



Review

Exploiting the unique interaction characteristics of fast neutrons for improved cancer therapy: A radiobiological perspective

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ARTICLE INFO

Keywords:

Neutrons

Radiation therapy

Energy

Double-strand break (DSB)

ABSTRACT

Fast neutrons have sufficient energy to liberate recoil protons, alpha particles, and other products when they interact with the nuclei of the target material through scattering and absorption processes. Physical interactions with biological tissues occur mainly with hydrogen nuclei and as the protons interact with the hydrogen in tissues, they create dense ionization chains along their tracks thus depositing energy. Fast neutron therapy was pioneered by Robert Stone in 1938 a few years after the discovery of the neutron. Its main advantage is the limited sensitivity to hypoxia and treatment of slow-growing tumors hence better local control. This is where photon therapy has yet to have much success. Energy deposition by fast neutrons in living tissues is higher than in conventional radiotherapy using mega voltage (MV) photon beams. This higher energy deposition gives fast neutrons a higher relative biological effectiveness (RBE) in dealing with certain tumors. Fast neutrons also have a higher linear energy transfer (LET) and can reach deep-seated tumors better than photon therapy. The main challenge with Fast neutron therapy has been extreme toxicity in late-reacting tissues. Overall, fast neutron therapy holds potential for the treatment of certain tumors by leveraging the unique interaction characteristics of fast neutrons with biological tissues. This review therefore intends to bring this uniqueness to light to enhance the understanding of the radiobiological properties of fast neutrons and the advantages associated with its therapy.

1. Introduction

High-energy X-rays and gamma rays are always the first stop whenever a referral for cancer therapy is made. They're known to penetrate more deeply into tissues with an increase in energy although the cellular effects (useful for cancer killing) may not be increased. On the wrong end, however, they exhibit larger penumbras and large exit doses which result in higher toxicity to normal tissues. An alternative approach to this therapy has been the use of fast neutrons.¹

Fast neutrons are those neutrons with sufficient energy to liberate recoil protons, alpha particles, and heavier nuclear fragments from matter when they interact with the nuclei of the target material. Neutrons are uncharged, cannot be accelerated or deflected, and do not interact with the electron cloud. This interaction might either scatter off the nuclei or absorb the incident neutron. Photons interact with orbital electrons of the target material through Compton or photo-electric processes to liberate fast electrons. Clinical oncologists have had issues regarding the usage of fast neutrons for cancer therapy because of the challenges it has had in the past related to excessive toxicity in late-responding tissues, but these have been partly due to inadequate

radiobiological understanding.²

The challenge facing any radiation therapy modality today is how to minimize dose-related complications while enhancing cell killing within malignant tumors in organs containing rapidly proliferating cell populations. The goal in all this is a double-strand break (DSB) at every opportunity when radiation interacts with any biological tissue. Radiation can cause the death of hematopoietic stem cells in the bone marrow and crypts which leads to secondary damage caused by immunosuppression and infection.³

Dr. Robert Stone's work at the Lawrence Berkeley laboratories is credited for pioneering the work in fast neutron therapy in 1938. It is reported that nearly 250 patients were treated with fast neutrons between 1938 and 1942. Similar follow-up efforts were initiated in 1970 at the Hammersmith Hospital in London and a few years later in several centers across Europe and the United States.⁴

Successful eradication of cancer relies on a deep understanding of radioactive isotopes characterized by high linear energy transfer (LET), including their half-lives, charge particle reactions, tissue penetration, and the patterns of energy deposition associated with different radiation types (such as alpha, beta, or gamma radiation).⁵ Fast neutron therapy

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<https://doi.org/10.1016/j.radmp.2023.12.004>

Received 31 August 2023; Received in revised form 27 December 2023; Accepted 29 December 2023

Available online 1 January 2024

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has been found useful in particular tumors where photon therapy has had limited success.⁶

