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ABSTRACT
The use of boron (11\(^{\text{B}}\)) is recently being investigated to be applied in proton therapy as a proton boron fusion dose enhancement agent. Alpha particles are emitted from the p + \(^{11}\text{B}\) → 3\(^{\alpha}\) reaction analogous to the \(^{10}\text{B}(n,^7\text{Li})\alpha\) capture (BNC) reaction. If a natural boron content (80\% \(^{11}\text{B}\) and 20\% \(^{10}\text{B}\)) is used in proton therapy, the contaminated neutrons, induced by the proton beam traversing a water medium, will react with \(^{10}\text{B}\) and the primary protons will react with \(^{11}\text{B}\). Each reaction will emit alpha particles according to its reaction cross section. The dose due to these alpha particles, together with the primary proton beam, can induce tumor cell kill. The purpose of this study is to computationally investigate these synergy effects using the Monte Carlo simulation with the target region located in the water medium. A 79.9 MeV proton beam (proton density: 1.9 \times 10^{8} \text{ cm}^{-2}) with 4 monitor unit was used to irradiate the target consisting of water, \(^{10}\text{B}\), \(^{11}\text{B}\), and natural B. The variation of the dose, the location of the reaction, and the energy distribution of the alpha particles were calculated according to the target material. As a result, we confirmed contributions of both BNC and PBF reactions to emitting alpha particles from proton beam irradiation with natural boron. This synergy effect induced an additional 7.29\% enhanced dose by 331,984 alpha particles. This enhanced dose can sufficiently reduce the number of treatment fractions in proton therapy.

A natural boron (B) content consists of 20\% \(^{10}\text{B}\) and 80\% \(^{11}\text{B}\). \(^{10}\text{B}\) has a high cross section to capture thermal neutrons (0.025 eV) as 3840 b.\(^{1,2}\) Alpha particles, with high linear energy transfer, are emitted from the \(^{10}\text{B}(n,^7\text{Li})\alpha\) reaction, and these alpha particles could critically damage the nearby tumor cells. Since 1950, boron neutron capture therapy is still actively used in the USA and Japan to treat cancer patients.\(^{3-9}\) Since 1960, the principle of proton boron (\(^{11}\text{B}\)) fusion (PBF) in the form of the p + \(^{11}\text{B}\) → 3\(^{\alpha}\) reaction has been investigated.\(^{10-14}\) In proton therapy, because the absorbed dose at the tumor region can be dramatically increased when the proton energy is adjusted to have the Bragg-peak within the tumor region, the feasibility of the p + \(^{11}\text{B}\) → 3\(^{\alpha}\) reaction has been recently studied by the Monte Carlo method.\(^{15-17}\) Since then, there have been continuous research interests to investigate the enhanced effectiveness of the p + \(^{11}\text{B}\) → 3\(^{\alpha}\) reaction applied in cancer treatment.\(^{16,19}\) In the current study, a hypothesis is proposed to further enhance the therapeutic effect of proton therapy in that secondary neutrons are induced with the proton beam traversing the water medium. To prevent the neutrons from depositing their energy beyond the target, the boron content containing \(^{10}\text{B}\) may be used.
within the target region to capture the induced neutrons through the $^{10}\text{B}(n,^7\text{Li})\alpha$ reaction. The generated alpha particles will impose cell kill due to the short range and high linear energy transfer within the target region. Therefore, if natural boron is applied to proton therapy, two types of dose contributions are induced by the alpha particles from $^{10}\text{B}(n,^7\text{Li})\alpha$ and $p + ^{11}\text{B} \rightarrow 3\alpha$ reactions.\textsuperscript{5–15}

The purpose of this study is to verify these contributions by the alpha particles via each nuclear reaction and to investigate if it can reach a synergy effect for dose enhancement using the Monte Carlo simulation.

