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Cancer Treatment Using Neutron Capture with Boron: Comparing the Effectiveness of Neutron Energy Generating Sources

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ABSTRACT

Cancer treatment with neutron radiation is a significant scientific advancement. Neutrons are produced through nuclear fission in reactors, nuclear reactions in accelerators and neutron generators, and are also emitted by radioisotopes. The purpose of this article is to review and compare neutron sources obtained from various natural and artificial sources/methods; they can be used in the treatment of various diseases, especially cancers, in a therapeutic technique known as boron neutron capture therapy (BNCT), which, like proton accelerators, relies on external neutron sources, but with enhanced characteristics, can serve as a promising method for treatment. The results show that whenever hyperthermal and fast neutrons are produced, neutron modulators can be used to convert them into thermal neutrons. In conclusion, given the operational advantages of accelerators—such as no radiation emission when turned off, ease of adjustment, lower cost, compact size, and higher safety—they are more suitable than other sources for medical applications.

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INTRODUCTION

The development and advancement of technology have prompted scientists to conduct increasingly extensive research and efforts in the field of disease diagnosis and treatment. The method of treating cancer with neutron radiation has also made significant progress in recent years (Farhood et al., 2018), and various types of cancers, including brain cancer (Miyatake et al., 2016), are being treated. Cancer is one of the most important global health challenges, claiming the lives of millions of people every year. There are various methods for treating cancer, including surgery, chemotherapy, radiation therapy, and new methods such as immunotherapy. One of the advanced methods in radiation therapy is the use of neutrons, which, due to their unique properties, are used in the treatment of some types of cancer.

Regarding the properties of neutrons in radiotherapy, it is worth noting that neutrons are subatomic particles with no electrical charge that can penetrate deeper into body tissues. This property allows neutron therapy to reach tumors located deep in the body. In addition, neutrons have a significant biological effect and are capable of destroying the DNA of cancer cells (Kondo, 2022) with greater efficiency than photons and electrons. Neutron capture therapy with boron is a new method that uses neutron trapping by the element boron 10(^{10}Be) (Barth et al., 2018), which is also used to treat brain, stomach, salivary gland, and head and neck cancers. The Sources used to produce neutrons for the treatment of the aforementioned cancers are divided into two main groups: natural and artificial. These sources, which have different neutron energies, have wide applications in various fields, including industry, research, medicine, and agriculture. The primary sources of energetic neutrons include reactors, accelerators, radioisotopes, and neutron generators. In most health centers where radiation therapy is used for cancer treatment, the neutron sources used are accelerator sources (Hirose et al., 2021). In this article, sources of neutrons produced by nuclear interactions are compared in terms of the dose used, irradiation time, and accelerator particle flow to facilitate possible nuclear interactions in neutron production.

Boron neutron capture radiotherapy (BNCT) is a method used for the diagnosis and treatment of various diseases, including cancer (Khavari & Mirzaee, 2024), (Sosilowati & Yohannes, 2016), (Nakai et al., 2014) and is based on nuclear interaction (Agrahari et al., 2021). In this method, when boron is irradiated with low-energy thermal neutrons, it produces large amounts of alpha and lithium particles characterized by linear energy transfer (IAEA, 2001). The high energy of the alpha particle within the same cell dimension (a short distance) causes tumor destruction (Sauerwein et al., 2012).

The hyperthermal neutrons are converted into thermal neutrons as they pass through different cells when reaching the tumor. The boron atom is transported to the cancer cells by carriers such as (BSH and BPA). It destroys them by irradiating the neutron beam on the cells (He et al., 2021) which is a crucial aspect of this treatment, as the adjacent cells are largely protected. Cancer cells absorb the energy of charged lithium and alpha-ionizing particles, causing damage to their DNA structure and causing them to be destroyed (Belyakov et al., 2023).

One of the key factors for the success of BNCT is the provision of a sufficiently intense neutron beam, which requires the availability of adequate neutron sources (Podgorask, 2016). Clinical trials of this method are underway or have been completed in many countries. The initial treatment involves surgical removal of as much of the tumor as possible, followed by BNCT at various intervals after surgery (Masoud Zadeh et al., 2012). The BNCT method can also be used as an adjuvant treatment for other tumors, allowing it to be combined with other methods (Belyakov et al., 2023), including surgery, chemotherapy, and external radiotherapy, which may lead to improved patient survival. According to preliminary clinical studies, BNCT is an emerging targeted therapy with promising and acceptable results (Calvo et al., 2006).

