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Dose evaluation of boron neutron capture synovectomy using the THOR epithermal neutron beam: a feasibility study

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Abstract

Rheumatoid arthritis is one of the most common epidemic diseases in the world. For some patients, the treatment with steroids or nonsteroidal anti-inflammatory drugs is not effective, thus necessitating physical removal of the inflamed synovium. Alternative approaches other than surgery will provide appropriate disease control and improve the patient's quality of life. In this research, we evaluated the feasibility of conducting boron neutron capture synovectomy (BNCS) with the Tsing Hua open-pool reactor (THOR) as a neutron source. Monte Carlo simulations were performed with arthritic joint models and uncertainties were within 5%. The collimator, reflector and boron concentration were optimized to reduce the treatment time and normal tissue doses. For the knee joint, polyethylene with 40%-enriched Li_2CO_3 was used as the collimator material, and a rear reflector of 15 cm thick graphite and side reflector of 10 cm thick graphite were chosen. The optimized treatment time was 5.4 min for the parallel-opposed irradiation. For the finger joint, polymethyl methacrylate was used as the reflector material. The treatment time can be reduced to 3.1 min, while skin and bone doses can be effectively reduced by approximately 9% compared with treatment using the graphite reflector. We conclude that using THOR as a treatment modality for BNCS could be a feasible alternative in clinical practice.

1. Introduction

Around the world, 3% of the total population (Pandey *et al* 2001) and 5% of the people in Taiwan (DOH 2006) suffer from rheumatoid arthritis, which causes inflammation of the synovial membrane (synovium) and leads to great pain in the affected joints. For most patients, there is no permanent cure. Symptomatic relief, therefore, becomes a primary aim to avoid deformation of the diseased joint and to achieve better quality of life. The treatment with steroids or nonsteroidal anti-inflammatory drugs (NSAIDs) for most patients is effective. However, for some patients, their joints do not respond to these drugs (Fleming *et al* 1976). Physical removal of the synovium is thus necessary to preserve the mobility of the inflamed joint.

Synovectomy can be done by arthroscopy, surgical operation or radiation therapy. Radiation synovectomy using intra-articular injection of beta-emitting radioisotopes has proven to be an effective alternative for killing macrophages, thus terminating the inflammation mechanism (Hosain *et al* 1990, Kresnik *et al* 2002). Studies indicate that the success rate reaches 72–81% (Zuckerman *et al* 1987), and this percentage could be even higher if ideal candidates are selected (Pelosi *et al* 2004). However, the potential problems regarding the leakage of beta emitters and the continuous exposure during the effective half-life of radioisotopes may increase the risk of cancer (Davis and Chinol 1989, Klett *et al* 1999). Consequently, the use of radiation synovectomy has been limited in the United States.

Boron neutron capture synovectomy (BNCS), which uses an epithermal neutron beam with the $^{10}B(n,\alpha)^{7}Li$ nuclear reaction, is a potential application for the treatment of rheumatoid arthritis. Similar to boron neutron capture therapy (BNCT), the alpha particle having high LET can deposit all its energy within an extremely short range to ablate the synovium without killing normal tissues. Recent studies have been conducted using an accelerator to produce a neutron beam (Yanch *et al* 1999, Gierga *et al* 2000). Different target reactions including $^{7}Li(p,n)$, $^{9}Be(p,n)$ and $^{9}Be(d,n)$ were investigated. After optimizing the neutron moderator, reflector and filter geometry of the beam line, it has been proven that accelerator-based BNCS appears to be feasible as a treatment modality for rheumatoid arthritis. Another neutron source for BNCS is based on the utilization of a ^{239}PuBe isotopic neutron source (Vega-Carrillo and Torres-Muhech 2002). Monte Carlo simulations were carried out to estimate the neutron spectra with different moderators (Vega-Carrillo and Manzanares-Acuña 2003). The results suggest that the polyethylene/D_2O moderator and neutron reflector should be used to increase the neutron field inside the knee.

