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PROSPECTS OF NEUTRON CAPTURE SYNOVECTOMY AT THERMAL NUCLEAR REACTORS

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Evaluative dose calculations were performed for the irradiation of a human knee-joint with neutrons at a horizontal channel of the WWR-M nuclear research reactor. It was shown that therapeutic dose of 100 Sv, necessary for the destruction of a pathological synovial membrane of an inner joint capsule at Reumatoid Arthritis, can be delivered in several minutes if a boron compound is injected into the capsule before irradiation. Evaluated doses on other tissues of a joint were found to be one order of magnitude lower than permissible levels. Neutron filters and reflectors are supposed to be used for forming necessary neutron spectrum and obtaining adequate neutron flux at the irradiation position. The calculations were done by the Monte Carlo method on the assumption that the content of ^{10}B in a synovial membrane was 1,9 %. From the results obtained a conclusion was drawn about the possibility of creation of an irradiating facility for Neutron Capture Synovectomy (NCS) on the basis of the nuclear research reactor with no alterations in its construction or operating mode.

Introduction

NCS was proposed as an alternative method for treating Reumatoid Arthritis (RA) [1]. RA is a painful infectious disease affecting joints. When RA happens, an inner membrane of a joint capsule, which is called synovium, becomes inflamed and grows thick up to 1,0 - 1,5 cm (normally it is 1 - 2 layers of cells). At the same time excrescences appear on the inner surface of a synovium, joint components degrade, and the joint loses its function. RA proceeds very painfully and it is often a reason for disablement. Up to 3 % of population suffers from this disease and for the most part its conservative treatment is ineffective. The usual way out is a surgical ablation of a synovium, which is called synovectomy. The operation is extremely traumatic, and, as a rule, a recurrence follows in 2 - 5 years. Radiation synovectomy presents an alternative method [2], where synovium is destructed by β-radiation of radioactive liquid injected into a joint. Possible proliferation of the radioactivity over a body through lymph and blood flows is an evident disadvantage of the method. Because of this, it is under a ban in some countries, for example, in USA.

In NCS destruction of a synovium is achieved as a result of the irradiation of a joint by neutrons after a medication, containing stable isotopes with high neutron cross section, is injected into a joint capsule. Destructive radiation effect is produced by high-energy charged particles, the products of nuclear reactions. Ordinarily $^{10}B(n, \alpha)^{7}Li$ reaction is employed, where α-particle and ^{7}Li recoil nucleus with a total kinetic energy of 2,33 MeV are produced. The use of compounds containing ^{157}Gd is also promising because of the record capture cross section (255000 barns) of the isotope and high yield of conversion (0,69), Auger and Coster-Kronig (4,93) electrons per capture [3]. One may hope that with NCS it would be possible to treat patients without a traumatic operation and injection of radioactive substances into their organisms.

Although NCS is based on the same principles as neutron capture therapy (NCT), a well- known method for curing brain tumors [4], there are some essential differences between them, which are associated with distinctions in anatomy and physiology of joints and brain. Firstly, the tissues to be irradiated in NCS are located relatively close (~1 cm) to the skin surface, whereas NCT is applied for treating tumors on depths up to 8 cm. Secondly, a direct injection of a boron containing medication into a joint is possible, hence much higher (about 500 times) concentration of boron in a synovium than in malignant cells of brain is achievable. Thirdly, joints are located far from vital organs, and they are less radiosensitive and more toxic resistant than brain. Fourthly, wide neutron beams are suitable for NCS where a joint is irradiated as a whole, whereas NCT requires application of narrow beams since only a small part of a head usually needs radiation treatment. Fifthly, in NCT the selectivity of uptake of neutron capture agents is usually referred to their ability to accumulate in malignant and not to accumulate in benign cells of the same type, whereas in NCS it is a question of accumulation in different tissues. Thus, in principle, one could expect achieving higher uptake selectivity of neutron capture agents in a synovium than in the malignant brain cells. All these, on the one hand, make easier the selection of a boron carrier compound in NCS, and, on the other hand, enables creating a neutron source for NCS in such nuclear facilities, where the construction of a neutron source for NCT encounters definite technical and economical difficulties.

At present NCS is on the stage of laboratory research. This method is being actively developed at the Department of Nuclear Engineering and Whitaker College of Health Sciences, Massachusetts Institute of Technology, USA, with the participation of specialists from other US institutions and laboratories. For the needs of NCS a neutron source was developed [5] on the basis of 4,1 MeV tandem accelerator with deuteron current 1 mA at a Be target. In the present work we are going to evaluate capabilities and practical value of the method for the case of using thermal nuclear reactor as a neutron source.