METHODS AND MATERIALS

In this article, the results of research and various methods of neutron production from different sources, as reviewed in more than 25 articles, books, and research papers, have been examined and their findings utilized. The classification and quantitative and qualitative examination of each research source and method, along with their graphical analysis, have yielded the results presented below. Systems have been classified and evaluated based on their novelty and widespread use in cancer treatment using the BNCT method. Neutron generation sources have been classified into two groups: reactors and accelerators. These two groups have been selected based on their widespread use, particularly in cancer treatment centers that utilize isotopic dosing. Consequently, these two groups of neutron sources have been widely employed.

Neutron Production Sources

A neutron is a particle that has its properties and characteristics, interacts with matter, and is used to bombard nuclei and targets to produce energy (Naito, 2018).

Reactors

As the primary source of neutron production and, the most powerful in terms of producing the highest neutron flux, they have been considered since the inception of BNCT. The neutron spectrum produced by this source is broad; however, due to its ability to produce a high neutron flux, the desired spectrum can be achieved by filtering out fast and thermal neutrons. For this reason, many reactors in different countries of the world are operating as a source for BNCT, but for reasons such as:

- Public disapproval of using reactors for safe treatment.
- Being far from hospitals.
- High cost of starting and working with reactors.
- High gamma contamination compared to other sources.
- Presence of neutron and gamma contamination even after the reactor is turned off.

The researchers decided to focus their studies on other suitable alternative sources (Sauerwein et al., 2012).

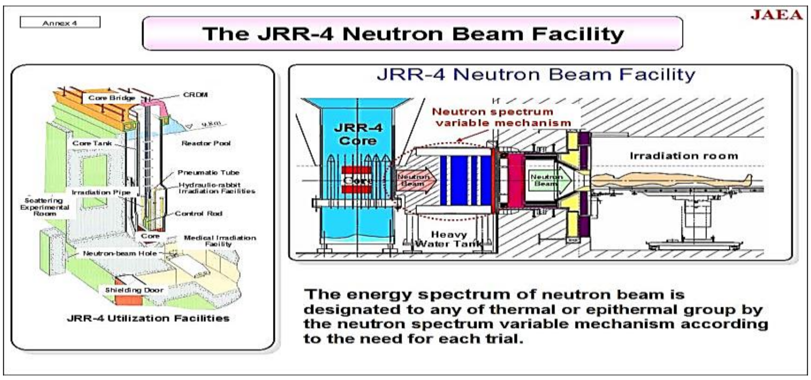

Figure 1: *It is a research reactor in Japan that has been used as a neutron source (IAEA, 2006)*

As can be seen, fast neutrons are first produced in the reactor. By passing through the Beam Shaping Assembly, they are converted into the desired neutrons, which interact with the boron element that was previously injected into the cancerous gland, destroying the cancer cells.

Accelerators

Many efforts have been made to make neutron sources more affordable, compact, and acceptable to the public. In this area, the use of accelerators has received more attention (Kiyanagi, 2018). The process of producing neutrons is carried out by accelerating light-charged particles to a specific energy and bombarding a suitable target (a source that produces neutrons) with these particles (Gholami & Eskandari , 2011). The use of accelerators instead of reactors has many advantages, the most important of which are:

- They are safer.
- They are cheaper.
- The neutrons produced by them are often low-energy.
- The energy spectrum of the neutrons produced by them is more limited.
- They occupy less space.
- They are easier to manufacture and maintain.
- They can be installed in or near hospitals.

Accelerators are considered a suitable option for BNCT due to their numerous advantages and the absence of significant barriers to their use (Copoulat & Kreaner, 2017). Numerous studies have been conducted in this field, and various treatment procedures have been developed for their different types (Godley & Xia, 2019).