The Tsing Hua open-pool reactor (THOR) in Taiwan was a 1 MW reactor. Since 1998, its neutron beam line has been used for animal studies related to BNCT drug developments (Liu and Teng 1998). Nowadays, THOR is upgraded for renovation of an epithermal neutron beam for BNCT exclusively and can be operated up to 2 MW (Liu *et al* 2004). The use of this beam line for BNCS requires further investigations because it differs considerably from BNCT in several aspects. In BNCT, boronated compounds are accumulated through the vascular system. The tumour/normal tissue boron concentration ratio is typically 4 using current boron-labelled pharmaceuticals (Liberman *et al* 2004). In contrast, in BNCS, the boron-labelled compounds are directly injected into the joint space. The synovium/adjacent tissue boron concentration ratio can thus exceed 1000 (Binello *et al* 1999). Moreover, the depth of a target treated by BNCT can be up to 8 cm in brain therapy, whereas the depth of an inflamed synovium in the knee treated by BNCS is only about 1 cm under the skin surface. The above factors result in different requirements of the neutron beam.

In this study, we attempted to evaluate the feasibility of using THOR for BNCS. Different configurations including the collimator, reflector and boron concentration were optimized

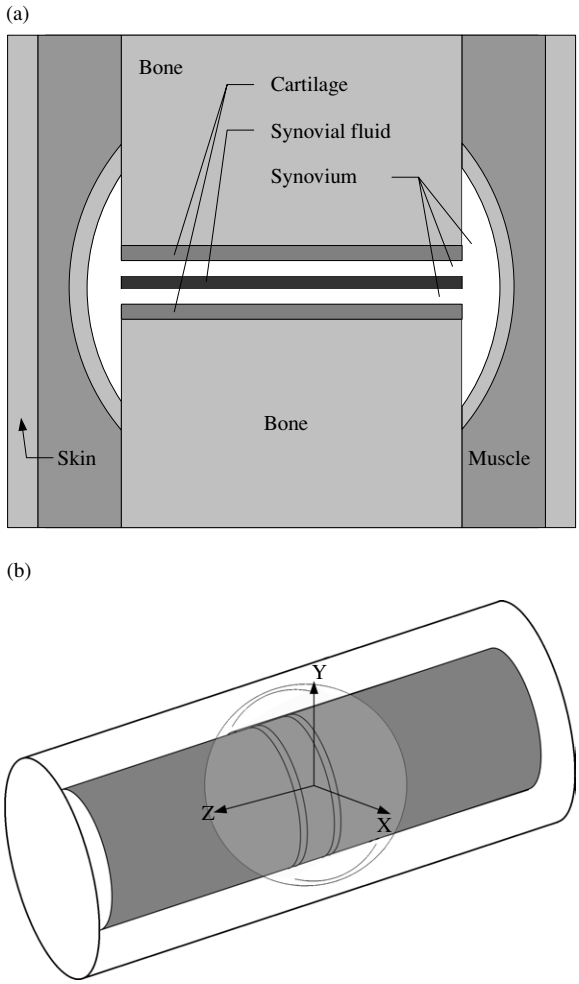

Figure 1. (a) Coronal section of the joint model and (b) its reference coordinates.

through Monte Carlo simulations. The treatment parameters of the estimated optimum configuration can be taken as reference for the clinical trial of BNCS conducted in the near future.

2. Materials and methods

2.1. Joint models

Arthritic joint models consisting of the skin, synovium, synovial fluid, cartilage, bone and muscle were created according to a patient's T1-weighted MR images. The elemental compositions of these tissues were taken from the ICRU Report No. 46 (ICRU 1992). The synovium and synovial fluid were modelled with the composition of blood. Figure 1 shows the coronal section of the joint model and its reference coordinates. For the knee joint, the diameter of the outer cylinder is 10 cm, and the thicknesses of the synovium, synovial fluid and cartilage are 0.5, 0.4 and 0.3 cm, respectively. For the finger joint, the size of the model

