: when depth is mentioned depending on the energy, actually is a SOBP achievable or the LhARA beams will have pristine Bragg peaks? Maybe this information could be provided/clarified/mentioned? It may not so obvious to the reader.**
It is possible to deliver a SOBP at LhARA; indeed our goal is to be able vary the beam energy within one bunch. Two cavities are provided for this purpose in the stage 1 beam line. In stage 2 the flexibility to manipulate the longitudinal phase space provided by the RF in the FFA is augmented by the 5-cavity module placed in the *in vivo* beam line. A statement to this effect has been added in the text.

24. **Lines 855-856 "tumour control probability" sound more appropriate than tumour-kill probability"**
The sentence has been modified to refer to "tumour-control probability".

References

[1] The LhARA consortium, "The Laser-hybrid Accelerator for Radiobiological Applications," Tech. Rep. CCAP-TN-01, 2020. https://ccap.hep.ph.ic.ac.uk/trac/raw-attachment/wiki/Research/DesignStudy/PreCDR/Review/2020-03-31-LhARA_pre_CDR-d2.0.pdf.

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1. Initial Validation ✓ 2. Editorial Assignment ✓ 3. Independent Review 6. Final Validation 4. Interactive Review 7. Final Decision

LhARA: The Laser-hybrid Accelerator for Radiobiological Applications

Galen Aymar, Tobias Becker, Stewart Boogert, Marco Borghesi, Robert Bingham, Ceri Brenner, Philip N Burrows, Oliver C Ettlinger, Titus-Stefan Dascalu, Stephen Gibson, Timothy Greenshaw, Sylvia Gruber, Dorothy Gujral, Claire Hardiman, Jonathan Hughes, W Gareth Jones, Karen Kirkby, Ajit Kurup* , Jean-Baptiste Lagrange, Kenneth Richard Long* , Wayne Luk, John Matheson, Paul McKenna, Ruth Mclauchlan, Zulfikar Najmudin, Hin Tung Lau, Jason Luke Parsons, Jaroslaw Pasternak, Juergen Pozimski, Kevin Prise, Monika Puchalska, Peter Ratoff, Giuseppe Schettino, William Shields, Susan Smith, John Thomason, Stephen Towe, Peter Weightman, Colin Whyte and Rachel Xiao

Original Research, Front. Phys. - Medical Physics and Imaging
Received on: 30 May 2020, **Edited by:** Vincenzo Patera
Manuscript ID: 567738
Research Topic: Applied Nuclear Physics at Accelerators
Keywords: Radiobiology, Novel acceleration, proton beam therapy (PBT), ion beam therapy, Laser-driven ...

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Reviewer 1
Independent review report submitted: 09 Jul 2020
Interactive review activated: 09 Jul 2020

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Submit all comments AND Re-submit manuscript

EVALUATION

Q 1 **Please summarize the main findings of the study.**

Reviewer 1 | 09 Jul 2020 | 11:44 #1

Since the paper is a design study on a novel facility based on an innovative particle acceleration system, there are no specific finding.
See a more detailed discussion in the detailed report attached.

Add comment

Q 2 **Please highlight the limitations and strengths.**

Reviewer 1 | 09 Jul 2020 | 11:44 #1

The main strength is that, if implemented, the facility envisioned in this study will potentially allow to gain insights on the radiobiological mechanisms at play in phenomena such as the reduced radiation-induced toxicity in normal tissue warranted by the FLASH effect as well as the use of proton mini/micro beams. The clinical relevance of the study in the outlined facility is also a major point. The major limitation is a dichotomy between excessive simplicity and verbosity in describing well-known concept (e.g. RBE) on one side and an excessive detail on technicalities regarding the design of the beam line. 1 In addition, there appears to be a vagueness about the actual implementation of such an ambitious and clearly extremely well-thought out programme: no time frame, no cost-effectiveness evaluation, no mention on the actual overall cost. 2 This may be important in light of the argued need to abate costs for hadrontherapy.
See a more detailed discussion in the detailed report attached.

Add comment

Q 3 **Please comment on the methods, results and data interpretation. If there are any objective errors, or if the conclusions are not supported, you should detail your concerns.**

Reviewer 1 | 09 Jul 2020 | 11:44 #1

I don't think this is rigorously applicable for this paper. The rationale, simulation-based approach and consequent results are sound.