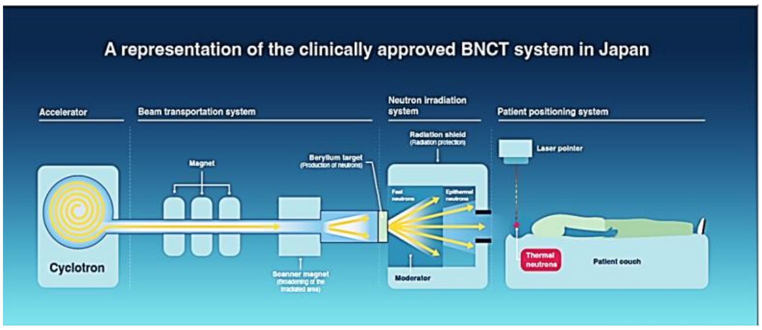

***Figure 2**: Accelerator used as a neutron source (Madsen, 2022)*

As can be seen in the figure, neutrons are produced through nuclear interactions (p, n). In the moderator, their speed is reduced, and they are converted into thermal neutrons, which interact with the boron element that has been previously injected into the cancerous gland and destroy the cancerous cells.

Neutron Generators

Neutron production in neutron generators is based on the interactions mentioned in the equations (1) and (2)

$$D + D \rightarrow n(2.45MeV) + {}^{3}_{1}H(0.82\ MeV) \qquad (1)$$

$$D + T \rightarrow n(14.1MeV) + {}^{4}_{2}He(3.5MeV) \qquad (2)$$

Generators generally consist of an ion source (ionizer), an acceleration system, and a neutron production target. In the ionizer section, deuterium or tritium gas is ionized, and the resulting ions are then bombarded by the acceleration system onto a moving deuterium or tritium target, producing neutrons during these interactions. The neutron flux resulting from the D-D and D-T interactions is $10^8 \frac{n}{s}$ and $10^9 \frac{n}{s}$n/s in the total solid angle, respectively (Koivunoro et al., 2003).

- The advantages of this neutron source are:
- They do not emit radiation in the off-state.
- They are adjustable.
- They are easy to use and maintain and are safe.
- They are less expensive to manufacture.
- They are small in size and can be installed in hospitals.

Neutron generators are not suitable for clinical treatment for BNCT because, considering the neutron flux mentioned, it is challenging to receive sufficient neutron flux for treatment due to the spatial neutron attenuation and the attenuation of at least 10^3times during deceleration (Calvo et al., 2006). However, a D-T-based neutron generator with a flux of $10^{13} \frac{n}{s}$ has been built in the United States, which meets the requirements of BNCT. However, numerous studies have been conducted to utilize this source in BNCT, and several treatment processes have been designed (Cerullo et al., 2014).

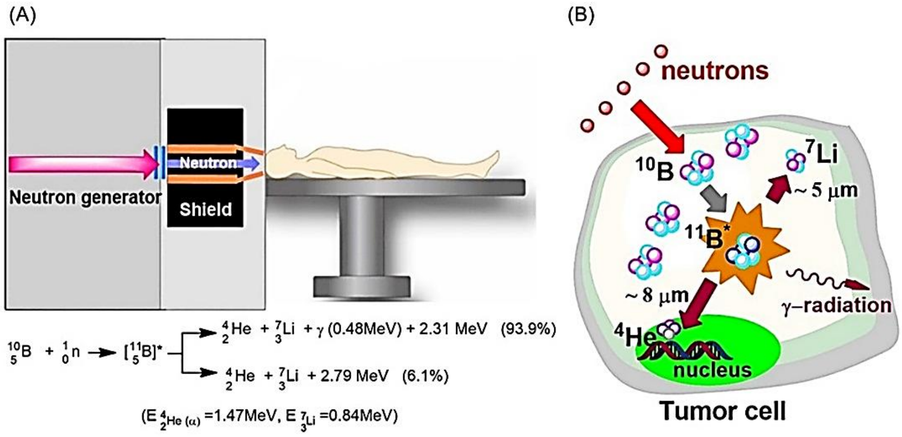

Figure 3. *A neutron generator used as a neutron source for cancer treatment (Zhang & Lin, 2023)*

As shown in the figure, the neutron produced by the nuclear interaction of deuterium and tritium, after being converted into a thermal neutron, interacts with the boron element that has been previously injected into the cancerous tumor and destroys the cancer cell.