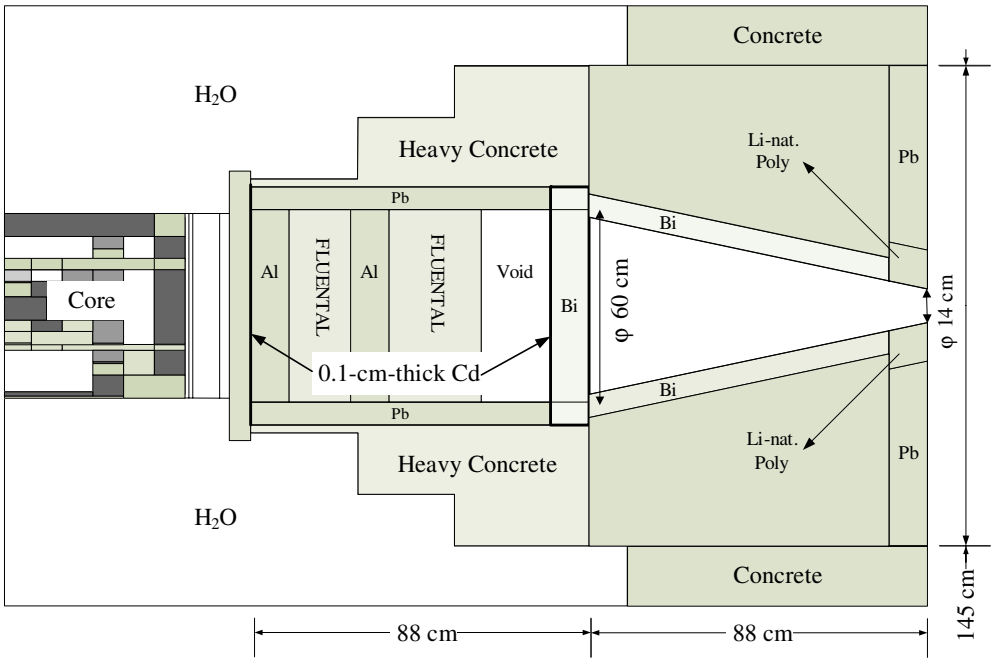

Figure 2. Beam design of THOR.

was scaled to 2 cm. Therefore, the synovium diminishes to 1 mm in thickness and 3 mm in depth.

2.2. Monte Carlo simulations

The Monte Carlo N-particle transport code 4C (MCNP 4C) (Briesmeister 2000) was employed to simulate the beam spectrum, knee joint, finger joint and other accessories. The cross sections were acquired from the ENDF/B-VI library (Hendricks *et al* 1994) and the neutron–photon mode was applied assuming that electrons deposit all their energy locally. The dose of the synovium and normal tissues was calculated by multiplying the flux with the kerma conversion factors (Caswell *et al* 1982). The standard deviations were generally within 5%. Owing to a significant decrease in the neutron flux caused by the neutron capture interaction, the effects of boron concentration were specifically considered to achieve more accurate dose estimation.

2.3. Beam design of THOR

The beam design of THOR is illustrated in figure 2, where the epithermal neutron flux is 1.7×10^9 n cm^{-2} s^{-1}, three times larger than the old beam design (Liu *et al* 2004). The joint model with ^{10}B concentration of 1000 ppm in the synovium was placed in front of the beam exit under the conditions of single and parallel-opposed irradiation. Different distances between the beam exit and joint model were considered.

2.4. Collimator optimization

The beam exit has a diameter of 14 cm (figure 2), which is generally larger than the size of the knee joint. Therefore, a collimator with a convergence angle of 22.4° was used to limit

the beam exit to a diameter of 10 cm, just covering the knee joint. Two different compositions of the collimators, including polyethylene (PE) with 25.79%-enriched Li_2CO_3 and with 40%-enriched Li_2CO_3, were compared under the condition of parallel-opposed irradiation.

2.5. Reflector optimization

Usually, the thickness of the knee joint is less than 15 cm. Adding an appropriate reflector around the knee could efficiently increase the neutron flux (Gierga *et al* 2000). We used graphite as the reflector material and estimated the effects of various thicknesses of the side and rear reflectors. The dimensions of the reflectors are $10 \times 10\ cm^2$, and the thickness ranges from 10 to 40 cm.

2.6. ^{10}B concentration optimization

The range of boron concentrations in the synovium was selected according to the *in vivo* experiments conducted by Yanch *et al* (1999). They found that only 265–950 ppm ^{10}B still remained in the rabbit synovium at 15 min post intra-articular injection of 5000 ppm boron. Therefore, we considered different ^{10}B concentrations in the synovium from 100 to 1000 ppm for the knee joint under the optimized configuration to evaluate the feasibility of BNCS using THOR.

