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FULL PAPER

Intracavitary moderator balloon combined with ^{252}Cf brachytherapy and boron neutron capture therapy, improving dosimetry in brain tumour and infiltrations

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Objective: This article proposes a combination of californium-252 (^{252}Cf) brachytherapy, boron neutron capture therapy (BNCT) and an intracavitary moderator balloon catheter applied to brain tumour and infiltrations.

Methods: Dosimetric evaluations were performed on three protocol set-ups: ^{252}Cf brachytherapy combined with BNCT (Cf-BNCT); Cf-BNCT with a balloon catheter filled with light water (LWB) and the same set-up with heavy water (HWB).

Results: Cf-BNCT-HWB has presented dosimetric advantages to Cf-BNCT-LWB and Cf-BNCT in infiltrations at 2.0–5.0 cm from the balloon surface. However, Cf-BNCT-LWB has shown superior dosimetry up to 2.0 cm from the balloon surface.

Conclusion: Cf-BNCT-HWB and Cf-BNCT-LWB protocols provide a selective dose distribution for brain tumour and infiltrations, mainly further from the ^{252}Cf source, sparing the normal brain tissue.

Advances in knowledge: Malignant brain tumours grow rapidly and often spread to adjacent brain tissues, leading to death. Improvements in brain radiation protocols have been continuously achieved; however, brain tumour recurrence is observed in most cases. Cf-BNCT-LWB and Cf-BNCT-HWB represent new modalities for selectively combating brain tumour infiltrations and metastasis.

Malignant brain tumours grow rapidly and often spread to the adjacent tissues. One of the most malignant and aggressive of brain tumours is glioblastoma multiforme (GBM),¹ which generally affects both brain hemispheres and, in some cases, presents multifocal growth.²

The tumour histology and anatomical location are significant factors in the choice of treatment. Tumour resection is often the first attempt, although tumour resection is not possible in some cases owing to the risk of inducing more damage to brain function. Additionally, in the case of a glioblastoma that is highly infiltrative, even with complete tumour resection, microscopic neoplasm extensions still remain in the surrounding tissues and cannot be removed.³ The main purpose of surgery is therefore the reduction of tumour cell population. Additionally, surgery is followed by radiation therapy and chemotherapy. Tumour resection has often produced an empty space occupied early by the tumour mass, resulting in a collapsed brain. The average patient's survival is usually less than 2 years; thus, treatment is considered palliative owing to the frequent local recurrence.⁴

Boron neutron capture therapy (BNCT) is an experimental radiotherapy for patients with glioblastoma. In this case,

a borate compound infusion that concentrates on the tumour is applied, and later, the entire brain is exposed to an epithermal neutron beam. The neutrons are captured by the boron in $^{10}\text{B}(n,\alpha)^7\text{Li}$ reactions, producing particles with high linear energy transfer and a mean range of 10 μm (approximately the cell diameter). Thus, the dose deposition resulting from the nuclear reaction with boron remains in the tumour. Additionally, owing to the higher cancer cell metabolism, the boron concentration is often lower in the normal tissue and blood but is higher in the tumour, promoting a selective absorbed dose effect.^{5,6}

BNCT is still considered experimental but has been under continuous development over the past few decades.^{5–7} Clinical trials have been developed in various international centres, strengthening the applicability of this technique in medicine and confirming the safety of the method.^{8–11}

One of the major difficulties in BNCT application is associated with neutron source generation required for brain irradiation. Usually, these neutrons are produced by nuclear reactors, which require complex installations, resulting in a very expensive protocol.^{12,13} According to Wagner et al,¹⁴ there are less than ten BNCT clinical facilities for

glioblastoma treatment in the world, and the number of treated patients is still low, <1000 patients since BNCT started.

A needle of californium-252 (^{252}Cf) can be an alternative neutron source for BNCT application in radiotherapy centres, and this technique can be combined with brachytherapy.^{15,16} The application of ^{252}Cf as a neutron source in BNCT has already been investigated.^{5,16,17} ^{252}Cf is an isotope that decays by spontaneous fission, emitting fast neutrons with an average energy of 2.1 MeV, followed by gamma radiation. Its half-life is 2.7 years, which is satisfactory for brain tumour brachytherapy.^{17–19}

Fast neutrons emitted by a ^{252}Cf source slow down in the human brain along their pathways because of nuclear interactions, especially with hydrogen nuclei. Thus, the neutrons reach the tumour with a suitable thermal spectrum, and their nuclear interaction with boron nuclei is 10^3 times higher than that with constituent elements of the human tissue. This article proposes a combination of ^{252}Cf brachytherapy, BNCT and an intracavitary balloon catheter filled with a moderator solution that should slow down the neutrons emitted by the discretely sealed ^{252}Cf source.