LET is directly proportional to the number of ionization events along a particle's path. It is defined as the average energy deposited in matter per unit length of the ionizing particle's track. X-rays or gamma rays are low LET while fast neutrons, α -particles, protons, and other particles are high LET. Low LET radiation is characterized by a sparse distribution of single-strand breaks (SSB) while DSB which are majorly a result of localized and dense ionization chains arise from high LET irradiation. This variation in LET impacts directly on the irradiated cells' DNA damage response (DDR). High LET sources also generate fewer but larger DSB foci per unit dose compared to the low LET sources. Furthermore, there is a difference in processing the DSB owing to the nature of irradiation. It is reported that the nuclear DSB resolution is faster in the case of low LET irradiation compared to the high LET.^{7,8}

Live cell imaging has been used on U2OS cells with excellent results in studying the kinetics and mechanism of DSB processing after irradiation with α -particles (high-LET) compared to photon (low-LET) irradiation. Firstly, this study noted that p53 binding protein 1 (53BP1) foci had vanished within a few hours for cells irradiated with photons while for those irradiated with α -particles, a consistent focus was observed in them. Secondly, the average pixel intensity didn't increase as time went by as was the case with X-rays. Thirdly, the 53BP1- green fluorescent protein (GFP) foci were initially smaller and increased in size progressively during X-ray irradiation which was contrary to α -particle irradiation. Lastly, the X-ray irradiated cells accumulated smaller amounts of 53BP1-GFP in foci than the α -particle induced cells.⁹ It has also been observed by Lees-Miller and Meek,¹⁰ that the repair of DSBs induced by X-rays is quicker compared to that induced by particle-irradiated cells.

Regardless of the multifaceted resistance offered by tumor cells and the developments in photon therapy, some scholars have argued that the exceptional radiobiological properties of fast neutrons offered the best option in terms of local control (LC) and overall survival (OS).^{11,12} The advantage of fast neutron therapy (FNT) is its limited sensitivity to hypoxia and treatment of slow-growing tumors among others mainly, prostate adenocarcinomas.^{13,14} Results have shown a 5-year LC of 89% against 68% for FNT versus conventional therapy in a cohort of 172 patients having prostate adenocarcinomas.¹⁵ Other data from a cohort of 1,171 patients from 11 clinics analyzed showed that FNT was a game changer for patients with primary radiotherapy of inoperable tumors and post-surgery macroscopic disease with a LC of 50% in these cases. Excellent results have also been reported in worldwide clinical surveys when using mixed beams of neutrons and photons versus pure fast neutrons or photon beams alone.^{16–18}

Another cancer affecting 3%–4% of people is the salivary gland tumor. Common in ages of 55 years and above, the affected persons have been treated with photons with limited success. A cohort of 32 patients with inoperable salivary gland tumors posted a median survival time of 22 months, complete tumor regression in 25 patients, and lasting LC in 21 of the patients after FNT in the Netherlands. Similarly, LC outcomes of 0–56% were found in patients with soft tissue sarcomas after high-dose radiotherapy. These suboptimal results led to trials with FNT. The downside of FNT has always been severe toxicity in late-reacting tissues.^{18–20}

Therefore, FNT offers a better therapeutic gain compared to photon therapy and should be the first option for certain kinds of tumors like salivary gland tumors, which are partially resected and recurrent.

2. Neutron interaction with matter

2.1. Neutron properties

As mentioned earlier, a neutron is an electrically neutral elementary subatomic particle with a mass almost 2,000 times that of an electron. Its lifetime as a free particle is about 15 min although neutrons are stable when bound in atomic nuclei. Neutrons interact weakly with matter and

are therefore very penetrative beyond photons. Fast neutrons typically have energies ranging from 0.5 to 20 MeV. These energy levels are characteristic of neutrons emitted by fission sources. After being emitted, they travel in straight lines until they collide with a nucleus, at which point they may either be scattered or absorbed. This can result in the emission of particles such as protons, alpha particles, or prompt gamma rays. The likelihood of a specific reaction occurring depends on two factors: (a) the kinetic energy of the neutron and (b) the identity of the target nucleus. Neutrons are not affected by the atomic electron cloud, the nucleus itself, or the electric field caused by a positively charged nucleus during their flight.²¹

