Original Article

Investigation of Dose Distribution in Mixed Neutron-Gamma Field of Boron Neutron Capture Therapy using N-Isopropylacrylamide Gel

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ABSTRACT

Gel dosimeters have unique advantages in comparison with other dosimeters. Until now, these gels have been used in different radiotherapy techniques as a reliable dosimetric tool. Because dose distribution measurement is an important factor for appropriate treatment planning in different radiotherapy techniques, in this study, we evaluated the ability of the N-isopropylacrylamide (NIPAM) polymer gel to record the dose distribution resulting from the mixed neutron-gamma field of boron neutron capture therapy (BNCT). In this regard, a head phantom containing NIPAM gel was irradiated using the Tehran Research Reactor BNCT beam line, and then by a magnetic resonance scanner. Eventually, the R_2 maps were obtained in different slices of the phantom by analyzing T2-weighted images. The results show that NIPAM gel has a suitable potential for recording three-dimensional dose distribution in mixed neutron-gamma field dosimetry.

1. Introduction

Boron neutron capture therapy (BNCT) is a chemically targeted radiotherapy that uses the high neutron capture cross section of ^{10}B at thermal neutron energies to achieve a preferential dose increase within the tumor volume. In this radiotherapy technique, boron is first selectively accumulated in the tumor cells by a tumor-specific boron carrier, and then the patient is exposed with a neutron beam from a nuclear reactor or an accelerator. A variety of boron delivery agents have been investigated to date, including amino acids, porphyrins, nanoparticles, polyamines, biochemical precursors, DNA-binding agents, sugars, anti-sense agents, peptides, proteins, monoclonal antibodies, and

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liposomes. However, there are only two boron delivery agents available for clinical BNCT trials for malignant glioma: ^{10}B-enriched boronophenylalanine and biodistribution of sodium borocaptate. These drugs are distributed through passive diffusion from the blood to tumor tissues via the disrupted blood−brain barrier. The boron concentration in a normal brain with an intact blood−brain barrier remains minimal, whereas the tumor ^{10}B concentration is related to both the tumor vessel density and the blood ^{10}B level [1].

In BNCT, the energy of the neutron beam is chosen with respect to the depth of the tumor. Thus, for treating superficial tumors such as melanoma and meningioma, a thermal neutron ($E < 0.5$ eV) or a mixed thermal−epithermal neutron beam is used, whereas epithermal neutron beams (0.5 eV $< E < 10$ keV) are used for the treatment of deep-seated tumors such as glioblastoma multiforme. Epithermal neutrons are thermalized in tissue, and when they reach the boron-labeled tumor cells, their capture reaction probability by ^{10}B isotopes is thus increased. This reaction produces alpha and lithium particles that have high linear energy transfer and release their energy at the cellular level. In addition to the dose resulting from the boron neutron capture reaction, there are three other dose components in BNCT [2]:

1. The gamma dose from neutron beam and ^{1}H(n_{th}, γ)^{2}H reaction
2. The dose resulting from thermal neutron capture in nitrogen [^{14}N(n_{th}, p)^{14}C]
3. Fast and epithermal neutrons dose from the ^{1}H(n,n')^{2}H reaction

As with other radiotherapy techniques, the goal of BNCT is to deliver the maximum dose to the tumor and the least dose to the normal healthy tissue for obtaining a high cure rate and limiting radiation toxicity. This goal necessitates the measurement of radiation dose and exact knowledge of radiation effects. Therefore, understanding the radiation field characteristics through measurement of the radiation dose at the desired location of the body is very important. Radiation dosimetry is a process to quantitatively measure the energy deposited in various organs using dosimetric systems with the highest level of accuracy. Dosimetry for BNCT is much more complicated than other radiotherapies because of the various dose components with different relative biological effectiveness. Commonly in the clinical dosimetry of BNCT, the dose from thermal neutron reactions with ^{14}N and ^{10}B is calculated using the kerma approach, after measuring the thermal neutron flux using the neutron activation technique [2]. Moreover, the dose resulting from fast and epithermal neutrons and photons are determined using the dual ionization chamber technique as described in International Commission on Radiation Units (ICRU) Report 45 [2]. These techniques have several drawbacks [3]:

1. These methods are very time consuming.
2. Thermal neutron and boron doses are not measured directly, and the measured thermal neutron flux should be multiplied by the appropriate kerma coefficient for dose evaluation.
3. At least two dosimetry methods are required for calculation of total absorbed dose.
4. Ionization chambers require several correction factors.