METHODS AND MATERIALS

A computational phantom of a human head was used in the simulations. This computational phantom represents a voxel model that was built based on images of the Visible Human Project²⁰ according to dimensions and materials of the BNCT protocol.²¹ A simulated brain tumour was established in the left temporal lobe of the phantom.^{16,22,23} Two hypothetical infiltrations were also incorporated in the computational phantom, each one in a side of the temporal lobe. The tumour, and infiltrations in the left (I_1) and right (I_2) temporal lobes had volumes of 13.7, 0.43 and 0.27 cm³, respectively. The model was constructed and modified using SISCODES (stochastic model-based computational dosimetric system)²⁴ that exports the brain model to MCNP5²⁵ (Monte Carlo N-Particle Transport Code, version 5) in a readable format by this code.

The following boron concentrations were established in the computational phantom for the BNCT simulations: 52.5 $\mu\text{g g}^{-1}$ in tumours and infiltrations, and 15 $\mu\text{g g}^{-1}$ in the adjacent normal tissue, such as white and grey matter and the limbic system, resulting in a realistic tumour concentration ratio of 1:3.5; these values were based on the literature.^{10,11}

The ^{252}Cf source was a cylinder filled with a Pd-Cf₂O₃ cermet wire with an active length of 7.6 mm and a diameter of 0.7 mm. The cylinder case was 0.2-mm thick and was made of stainless steel. The neutron energy spectrum of the ^{252}Cf source was assumed to be a Watt distribution, with an average energy of 2.1 MeV, as recommended by the MCNP manual.²⁵ The moderator balloon was defined as a sphere of 4 cm in diameter, filled with heavy water (D₂O) or light water (H₂O). The centre of the moderator balloon was matched with the centre of the ^{252}Cf source and with the centre of the tumour, at 4.3 cm below the surface of the skin. The MCNP5 simulation geometry represents a real partial resection of the tumour and the occupation of its original space by the water balloon.

The neutron and gamma spectra from the ^{252}Cf -emitting source were considered to perform dosimetry. The chemical composition

of a human brain tissue was adopted. All possible nuclear and atomic interactions were considered. The microscopic cross-sections of each chemical element present were taken at ENDF-B7 (evaluated nuclear data files-type B, version 7). The dose rate of the BNCT combined with ^{252}Cf brachytherapy addressed the following components: D_H , D_G , D_γ , D_N and D_B . The variable D_H represents the dose component owing to the elastic interaction of fast neutrons with hydrogen, $^1\text{H}(n,n)^1\text{H}$. The variables D_G and D_γ address the dose components related to the γ -rays emitted by the source and by thermal neutrons captured by hydrogen, $^1\text{H}(n,\gamma)^2\text{H}$, respectively. D_N is the dose component that represents thermal neutrons captured by nitrogen, $^{14}\text{N}(n,p)^{14}\text{C}$. Finally, D_B represents the dose owing to thermal neutrons captured by boron, $^{10}\text{B}(n,\alpha)^7\text{Li}$.

The D_H , D_G and D_γ components were evaluated by MCNP5, which conducted the average energy deposition (MeV g^{-1}) in the cerebral tissues and transformed it to the absorbed dose rate ($\text{Gy h}^{-1} \text{p}^{-1} \text{s}$) through a conversion factor (CF). Then, it was multiplied by 10^9p s^{-1} to consider the differences in neutron and photon particle ^{252}Cf emissions for a specific Cf source activity. This unit means that a dose rate of a unitary gray per hour is absorbed in brain tissue if exposed to a fluency of 10^9 neutron particles emitted per second by the Cf source.

The version of the code used in this study does not track protons and ions of ^{14}C [generated in $^{14}\text{N}(n,p)^{14}\text{C}$] or α particles and ^7Li nuclei [generated in $^{10}\text{B}(n,\alpha)^7\text{Li}$ reactions]. Therefore, the D_N and D_B components were calculated from the manipulation of fluency values obtained in the MCNP5 simulation, which represented the neutron fluency in the cerebral tissues. Similar to boron, the sum of the product of nitrogen cross-sections and neutron fluency over the neutron spectra was obtained from MCNP5 and multiplied by the elemental atomic density in each voxel. Thus, the reaction rates for the $^{14}\text{N}(n,p)^{14}\text{C}$ and $^{10}\text{B}(n,\alpha)^7\text{Li}$ were evaluated.²⁶ Using the reaction rates and the exothermic energy values of the reactions, the average energy deposited was calculated and divided by the voxel weight. This absorbed dose was multiplied by CF. Thus, the absorbed dose rates from the two components were determined by the voxels of the model. In all MCNP5 simulations, the cerebral tissues were irradiated by 1×10^8 particles emitted by the source.