2.7. Finger joint simulations

The finger joint with a 3 cm diameter collimator was simulated under the optimized configuration. Two convergence angles of collimators, including 22.4° used for the knee and 45.0°, were compared. By considering different depths of the synovium between the knee and finger models, polymethyl methacrylate (PMMA) was additionally used as the reflector material and compared with the graphite reflector.

2.8. Treatment parameters

The treatment parameters were selected according to two criteria: achievement of the minimum synovium dose and reduction of the normal tissue dose. From the clinical evaluations of radiation synovectomy (Deutsch *et al* 1993), the minimum synovium dose has to reach 100 RBE Gy to effectively ablate the synovium. With respect to normal tissues, the skin and bone doses were considered important. Radiation-induced skin erythema is a deterministic effect with a threshold of 8 RBE Gy (Nias 1990). Therefore, the skin dose must not exceed this level. In addition, radiation-induced bone cancer is a stochastic effect whose probability of occurrence increases in proportion to the magnitude of the dose received. Therefore, the bone dose has to be kept as low as possible.

Three figures of merit were used in this study, including the treatment time, therapeutic ratio of bone and skin dose. The treatment time (T) is the ratio of the minimum dose required for synovium to the minimum dose rate of synovium,

$$T = D_{\text{synovium}}/\dot{D}_{\text{syn}} = 100\,\text{RBE Gy}/\dot{D}_{\text{syn}}. \tag{1}$$

Tissue doses can then be calculated according to $D_{\text{tissue}} = T \times \dot{D}_{\text{tissue}}$, where $\dot{D}_{\text{tissue}}$ is the maximum dose rate of the tissue. Moreover, the therapeutic ratio is defined by

$$TR_{\text{tissue}} = \frac{D_{\text{synovium}}}{D_{\text{tissue}}}. \tag{2}$$

Table 1. Treatment parameters for single beam and parallel-opposed beams at various distances without collimators and reflectors.

	Single beam			Parallel-opposed beams		
Distance (cm)	0	5	10	0	5	10
TR_{skin}	26.1	25.6	23.0	76.8	75.8	71.7
TR_{bone}	28.6	29.1	26.4	74.3	74.6	71.1
Skin dose (RBE cGy)	383	390	435	130	132	139
Bone dose (RBE cGy)	349	343	379	135	134	141
Treatment time (min)	9.8	12.1	16.1	5.1	6.3	8.1

For the skin, this ratio must be larger than 12.5 according to the threshold of the acute radiation syndrome, whereas for the bone it should be kept as large as possible to minimize the probability of the chronic effect of ionizing radiation. Note that the relative biological effectivenesses (RBEs) used in this study for photon, neutron and ^{10}B reactions are 1.0, 3.8 and 4.0, respectively (Gierga *et al* 2000).

3. Results and discussion

The treatment parameters for single beam and parallel-opposed beams without collimators and reflectors are listed in table 1, where the boron concentration is assumed to be 1000 ppm. For the parallel-opposed beams, the treatment time was reduced by nearly half compared with that needed for the single beam because more uniform dose distribution in the synovium is achieved. Figure 3 shows the dose-rate volume histograms, indicating that parallel-opposed irradiation can increase the dose-rate coverage of the synovium. Although the dose rates of normal tissues are increased as well, the tissue doses can be decreased due to the shortening of treatment time. Table 1 also shows that when we increased the distance between the beam exit and knee joint model, the required treatment time was prolonged and the skin dose was increased.

The treatment parameters for parallel-opposed beams with different collimators are given in table 2, where the ^{10}B concentration is 1000 ppm. The treatment time for both collimators was increased by approximately 1 min because inserting a collimator will inevitably increase the distance between the original beam exit and knee joint. For this reason, the maximum epithermal neutron flux decreases by a factor of 0.25. The collimator 2 (PE with 40%-enriched Li_2CO_3) and collimator 1 (PE with 25.79%-enriched Li_2CO_3) achieved similar skin and bone doses. This contradicts Gierga's results. Their data show that the ^{6}Li thermal neutron filter placed at the moderator exit removes not only thermal neutrons but also epithermal neutrons, leading to prolonging the treatment time. In our simulations, ^{6}Li was only added in the collimators to remove the thermal neutrons. The effects on the epithermal neutrons are relatively small. Therefore, the treatment times for both collimators are similar.