To date, numerous studies have been conducted to overcome these drawbacks and improve the absorbed radiation dose measurement in BNCT. In this context, several dosimeters have been evaluated for acceptable application in BNCT dosimetry, considering all advantages and disadvantages, including GafChromic films, Thermoluminescent Dosimeters (TLDs), alanine detectors, and gel dosimeters [3−6]. The radiation-sensitive gels have unique advantages in comparison with other dosimeters. In general, they are tissue equivalent phantom dosimeters capable of measuring three-dimensional (3D) dose distributions with high spatial resolution [7]. To date, several attempts have been made to use gel dosimeters in BNCT dosimetry [8−13]. The results of such studies indicate that dosimeters have significant potential for dose measurement in BNCT.

The main objective of this study is to evaluate the potential of N-isopropylacrylamid (NIPAM) gel for recording the 3D dose distribution in Tehran Research Reactor (TRR) BNCT beam line. In this regard, NIPAM gel was irradiated with the neutron beam in an acrylic ellipsoidal head phantom and then imaged by a magnetic resonance (MR) scanner. Subsequently, the T2-weighted images were obtained from different slices of the phantom containing the gel. These images were analyzed using the Matlab software in order to extract the relaxation rate (R_2) values. Finally, it was shown that NIPAM gel as a 3D dosimeter has suitable potential for applying in the mixed neutron-gamma field of BNCT.

2. Materials and methods

2.1. Gel preparation

A NIPAM gel dosimeter was prepared using the method proposed by Senden et al [14], inside of a fume hood, and under normal atmospheric conditions. According to this method, gelatin (300 Bloom Type A; Sigma-Aldrich) was added to 80% of deionized water. While the gelatin was dissolving, the temperature was increased to 50°C, and then N-N′-methylene-bis acrylamide (BIS) (Sigma-Aldrich) was added to the solution as a crosslinker agent for the radiation-induced polymerization process. Following BIS, N-isopropylacrylamide (NIPAM; Sigma-Aldrich) was added to the gelatin−BIS mixture after cooling the temperature down to 37°C. When the monomers were completely dissolved, a solution of the antioxidant tetrakis(hydroxymethyl)phosphonium chloride (THPC) with the remaining water was prepared, and added to the solution at 35°C. All chemicals were sourced from Sigma-Aldrich, and

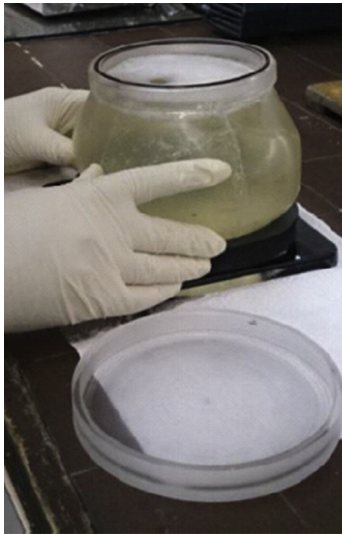| Table 1 — Elemental composition of NIPAM gel and Kerma factor for each element.	
Elements	Weight percent
H	10.81
C	6.51
N	1.65
O	80.42
P	0.29
Cl	0.33
NIPAM, N-isopropylacrylamide.	

Fig. 1 − The head phantom containing NIPAM gel. NIPAM, N-isopropylacrylamide.

their weight percentages in the NIPAM gel formulation are presented in Table 1.

Eventually, the prepared gel was poured into an acrylic ellipsoidal head phantom (Fig. 1). The head phantom presented here is an ellipsoidal head phantom close to the Snyder head model [15,16].

As light can cause polymerization in gel, the gels were completely sealed in aluminum foil and then transferred to a refrigerator for solidification [14].