2.1.1. Neutron interactions – general principles

Neutrons interact with matter primarily through two main mechanisms: scattering and absorption. These interactions can occur at any energy level, but scattering reactions tend to dominate once the neutron energy exceeds a few hundred keV. The likelihood of neutron interactions is quantified using cross-sections, which express the probability of a specific interaction occurring between an incident neutron and a target nucleus. Importantly, cross-sections are independent of the actual dimensions of the target and are typically measured in barns ($1 \text{ b} = 10^{-24} \text{ cm}^2$). The human body comprises elements such as hydrogen, oxygen, carbon, and nitrogen. Although the individual neutron capture cross-sections for these elements are relatively small, the large quantity of atoms in all tissues becomes a significant factor to consider when assessing radiation doses absorbed by healthy tissues.^{21,22} The neutron cross-section depends on factors such as the target nucleus, type of reaction, neutron energy, and, to a lesser extent, target energy. To generate fast neutrons, cyclotrons within a reactor facility accelerate either protons or deuterons to very high speeds and then direct them toward a beryllium target.⁴

2.1.2. Scattering reactions

Elastic scattering is often referred to as a “knock on” reaction or “billiard ball” collision where the kinetic energy is conserved. In this collision, the total kinetic energy remains the same before and after the interaction. Elastic scattering is the most probable interaction between neutrons and all types of nuclides. When a neutron interacts with a target nucleus of the same mass, the maximum amount of energy can be transferred. Additionally, target nuclei with lower atomic mass numbers are more effective as moderators. Typical moderators such as water, paraffin, plastic, and graphite slow down neutrons through elastic scattering. In contrast, inelastic scattering is a type of interaction where kinetic energy is not conserved; specifically, the total kinetic energy before the collision is greater than the total kinetic energy after the collision. Inelastic scattering is relatively uncommon, but when it occurs, it is most likely to involve high atomic number (Z) nuclei and high-energy neutrons.³

2.1.3. Absorption of neutrons

Incident radiation directly or indirectly ionizes a medium in which it is absorbed. Directly ionizing particles can disrupt the atomic structure of the absorbing medium through which they pass directly hence producing chemical and biological changes. This is through the Compton and photoelectric processes. X-rays, γ -rays, and neutron radiation are indirectly ionizing as they do not produce chemical and biological damage themselves. However, they give up their energy to produce fast-moving charged particles that “terrorize” the absorbing medium.²³ The incident neutron collides with the target nucleus, releases part of its kinetic energy to it and retains a part as it is deflected. Additionally, there will be elastic collisions of neutrons with heavy elements in tissues but their contribution to the total dose is quite small although it is deposited at a high LET. Inelastic collision takes effect at energies higher than 6 MeV and continues to dominate thereafter as the neutron energy increases. A new set of products called spallation products is released at these higher energies for example a neutron and a ^{12}C reaction yields three α -particles.

As the energy of the neutron beam rises, the chances of having spallation products increase. Although the contribution of these spallation products (α -particles) to the total absorbed dose is less significant, their ability to create dense ionization chains makes them have an important biological effect on the infected organs.

2.2. Interaction of particles with biological tissues

In this interaction, energy is deposited in a random and discrete nature in the medium in which the particle passes. The deposition increases in magnitude along the track and this is delivered in packets commonly known as “spurs” with 100 eV or less, “blobs” (100–500 eV), or even “short tracks” (500–5,000 eV). Each of these deposits can make not less than three dozen ionisations.³

The interaction between the fast neutrons and hydrogen nuclei is the most dominant process of energy transfer in tissues. This is because (a) hydrogen (^1H) is the most abundant atom in the tissues since the human body is about 60% water, (b) hydrogen provides a large collision cross-section compared to other atoms, (c) hydrogen being nearly of the same mass as the neutron, much of the energy is easily transferred to the hydrogen in this interaction. Therefore, uncharged fast neutrons will always look for a hydrogen nucleus for interaction, thus producing recoil protons and alpha particles that create dense ionization chains along the track of the particle. Such chains will be created in water and other biological macromolecules containing a reasonable volume of hydrogen-like lipids and lipoproteins, for example myelin and sphingomyelin in the brain, spinal cord white matter, and bodily fat. In this way, large quantities of energy KERMA (kinetic energy released in matter) are deposited into these tissues which breaks the double strands of the DNA of cancer cells making repair more difficult. The KERMA ranges between 20 keV/ μm to 100 keV/ μm which is higher than MV photon beams in conventional radiotherapy. This gives fast neutrons a higher relative biologic effectiveness (RBE) in dealing with certain tumors like salivary glands over other conventional approaches.^{2,3,23,24}