Radioisotopes

Radioisotopes are nuclei of a single element that have different numbers of neutrons. In terms of their chemical properties, they are the same; however, in terms of their physical properties, due to the differences in mass, magnetic properties, and nuclear properties resulting from the difference in neutrons, they are distinct. The isotope $^{256}_{126}Cf$ has long been used in industry (such as radiography of military equipment) and medicine as a portable source for neutron production. Each milligram of it is capable of emitting a flux of $2.3 \times 10^9 \frac{n}{s}$ With an average energy of $10MeV$. This number of neutrons is significant, but if it is shaped into a retarder (given that the neutron radiation spectrum must be suitable for treatment with the BNCT method), it is reduced by at least a thousand to ten thousand times and, therefore, cannot provide the neutron flux required for treatment. Due to the isotope's half-life of 2.6 years, it requires frequent replacement of $^{256}_{126}Cf$. It has a large amount. In addition, a source of 1g is required, which is very difficult to obtain, and is therefore rare (Martin et al., 2000).

Am-Be neutron source. The possibility of using radioisotope neutron sources in BNCT was investigated. Given the characteristics of the radioisotope source, which include affordability, ease of transport, availability, and compact dimensions, further studies in this field can help address many of the problems associated with reactor neutron sources. Considering the importance of BNCT experiments and their practicality, it has been decided to investigate the possibility of using radioisotope neutron sources for BNCT research to advance these goals. This method is not suitable due to the low intensity of neutrons, but it is suitable and relatively usable for reactors (Kalantari et al., 2013).

FINDINGS

Various studies and findings from research institutions show that several factors are important in determining the effectiveness of a neutron source for BNCT, which are (neutron producing source in terms of flux produced from the source, flux used in the tumor, energy and flow of bombarding particles to create nuclear interaction to produce neutrons, dose used to destroy the tumor, time of irradiation of neutron radiation in the tumor) and considering the type of neutron used for tumor treatment.

From the comparison of nuclear interactions, it was observed that the neutron flux produced by nuclear interactions (P-n) in the use of accelerators to produce neutrons is greater and more significant.

From Table 1 below, it can be concluded that the flux produced from the D-T nuclear interaction is in the first place, that from the (p,n) nuclear interaction is in the second place, and that from the (d,n) nuclear interaction and the IAEA proposed flux is in the third place.

***Table 1**: Comparison of the flux received from neutron sources*

Nu.	Reported by references	Neutron source interaction	Flux ($\frac{n}{s}$)	Flux ($\frac{n}{cm^2.s}$)
	(Sosilowati & Yohannes, 2016)	D-D	10^{11}	Not calculated
	(Verbeke et al., 1998)	D-T	10^{14}	Not calculated
	(Gholami & Eskandari , 2011)	$X(\gamma, n)Y$	Not calculated	$10^8 - 10^9$
	(Copoulat & Kreaner, 2017)	(p, n)	$10^{11} - 10^{12}$	10^9
	(Copoulat & Kreaner, 2017)	(d, n)	10^{11}	10^9
	(Belyakov et al., 2023)	IEAE	Not calculated	10^9

To destroy brain tumors, rays with an appropriate dose produced from nuclear interactions that generate neutrons enter the tumor and, by cutting the DNA strands in the target area, are destroyed as a result.

From the comparison of nuclear interactions, it can be seen that the dose produced by nuclear interactions (P-n) in the use of accelerators to produce neutrons is higher and more significant than that from nuclear interactions (D-D, D-T, γ,n).

Table 2: *Comparison of neutron sources in terms of dose used for the tumor*

Nu.	Reported by references	Neutron source interaction	Used dose (Gy=Eq)	Comparative percentage of interactions
1	(Copoulat & Kreaner, 2017)	$Li(p,n)Be$	57	36%
2	(Copoulat & Kreaner, 2017)	$C(d,n)N$	56.7	35%
3	(Copoulat & Kreaner, 2017)	$Be(d,n)B$	47	29%

From Table 2, it can be concluded that the most effective dose for eliminating a brain tumor comes from the (p,n) interaction. This is followed by the (d,n)… interaction producing nitrogen, while another (d,n) interaction involving boron as a target is considered third in effectiveness, and from the interaction (d,n) whose product is a boron atom in the third order.