2.2. Irradiation in TRR BNCT beam line

As previously noted, one of the important sources for BNCT is a nuclear reactor. There are several nuclear reactors worldwide that have been used for BNCT [17−19]. The feasibility of the TRR as a neutron source for BNCT has been demonstrated, and many attempts have been conducted to produce a suitable BNCT beam [20−22]. The thermal column of the TRR has been modified to provide an appropriate neutron beam for use in the BNCT treatment method [22,23]. The criteria for a qualified neutron beam for BNCT are given by the International Atomic Energy Agency [2]. Table 2 shows the

recommended beam parameters and measured values of the TRR in-air beam parameters in comparison with other BNCT facilities around the world [2,22]. As shown in Table 2, TRR BNCT beam parameters are close to those of other BNCT facilities and satisfy the International Atomic Energy Agency criteria to a reasonable approximation [21].

The phantom containing gel dosimeter was irradiated in front of the TRR thermal BNCT beam line at a reactor power of 3 MW. The thermal column is about 3 m in length with a wide square shape cross section of 1.2×1.2 m². It is filled with removable graphite blocks. In order to produce a proper thermal neutron beam, the configuration of graphite blocks has been rearranged in such a way that it is possible to create a $2.6 \times 0.3 \times 0.3$ m³ empty channel. Additionally, a $30 \times 30 \times 12$ cm³ lead block as a gamma shield and a collimator have been constructed and installed in the beam line (Fig. 2).

2.3. MR imaging

In polymer gel dosimetry, upon irradiation, radiation-induced polymerization occurs in the dosimeter, limiting the movement of water molecules, and increasing the R_2 values as a function of the absorbed radiation dose. Therefore, MR imaging is a commonly used technique in reading out the polymer gel dosimeters [7]. In this study, the phantom containing NIPAM polymer gel were imaged by a 1.5-T Siemens MR scanner 24 hours after irradiation. Because temperature fluctuations affect the dosimeter responses, the phantom was maintained at room temperature level and was finally imaged inside the head coil of the scanner [24].

Eventually, T2-weighted images in multiple spin−echo sequence were obtained, from five slices of the different sections of the phantom, and one slice from the center of the vials. Other characteristics of the MRI protocol used are presented in Table 3.

In order to obtain the R_2 map, the MR images were analyzed by code written using the MATLAB software (2014).

3. Results

After irradiation and MR imaging of the phantom containing gel, the R_2 values were obtained by analyzing the MR image

Table 2 − TRR in-air BNCT parameters.				
Reactor	Power (MW)	$\varphi_{\text{thermal}}\left(\times 10^9 \frac{\text{n}}{\text{cm}^2 \cdot \text{s}} \right)$	Cadmium ratio	$\frac{\dot{D}_\gamma}{\phi_{\text{thermal}}}\left(\times 10^{-13} \frac{\text{Gy cm}^2}{\text{n}} \right)$
IAEA	−	>1		<2
RA-3	10	9	4100	1/73
JRR-2	10	1/1	64	1/21
JRR-4 (mode 1)	3/5	2	2/5	5
JRR-4 (mode 2)	3/5	0/6	13/5	3/24
TRR	5	0.56 ± 0.09	180	2/8