We compared the treatment time, therapeutic ratio of bone and skin dose for the side and rear reflectors of different thicknesses. When a 10 cm side reflector was used alone, the treatment times were reduced to 8.2 min and 4.3 min for the single and parallel-opposed beams, respectively. When a 15 cm rear reflector was used alone, the treatment times were reduced to 8.5 min and 4.8 min, respectively. Once the thicknesses of the side and rear reflectors exceed the above levels, no further improvement can be found. Both reflectors significantly elevated the therapeutic ratio of bone and reduced the skin dose for the single-beam irradiation, whereas

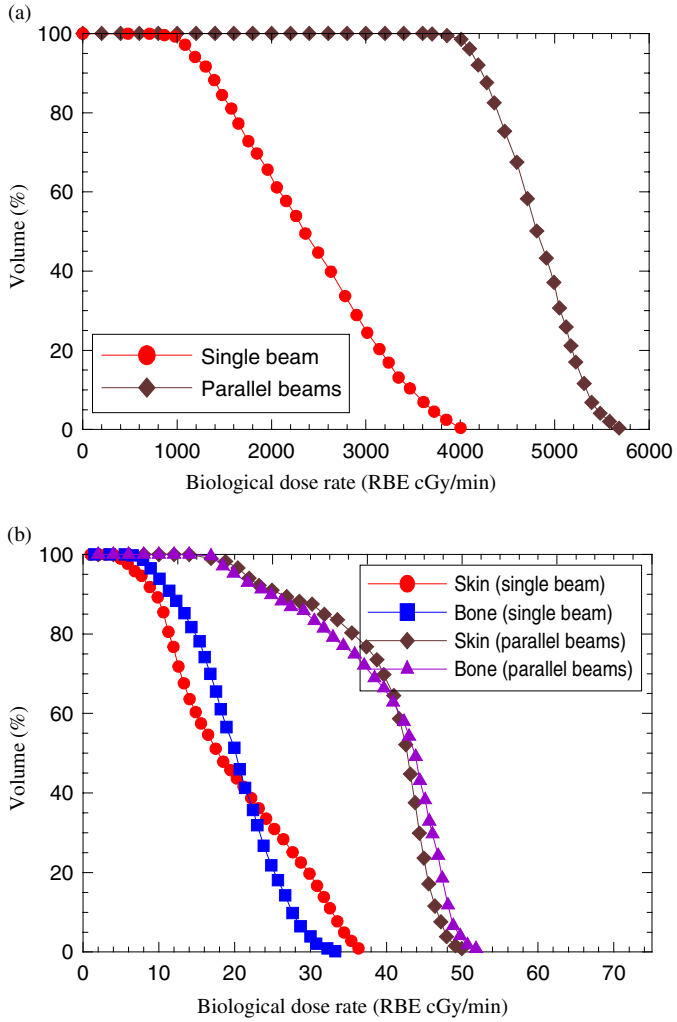

Figure 3. Dose-rate volume histograms of (a) the synovium and (b) normal tissues.

Table 2. Treatment parameters for parallel-opposed beams with different collimators at the ^{10}B concentration of 1000 ppm.

Type of collimators	Collimator 1 (PE+25.79%-enriched Li_2CO_3)	Collimator 2 (PE+40.0%-enriched Li_2CO_3)
TR_{skin}	71.9	74.1
TR_{bone}	76.5	78.0
Skin dose (RBE cGy)	139	135
Bone dose (RBE cGy)	131	128
Treatment time (min)	6.0	6.0

the effects were not significant for the parallel-opposed beams. Note that this optimization leads to similar results as those presented by Gierga *et al*.

Table 3. Treatment parameters for various ^{10}B concentrations in the synovium under the optimized configuration.

Boron concentration (ppm)	100	200	400	600	800	1000
TR_{skin}	12.6	23.3	41.2	55.2	65.4	73.2
TR_{bone}	12.8	23.3	42.0	55.4	61.9	71.0
Skin dose (RBE cGy)	795	429	243	181	153	137
Bone dose (RBE cGy)	779	428	238	180	162	141
Treatment time (min)	26.5	14.9	8.9	6.9	5.9	5.4

Table 4. Treatment parameters for the finger joint. The optimized configuration was used with various convergence angles of collimators.