Employed model and approach

Dose calculations were carried out for a model of NCS irradiation unit as if it were installed at one of the horizontal beams of Kiev nuclear research reactor WWR-M. This is a pool-type reactor with thermal power 10 megawatts and in-core neutron flux about 10^{14} cm$^{-2}\cdot$ s^{-1}. The reactor core is surrounded by a beryllium reflector with external diameter 93,6 cm. 10 radial horizontal channels with internal diameters 10 or 6 cm diverge from the core. The channels begin from the side surface of the core or from various depths in the reflector, pass through a water tank and concrete biological shielding and end by shutters. External ends of the channels are located at 365 cm distance from the center of the reactor core.

Calculations were performed for a model of NCS irradiation unit, whose scheme is shown in Figure, *a*. It is assumed that the horizontal beam has 10 cm diameter and begins at the external surface of the reactor core. A joint being irradiated is located 40 cm far from the outlet of the channel. On sides and from behind a joint is surrounded by additional reflectors made of carbon, lead and nickel. A vertical cylinder with 10 cm diameter and 23 cm height represents a joint. The external layer is skin, the next one is synovium (both are 3 mm thick). The rest of a joint volume is filled with bone tissue. Although the accepted model of a joint is rather simple, we consider it sufficient for making evaluative dose calculations.

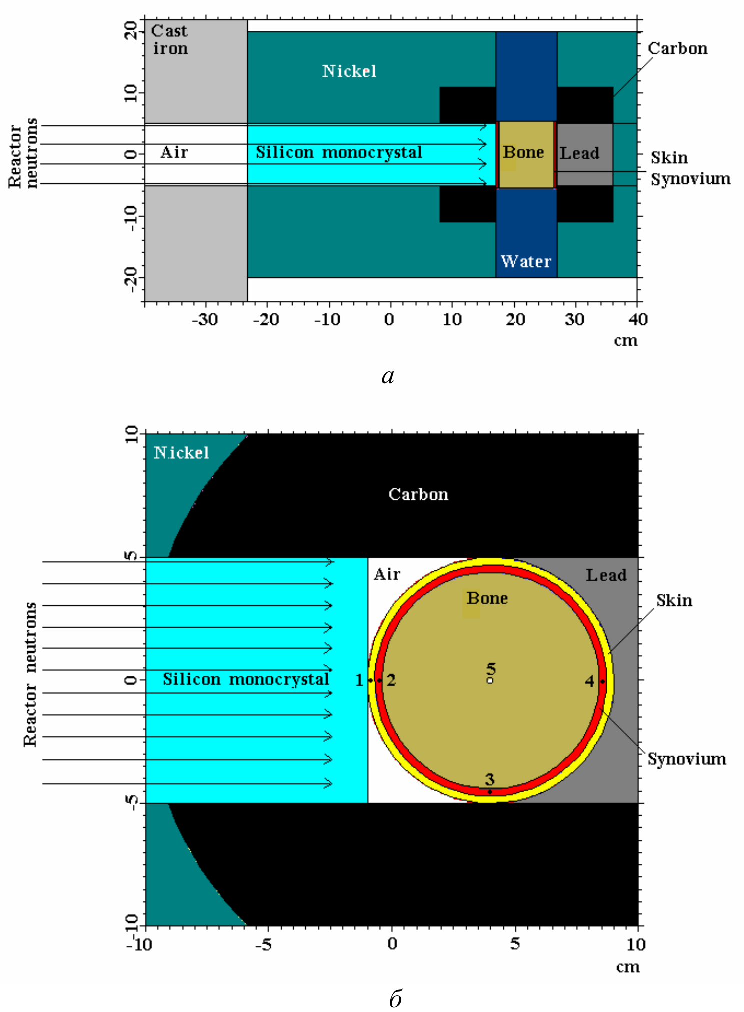
Elemental compositions for skin and bone tissues were taken from [6]. It was assumed that synovium has the same composition as skin but with addition of 1,9 mas. % of ^{10}B. This is very high concentration, which is unreachable in brain tumors. But according to the experimental data obtained with laboratory animals [7, 8], it is possible to achieve and keep such concentration of boron in a synovial membrane for a relatively long period of time (at least 25 min).

A typical thermal reactor spectrum [9] was taken for neutrons coming out from the reactor core. Contributions of different spectrum components were as follows: thermal neutrons ($E < 0{,}1$ eV) – 22 %, epithermal neutrons ($0{,}1$ eV $\le E < 10$ keV) – 49 %, fission neutrons (10 keV $\le E < 20$ MeV) – 29 %. Total neutron flux at the core surface was evaluated based on the measurements in the beryllium reflector [10], which yielded $3 \cdot 10^{13}$ cm$^{-2}\cdot$ s^{-1}. The spectrum of the gamma-rays emerging from the reactor core (primary gamma-rays) was taken from the experimental work [11]. The gamma-ray flux was evaluated to be $7{,}6 \cdot 10^{13}$ cm$^{-2}\cdot$ s^{-1}.