Note. From "Design of an epithermal neutron beam for BNCT in thermal column of Tehran research reactor," by Y. Kasesaz, H. Khalafi, F. Rahmani, 2014, *Ann. Nucl. Energy*, 68, p. 234−238. Copyright 2014, Elsevier Ltd. With permission. "Design and construction of a thermal neutron beam for BNCT at Tehran Research Reactor," by Y. Kasesaz, H. Khalafi, F. Rahmani, A. Ezzati, M. Keyvani, A. Hossnirokh, M.A. Shamami, S. Amini, 2014, *Appl. Radiat. Isot.*, 94, p. 149−151. Copyright 2015, Elsevier Ltd. With permission.
IAEA, International Atomic Energy Agency; JRR, ; TRR, Tehran Research Reactor.
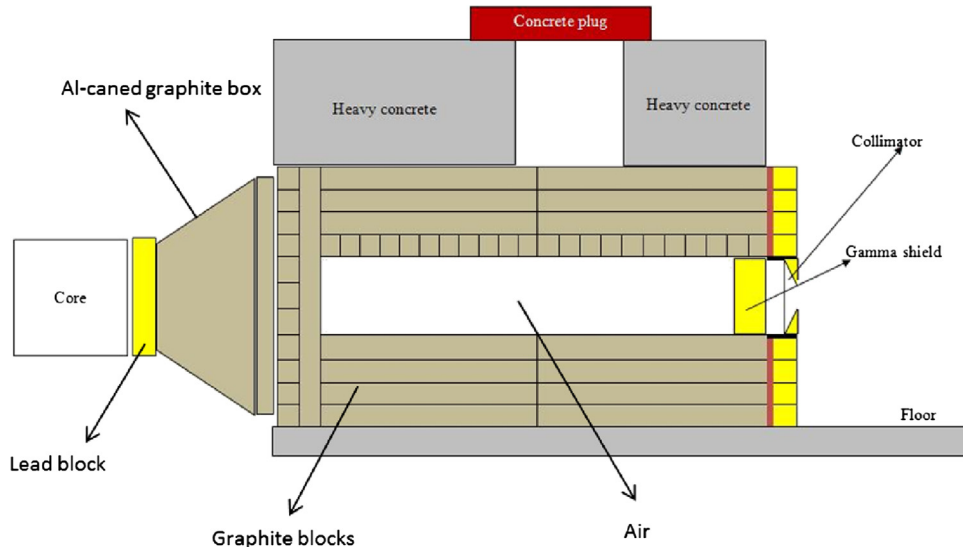
Fig. 2 – The Tehran Research Reactor (TRR) thermal boron neutron capture therapy (BNCT) beam line.

using a code written in MATLAB. In order to evaluate the dose response of the gel in the irradiated phantom, the extracted R_2 maps from the T2-weighted MR images were normalized to the maximum R_2 value, and the relative dose response of the gel in the different slices of the phantom was obtained (Fig. 3).

Table 3 – The magnetic resonance imaging (MRI) protocol used for scanning gel dosimeters.	
Sequence	T2-weighted multiple spin echoes
Matrix size	512×512
Slice thickness (mm)	5
Repetition time (TR) (ms)	4000
Echo time (TE) (ms)	20
Inter echo time spacing (ms)	20
Number of echoes	32
Number of accusation	1

The R_2 profiles along and perpendicular to the beam line at the center of each phantom slice are presented in Fig. 4.

The figure shows that the R_2 value decreases with increasing depth in different sections of the head phantom. Also, the dose profiles perpendicular to the beam line show very little variation, indicating sufficient beam uniformity.

NIPAM polymer gel was first introduced by Senden et al [14] as a lower toxicity polymer gel dosimeter in 2006. Studies carried out to investigate the basic dosimetric characteristics of NIPAM gel have shown that the gel's response in photon irradiation is reproducible, with energy and dose rates being independent. It was also shown that NIPAM gel is tissue-equivalent in terms of electron and mass density [25]. As the elemental composition of the dosimeter is the most important parameter in tissue equivalency, especially in neutron dosimetry, in Khajeali et al's [13] study, the elemental composition of NIPAM gel was compared to the adult brain
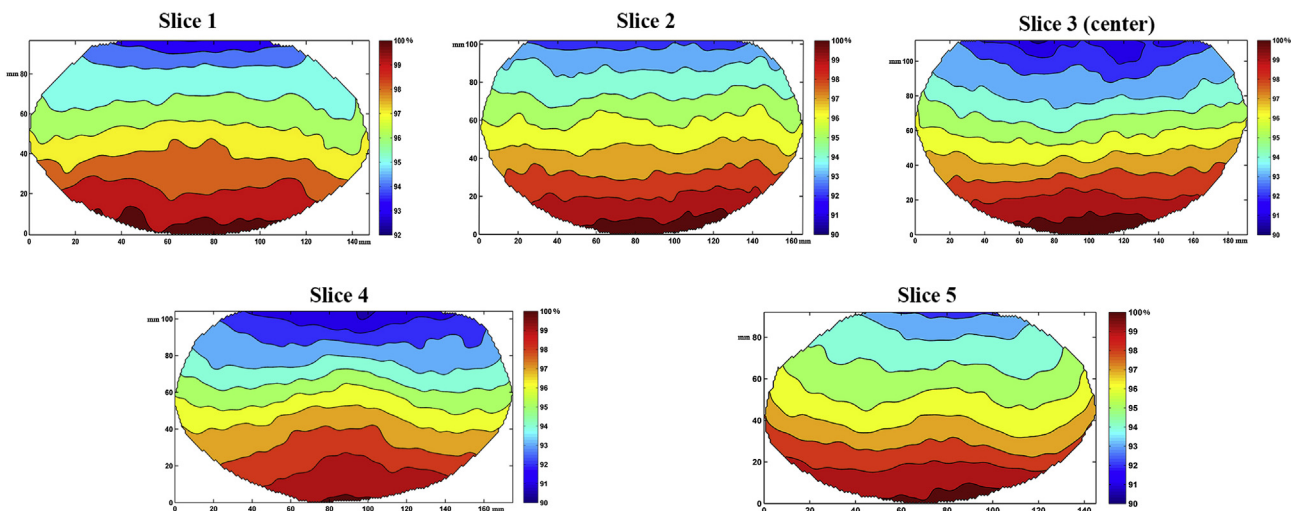