Convergence angle of collimators	22.4°	45.0°	45.0°[a]
TR_{skin}	58.6	72.4	80.0
TR_{bone}	55.8	69.6	74.9
Skin dose (RBE cGy)	171	138	125
Bone dose (RBE cGy)	180	144	134
Treatment time (min)	6.3	4.3	3.1

[a] PMMA was used as the reflector material.

Different ^{10}B concentrations in the synovium under the optimized configuration, that is the parallel-opposed beam irradiation, PE with 40%-enriched Li_2CO_3 collimator, 15 cm thick rear reflector and 10 cm thick side reflector, were simulated. The treatment parameters are shown in table 3. As the concentration increased, the treatment time, skin dose and bone dose were reduced. This downward trend indicates that if higher concentration of the boronated compound is administered, the treatment parameters could be further improved. At 100 ppm, the skin dose almost reached the threshold of 800 RBE cGy for skin erythema. The ^{10}B concentration below this level should not be administered owing to the deterministic effect of the skin induced.

Table 4 lists the treatment parameters for the finger joint, where the optimized configuration was used with various types of 3 cm diameter collimators. The treatment time of the collimator with a convergence angle of 22.4° for the finger joint was longer than that for the knee joint because the collimator used for the former is longer. If we further increase the convergence angle from 22.4° to 45.0°, the length of the collimator can be shortened to 5.5 cm, reducing the time consumed to 4.3 min. Better therapeutic ratios and lower normal tissue doses can be achieved as well. Table 4 also shows that using PMMA as the reflector material further reduces the treatment time by 28%, while skin and bone doses are reduced by approximately 9% compared with treatment using the graphite reflector. This is mainly because the ^{1}H in PMMA can effectively reflect the neutrons with lower energy, which significantly contributes the dose to the synovium near the skin.

Table 5 compares the treatment parameters for the knee joint and finger joint using THOR as the neutron source with the results obtained using accelerator-based neutron beam lines constructed at the Laboratory for Accelerator Beam Applications (LABA) (Gierga *et al* 2000). Under both the optimized configurations, our results are superior or comparable to their data. We believe this could be due to more forward neutrons and fewer fast and thermal neutrons present in the energy spectrum. Moreover, less γ-ray contamination could also reduce the skin and bone doses effectively. Other possible reasons causing the differences between THOR and

Table 5. Comparison of treatment parameters using THOR and LABA's accelerator-based beam lines as neutron sources.

	Knee joint		Finger joint	
Neutron source	THOR	4.0 MeV ^{9}Be(p,n)[a]	THOR	4.0 MeV ^{9}Be(p,n)[a]
TR_{bone}	71.0	73.0	74.9	62.0
Skin dose (RBE cGy)	137	203	125	161
Treatment time (min)	5.4	7.3	3.1	3.6

[a] The results were based on 1 mA current of LABA's beam line (Gierga *et al* 2000).

LABA's results include flux to dose kerma factors and geometric differences in the phantom models. Note that the results of LABA were based on 1 mA accelerator current. Higher accelerator currents could lead to shorter treatment times.

In this study, the RBE values applied in dose calculations are commonly used for BNCT. Further investigations should focus on determining these values according to the THOR epithermal neutron beam with the specific end point for BNCS. In addition, dose measurement in the clinical trial is essential, by which we can further verify the accuracy of dose estimation.

4. Conclusions

In this research, we used Monte Carlo simulations to evaluate the feasibility of using the epithermal neutron beam of THOR as the neutron source for BNCS. After optimizing the collimator, reflector and boron concentration, the treatment time for the knee joint was less than 5.5 min, the skin dose was far less than the dose limit of deterministic effects and the bone dose was minimized. For the finger joint, when PMMA was used as the reflector material, the treatment time can be less than 3.5 min, and both skin and bone doses can be effectively reduced. We conclude that using THOR as a treatment modality for rheumatoid arthritis appears to be a feasible alternative in clinical practice.

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