Neutrons applications in cancer treatment and in specific diagnostics

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Abstract

The major effect of ionizing radiation in cells is to destroy the ability of cells to divide by damaging their DNA strands. Extensive researches are leading to an understanding that the characteristics of high LET radiations such as fast neutrons and low LET radiations like protons, photons and electrons are different; because of different types of their interactions with tissue. Low LET radiations mostly damage tissue by producing free radicals. Oxygen has an effect of enhancing free radical formation in cells. Indeed hypoxic cells, which exist in malignant tumors, are radio resistant under irradiation with low LET radiations. In contrast, neutron interacts with tissue primarily via nuclear interactions, so its biological effectiveness is not affected on the presence of oxygen. The required dose to kill the same number of cancerous cells by neutrons is about one third in comparison with photons. Clinical reports show that a full course of treatment with neutrons consists of 12 treatment sessions, compared to 30-40 treatments with photons or electrons. *In conclusion*, in this review we describe which cancers or tumors could be better treated with neutrons. We also refer to whether neutrons could be used for diagnosis.

Introduction

Nuclear medicine is the branch of medicine that deals with the use of radioactive substances in research, diagnosis and treatment. Applications of neutrons have a long history in "nuclear" medicine, starting six years after the discovery of neutrons by Chadwick in 1932 [1]. Dr. Robert Stone (1938) first showed clinical trials for treating cancer with fast neutrons in Berkeley, California [2]. These trials were terminated during World War II and restarted by Dr. Mary Catterall (1965) at Hammersmith Hospital in London [3]. By 1969, it was obvious that neutron irradiations were more effective than other irradiations for certain malignant tumors [4]. Following these results, the M.D. Anderson Hospital and Tumor Institute in Houston, the Naval Research Laboratory in Washington, D.C., and the University of Washington in Seattle commenced neutron treatment research [5]. Patients were first treated in these institutes in the early 1970s [3]. Many therapeutic centers have started fast neutron treatment since 1976 and this treatment is now routinely performed. Table 1 lists some neutron treatment centers worldwide [6]. Typical neutron energies used for treatment are up to 70MeV and are mostly produced by neutron sources such as reactors, cyclotrons (d+Be) and linear accelerators [7].

The advantages of neutron treatment

The most destructive effect of ionizing radiation is to damage cellular DNA strands and thus prevent cell proliferation. High LET radiations such as fast neutrons cause tissue damage primarily by nuclear interactions. Low LET radiation like electrons, photons and protons cause damage by activated radicals produced from atomic interactions. Oxygen plays an important role in free radicals production in the body. The body is deprived of adequate oxygen supply in special pathological "hypoxic" conditions. Hypoxic cells exist in malignant tumors [8-10] therefore the probability of produce free radicals is decreased. Indeed, hypoxic cells when irradiated with low LET radiations are radio resistant while neutrons do not depend on the presence of oxygen in order to damage cancer cells [8, 11].

The microdosimetric characteristics of neutrons and X-rays beams are different. Recoil protons and other secondary particles produced by nuclei, deposit about 50-100 times more energy per unit path length than do electrons. The probability of fatal injury to cell nucleus, when affected by recoil protons from neutron scattering in tissue, is very much higher than that of recoil electrons [8, 12]. In addition, if a cancer cell is damaged by high LET radiation the probability to repair itself and continue to grow is much less that if damaged by low LET radiation [13, 14].

The required dose to kill the same number of cancerous cells by neutrons is about one third in comparison with photons [8, 13]. Clinical reports indicate that a full course of treatment with neutrons consists of 12 treatment sessions, three times a week for four weeks, compared to 30-40 treatments, five times a week for six weeks with photons or electrons [15].

Various clinical studies were performed in the 1970s to determine the side effects of neutron treatment. The acquired results showed that the side effects for fast neutron treatment were similar to those of low LET treatment [15] depending on the total dose transferred and the general health of the patients. Most of the more serious side effects are temporary and normal tissue recovery finally occurs. Fast neutron treatment in comparison with photon treatment has fewer local symptoms such as pain or bleeding [13].

Which cancers or tumors could be better treated with neutrons?

Locally extended, inoperable *salivary gland* tumors are the first type of tumors in which it has been accepted that treatment by fast neutrons were superior over usual

Figure 1. A: a man suffers from a large tumor of squamous cell carcinoma. **B**: the same man a few months after a full course of neutrons treatment [40].