Fig. 3 – Relative dose response of N-isopropylacrylamide (NIPAM) gel in different slices of the head phantom. Results are normalized to the maximum R_2 value.
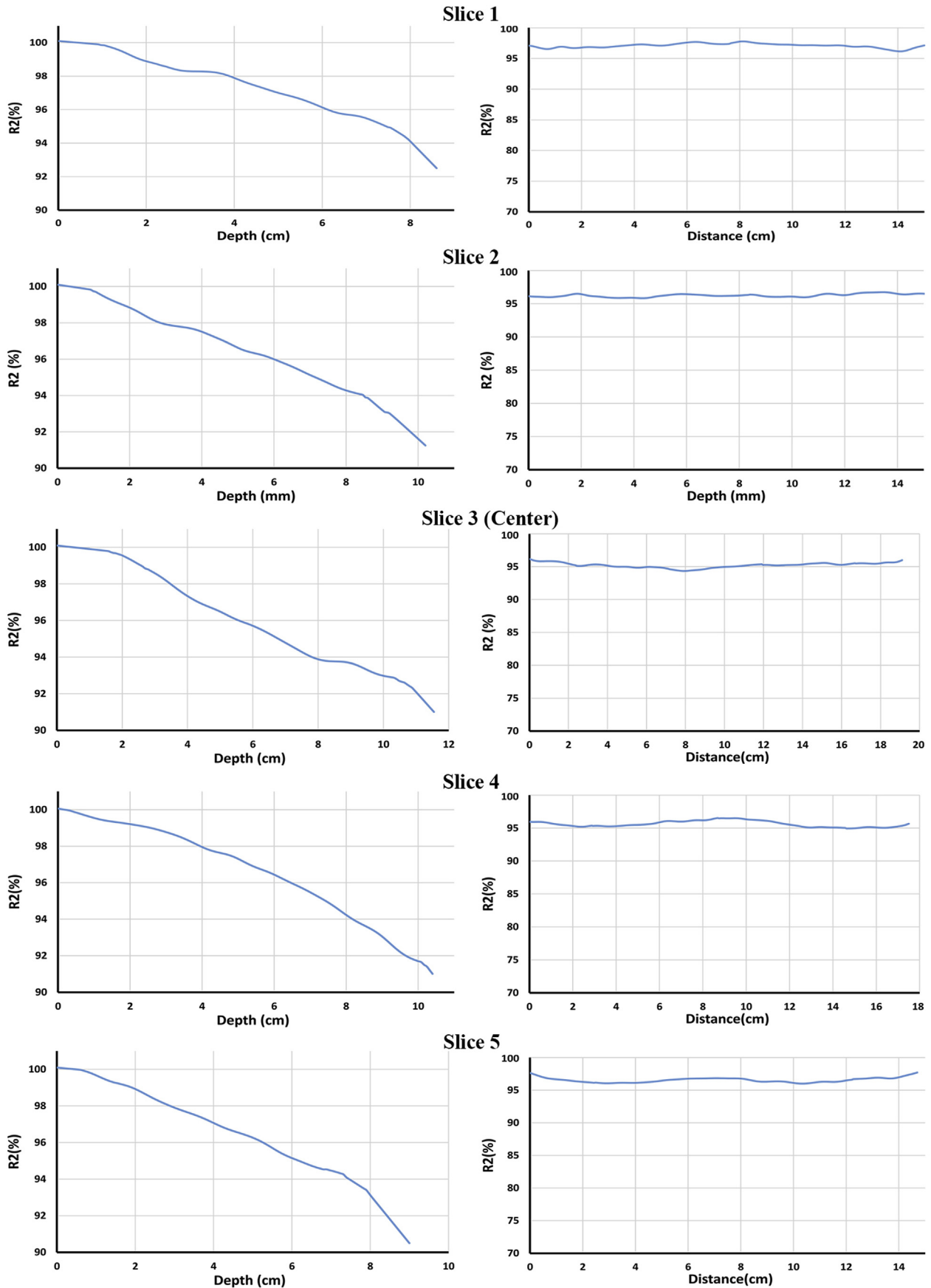
Fig. 4 − R_2 profiles along (left) and perpendicular (right) to the beam line at the center of each phantom slice. Results are normalized to the maximum R_2 value.