In accelerators, first, particles are accelerated to a specific energy and then directed at the target. As a result, the produced particle hits the target and produces a neutron, which is considered in Table 3 for three interactions.

In the interactions, it was found that the lithium element, with a lighter nucleus compared to carbon and beryllium, produces a higher dose, and its effectiveness in using accelerators to produce neutrons is higher than that of the other two nuclei (carbon and beryllium elements).

Based on the data presented in Table 3 below, it can be concluded that among the nuclear interactions used for neutron production in particle accelerators, the D-T (deuterium-tritium) reaction produces the highest neutron flux.

Table 3: *Comparison of neutron sources in terms of particle flow used to bombard the target to produce neutrons in accelerators*

Nu.	Reported by references	Neutron source interaction	Applied currents (mA)	Comparative percentage of interactions
1	(Copoulat & Kreaner, 2017)	$Li(p,n)Be$	30	13%
2	(Copoulat & Kreaner, 2017)	$C(d,n)N$	30	14%
3	(Sosilowati & Yohannes, 2016)	$D-T$	160	73%

This is followed by the (p,n) and (d,n) interactions, which generate comparatively lower neutron yields.

For the effective destruction of brain tumors and other cancerous tissues via neutron irradiation, the neutron beam must be precisely targeted at the tumor site for a specified duration to achieve optimal therapeutic results.

Table 4 below presents four neutron sources and compares the irradiation times required for brain tumor treatment using the boron neutron capture therapy (BNCT) technique. From the comparison of nuclear interactions, it was observed that the irradiation time of the neutron beam resulting from the nuclear interaction (P-n) in the use of accelerators for producing neutrons is less than that of nuclear interactions (D-n, D-T), which means that we can treat many patients in a short time, which is also important.

***Table 4**: Comparison of the time of neutron sources used for tumor treatment*

Nu.	Reported by references	Neutron source	Time in minutes	Comparative percentage of interactions
1	(Copoulat & Kreaner, 2017)	$Li(p,n)Be$	38.5	14%
2	(Copoulat & Kreaner, 2017)	$C(d,n)N$	60-120	21%
3	(Copoulat & Kreaner, 2017)	$Be(d,n)B$	64	23%
4	(Sosilowati & Yohannes, 2016)	$D-T$	120	42%

From Table 4, it can be concluded that the radiation dose time for destroying a brain tumor, from the first to the third number, spans a more extended period.
To produce neutrons, particles with the desired energies are introduced to the target, and through nuclear interaction, neutrons are produced, which are used for tumor treatment by the BNCT method.

***Table 5:** Energy required for particles used to produce neutrons in accelerators*

Nu.	Bombarding particles on neutron-producing target	Neutron source interactions	The energy required in MeV	Comparative percentage of interactions
1	Neutron	$Li(p,n)Be$	2.3	34%
2	Neutron	(d,n)	1.5	17%
3	Proton	(p,n)	2	13%
4	Proton	(p,n)	4	20%
5	Deuteron	(d,n)	1.45	13%
6	Deuteron	$D-T$	0.4	3%

Table 5 illustrates that, in accelerator-based neutron production, particles with specific energies are directed at a target to induce nuclear interactions that generate neutrons. Among these, the deuterium-tritium (D-T) reaction requires the least amount of input energy compared to other interactions.

Although various neutron sources are utilized in cancer therapy, and their suitability may depend on factors such as tumor location, size, depth, malignancy level, and the patient's radiation tolerance, a general comparison shows that the D-T interaction is more energy-efficient in terms of neutron generation. However, in practice, the (p,n) nuclear interaction — where a proton is accelerated toward a target nucleus to produce neutrons — is currently more widely used and considered significant in clinical applications.

Figure 2 provides a comparative graphical analysis of these four neutron sources, evaluated across four categories.