The absorbed dose rate for each component, in units of Gy h^{-1} , was multiplied by a weighting factor. The biological weighting factors were considered a guide to achieve dose prescription and used to compare doses across various institutions. The diverse BNCT dose components have their own radiation quality or their own relative biological effectiveness (RBE). Thus, the weighting factors were established to the dose components addressed by the particle emissions of the Cf source. These weighting factors consider the diversity of biological effects on a specific tissue composition owing to a mixed field of high- and low-linear energy transfer (LET) radiation, such as the radiation provided by neutrons, alpha particles and γ -rays on tumour, brain, skin or skull. The DNA breaks caused by the gamma component of the dose undergo repair after ^{252}Cf irradiation. A low-dose rate implies a dose reduction factor, which was incorporated in the weighting factor for γ -rays, w_γ . The choice of the remaining three weighting factors considered their respective RBEs.²¹

Table 1. Weighting factor (W) for conventional boron neutron capture therapy (BNCT)^{9,25,26} and californium-252 coupled to BNCT,^{1,10} followed by weight percentage of nitrogen (N) and hydrogen (H) in main tissues

Main tissues	Weighting factors					W (%)	
	w_G	w_H	w_γ	w_N	w_B	N	H
Tumour and metastasis	0.5	3.2	0.5	3.2	3.8	2.2	10.6
Normal brain	0.5	3.2	0.5	3.2	1.3	2.2	10.6
Skin	0.5	3.2	0.5	3.2	2.5	4.2	10.0

The weighting factor for BNCT based on ^{252}Cf emission is presented in Table 1 and is compared with parameters taken from the literature.^{9–11,27,28} Table 1 also shows the weight percentage of nitrogen, hydrogen and boron concentrations on the main tissues of the model.

The weighting factors w_G and w_γ for the components of dose rates D_G and D_γ , respectively, were lower than the general values used for photons owing to reduced dose rates produced by these components. We included a reduction factor in the coefficients for calculating the probability of induction of deterministic biological effects owing to dose rates $<0.19\text{ Gy h}^{-1}$ of low LET radiation, as in the case of gamma radiation.

The energy per unit of mass generated in the MCNP5 simulation on all voxels of the model was exported to SISCODES. The absorbed dose rates were multiplied by the respective biologic weighting factors. Thus, the SISCODES generated the isodose surfaces superposing them to the computational phantom. These regions represent the total biologically weighted dose rate (D_w) in cerebral tissues.

Dosimetric evaluations were performed with a moderator balloon filled with light or heavy water (H_2O or D_2O) by applying the same methodology described above. The same evaluations were performed for the ^{252}Cf source without the moderator balloon to have parameters for comparison. To distinguish the proposed radiation therapy protocols in this article, BNCT combined with ^{252}Cf brachytherapy is denoted Cf-BNCT; BNCT combined with ^{252}Cf brachytherapy and moderator balloon filled with heavy water is denoted Cf-BNCT-HWB; and BNCT combined with ^{252}Cf brachytherapy and moderator balloon filled with light water is denoted Cf-BNCT-LWB.

RESULTS

The head voxel model provided a human brain equivalent environment for the simulations. Figure 1 presents the section of the computational human head phantom wherein the centres of ^{252}Cf source and moderator balloon can be identified.

The dosimetric analyses performed in this study were based on the dose deposition in the tumour tissue (tumour and infiltrations), in the adjacent normal tissue (at surface balloon or infiltrations) and in the overall normal tissue, in positions following a linear axis crossing the tumour or balloon centre.

The total biologically weighted dose rates of Cf-BNCT, Cf-BNCT-HWB and Cf-BNCT-LWB are presented in Figure 2. The

hypothetical non-resectable tumour was 3.0–5.1 cm below the surface of the skin in the case of the Cf-BNCT protocol. The Cf-BNCT-HWB and Cf-BNCT-LWB protocols received a moderator balloon at a depth of 2.25–6.25 cm in the supposed tumour bed. Tumour infiltrations I_1 and I_2 were at 6.8–7.7 and 11.0–12.5 cm depth, respectively.