2.3. Linear energy transfer (LET) and relative biological effectiveness (RBE) of neutrons

LET is influenced by both the mass of the ionizing particles and their associated charge. For protons, the rate of energy deposition in a target volume increases as the particle slows down, leading to greater damage inflicted on the tumor. As a result, LET is inversely proportional to the speed of the ionizing particle. RBE is defined as the ratio between two absorbed doses delivered using two different radiation qualities, one of which serves as the reference radiation (usually 250 kVp X-rays, but ^{60}Co γ -rays can also be used). This ratio reflects the equivalence of two doses in terms of producing the same biological endpoint in a given biological system under identical irradiation conditions.

$$RBE = \frac{\text{Dose (photons)}}{\text{Dose (neutrons)}} \quad (1)$$

From a radiobiological perspective, neutrons are high LET radiation while X-rays or photons are low LET. The maximum LET that protons reach is around 100 keV/ μm and then drops sharply. This is because, at this point, the average distance between any two ionizing events is proportional to the diameter of the DNA double helix (about 2 nm). Fast neutrons of such a LET have the highest chance of making a DSB and this is when the RBE is highest. So RBE strongly depends on LET although other predisposing factors are well documented in the literature.^{2,3,25} There is less dependency on the energy of the incident radiation as fast neutrons even though show weak RBE values, they are still high LET particles.⁵ Apart from the particle LET, other factors affect the RBE: (a) the dose per fraction – the RBE is inversely proportional to dose per fraction, (b) tissue type – there are differences between RBE values of early and late effects, (c) the particle energy – it is shown that RBE is

higher for neutrons with lower energy and (d) cell cycle – there are noticeable changes in radio-sensitivity at different stages of the cell cycle.²⁶

2.3.1. Historical challenges with fast neutron therapy (FNT)

Efficient cell killing and a mild dependency on tissue oxygen per unit dose were the medical rationale for the use of FNT. Earlier scientific discoveries based on *in vitro* data from biological systems done by Gray et al.²⁷ had shown that it was possible to achieve better clinical outcomes with low-dose neutrons than photons. However, Gray later had misgivings about this proposal in the first human treatments in the 1940s in the USA as these were found with excessive toxicity as the issue of RBE hadn't been fully explored. Radiobiological evidence would later exonerate Gray as it was discovered that RBE was inversely proportional to dose such that at the dose fall-off, the RBE was highest and yet this was beyond any cancer target.²

The lack of experience in dosimetry and knowledge of radiobiological interactions of neutrons with tissues resulted in unbearable treatment outcomes which brought a temporary suspension of this technique in the early 1940s. Later, with more experience and knowledge, FNT resumed in the 1960s in the UK. The persistent challenge of FNT has also been that of distant metastases for some patients.¹⁸

The prevalence of severe late effects also became a common phenomenon in the early days of FNT. Results from a study cohort of 232 patients reported these in 19% of the cases. This was attributed to patients being irradiated with inadequate neutron beams and that many of the patients had a history of radical surgery or had done radiotherapy before.^{28,29}

Additionally, in the early days, many of the treatments were done with first-generation machines which were of poor technical quality. This led to the high levels of severe late effects reported between 6.6% and 50%. The other reasons for late complications were: large treatment numbers, pretreatment conditions, and dose inhomogeneities.¹⁸ Moffitt et al.³⁰ have highlighted a need for more quality assurance (QA) tools to critically analyze the impact of tissue density and composition. Such tools will assist in the use of advanced radiotherapy techniques such as intensity modulated neutron therapy (IMNT).