In this study, the simulation was performed with the Monte Carlo n-particle code MCNPX (2.6.0 ver, LANL, USA) to acquire 2D and 3D dose maps for the reaction coordinates and energy spectra of alpha particles induced by each reaction under different boron and tally cards. The simulation geometry was set in a water phantom [40 mm (W: width) × 40 mm (H: height) × 100 mm (D: depth)] with a target region [8 mm (W) × 40 mm (H) × 6 mm (D)]. The location of the target region was at the position of the Bragg-peak of the incident proton beam. The location of the Bragg-peak in water without a boron uptake region was 48 mm from the water surface, and the end point of the tail was 51 mm. For this reason, the target region was located from 46 mm to 52 mm from the water surface to show an overall variation of the dose. From a previous study, we confirmed that the proton can also react with boron which is not located at the Bragg-peak position. However, in order to induce maximum dose enhancement, the position of the Bragg-peak has been adjusted to be within the boron uptake region. For this reason, the locations of both the Bragg-peak and the boron uptake region were the most important for setting the simulation.\textsuperscript{16}

The specification of the proton beam was reflected from the measured information using the proton accelerator beam (PROBEAT III, Hitachi Ltd., Japan) of spot scanning mode in 79.7 MeV with 4 monitor unit (MU; proton density: $1.9 \times 10^{8}$ cm$^{-2}$) in Nagoya Proton Therapy Center.\textsuperscript{17} Thus, this proton density value and monoenergy value were reflected as the number of source-particle (NPS) and ERG (energy parameter), the MCNPX simulation code, respectively. The proton beam has a source to surface distance with the water phantom of 280 cm. The beam passed through the midpoint of the water surface, and the outer space was filled with air (density: 0.001 294 g/cm$^3$). We made 8 simulation codes according to two variable conditions for the acquisition of the 2D dose map. First, there were four uptake setups for the target region, namely, water (H$_2$O, density: 1 g/cm$^3$), $^{10}\text{B}$ (normalized as 20%, total density: 1 g/cm$^3$), $^{11}\text{B}$ (normalized as 80%, total density: 1 g/cm$^3$), and natural B (20% $^{10}\text{B}$ + 80% $^{11}\text{B}$, total density: 1 g/cm$^3$). In addition, two kinds of F6 tally cards were used, namely, the proton tally (F6h) and the alpha particle tally (F6a), under the same proton beam characteristic. The mode card and cell importance (imp) used both h (first: proton) and a (second: alpha) in the code. For the composition of the dose map, the 2D pixel size was set as 1 mm × 1 mm, and each pixel counted the absorbed dose according to the F6 tally setup.\textsuperscript{16,17} The absorbed doses were rearranged as a matrix and then reconstructed as a 2D dose map using the MATLAB (2019b, Mathworks, MA, USA). Also, we extracted the dose profiles according to the proton beam path from all the 2D dose maps and collected the absorbed doses at the only target region. Second, we changed the output factor in these simulation codes from tally to particle track output (P-trac) and repeated the simulations again.

**FIG. 1**. Dose maps for the proton beam and the emitted alpha particle according to the variation of target materials [(a) water; (b) $^{10}\text{B}$; (c) $^{11}\text{B}$; and (d) 20% $^{10}\text{B}$ + 80% $^{11}\text{B}$] and dose profiles extracted from the dose maps [(e) for protons and (f) for alpha particles].
TABLE I. Collected doses in the only target region from the dose maps for both the proton beam and the alpha particle. The unit of absorbed dose was MeV/g, and the variation ratio (increment ratio) was also calculated with respect to that of water in the target.

| Source | Tally | Target | Absorbed dose (error rate: %) | Variation (%) |
|--------|-------|--------|-------------------------------|--------------|
| Proton | Proton | Water  | 296.42 (±0.16%)              |              |
| 4 MU   | 10B (20%) |        | 300.71 (±0.24%)              | 1.45%↑       |
|        | 11B (80%) |        | 313.75 (±0.91%)              | 5.85%↑       |
| 79.7 MeV | 11B (80%) + 10B (20%) | | 318.04 (±0.11%) | 7.29%↑ |
| Alpha particle | 10B (20%) | Water  | 0.2367 (±0.91%)              | 911.54%↑     |
|        | 11B (80%) |        | 0.9537 (±0.34%)              | 3975.64%↑    |
|        | 11B (80%) + 10B (20%) | | 1.1891 (±0.45%) | 4985.47%↑ |

P-trac could provide event information of each particle, such as reactions, positions, and energies, so that only the events of emitted alpha particles within the target region could be extracted using the sorting process. From the sorted data, the coordinates (x, y, z) of all alpha particles were demonstrated in the 3D phantom structure. Finally, energy information of the emitted alpha particles was collected within the target region from the sorted data in order to obtain their energy spectra from which the minimum, maximum, average with standard deviation in energy, and their maximum events were obtained.21,22