In the Cf-BNCT-LWB protocol, the balloon filled with light water generated an overall dosimetric advantage in normal tissue because the dose depositions in the overall voxel's positions in normal tissues were lower than in the Cf-BNCT and Cf-BNCT-HWB protocols, per unit of time and source yield. However, a higher normal-to-tumour dose ratio was found only near the balloon surface at the I_1 infiltration. Apparently, the balloon filled with light water did not generate overall dosimetric

Figure 1. A section of the computational human head phantom containing the hypothetical tumour and infiltrations. The sphere represents the moderator balloon with the californium-252 source placed at the central position.

Figure 2. Total biologically weighted dose rate for californium-252 brachytherapy combined with boron neutron capture therapy (Cf-BNCT), Cf-BNCT combined with a moderator balloon filled with heavy water (Cf-BNCT-HWB) and Cf-BNCT with balloon filled with light water (Cf-BNCT-LWB) protocols at 432- μg ^{252}Cf source.

advantage in distant infiltrations. Indeed, the dose deposition for Cf-BNCT-LWB was lower than that of Cf-BNCT at I_2 infiltration, and the dose rate found in adjacent normal tissue and I_2 were equivalent for both techniques.

In the Cf-BNCT-HWB protocol, although the dose deposition was only slightly larger than that of the Cf-BNCT, in voxels filled with tumour tissue, the higher values occurred in the two infiltrations distant from the ^{252}Cf source.

Near the balloon surface, there were some interesting values in the normal tissue and infiltrations. The remarkable findings of the dose distribution from the three protocols near the moderator balloon and infiltrations can be better analysed in Figures 3–5.

Figure 3 compares the total biologically weighted dose rate in the adjacent normal tissue to the surface's balloon. The total biologically weighted dose rates owing to Cf-BNCT-HWB and Cf-BNCT-LWB were, respectively, 37% and 50% lower in the left side of the balloon and 11% and 29% lower in the right side than were the dose rates in Cf-BNCT. The lower doses near the balloon surface in the moderator balloon protocols, compared with Cf-BNCT, occurred owing to the improved slowing of the source's neutrons, providing a lower fast neutron dose in the normal tissue. This result is relevant because the balloon protocols provide lower doses in the normal tissue near the source.

Figure 4 depicts the dose values in the region of I_1 . Dose values in the voxels that represents the I_1 infiltration and the normal surrounding tissues were determined. Both the heavy water- and the light water-filled balloon protocols showed dose advantages promoting a larger average total biologically weighted dose rate in tumour tissue and lower dose in the adjacent normal tissues than did the Cf-BNCT. One can observe the inversion of values at 6.45 and 6.95 cm in the Cf-BNCT-LWB protocol, for example. Indeed, Cf-BNCT-LWB provided an average tumour dose in I_1 ,

194% larger than in the normal tissue in the same region, whereas Cf-BNCT-HWB and Cf-BNCT provided 121% and 84% larger doses, respectively. At the volume up to 19 mm from the balloon surface (6.25 up to 8.15 cm—studied region), there was a lower dose in the normal tissue in all protocols in relation to the tumour tissue in the same region.

Figure 5 presents the total biologically weighted dose rate in the region of I_2 . It clearly shows a larger dose in the tumour tissue in the Cf-BNCT-HWB and Cf-BNCT protocols than in the Cf-

Figure 3. Total biologically weighted dose rate in the adjacent normal tissue near moderator balloon, which had its radial surface located at 2.25–6.25 cm depth at 432 μg californium-252 (^{252}Cf) source. Cf-BNCT, ^{252}Cf brachytherapy combined with boron neutron capture therapy; Cf-BNCT-HWB, Cf-BNCT combined with a moderator balloon filled with heavy water; Cf-BNCT-LWB, Cf-BNCT with balloon filled with light water.

Figure 4. Total biologically weighted dose rate in infiltrations in the left temporal lobe (I_1), located at 6.95–7.55 cm depth, and in I_1 adjacent normal tissue, at 432 μg californium-252 (^{252}Cf) source. Cf-BNCT, ^{252}Cf brachytherapy combined with boron neutron capture therapy; Cf-BNCT-HWB, Cf-BNCT combined with a moderator balloon filled with heavy water; Cf-BNCT-LWB, Cf-BNCT with balloon filled with light water.