Mathematical modeling of the biological effect of fast neutrons in a cancer target using the concept of fractionation has been carried by various scholars. These models apply the concept of biologically effective dose (BED) and also consider RBE in its varying forms as high LET radiation traverses through the biological tissues.²

In summary, from a radiobiological perspective, the poor clinical outcomes have been a result of (a) the apparent increase of RBE with dose fall-off which affected local control relative to normal tissue complications, (b) the fact that neutrons did not have Bragg peaks to enable them to spare many tissues, (c) the treatment protocols maintaining a constant RBE tumor prescription and yet there was a probability of having higher values of RBE for late reacting tissues, and (d) some tissues having a higher percentage of hydrogen, for example, myelin and sphingomyelin in the brain had the highest RBEs.²

2.4. Energy deposition

Neutrons have no Bragg peaks but can liberate protons from tissues. The Bragg peak is a pronounced peak on the Bragg curve which plots the energy loss of ionizing radiation during its travel through matter. As protons traverse through tissues, they will deposit energy along their track as they continuously slow down and the peak occurs immediately before the particles come to rest. This energy will be deposited up to a certain depth of penetration and the maximum energy will be at the so-called Bragg peak with a sharp dose falloff following this.^{2,14} Experimentally, the Bragg depth can be determined depending on the energy of the incident beam. However, to match this to the depth of the tumor, uniform slabs of plastic can be used to attenuate the beam to generate a series of Bragg peaks at different depths.^{1,31}

2.4.1. Cellular effects of high LET energy deposition

Whether it is low LET or high LET radiation, any exposure to radiation affects the macromolecules and structures in tissue. Ionizing radiation can break chemical bonds, such as C–H, O–H, S–H, and N–H bonds. Consequently, this leads to cell death and loss of clonogenicity due to DNA damage, including DSBs and SSBs. Multiple instances of DNA damage caused by irradiation result in the accumulation of irreparable DNA fragments, destabilization of chromosomes, the induction of toxic mutations, and other related effects. Additionally, there are secondary effects observed, such as the release of reactive nitrogen (RNS) and oxygen (ROS) species, with ROS being the primary species generated. The most commonly produced ROS are oxygen and hydroxide free radicals. Considering that the extent of macromolecular damage is directly proportional to the energy deposited within a specific volume of tissue, high LET radiation generates a greater number of ROS per nanogram of tissue compared to low LET radiation.^{1,32}

2.4.2. Reaction of cancer cells to high LET radiation

Following a high LET radiation exposure, the extent of damage to the tumor determines whether sublethal DNA damage occurs, which can potentially be repaired by the tumor itself using available repair enzymes, albeit at varying rates. Subsequently, the proliferation and redistribution of tumor cells into different phases of the cell cycle commences, each exhibiting different sensitivities to radiation. The G₂ or M phase displays the highest radiation sensitivity, while the G₀ phase and late S phase exhibit strong resistance.^{1,33} Moreover, reduced oxygen supply (hypoxia) within the tumor microenvironment enhances resistance to radiation, whereas an irradiation-induced shrinkage known as “debulking” can increase oxygen supply, leading to heightened sensitivity.³⁴ High LET radiation generates complex and clustered DSBs that often remain unreparable, while X-rays are capable of inducing sublethal damage. Live-cell microscopy studies conducted by Roobol et al.³⁵ have demonstrated that high LET radiation can induce up to 500 DSBs per μm^3 of tissue volume more than low LET radiation. Consequently, a high concentration of repair proteins within the local volume is experienced.

2.5. Mathematical modeling of radiobiological considerations

In fractionated therapy, the linear quadratic (LQ or α/β) model is now widely accepted as the basis for weighting differences in fraction size to determine the absorbed dose. Without specific information, it is assumed that the α/β ratio is equal to 10 Gy on average for early responding tissues for example the intestinal epithelium and the skin while a 3 Gy for late responding tissues e.g., the spinal cord. This classification of early or late reacting depends on the time of the onset of repopulation. Tumors are usually called early-reacting as they possess short repopulation times. The terms α and β are related to the lethality of directly ionizing actions and due to the accumulation of sublethal damage respectively. Before the advent of the LQ model, the Target theory guided the clinical practice at the time. According to Lea,³⁶ it was assumed that there are many specific sensitive targets within a cell that needed to be irradiated and this determined whether a cell survives or not. Moreover, it was postulated that irradiating one of the n -sensitive targets on the cell caused cell kill. It was based on Poisson's statistics and thus, the probability of hitting no specific target was expressed as,

$$P(0 \text{ specific target hits}) = e^{(-D/D_0)}. \quad (2)$$

Generally, the probability of survival, that is,

$$P(\text{not deactivating any target}) = 1 - \left[1 - e^{\left(-\frac{D}{D_0}\right)} \right]^n \quad (3)$$