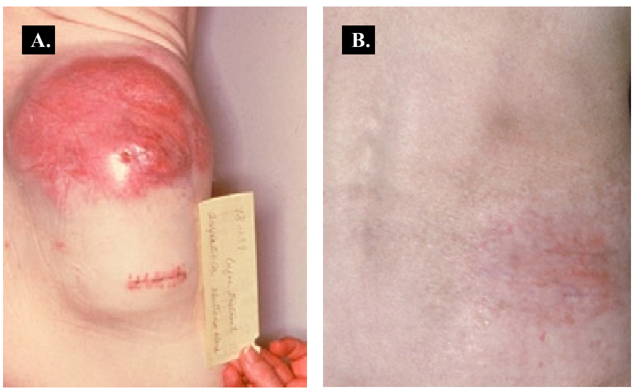

Figure 2. A: large soft tissue sarcoma on the hip. **B**: the same patient at two months after being treated with fast neutrons for two months [41].

low LET radiations (Fig.1) [16, 17]. Later, remarkable results of neutron treatment have been reported: for locally advanced tumors of the *paranasal sinuses* [18-20], for advanced *squamous cell carcinomas of the head and neck* [21-23] and for advanced *prostate cancer* [24, 25]. For example, K100 cyclotron is now in use to produce a high energy neutron in Harper University Hospital, for the treatment of advanced prostate cancer [26]. Furthermore, treatment of *soft tissue sarcomas* [27, 28] (Fig. 2), *melanomas* [29-31] and *brain tumors* [32, 33] showed much better treatment results when treated by neutrons as compared with photons, because these tumors are resistant to photon irradiation. Moreover, usual radiation treatment such as photon treatment has been defeated generally for the control of *sarcomas of bone* and *cartilage*, because of radiation-induced osteoradionecrosis. In these cases, absorbed dose is decreased to about 25% or more by the low neutron "kerma" radiation in osseous cavities [34]. Hence, treatment of bone and cartilage tumors is a main part of clinical neutron treatment [35, 36].

Furthermore, neutron branchy therapy is an effective treatment for cervix, prostate, skin and breast cancers and more suitable than radiotherapy for cervix and prostate cancers [37, 38] using a californium-252 neutron source branchy therapy [39].

Could neutrons be used for diagnosis?

The *in vivo neutron activation analysis* (IVNAA) is now used for measurements and for the diagnosis of clinical syndromes due to abnormal body elements like calcium, nitrogen, hydrogen, oxygen, carbon, iron, iodine, chlorine, sodium, etc. [42, 43] in some hospitals such as the U.S. Department of Agriculture/Agricultural Research Service the

Table 1. *Some active neutrons treatment centers, worldwide*

Centre	Country	Neutron source	Patients treated	Comments
FRM II Munich,	Germany	Reactor	80	
Snezhinsk	Russia		990	Two treatment rooms (one vertical and one horizontal beam). No multi-leaf collimator
Tomsk	Russia		1,200	
iThemba Labs	S. Africa	Separated sector cyclotron, 66MeV p^+ on a Be target	1,700	Isocentric unit with multi-blade trimmer.
Detroit	USA	Cyclotron d(48.5)+Be	2,200	
Fermilab	USA	Proton linear accelerator ~70MeV	3,000+	Currently 30-40 annually
Seattle	USA	Cyclotron 50MeV	2,750	

Children's Nutrition Research Center, the Monash Medical Center Melbourne and the Brook Heaven National Laboratory [44-46]. The tissue examined is irradiated with thermal neutrons, causing the various elements to become radioactive. As these radioactive elements decay, they emit prompt and delayed gamma rays the spectra of which are measured by special detectors and finally the quality and quantity of these elements in the target organs such as liver, kidneys and the heart are determined.

The most recent spectroscopic imaging technique is: n*eutron stimulated emission computed tomography* (NSECT), currently being developed to non-invasively measure and image elemental concentrations, by using inelastic scattering of fast neutrons within the body. For that an incident neutron excites the target atomic nucleus like in the IVNAA method. The energy of the prompt gamma radiation emitted is like a signature of the emitting atom, identifying this atom and its concentration in the tissue sample. Experiments demonstrate the ability of this method to obtain element information from an intact small animal such as mouse [47]. In addition, NSECT is the novel diagnosis method to detect breast cancer at very early stages; it detects changes in trace element concentrations in the breast, which usually occur before anatomical features such as the formation of tumors [48, 49]. Such a technique can be used for the diagnosis of hemochromatosis iron overload mainly in the liver that causes serious consequences for the patient through an increase in the body's iron stores [50, 51].

As for dosimetry of neutron applications, it is necessary to calculate the neutron absorbed dose and the neutron effective dose to different organs, since direct measurement of these quantities in the human body is impossible.

In conclusion, neutrons applications in treatment and in diagnosis have many advantages as compared to other radioactive applications but they need proper equipment that are available only in few medical centers.

The authors declare that they have no conflicts of interest.

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