Figure 1 shows the 2D dose maps for the proton and the alpha particle according to the target [(a) water, (b) 10B, (c) 11B, and (d) 20% 10B + 80% 11B] and the extracted dose profiles [(e) for protons and (f) for alpha particles]. Alpha particles, as emitted by the reaction between 10B and neutrons induced by the incident proton beam, were clearly observed [Figs. 1(b) and 1(f)], and the alpha dose distribution is shown at the location within the target [Fig. 1(f), blue line]. Especially, the dose region of the alpha particles in Fig. 1(d) originated from both the BNC reaction and the PBF reaction. Because a color scale of these dose maps, including

**Figure 2.** 3D maps for the positions of alpha particle deposition: (a) 10B in target, (b) 11B in target, and (c) 11B + 10B in target. When the number of incident protons was $1.9 \times 10^8$, the alpha particles from (a)–(c) were counted to be 61 231, 271 664, and 331 984, respectively.
that in Fig. 1(c), was adjusted relatively, the colors for the background of the alpha dose according to the proton beam path are observed to be less intense than that in Fig. 1(b). This means that the doses of alpha particles induced by the PBF reaction ($^{11}$B or $^{11}$B + $^{10}$B) were overwhelmingly high as shown in Fig. 1(f). If the natural boron content is preferably absorbed by the tumor target in clinical management, the alpha particles are produced by both BNC and PBF reactions in the target despite the low concentration of the natural boron content being absorbed in the vicinity of the target [Fig. 1(f)]. It is also interesting to observe the dose enhancement relative to the Bragg-peak position of the incident proton. The dose of the proton has been enhanced at the location beyond the Bragg-peak [Fig. 1(e)]. Since the dose enhancement of the incident proton beam is dominated by the PBF reaction to produce the alpha particles, the location of PBF is about 2 mm beyond the Bragg-peak that the incident proton energy sharply decreases to kiloelectronvolt. This shows that the dose enhancement occurs 2 mm downstream to the Bragg-peak. For this reason, the shift of downstream should be considered when the proton therapy with the spot scanning mode is progressed using the natural boron.

Table I shows the collected doses on the target region from the 2D dose map in Figs. 1(a)-1(d). The absorbed proton dose was calculated to be 296.42 MeV/g in water. However, the absorbed dose at the natural boron target was calculated to be 318.04 MeV/g. The increment ratio of the proton dose was 7.29%, and the variation of the alpha dose was increased dramatically as 4985.47%. The alpha dose at the natural boron target was calculated to be 1.19 MeV/g. The reason for the proton dose increase was the increase of the alpha dose. The variation ratio of the proton dose was calculated using the following equation: 

\[
\frac{[318.04 \text{ (p + natural B)} - 296.42\text{(p)}]}{296.42\text{(p)} \times 100\%} = 7.29\%.
\]

Moreover, this value absolutely agreed with the dose contribution of the alpha particle as follows: 

\[
[1.1891 \text{ (alpha)/296.42 (p)}] \times 20 \text{ (alpha quality factor)/1.1 (proton quality factor)} \times 100\% = 7.29\%.
\]

We also confirmed the same trend from the other cases. Normally, irradiation of the proton progresses from 1.8 GyE (1 Gy equivalent) to 2.0 GyE per one fraction (Fr). For example, as a simple calculation, a previous clinical study reported that pediatric glioma was treated with 50.4 GyE/28 Fr (1.8 GyE per 1 Fr). If boron was used for this treatment, because the dose contribution of the alpha particle can make the total dose as 7.3%, the total dose will be decreased to 46.97 GyE and the Fr number will be 26 Fr. In the case of 2.0 GyE per 1 Fr, Nishioka et al. reported the dose for treatment for tumor at bone/soft tissue as 70.0 GyE/35 Fr. However, the total dose and Fr number will be changed to 65.23 GyE/32.6 Fr. From the couple of cases, we can recognize that about 2 Fr can be saved when boron is used for proton therapy.

