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PHYSICAL INTERACTION OF FAST NEUTRONS WITH BIOLOGICAL TISSUES FOR RADIOLOGICAL THERAPY – A RADIOBIOLOGICAL REVIEW

Abstract

From the discovery of neutrons by James Chadwick in 1932, research into the clinical applications of fast neutrons has been going on for almost a century regardless of the several bottlenecks. The uncharged neutrons do not interact directly with the electron cloud of atoms like X-rays or photons. They however interact with water or hydrogen in biomolecules, liberating the highly ionising protons which create dense ionisation chains along their paths. Along these paths, they transfer energy to the body in a process called Linear Energy Transfer (LET). It's this energy that is responsible for the Double Strand Breaks (DSB) that cause lethal damage to DNA. The lack of proper understanding of this radiobiological phenomenon is likely to be a major hindrance to the scientific progress.

Introduction

Fast neutrons are those with sufficient energy to liberate recoil protons from matter after which these liberated particles ionise materials. Neutrons are uncharged, cannot be accelerated or deflected and do not interact with electrons. This interaction might either scatter off or absorb the incident neutron. Clinicians have had issues regarding the usage of fast neutrons for therapy because of the challenges it has had in the past related to excessive toxicity [1]. The main aim of radiation therapy is a Double Strand Break (DSB) at every irradiation. Radiation can cause the death of hematopoietic stem cells in the bone marrow [2]. 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 – 1942. Similar follow-up efforts were initiated in 1970 at the Hammersmith Hospital in London [3]. Fast neutron therapy has been found useful in particular tumors where photon therapy has had limited success [4].

The case for neutron therapy

Although photon therapy has taken greater strides in terms of specification of the target and accuracy limits, there remains a need for neutron therapy for certain types of tumors. The main radiobiological advantages of fast neutrons or high Linear Energy Transfer (LET) radiation are mainly three: (a) the

suppressed oxygen effect, (b) reduced repair of sub-lethal damage and increased cell kill per fraction of absorbed dose, and (c) a reduced variation in cell response within the phase of the mitotic cell cycle. Whereas the biological effectiveness of neutron irradiation has been found to increase with LET, the number of DSBs also increases as LET decreases [5, 6]

Neutron properties

A neutron is a neutral elementary subatomic particle with a mass of almost 2000 times that of an electron. It's lifetime as a free particle is about 15 min inspite of the fact that neutrons are stable when bound in atomic nuclei. Neutrons interact weakly with matter and are therefore very penetrative beyond photons. Fast neutrons generally have energies between 0.5 - 20 MeV. These are the energies of neutrons emitted by fission sources and after emission, they travel in **straight lines only**, deviating from their original path when they collide with a nucleus [7].

Neutron interaction with biological tissue

Uncharged fast neutrons will always look for a hydrogen nucleus (^{1}H) for interaction since it passes through the electron cloud uninterrupted and thus producing recoil protons that create dense ionisation chains along the track. Such dense ionisation 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 the process, large quantities of energy Kinetic Energy (KERMA) is deposited into these tissues containing hydrogen which breaks the double strands of the DNA of cancer cells making repair more difficult. It is this higher energy deposited that gives fast neutrons a higher Relative Biological Effectiveness (RBE) [1, 2, 9].

Linear Energy transfer (LET) and RBE

LET is a function of both the mass of the ionising particles and its associated charge. For a given ionizing particle like a proton, the rate of energy deposition in a target volume increases as the particle slows down and in so doing, more damage is done to the tumor Therefore, LET is inversely proportional to the speed of the ionising particle. Another factor greater relevance is the RBE. It is defined as the ratio between two absorbed doses delivered with two radiation qualities, the reference radiation (250 kVp x-rays or ^{60}Co γ-rays) and non-reference radiation that results in the same effect in a given biological system. From a radiobiological point of view, neutrons are high LET radiation while X-rays or photons are low LET.