To obtain recommendations for optimal spectrum of neutrons incident upon a joint, preliminary calculations with a monoenergy neutron source ($E = 0{,}025$ eV, 10 keV and 1 MeV) were carried out. The obtained results showed that when a joint is irradiated in wide beam geometry and in the presence of reflectors on its sides and from behind, the highest reaction rate on ^{10}B (at depths up to 1 cm) per one neutron incident upon a joint is predicted for incident thermal neutrons. It must be pointed out that in this respect the situation differs from that in NCT, where epithermal neutrons known to be an optimal choice for irradiating deep brain tumors in narrow beam geometry.

To reduce the fraction of fission neutrons in the incident beam, which can cause an overirradiation of the skin, it was decided to pass the reactor neutrons through 40 cm long single-crystal silicon placed just before a joint (see Figure, *a*). The idea is to use the advantage of difference in peculiarities of the interaction of thermal and above-thermal neutrons with a crystal lattice to form necessary spectrum of incident neutron flux. It is well known that thermal neutrons interact with a periodic structure of "fixed" atoms mainly by a coherent scattering (reflection) on the crystal plates. The scattering takes place only for particular energies of neutrons, which fulfill the Bragg's condition, while neutrons with other energies are "freely" (if neglecting by absorption) transported through a crystal. For neutrons with energies above ~ 0,1 eV the coherent effects become negligible and all the neutrons undergo scattering irrespective of their energy. Thus, the overall effect of a single-crystal filter on the incident neutron flux can be expressed roughly as removal (mainly as a result of scattering) of neutrons with energies higher than 0,1 eV.

Calculations were performed with the use of the Monte Carlo computer code MCNP-4c [12], which is widely applied for making such type of evaluations [13]. A KERMA approach was used based on a point detector tally F5 and multiplier cards FM –1 –4 and FM –5 –6, representing stan-



Model geometry of a NCS irradiation unit in one of horizontal channels of WWR-M nuclear research reactor:
a - cross-section by a vertical plane; *b* - cross-section by a horizontal plane.
Figures indicate numbers of points where doses were evaluated.

Calculated total and partial dose rates in different points of a joint, Sv/hr

Tissue	Skin	Synovium			Bone
Point number	1	2	3	4	5
Thermal neutrons (E < 0,1 eV)	3,1	4756,0	440,0	31,4	2,6
Epithermal and fast neutrons (E > 0,1 eV)	7,2	273,6	172,0	64,4	2,1
Primary γ-rays	21,1	21,0	17,8	14,0	17,0
Secondary γ-rays	0,66	0,87	0,50	0,27	0,42
Total	**32,1**	**5051,5**	**630,3**	**110,1**	**22,1**

dard heating functions for neutrons and photons respectively. To convert to equivalent doses, RBE-factors 4, 3,8 and 1,0 were applied for $^{10}B(n, \alpha)^7Li$ reaction products, neutrons and photons respectively [5].

Since MCNP-4c does not consider peculiarities of the neutron transport in crystalline structures, the attenuation of thermal neutron flux in the single-crystal silicon filter was considered deterministically by applying a damping factor. Its value (0,285) was evaluated assuming that the attenuation is occurred mostly due to the capture on silicon nuclei (thermal cross section 168 mb). Thermal neutron transport outside the filter as well as transport of epithermal and fission neutrons, primary and secondary photons in the whole problem geometry were considered on the basis of a consistent Monte Carlo approach realized in MCNP-4c.

Results and discussion

Dose rates were calculated in different tissues (skin, synovium, bone) of a joint as indicated in Figure, *b*. Doses in synovium were evaluated in three points – on the front, on the side, and from the rear of a joint. Total dose rate and partial contributions from thermal, epithermal and fission neutrons, as well as from primary and secondary gamma-rays were evaluated. The results are summarized in Table.

Maximum dose rate of about 5000 Sv/hr is predicted for a part of a synovial membrane, which is located near to the front side of a joint hit by the incident neutron beam. From this estimate one may readily deduce that a therapeutic dose of 100 Sv in this part of a synovial membrane can be accumulated in 1,2 min, which can be considered as more than acceptable irradiation time. At the same time the dose on skin is predicted to be about 0,64 Sv that is acceptable as well (maximum permissible dose is 8 Sv). This dose can be even more reduced, for example, by increasing the length of a silicon filter. In fact, according to the performed evaluations, addition of another 40 cm long silicon single-crystal would reduce the skin dose at least by a factor of two.

Dose rates in the other parts of synovium are 8 - 45 times lower if compared with that near the front side of a joint. Therefore it seems to be advisable to change orientation of a joint during the irradiation with respect to the direction of the incident neutron beam to obtain necessary spatial dose distribution within pathological synovial membrane. In this respect the combination of the NCS with computer tomographic imaging system would be useful for providing an efficient and optimal treatment to a patient.