Add comment

Q 4 **Check List**

Reviewer 1 | 09 Jul 2020 | 11:44 #1

Is the English language of sufficient quality?
- Yes

Is the quality of the figures and tables satisfactory?
- Yes

Does the reference list cover the relevant literature adequately and in an unbiased manner?
- Yes

Are the statistical methods valid and correctly applied? (e.g. sample size, choice of test)
- Not Applicable

Are the methods sufficiently documented to allow replication studies?
- Yes

Are the data underlying the study available in either the article, supplement, or deposited in a repository? (Sequence/expression data, protein/molecule characterizations, annotations, and taxonomy data are required to be deposited in public repositories prior to publication)
- Not Applicable

Does the study adhere to ethical standards including ethics committee approval and consent procedure?
- Not Applicable

Have standard biosecurity and institutional safety procedures been adhered to?
- Not Applicable

Add comment

Q 5 **Please provide your detailed review report to the editor and authors (including any comments on the Q4 Check List):**

Reviewer 1 | 09 Jul 2020 | 11:44 #1

Although I checked that the reference list is adequate, there is a disagreement on two of those, which I strongly believe must be replaced as illustrated in the attached detailed report.

Review supporting file - 48618 3

Add comment

QUALITY ASSESSMENT

Q 6	Originality	■■■■■
Q 7	Rigor	■■■■□
Q 8	Significance to the field	■■■■■
Q 9	Interest to a general audience	■■■□□
Q 10	Quality of the writing	■■■■■
Q 11	Overall quality of the study	■■■■□

REVISION LEVEL

Q 12 **What is the level of revision required based on your comments:**

Reviewer 1 | 09 Jul 2020 | 11:44 #1

Minor revisions

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Reviewer's comments for review article ID 567738

Title: LhARA: The Laser-hybrid Accelerator for Radiobiological Applications

General comments

This paper describes the conceptual and technical design of a novel particle accelerating facility, LhARA, which by assembling an innovative combination of high intensity-powered laser-driven generation and plasma lenses-assisted focussing of ions with fixed-field alternating-gradient accelerator (FFA), promises to deliver a uniquely flexible research environment for carrying out basic research in the radiobiology of charged particles. The ultimate objective is to allow faster proton and ion-beam therapy (PBT), which should be also better biology-based, hence suitably targeting the individual patient characteristics, thanks to the new insights that the peculiar and so far unattained physical features on the spatio-temporal structure of mechanisms through which ionizing radiation (IR) interacts with the biological matter. The authors state that the system envisaged by the LhARA system, will allow unprecedented flexibility in terms of switching between ion type and energies, which in turn should lead to the possibility of exploring the therapeutically beneficial promises (and the radiobiological mechanisms at play thereof) held by the recently discovered FLASH effect and by the micro-beam approach, both pointing toward in the direction of reducing normal tissue radio-toxicity. It is also hinted at the fact that by making PBT delivering facilities more compact, such a form of treatment will be made more readily accessible to a wider cancer patient audience, with obvious societal consequences.

LhARA, as presented by the authors in this paper, arguably implies a huge technological effort and tremendous potential for scientific breakthroughs and fits within the scope of the Research Topic "Applied Nuclear Physics at Accelerators" that stemmed from the GSI Biophysical collaboration meeting held in 2019 aimed at creating a network of novel and existing applied physics research infrastructures.

The paper is extremely detailed and highly technical in the sections devoted to the description of the laser and plasma-based modalities, with a plethora of information. On the other hand, it seems extremely simplistic in some basic aspects particle radiobiology as is the case for the explanation of the difference of biological effectiveness and DNA damage between photons and high-LET particles. 1
This, incidentally, takes almost more than half page whereas it can be condensed in a sentence and appropriate reference. Such a dichotomy also creates an unbalance between what reads as a "lay explanation "of well-known concepts such as the long-debated RBE uncertainty for clinically used proton beams, for example, which according to the authors research performed at LhARA will contribute to solve, and instead highly specific descriptions of advanced laser acceleration and focussing techniques. At times, the reader has the impression that the original research part that is arguably present in the paper (see for instance the Monte-Carlo simulations and similar) is masked and suffocated by an engineer-like layout of the project. Details such as the length (17,225 metres) of a beamline, with tables (e.g. Table 2) that contain an amount of specifications down to the number of solenoids or the bending angle seem more useful on the workers on the constructing site than to the researcher who is interested to carry out his experiments in the new facility. I understand that this information was used in simulations, but is such a degree of detail necessary? The essential table is arguably the last one, Table 5, where the true relevant information for radiobiological experiments is reported, i.e. the dose per pulse, as the instantaneous and average dose rates achievable with the two types of particles chosen for the simulation, the low- and high-energy protons and C ions. 2