Figure 2 shows the 3D maps for the positions of alpha particle deposition. The coordinates of the emitted alpha particles were plotted in the 3D structure of the water phantom including the target region. According to the target content, the results for $^{10}$B, $^{11}$B, and $^{11}$B + $^{10}$B are shown in Figs. 2(a)-2(c), respectively. The top row of Fig. 2 shows the whole structure of the phantom with points plotted for alpha particle deposition. The target regions, including the plotting of the points for alpha particle deposition, are demonstrated in the zoomed-in view in the bottom row. When the number of incident protons was $1.9 \times 10^8$ cm$^{-2}$, the
numbers of alpha particles in the \(^{10}\)B, \(^{11}\)B, and \(^{11}\)B + \(^{10}\)B region were 61 231 (0.032%), 271 664 (0.143%), and 331 984 (0.175%), respectively. Because the number of alpha particles induced by the BNC reaction was counted to be 61 231 in the \(p + \(^{10}\)B\) simulation, the same number of induced neutrons were removed. Because the secondary neutrons induced by the proton beam can very easily react with \(^{10}\)B, most of the alpha particles via BNC reactions occurred in the proximal part of the boron region. However, the distribution of alpha particles via the PBF reaction was farther in depth. Because the location of the emission of alpha particles via the PBF reaction corresponds with that of the Bragg-peak, the distribution of alpha particles can be spread out farther. This is a reason why the highest point of the blue line in the target region in Fig. 1(f) was located a little proximal than the Bragg-peak. The sum of the numbers in both Fig. 2(a) and Fig. 2(b) has been about the same as the number of alpha particles produced via the PBF reaction with the natural boron content [Fig. 2(c)]. Moreover, the same simulation with a different NPS number of 3 000 000 has been repeated to compare the trend of the generation ratio of the alpha particle. The numbers of alpha particles in the \(^{10}\)B, \(^{11}\)B, and \(^{11}\)B + \(^{10}\)B region were 815 (0.027%), 4080 (0.136%), and 4977 (0.166%), respectively. Although this case for a small NPS number shows almost the same trend with the main results, when a larger NPS number was used, a higher generation ratio of the alpha particle was observed for all cases.

Figure 3 shows the energy spectra regarding the alpha particles via the reaction between the proton and boron [\(a + \(^{10}\)B\), \(a + \(^{11}\)B\), and \(a + \(^{11}\)B + \(^{10}\)B\)]. In the case of the reaction \(p + \(^{10}\)B\), the maximum energy and the average energy of the alpha particle were 14.6 MeV and 5.6 MeV, respectively, and the highest event peak was at 4.1 MeV. This range originated from the reaction \(n + \(^{12}\)B\). However, from the results of the reactions \(p + \(^{11}\)B\) and \(p + \(^{10}\)B + \(^{11}\)B\), the maximum energies of alpha particles were the same (22.0 MeV). The average energy and the highest peak energy were 6.5 MeV and 8.1 MeV, respectively, for \(p + \(^{10}\)B\) and correspondingly 6.1 MeV and 8.0 MeV for \(p + \(^{11}\)B + \(^{10}\)B\). The average energy in Fig. 3(c) is lower than the average energy in Fig. 3(b) due to the inclusion of the low energy alpha particles induced by the BNC reaction. In addition, the alpha contribution was mostly due to the inclusion of PBF with a minor contribution by the alpha particle via the BNC reaction.

In conclusion, we confirmed the enhanced dose as 7.29% when a 79.7 MeV proton beam with \(1.9 \times 10^{6} \text{ cm}^{-2}\) density was irradiated onto natural boron. In addition, we quantitatively investigated the synergy effect for the two types of contributions as both the BNC reaction and the PBF reaction. The results show the strong possibility to reduce the number of fractions for proton beam treatment. This can allow treatment of more cancer patients within the same duration by using natural boron for proton beam therapy.