It must be pointed out that the obtained estimates are preliminary and require refinements. Both joint and irradiation unit models need more detailed elaboration and optimization. As a continuation of this research we plan to perform variety of calculations with various combinations of filters, moderators and reflectors, their geometry, dimensions and composition. At the same time the obtained estimates do show the principal possibility of the employment of thermal reactor neutrons for the purposes of NCS. It must be pointed out that the creation of a NCS irradiation unit at one of the horizontal beams of the nuclear research reactor does not require significant investments, labor efforts or re-construction of the facility, unlike it is in case of the NCT [14].

Conclusions

A principal possibility of creation of an NCS irradiation unit on the basis of a 10 megawatt WWR nuclear research reactor was demonstrated based on the Monte Carlo calculations with the use of MCNP-4c code. The obtained evaluations showed that using an appropriately configured irradiation unit installed at the outlet of a horizontal channel a therapeutic dose of 100 Sv could be delivered to a pathological synovial membrane of an articular capsule in several minutes. The dose in skin turned out to be several tens times less than the maximum permissible value. The main features of the unit construction are the use of reflectors and single-crystal silicon filter, forming a required spectrum of neutrons incident upon a joint.

The unit can be used for both patient treatment and research purposes. Its creation will not require alteration of neither reactor construction nor its technological regime and it can be done within a moderate budget. Obviously, the same facility could be applied for treating other painful illnesses, such as skin melanoma, malignant bone tissue neoplasms and, perhaps, some urological diseases.

As a concluding remark it must be noted that putting NCS into practice requires solving another actual problem, connected with the choice of an appropriate neutron capture agent compound. As it was shown in the model experiments [15], the destruction of a synovium in NCS is often accompanied by an undesired effect, which is the damage of a joint cartilage as a result of penetrating of neutron capture agent into the cartilage tissue. For example, this fact made it impossible a clinical application of compound $K_2B_{12}H_{12}$, which was considered as the most promising among tested agents. Therefore search of new suitable agents is of great importance and it can be done only within a co-operative research of specialists working in different fields of science, such as physics, medicine, biology, and chemistry. Presence of such specialists in Kiev constitutes a favorable ground for the development and practical application of the NCS method on the basis of the WWR-M nuclear research reactor of the Institute for Nuclear Research of the NAS of Ukraine.

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ПЕРСПЕКТИВИ НЕЙТРОНОЗАХВАТНОЇ СИНОВЕКТОМІЇ НА ТЕПЛОВИХ ЯДЕРНИХ РЕАКТОРАХ

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Виконано оціночні розрахунки доз при опроміненні нейтронами колінного суглоба людини на горизонтальному каналі реактора ВВР-М. Показано, що терапевтична доза 100 Зв, яка необхідна для радіаційного руйнування патологічної синовіальної мембрани суглобної сумки, може бути накопиченою за кілька хвилин при умові введення перед опроміненням у суглобну сумку сполуки бору. Оцінені дози на інших тканинах суглобу виявились на порядок нижче допустимих величин. Припускалось, що для формування спектра випромінювання й досягнення необхідного потоку нейтронів на місці опромінення будуть використані нейтронні фільтри та додаткові нейтронні відбивачі. Розрахунки було виконано методом Монте-Карло у припущенні, що концентрація ізотопу ^{10}B у синовіальній мембрані становить 1,9 %. За результатами розрахунків зроблено висновок про можливість створення установки для нейтронозахватної синовектомії на базі дослідницького ядерного реактора без внесення змін у його конструкцію та технологічний режим.

ПЕРСПЕКТИВЫ НЕЙТРОНОЗАХВАТНОЙ СИНОВЕКТОМИИ НА ТЕПЛОВЫХ ЯДЕРНЫХ РЕАКТОРАХ

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Выполнены оценочные расчеты доз при облучении нейтронами коленного сустава человека на горизонтальном канале реактора ВВР-М. Показано, что терапевтическая доза 100 Зв, необходимая для радиационного разрушения патологической синовиальной мембраны суставной сумки, может быть накоплена за несколько минут при условии введения перед облучением в суставную сумку соединения бора. Оцененные дозы на других тканях сустава оказались на порядок ниже допустимых величин. Предполагалось, что для формирования спектра излучения и достижения необходимого потока нейтронов на месте облучения будут использованы нейтронные фильтры и дополнительные нейтронные отражатели. Расчеты были выполнены методом Монте-Карло в предположении, что концентрация изотопа ^{10}B в синовиальной мембране составляла 1,9 %. По результатам расчетов сделан вывод о возможности создания облучательной установки для нейтронозахватной синовектомии на базе исследовательского ядерного реактора без внесения изменений в его конструкцию и технологический режим.

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