Within the wealth of information provided, there are some points that may be of interest, and actually important in the presentation of such a massive R6D programme: what is the time scale of the project? Can the authors say a date by which stage 1 and/or stage 2 will be initiated/completed? What is actually the funding status? It is understood this is part of a well-structured Consortium but has

LhARA, as described, been already granted funding for its complete implementation? Also, only towards the very end of the manuscript (line 758) the reader learns that "It is envisaged that LhARA will be built at an STFC National Laboratory or equivalent research institute which has an established safety-management system and culture in place". So, hasn't even the building site been decided yet? This may also help to corroborate a rather important statement at line 273 " At present, a dedicated ion beam for radiobiology, based on a laser-driven source, is not available anywhere in the world. Therefore, LhARA will be a unique, state-of-the-art system, able to explore the radiobiological benefits of a laser-accelerated ion source". Yes, true, that depends on the time scale and the implementation feasibility. 3

One important innovation among the so many proposed here, it seems to me, will be the use of Gabor lenses. Of course, it is going to be exciting research to see if the criticalities that are pointed out by the authors can be overcome, i.e. the instability of the electron cloud. However, I find the statement on line 393 of a rather disarming naivety "The research project is time limited such that, should it not prove possible to produce a suitable Gabor lens, there will remain time sufficient to procure conventional solenoids in their place". Well, then one may wonder: a) what about all the work presented after this line, based on the use of Gabor lenses, completely useless? For instance, all the work described in lines 419-426, and the whole design, really seems heavily Gabor lens-depdent; b) if there is really an alternative in conventional solenoids, why propose Gabor lenses in the first place? Or is there something I cannot grasp? 4

Conceptually, one of the motivations to think of an alternative to conventional accelerators for hadrontherapy, besides their limitations in term of time to dedicate to pre-clinical research, is, of course, cost and size, hence complexity. This has driven researchers such as those involved in this ambitious programme to strive for compactness and cost-effectiveness. Moreover, it is stated in the introduction "It is estimated that 26.9 million life-years could be saved in low- and middle-income countries if radiotherapy capacity could be scaled up [Atun et al. (2015)]. Novel techniques incorporated in facilities that are at once robust, automated, efficient, and cost-effective are required to deliver the required scale-up in provision". This hints at the possibility that facilities such as LhARA, or at least based on the hybrid acceleration system proposed for LhARA, will help in the direction of making PBT accessible also to those vast part of the world population that are now excluded. Am I right in understanding this statement in this sense? If so, it should be probably better argued exactly how: the whole design for LhARA does not come cheap and does require R&D investments that do not look trivial to me. Or are the authors saying that LhARA could serve as a prototype for similar facility for delivering PBT? 5

Still, on the conceptual side: it is stated repeatedly that LhARA will allow radiobiology research that is not possible to do now at existing facilities. However, one thing is the time scale of dose administration that will be achievable, which is indeed a "terra incognita" as correctly stated by the authors, since the mechanistical bases for such effects are not known (nowhere it is cited for instance that hypothesis such as the oxygen depletion or other radiochemical phenomena will be investigated with an array of energies and ion species which will be truly unique), another thing is the "type" of endpoints. These are unrelated to the specifications of LhARA. There possibility of performing experiments using endpoints other than clonogenic survival, such as senescence or study of pro-inflammatory mechanisms or more sophisticated biomolecular investigations. This will be made possible by the state-of-the art radiobiology laboratory that will be annexed to the accelerating complex, and of course by the ability and expertise of the users. I am specifically referring to the sentence at line 205 "In addition, LhARA will enable exhaustive evaluations of RBE using more complex end-points (e.g. angiogenesis and inflammation) in addition to routine survival measurements", and this concept is repeated elsewhere as well. 6 7