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REFERENCES

1. A. Maity, T. C. Duan, J. Li, J. Y. Lin, and H. X. Jiang, Appl. Phys. Lett. 109, 072101 (2016).
2. B. Smilgysa, S. Guedesa, J. Hadlera, P. Coelhoa, I. Alencara, C. Soaresc, and L. Salme, Proc. Sci. 035, 1 (2011); available at https://pos.sissa.it/142/035/pdf.
3. D. Slatkin, Brain 114, 1609 (1991).
4. S. Belousov, M. Mitiev, K. Ilieva, K. Riley, and O. Harling, Appl. Radiat. Isot. 69, 1936 (2011).
5. S. Savolainen, M. Kortesniemi, M. Timonen, V. Reijonen, L. Kuusela, J. Uusis-Simola, E. Salli, H. Koivunoro, T. Seppala, N. Lonroth, P. Yalimaki, H. Hyyvonen, P. Kotiluoto, T. Seren, A. Kuronen, S. Heikkinen, A. Kosunen, and I. Auterinen, Phys. Med. 29, 233 (2013).
6. E. Bavarnegin, Y. Kassas, and F. M. Wagner, J. Instrum. 12, P05005 (2017).
7. C. Fantidis and A. Antoniadis, Int. J. Radiat. Res. 13, 13 (2015).
8. D. Y. Koon, J. Y. Jung, K. J. Hong, and T. S. Suk, Appl. Phys. Lett. 104, 083521 (2014).
9. S. Nakamura, S. Imamichi, K. Masumoto, M. Ito, A. Wakita, H. Okamoto, S. Nishioka, K. Iijima, K. Kobayashi, Y. Abe, H. Igaki, K. Kurita, T. Nishio, M. Masutani, and J. Itami, Proc. Jpn. Acad. Ser. B 93, 821 (2017).
10. C. Labaune, C. Baccou, S. Depiereux, C. Goyon, G. Loisel, V. Yahia, and J. Rafelski, Nat. Commun. 4, 2506 (2013).
11. M. Martinez-Val, S. Eliezer, M. Piera, and G. Velarde, Phys. Lett. A 216(1), 142 (1996).
12. D. C. Moreau, Nucl. Fusion 17(1), 13 (1997).
13. B. Levush and S. Cuperman, Nucl. Fusion 22(11), 1519 (1982).
14. T. Kobayashi, Y. Sakurai, and M. Ishikawa, Med. Phys. 27(9), 2124 (2000).
15. D. K. Yoon, J. Y. Jung, and T. S. Suk, Appl. Phys. Lett. 105, 223507 (2014).
16. H. B. Shin, D. K. Yoon, J. Y. Jung, M. S. Kim, and T. S. Suh, Phys. Med. 32, 1271 (2016).
17. J. Y. Jung, D. K. Yoon, B. Barracough, H. C. Lee, T. S. Suh, and B. Lu, Oncotarget 8, 39774 (2017).
18. G. A. P. Cirrone, L. Manti, D. Margarone, G. Petringa, L. Giuffrida, A. Minopoli, M. Picciotto, G. Russo, F. Cammarata, P. Piscitella, F. M. Perozziello, F. Romano, V. Marchese, G. Milluzzo, V. Scuderi, G. Cuttone, and G. Korn, Sci. Rep. 8, 1141 (2018).
19. G. Petringa, G. A. P. Cirrone, C. Caliri, G. Cuttone, L. Giuffrida, G. Larosa, R. Ranna, L. Manti, V. Marchese, C. Marchettla, D. Margarone, G. Milluzzo, A. Picciotto, F. Romano, P. F. Romano, A. D. Russo, G. Russo, D. Santoncino, and V. Scuderi, J. Instrum. 12, C03049 (2017).
20. T. Toshito, C. Omachi, Y. Kibe, H. Sugai, K. Hayashi, H. Shibata, K. Yassui, K. Tanaka, T. Yamamoto, A. Yoshida, E. Nikiwa, K. Asai, A. Shimomura, I. Okumura, T. Suzuki, H. Kinou, S. Isayama, H. Ogino, H. Iwata, Y. Shihamato, and J. Mizoz, Australas. Phys. Eng. Sci. Med. 39, 645 (2016).
21. N. Naganawa, S. Amano, M. Hino, M. Hirose, K. Hirota, H. Kawahara, M. Kitaguchi, K. Mishima, T. Nagae, H. M. Shimizu, S. Tasaki, and A. Umemoto, Phys. Procedia 88, 224 (2017).
22. N. Naganawa, T. Ariga, S. Amano, M. Hino, M. Hirose, K. Hirota, H. Kawahara, M. Kitaguchi, K. Mishima, H. M. Shimizu, S. Tada, S. Tasaki, and A. Umemoto, Eur. Phys. J. C 78, 959 (2018).
23. S. B. Jia, M. H. Hadizadeh, A. A. Mowlavi, and M. E. Loushab, Rep. Pract. Oncol. Radiother. 19, 376 (2014).
24. E. B. Hug, M. W. Muentner, J. O. Archambeau, A. DeVries, B. Liwnicz, L. N. Loredo, R. I. Grove, and J. D. Slater, Strahlenther. Onkol. 178, 10 (2002).
25. K. Nishioka, A. Prayongrat, K. Ono, S. Onodera, T. Hashimoto, N. Kato, T. Inoue, R. Kinoshita, K. Yasuda, T. Mori, R. Onimaru, H. Shirato, and S. Shimizu, J. Radiat. Res. 59, 463 (2018).