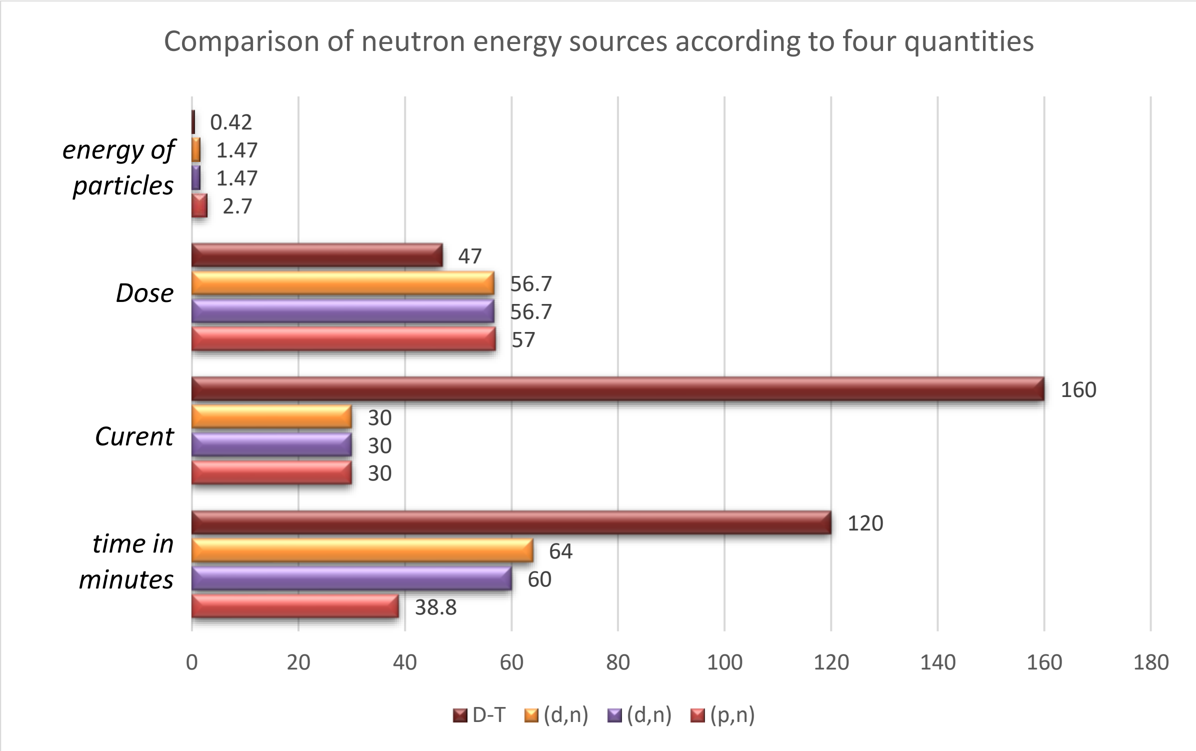

***Figure 2**: Comparison of neutron sources according to their components*

The graph above presents the results of four nuclear interactions, taking into account key parameters such as the energy of the incident particle on the target nucleus, the applied dose, the electric current, and the irradiation time in the context of cancer treatment. Among these, neutrons produced through (p,n) nuclear interactions are more commonly used and have demonstrated high effectiveness and clinical significance.

DISCUSSION

Based on the results obtained on the most effective neutron production sources for cancer treatment using boron neutron absorption, which sources are produced by particle accelerators? These sources (production systems) are currently the most widely used in the treatment sector due to their advantages (Kumada et al., 2023). Which opinion does the comparison of the results support? In a comparative discussion of the quantitative results obtained from the research results presented by the authors in the field of cancer treatment with the BNCT method, it is shown that the neutron flux produced from the nuclear interaction (P-n) in the use of accelerators for neutron production is higher and is significant compared to the nuclear interactions (D-D, D-T). The dose used to destroy a brain tumor resulting from the interaction (p,n) is in the first place (Nakamura et al., 2024), from the nuclear interaction (d,n), whose product is nitrogen, is in the second place, and from the interaction (d,n) whose product is a boron atom is in the third place. What is the main reason for choosing the first order of the interaction (p,n)? When we consider the comparison based on the element used, it is observed that in the interactions studied, the lithium element is a lighter nucleus compared to carbon and beryllium, produces a higher dose, and its effectiveness in using accelerators to produce neutrons is greater than the other two nuclei (carbon and beryllium elements). Regarding the radiation time, the results indicate that the radiation time of the neutron beam resulting from the nuclear interaction (P-n) in using accelerators to produce neutrons was less than that of the nuclear interactions (D-n, D-T), meaning that we can treat many patients in a short period, which is also important. There is no question that the radiation time and radiation dose have a direct effect on the cancer treatment process, but what precautions should be taken to avoid the side effects of radiation?