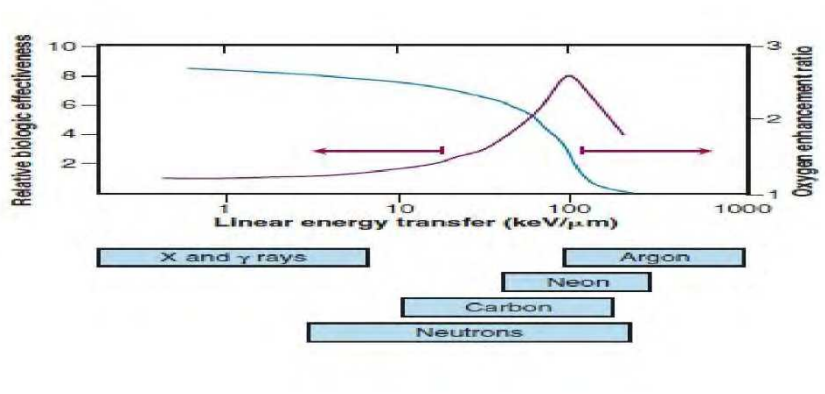

Fig. 1.1. RBE variation with LET adapted from [2]

From Fig 1.2, it can be observed that LET reaches its peak at around 100 Kev/μm and then drops sharply. This is attributed to the fact that at this point, the average distance between any two ionising events is proportional to the diameter of the DNA double helix (about 2mm). This is when the RBE is highest as well [1, 2, 10]. Table 1.2 summarises the dependence of RBE on LET for various particles. Alpha particles although have less penetration in tissues, their energy and RBE on the surface of the skin is noticeably very high. Fast neutrons have greater penetration on the other hand even though their energy is low compared to gamma rays and X-rays [12].

Table 1.1

Variation of RBE with nature of incident radiation [11]

Radiation type	**RBE**	**Energy range**
Alpha particles	$4 - 20$	$3.2 - 9MeV$
Beta particles	$1 - 3.5$	$0.019 - 1.7MeV$
Slow neutrons	$\sim 2.5 - 20$	$\sim 10 - 100KeV$
Fast neutrons	$\sim 5 - 20$	$0.1 - 3MeV$
Protons	$\sim 0.89 - 20$	$50 - 1000MeV$
Gamma rays	~ 1	$1.2 - 6MeV$
X-rays	$\sim 1 - 1.1$	$200 - 50MeV$

Apart from the particle LET mentioned above, there are other factors that affect the expected RBE and these include: (a) the dose per fraction (b) tissue type (c) the particle energy and (d) cell cycle [13].

Energy deposition

Neutrons have no Bragg peaks but can liberate protons from tissues. As protons traverse through tissue, they will deposit energy along their track as they continuously slow down. This energy will be deposited up to a certain

depth of penetration and the maximum energy will be at the so-called Bragg peak (Fig 2.3) and thereafter, a sharp dose falloff follows from this [8, 1].

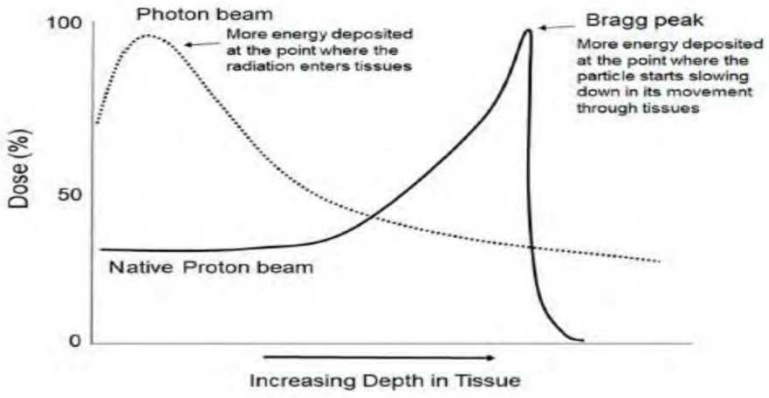

Fig. 1.2. Energy deposit in tissues (Adopted from [11])

Experimentally, the depth of the Bragg depth can be determined depending on the energy of the incident beam [11, 8]. Comparisons have been made between neutron therapy and "FLASH" radiotherapy (Ultra High Dose rate – UHDR) [1].

Conclusion

This mini-review has focused more on the radiobiological aspects of the interaction between fast neutrons and biological tissues. Neutrons interact with hydrogen-containing tissues like lipids and lipoproteins creating a dense cloud of ionisation chains along the track of the liberated protons. Energy in the process is deposited along the track of the particle in a process called Linear Energy Transfer (LET).

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