However, the target theory was later criticized when the first batch of survival data was used. Its predictions were contrary to the available data. The discovery of the DNA further led to this model's extinction. To

have any therapeutic gain using any radiation type, the treatment optimization process should aim at increasing the tumor control probability (TCP) and/or decreasing the normal tissue complications probability (NTCP). This involves both the physical linear accelerator (LINAC) controls and biological means by considering the different radiobiological properties of the tissues involved.^{25,37}

For the effective use of fast neutrons, an extensive theoretical and experimental study into their radiobiological parameters, particularly the RBE has been undertaken. This has been very useful as the number of radiotherapy centers using high LET radiation is increasing globally although more needs to be done.²⁶

The use of mathematical modeling of the RBE in a clinical environment is to give the oncologists an idea of the effectiveness of a new treatment modality compared to the one for which he/she has generated considerable experience. The BED as coined by John F. Fowler in 1989 has long stood as a clinically viable expression for any fractionated scheme taking into consideration a variety of tissues. BED is expressed in units of Gy α/β with the α/β depending on the nature of tissues, whether early reacting or late responding. BED relates to a quantified effect of any fractionated regime. In the event of unplanned gaps in treatment, the “BED” can be modified with a time factor ($e^{-\gamma t}$) such that,

$$\text{BED} = nd \left(1 + \frac{1}{(\alpha/\beta)} \right) - \frac{\gamma T}{\beta} \quad (4)$$

Subsequent suggestions and modifications of Eq (4) into a more precise equation were also later dropped as it was too bulky for clinical applications as the parameters involved were too many to be specified accurately.³⁶

In high LET radiation exposure, the BED is also necessary to attain an isoeffective fractionation schedule comparable to that in photon therapy. For the low-LET (L) to have the same biological effect as the high-LET (H) radiation over a biological material, then there has to be a defined equivalent endpoint. Such an endpoint maybe an equal number of lethal events say X such that $X|_{\text{high-LET}} = X|_{\text{low-LET}}$ for both low and high LET irradiations.

The high LET BED can be expressed as;

$$\text{BED}_H = n_H d_H \left(\text{RBE}_{\max} + \frac{d_H}{(\alpha/\beta)_L} \right) \quad (5)$$

Where $\text{RBE}_{\max} = \text{RBE}|_{d=0 \text{ Gy}} = \frac{d_L}{d_H} = \frac{\alpha_H}{\alpha_L} = \frac{\text{BED}_L}{\text{BED}_H} = \frac{\alpha_H}{\alpha_L}$

The $\text{RBE}_{\max}$ helps in guiding treatment decisions in non-conventional therapy as it assists to calculate the equivalent dose of high LET radiation in comparison to a known photon dose.

The fact that $\text{RBE}_{\max}$ exists at $d = 0$ Gy suggests that there is another lower RBE at some dose $d \gg 0$ Gy. This is the minimum RBE ($\text{RBE}_{\min}$) and with a clear look at the two extremes, it is conclusive to say that as the number of fractions decreases, a higher dose per fraction ($d \rightarrow \infty \text{ Gy}$) is expected and with this, the RBE should decrease. The derived $\text{RBE}_{\min}$ is given by,

$$\text{RBE}_{\min} = \frac{d_H}{d_L} = \sqrt{\frac{\beta_H}{\beta_L}} \quad (6)$$

At this point, we can conclude that if β is independent of the radiation quality, then $\text{RBE}_{\min} = 1$ as $d \rightarrow \infty \text{ Gy}$. Eqs (5) and (6) can be recombined such that the high-LET BED is given by,

$$\text{BED}_H = n_H d_H \left(\text{RBE}_{\max} + \text{RBE}_{\min}^2 \frac{d_H}{(\alpha/\beta)_L} \right) \quad (7)$$

Eq (7) has got both high and low LET components which allows a comparison between radiation of different qualities.²²

