Peer Review File

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Reviewer A

The authors proposed a treatment method that adds the reaction of B-11 and protons to the current proton therapy which uses the Bragg peak of proton beam, and confirmed its effectiveness by Monte Carlo Simulation. Although this technique has been known for many years, there are two main problems in its clinical application.

1) Authors state that 200 ppm boron drug is introduced selectively into tumor cells, but what exactly is the drug?

Reply 1: Thanks to the reviewers for the questions! It can be the combination of B-10, B-11 and B-N with drugs, such as disodium salt of mercaptododecaborate (BSH, the concentration peaks at about 6 hours after injection), which can freely enter the tumor cells, but can not pass the blood-brain barrier, but can be concentrated in the tumor tissue after the destruction of the blood-brain barrier; ② L-p-boronylphenylalanine (BPA, the concentration peaks at about 2 hours after injection), belongs to the second generation of boron drugs, with low toxicity, which is good (T/NT) value, different from BSH, it can enter the cancer cells directly through the blood-brain barrier, so it can be used in the brain. The second generation of boron drugs, low toxicity, the good (T/NT) value, different from BSH is that it can directly enter the cancer cells through the blood-brain barrier, so it can be used in the treatment of brain tumors, but also for the treatment of melanoma.

At present, the research of boron-bearing drugs has entered the third generation development stage, researchers are trying to improve the tumor selectivity of boron drugs, making it possible to combine with tumor target molecules, such as synthesizing boron with condensed amino acids, amino acids, antibodies, nucleosides, sugars, porphyrin-like compounds, liposomes and nanoparticles, etc., so as to be able to achieve breakthroughs in therapeutic efficacy for specific tumors.

Changes in the text: None

2) The nuclear cross section between B-11 and protons, which is expected to be utilized, is a few barn at an incident proton beam energy of about 1 keV (assuming that the proton beam is decelerated in the body). On the other hand, the nuclear cross section of B-10 and neutrons used in boron neutron capture therapy (BNCT) is 3,800 barn, three orders of magnitude larger than that of thermal neutrons. The current value of the BNCT accelerator ranges from 1 mA to 30 mA. Considering that the output of proton therapy machines is currently about 1 μA at maximum, it is impossible to bridge the six orders of magnitude difference in collision probability produced by this situation, and the results of the authors' simulations do not lead to any significant results.

Reply 2: Thanks to the reviewer for raising this issue, which I hadn't considered before. The difference with BNCT is that BNCT requires a dedicated neutron source outside

the body for neutron generation, whereas here thermal neutrons from proton-target interactions are used (in this case neutrons are generated in vivo). Although conventional proton therapy has a beam strength of about 1 μA (much less than BNCT), this may be sufficient to increase the proton beam strength for proton FLASH therapy.
Changes in the text: None

Reviewer B

The authors addressed an interesting issue. However, I don't think the approach followed is the most appropriate. Your goal is to study this "ternary" model while considering the two reactions involving boron. However, your simulations were conducted by separately doping your material with B10 or B11. The integrated step to establish the model is absent. Furthermore, the analysis of alpha yields should be expanded, including distribution around the target and its relevance to clinically achievable boron concentrations.
Reply: Thanks to the reviewer for the questions!
Changes in the text: We are now working on a comprehensive model to simulate the effect of the natural abundance ratio of elemental boron introduced into the target area at the beam intensity corresponding to the dose rate of FLASH proton therapy (the dose rate of FLASH proton therapy is 40 Gy/s, which overcomes the problem of insufficient beam intensity of normal proton therapy in the model).

I have additional concerns regarding the absence of discussions about uncertainties and the manuscript's format. Please refer to my supplementary comments:

1. Line 83: include reference
Reply: Thanks to the reviewer for their comments on problems in the paper
Changes in the text: we added the reference. see Page 04, line 83

2. Line 91: what do you mean with "the surface?"
Reply: I'm sorry that the description given in the paper seemed to confuse the Reviewer.

The surface here is mainly the vicinity of the collision location of the proton sensitizer。

Changes in the text: we have modified our text as advised (see Page 4, line 91).

3. Line 103: reference should be included here
Reply: Thanks to the reviewer for their comments on problems in the paper.
Changes in the text: we added the reference. see Page 05, line 103

4. Line 135: flair
Reply: Thanks to the reviewer for their comments on problems in the paper
Changes in the text: we have modified our text as advised (see Page 6, line 135).

5. Line 149: Is this energy representative in a clinical proton beam?
Reply: I'm sorry that the description given in the paper seemed to confuse the Reviewer. Proton beam energies of 60-180 MeV are generally used in clinical practice, with 100-150 MeV energies being the most commonly used.
6. Line 162: All this belongs to M&M section?
Reply: Thanks to the reviewer for their comments on problems in the paper
Changes in the text: we have modified our text as advised (see Page 6, line153-156).

7. Line 167: It's not clear if you refer to all the curve or to the maximum position, please explain
Reply: Thanks to the reviewer for their comments on problems in the paper.
The entire alpha production curve was recorded throughout the experiment, but more attention was paid to alpha production at the peak site.

8. Line 172: Are there is no reference to uncertainties, how can you confirm that are different?
Reply: I'm sorry that the description given in the paper seemed to confuse the Reviewer. The data here are the results from Monte Carlo (fluka) simulations, in which the error has been controlled to a limited range (2%), so that these simulations may reflect the differences between them.