In medical centers, cancer treatment is often carried out using particle accelerators instead of reactors to produce suitable radioisotopes (including neutrons). In comparison, we see that when accelerators are used to produce neutrons, particles with specific energy are fired at the target to produce neutrons, and the D-T nuclear interaction requires less energy than other interactions. What is the main reason for the superiority of this interaction? Are there alternative particles for this nuclear interaction, and if so, what is its reliability in the treatment of cancer?

According to the analysis results, the dose used by the (p,n) interaction is higher than that of other interactions (Bleuel et al., 1998). For this reason, it is a suitable source of neutrons, as in the BNCT method, the dose is directly radiated to the tumor. The aforementioned interaction is a suitable source of neutrons for treating brain tumors. For (p,n) interactions, the proton is accelerated with a current of 30 mA, and the above-mentioned method can be used as the appropriate source for treating tumors. Although in the (d,n) interaction, the deuterium particle is also accelerated with the same current, the dose of the (p,n) interaction is higher due to the comparison of the doses used. In terms of comparing the energy of the bombarded particles to produce neutrons, the (p,n) interaction is also a suitable source, as shown in Figure 1, because the high-energy particle is bombarded in the target and produces neutrons in a shorter time. In terms of comparing neutron irradiation times, the (p,n) interaction is also a suitable source for neutron energy, as it allows for shorter treatment times. Although different neutron sources are used in cancer treatment and may vary depending on the location, size, and depth of the tumor, the degree of malignancy, and the conditions of radiation adaptation, in general, considering the radiation intensity and the time of activity and the energy required by the particle to produce a neutron, the type of deuteron-tritium interaction requires less energy, but currently, nuclear interactions (P-n) are used in which a proton particle is thrown into the target nucleus and produces a neutron (Horiike et al., 2015). Although nuclear interactions (P-n) are important (Nakamura et al., 2024), their significance remains open to debate until the results of new theoretical and practical research confirm this.

CONCLUSION

By accelerating light-charged particles with specific energies and bombarding appropriate targets to produce neutrons, the use of particle accelerators instead of nuclear reactors presents several notable advantages. In terms of radiation exposure time, (p,n) nuclear interactions are more favorable than other nuclear reactions. Regarding the radiation dose delivered to cancer cells, (d,n) nuclear interactions are more effective and impactful. Additionally, in terms of particle flux directed at the target, both (p,n) and (d,n) interactions offer advantages over alternative nuclear interactions.

When considering neutron flux and energy, deuterium-tritium sources, particularly when optimized through proper beam-forming assemblies, emerge as the most effective neutron energy sources for boron neutron capture therapy (BNCT) in brain cancer treatment. In contrast, nuclear reactors currently do not provide suitable conditions for this therapeutic approach. Likewise, radioisotope-based sources are not appropriate for BNCT due to their limited neutron energy and flux. Accelerators, therefore, are a more suitable and promising source of neutron energy for cancer treatment through boron neutron capture.

Given the complexity and evolving nature of this field, further research is essential. The present study draws on a limited number of sources, and expanding the scope to include more recent findings and broader datasets would enhance the reliability of conclusions. Additionally, key parameters—such as the specific characteristics of the study setting and the clinical profiles of patients—should be incorporated in future research to support more precise and applicable results.

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AUTHORS CONTRIBUTIONS

The contributions of the members of the writing team to this article in its preparation, analysis, and writing are as follows:

1- Yousufy, F. Collection of articles and references
2- Ebtekar, S. M. Analysis of data and references
3- Khavari R. A. Final arrangement and completion of the discussion and conclusion sections
4- All authors contributed to the completion of this article

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CONFLICT OF INTEREST STATEMENT

The authors declare that they have no conflict of interest.

DATA AVAILABILITY STATEMENT

All data and sources can be obtained online for free, accessible through the DOI addresses of the articles and websites.

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