Moreover, the variation of the β parameter with increasing LET has been considered controversial in some sections of the scientific community. Research shows that increments in β have an effect on RBE

especially at higher fractional doses. Although the largest effect with LET is considered to come from α , theoretical predictions have included β to fit experimental results.³⁸ Dale and Jones³⁷ had proposed that the variation of RBE was dependent upon only the $RBE_{\max}$ parameter and therefore mathematically found that,

$$RBE = \frac{(\alpha/\beta)_L RBE_{\max} + \sqrt{(\alpha/\beta)_L^2 RBE_{\max}^2 + 4d_L((\alpha/\beta)_L + d_L)}}{2((\alpha/\beta)_L + d_L)} \quad (8)$$

However, Carabe-Fernandez et al.³⁹ thought it was wise to incorporate the $RBE_{\min}$ parameter arguing that it is of critical importance for the accurate predication of the biological effect. The improved equation combined both the $RBE_{\min}$ and $RBE_{\max}$ into the same equation to predict that,

$$RBE = \frac{(\alpha/\beta)_L RBE_{\max} + \sqrt{(\alpha/\beta)_L^2 RBE_{\max}^2 + 4d_L RBE_{\min}^2((\alpha/\beta)_L + d_L)}}{2((\alpha/\beta)_L + d_L)} \quad (9)$$

It is observed that Eq (9) is filled with low LET parameters which are readily available in literature for most tissues and hence mathematically verifiable. Additionally, both Eq (8) and (9) are similar as $d_L \rightarrow 0$, implying that $RBE \rightarrow RBE_{\max}$. On the contrary, in the limit as $d_L \rightarrow \infty$, $RBE \rightarrow RBE_{\min}$. This signifies the importance of applying limits to both sides of d_L which had not been considered by Dale and Jones.³⁷ thus giving an inaccurate mathematical prediction. It's also been found that these parameters are relatively easier to determine in *in-vitro* experiments. However, their determination from simple regression analysis applied to survival data is error prone. Using Eq (7), we find that substituting for $D_H = n_H d_H$,

$$\frac{1}{D_H} = \frac{RBE_{\max}}{BED} + \frac{RBE_{\min}^2}{BED \left(\frac{\alpha}{\beta}\right)_L} d_H \quad (10)$$

And plotting the reciprocal of total dose against the high LET dose per fraction (d_H) would give the slope as $\frac{RBE_{\min}^2}{BED \left(\frac{\alpha}{\beta}\right)_L}$. The intercept on the $\frac{1}{D_H}$ axis would be $\frac{RBE_{\max}}{BED}$. This gives us an opportunity to find the $RBE_{\min}$ and $RBE_{\max}$ parameters.³⁹

3. Discussion and conclusion

The use of fast neutrons in cancer therapy has been explored as an alternative to high energy X-rays and gamma rays. Fast neutrons have different interactions with tissues compared to photons, offering potential advantages in certain tumor types. While local control can be achieved with fast neutron therapy, late complications or toxicity may be more severe compared to photon therapy. This has been highlighted in several study cohorts in the late 1980's. Understanding the properties of fast neutrons, their interactions with matter, and their effects on biological tissues is crucial for successful cancer treatment.

Fast neutrons, with energies between 0.5 and 20 MeV, interact with matter through scattering and absorption reactions. Scattering reactions dominate at higher neutron energies, while absorption reactions become more significant at energies above 6 MeV. Neutrons primarily interact with hydrogen nuclei in biological tissues, leading to the release of recoil protons and alpha particles that create dense ionization chains. The high energy deposition of fast neutrons, measured as KERMA, can cause DSB in DNA, making repair more challenging for cancer cells.

The LET of fast neutrons is an important factor in their biological effects. LET has been defined as the rate of energy deposition by ionizing particles and is inversely proportional to the particle's speed. Fast neutrons have high LET and exhibit a peak LET value at around 100 keV/ μ m, where the probability of causing a DSB in DNA is highest. The RBE of fast neutrons is higher compared to low-LET radiation, particularly at high

LET values. Other factors that influence RBE include the dose per fraction, tissue type, particle energy, and cell cycle stage.

In conclusion, fast neutron therapy holds promise for certain tumor types where conventional photon therapy has had limited success. The unique properties of fast neutrons, their interactions with matter, and their high LET effects on biological tissues contribute to their potential as a cancer treatment modality. Further research and understanding of these factors will continue to improve the efficacy and safety of fast neutron therapy.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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