9. Line 177: Table 2 and fig. 2 present the same date. I recommend to choose only one
Reply: Thanks to the reviewer for their comments on problems in the paper
Changes in the text: we have modified our text as advised (see Page 13, figure 369).

10. Line 180: Same concern about the uncertainties. Are all the figures significant?
Reply: Thanks to the reviewer for their comments on problems in the paper
Changes in the text: we have modified our text as advised (Tab. 2 has been removed from the paper so as not to duplicate Fig. 2.)

11. Line 181: value at 0 MeV? / what is the difference between left and right sides?
Reply: Thanks to the reviewer for their comments on problems in the paper
Changes in the text: we have modified our text as advised (Figure 2 has been revised. The right side of Figure 2 is a partial enlargement of the left side to show the differences between the three more clearly.)

12. Line 184: Description to belongs M&M section?
Reply: Thanks to the reviewer for their comments on problems in the paper
Changes in the text: we have modified our text as advised (see Page 6, line 157-158).

13. Line 190: This is an important concern about the work. You correctly state that boron absorbs neutons, so why assess the number of thermal neutrons? Logically, with more boron more neutrons are absorbed, leading to a decrease in their work.

I don't understanding the importance given within the work.
For the enhancement effect, the study of alphas(distribution and number)is the only which makes sense.
Reply: Thanks to the reviewer for their comments on problems in the paper
Changes in the text: we have modified our text as advised (Thermal neutrons produced by proton-target interactions produce alpha by reaction with B-10 ($\mathrm{B}^{10} + n_{th} \rightarrow [B^{11}]^{*} \rightarrow \alpha + Li^{7} + \gamma(2.31MeV)$). There is a possible dose-concentration relationship between the number of neutrons and the presence of B-10.
The proton ternary enhanced radiotherapy proposed in this paper is ultimately dependent on the amount and location of alpha production at the target site)

14. Line 193: What do you mean?
Reply: I'm sorry that the description given in the paper seemed to confuse the Reviewer.
Changes in the text: The idea here is that the maximum yield of alpha particles generated by exotic boron is also in the region of the Bragg peak position of the proton, which means that alpha particles generated by the interaction of protons and boron can also kill tumors at the target site, thus improving the effectiveness of radiation therapy for tumors.

15. Line 194: this is not a result
Reply: Thanks to the reviewer for their comments on problems in the paper
Changes in the text: we have modified our text as advised (Moved this section to the discussion section of the paper.

16. Line 200: here you are repeating the previous section.
Just focus on the analysis of the distance between peaks. it's important to clarifiy the scale to understand the negative values in the plots.
In any case, volumetric distribution around the target, and not only this distance would be more relevant to study.
Reply: Thanks to the reviewer for their comments on problems in the paper
Changes in the text: Section 4.3 focuses on the production location of the alpha particle peak and its comparison with the location of the proton Bragg peak.
The differences in the positions of the alpha and proton Bragg peaks are shown in Supplementary Figure 5.
It was analyzed mainly in terms of the amount and location of alpha production around the target.

17. Line 213: just one figure
Reply: Thanks to the reviewer for their comments on problems in the paper
Changes in the text: we have modified our text as advised (see Page 14, figure 376).

18. Line 225: neutrons are relevant for B10, why do you consider B11?
Reply: Thanks to the reviewer for their comments on problems in the paper
Changes in the text: Considering the extreme complexity of the physical processes

involved in the proposed ternary model, the two paths of B-10 and thermal neutrons and B-11 and low-energy protons are not completely separated, and there may be interactions and influences between them. Therefore, B-11 is temporarily included in the simulation process.

19. Line 229: which level? You should quantify it?

Reply: Thanks to the reviewer for their comments on problems in the paper

Changes in the text: The point here is that the amount of neutrons produced in the target area is still in the same order of magnitude as the number of neutron peaks, despite the fact that the peaks of neutrons produced are not in the target area.

20. Line 291:

I must admit that I don't understand this section.

A similar study that the one carried out with PMMA is even more interesting for the equivalent materials.

Reply: Thanks to the reviewer for their comments on problems in the paper

Changes in the text: Section 4.6 is an attempt to find out if other materials besides PMMA are more effective. However, it is out of context with the topic of this article and has been deleted during this revision process.

21. Line 246: ??

Reply: Thanks to the reviewer for their comments on problems in the paper

Changes in the text: we have modified our text as advised (see Page 9, figure 246).

22. Line 257: why extra? These are known neutrons produced by the interaction of protons with the material.

Reply: Thanks to the reviewer for their comments on problems in the paper

Changes in the text: The extra here is understood as follows: normal NCT must have a specialized neutron source (in vitro) to produce neutrons to treat tumors, whereas the extra here refers to not using a specialized neutron source, but rather using protons to interact with the target and thus produce thermal neutrons (in vivo production).

23. Line 260: ??

Reply: Thanks to the reviewer for their comments on problems in the paper

Changes in the text: we have modified our text as advised (see Page 9, line 260).

24. Line 305: error in the order

Reply: Thanks to the reviewer for their comments on problems in the paper

Changes in the text: we have modified our text as advised (see Page 11).