There is indeed a tendency on repeating over and over the same concept, i.e. that LhARA is going to be a novel facility allowing unprecedented research, and sometimes the same exact sentence. For example, "The laser-driven source allows protons and ions to be captured at energies significantly above those that pertain in conventional facilities, thus evading the current space-charge limit on the instantaneous dose rate that can be delivered" in the Abstract (line 10 and subsequent), in the Introduction (lines 72 and subsequent) and later on line 227, page 13. The same repetition occurs for the concepts of the exciting finding related to FLASH and microbeams from line 63 and from line 193 8

Reducing the length of the manuscript (28 pages without references), considering the above-mentioned unbalance, should be corrected maybe moving part of the more technical information to an appendix or supplemental material. 9

Punctual remarks

Paragraph 2 Motivation is unnecessarily long. Some concepts are trivialized, it seems that the Lay Summary extends into this section as well. For instance, "Dose delivered to healthy tissues can cause the death of the healthy cells and create adverse side effects" makes a lay reader believe that the RT side effects stems solely by cell killing, but this paper speaks to a community that is well aware that the scenario is more complex than that. 10

Line 117: maybe adding a reference? 11

Line 153: Is this statement really necessary, concerning the observed increase of RBE at distal position along proton SOBPs "Some of this variation may be due to the positioning of the cells during irradiation relative to the Bragg peak". Here the authors are broadly illustrating theoretical basis for uncertainties affecting particle radiobiology; implying that some published results may be due to banal positioning errors, that may be true, but it reads out of context here. 12

From line 156: as said before, most concepts can be summarized and also poised in a slightly more rigorous manner. RT does not just induced cell death by DNA damage, there is Therapy-Induced Senescence (TIS) affecting cancer cells' microenvironment with its related Senescence-Associated Secretory Phenotype (SASP), but it's just an example. 13

Line 184: apart from being a repetition of what already said in the introduction, the sentence saying that RT is administered in daily fractions of 2 Gy, here it is said at dose rates of 5 Gy/min or less, in the Intro of 10 Gy/min less. If this sentence really must be repeated, may it be done so consistently? 14

Lines 190 and subsequent, on the dose rate at which the FLASH effect is observed: I would strongly suggest the authors to change the references Systems (200) and IBA (2019). One actually points to a press release concerning the first patient treated with FLASH-RT. Please use a scientific paper, which was published exactly on that: Bourhis J, Sozzi WJ, Jorge PG, Gaide O, Bailat C, Duclos F, Patin D, Ozsahin M, Bochud F, Germond JF, Moeckli R, Vozenin MC. Radiother Oncol. 2019 Oct;139:18-22. doi: 10.1016/j.radonc.2019.06.019. Epub 2019 Jul 11. 15

From line 306 to 312 it reads as a repetition of a concept said abundantly before. 16

Caption of Fig.3: has really the figure relative to the length of the beam line to be given with this accuracy, 17.225 m? 17

Line 474: is the aberration issue observed in the simulations as in fig. 4 going to be solved/mitigated by using Gabor lenses? Because that is what seems to me the authors are stating when saying they will replace the solenoids used with a full electromagnetic simulation of these lenses. Again, what if the use of Gabor lenses will be not feasible? Is a risk mitigation plan in place? 18

Fig. 6: Are the numbers on both y-axes intended to be followed by a full stop, i.e. 50. 100. and -3. -2. and so forth? 19

Line 722: the sentence "will enable multiple groups of researchers to perform productive and high-quality biological research" referred to the state-of the-art lab..well, isnt' high-quality, productive research what we all strive to do? That is helped by having a good, fully equipped lab. I would omit that, please, it sounds appropriate in a Grant application, probably not here. 20

Line 757: the acronym STFC suddenly appears. It should be explicated, not all readers will be from the UK 21

Line 787: the 30-micron cell thickness was of course need to put a number to use in the simulations but I am confident the authors know that unless each single time they place a monoayer under the beam, they will not expect its thickness to be measured, right? And generally single monolayers are a bit thinner than that in normal cell culture conditions. 22

Line 793: when depth is mentioned depending on the energy, actually is a SOBP achievable or the LhARA beams will have pristine Bragg peaks? Maybe this information could be provided/clarified/mentioned? It may not so obvious to the reader. 23

Lines 855-856 “tumour control probability” sound more appropriate than tumour-kill probability” 24