tissue, and it was found that the gel could be considered as a tissue equivalent phantom-dosimeter in BNCT.

Gel dosimeters including Fricke and polymer were first used in BNCT dosimetry by Gambarini et al [8] and Farajollahi et al [26], respectively. So far, Fricke gels have been more frequently used in BNCT to measure different dose components [27—29]. These dosimeters have shown promising results in this regard, but they have several drawbacks associated with ferrous and ferric ion diffusion following irradiation, which lead to a decrease in the spatial stability in measuring dose distribution [3]. Unlike Fricke, polymer gels have high stability in recording 3D dose information. In 2000, Farajollahi et al [26], by irradiating BANG polymer gel containing different amounts of ^{10}B in front of the epithermal BNCT beam, showed that this dosimeter had a suitable potential in recording the enhanced dose owing to thermal neutron and ^{10}B reaction [26]. Subsequently, BANG-3 and MAGIC polymer gel were irradiated in an epithermal neutron beam from a Finnish BNCT facility at the FiR 1 nuclear reactor, and their responses were compared with the calculated radiation dose by simulation codes [12,30]. Although the results of these studies supported the potential of polymer gels in BNCT dosimetry, their toxicity formulation was the main limitation. The current study takes advantage of NIPAM gel, which is a polymer gel dosimeter with less toxicity than other polymer gels, for determination of dose distribution in BNCT. In order to determine the dose distribution resulting from the TRR BNCT beam, a head phantom containing the NIPAM gel was irradiated in the beam and then imaged by an MR scanner. The R_2 map and the relative dose response of the gel in the five slices of the phantom were obtained. The R_2 profiles along the beam show how to decrease the dose resulting from the beam by increasing the depth in different sections of the irradiated head phantom. There is a direct relation between R_2 values and dose. A high R_2 value corresponds to high dose and high polymerization, which results in increasing the dose value. With an increase in the depth of phantom, the neutron flux was attenuated and so there was a decrease in the dose and R_2 values.

As can be seen in Fig. 4, there is about 10% difference between the dose response of the gel at the start and end points of the phantom. The dose profiles perpendicular to the beam line show little variation, confirming the uniformity of the TRR BNCT beam line.

4. Conclusion

The results show that NIPAM gel as a lower toxicity polymer gel and a tissue equivalent phantom dosimeter, is suitable for recording 3D dose distribution in mixed neutron-gamma field dosimetry. Moreover, this gel can be a reliable tool for overcoming the drawbacks associated with conventional BNCT dosimetry, and useful in dosimetric verification of BNCT treatment planning because of its capabilities—especially its ability to record dose in 3D with high spatial resolution. Further studies are required to investigate the use of NIPAM gel in clinical situations of BNCT, and its capacity for obtaining dose information in tumor and nontumoral surrounding tissues.

Conflict of interest

The authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

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