BNCT-LWB protocol, with an average additional dose of 104% and 79%, respectively. The heavy water balloon provided an additional 16.7% total biologically weighted dose rate in comparison with Cf-BNCT. In the adjacent normal tissue, the average biologically weighted dose was the same in both Cf-BNCT and Cf-BNCT-HWB protocols. The light water balloon showed a dose reduction in I_2 . In the adjacent normal tissue, 58.3% and 54.2% of the dose produced in Cf-BNCT was observed in both sides of the infiltration, respectively.

Thus, Cf-BNCT-HWB demonstrated better dosimetric advantages than those of Cf-BNCT-LWB and Cf-BNCT at infiltrations 5.0 cm from the balloon surface.

Figure 6 presents the spatial isodose distribution on a section of the computational phantom, representing the total biologically weighted dose rate (D_w) in the cerebral tissues owing to Cf-BNCT-HWB.

As shown in Figure 6, the dose values in the periphery of the balloon, up to 7.7 cm from the surface, presented 25.0–49.9% of the maximal total biologically weighted dose. The regions of infiltrations were highlighted, showing the dose selectivity at these tumour regions. In I_1 , the average dose was 77% of the maximum dose, whereas I_2 received an average dose of 23% of the maximum dose. Additionally, a dose >75% of the maximum dose can also be seen on the right and above the I_1 , in a small region comprising residual tumour tissue. In the interior of the nasal cavity, the dose between 25% and 49.9% was owing to $^{14}\text{N}(n,p)^{14}\text{C}$ reactions owing to the air composition in the voxels filled with this material. This larger dose in air is not relevant to these analyses.

The advantage of the ^{252}Cf brachytherapy associated with BNCT and combined with a heavy or light water balloon compared with Cf-BNCT was also confirmed by analysing the neutron fluency in the brain, particularly fast neutrons and thermal neutrons. In comparing the average fluency in the Cf-BNCT and Cf-BNCT-HWB protocols (Figure 7), a 25% reduction of fast neutrons and 20% increase of thermal neutrons were observed with the presence of a moderator balloon. The Cf-BNCT-LWB protocol provided more thermal neutrons near the balloon surface up to 1.5 cm from the surface with lower fast neutrons; however, the Cf-BNCT-HWB protocol provided more thermal neutrons at 1.5 cm and further from the surface.

Table 2 shows the possible doses and exposure times to achieve a prescribed biologically weighted dose of 60 Gy in the tumour and in the adjacent normal tissue near the balloon. A surgency of $1.66 \times 10^8 \text{ n s}^{-1}$ to the ^{252}Cf source was considered for this analysis, referring to 72 μg of the californium mass, which is in agreement with the dimensions of the simulated source applied in this study. Table 2 also shows that it took 1.0 h to reach a biologically weighted dose of 60 Gy in the tumour tissue, adjacent to the ^{252}Cf source, in the Cf-BNCT protocol. In this case, the prescribed dose of 60 Gy was achieved at 0.25 cm from the source. The time can be scaled to 9.4 h to produce 60 Gy in the adjacent normal tissue to the tumour (the edge of the tumour, at 0.95 cm from the source). Thus, the dose at 0.25 cm should be 554 Gy and 15.1 and 4.5 Gy at infiltrations I_1 and I_2 , respectively.

The exposure times of 54.0 and 68.2 h in the Cf-BNCT-HWB and Cf-BNCT-LWB protocols were required to reach 60 Gy in the adjacent tissue to the balloon (at tumour bed), respectively. In the Cf-BNCT-HWB or Cf-BNCT-LWB protocols, the

Figure 5. Total biologically weighted dose rate in infiltrations in the right temporal lobe (I_2), located at 11.15–12.35 cm depth, and in the adjacent normal tissue, at 432- μg californium-252 (^{252}Cf) source. Cf-BNCT, ^{252}Cf brachytherapy combined with boron neutron capture therapy; Cf-BNCT-HWB, Cf-BNCT combined with a moderator balloon filled with heavy water; Cf-BNCT-LWB, Cf-BNCT with balloon filled with light water.

Figure 6. Spatial isodose distribution of the total biologically weighted dose rate in an axial plane of the computational phantom produced in californium (Cf)-boron neutron capture therapy combined with a moderator balloon filled with heavy water with a balloon 4 cm in diameter. The scale represent the percentage of the maximum dose rate of 12.0 Gy h^{-1} at $432 \mu\text{g } ^{252}\text{Cf}$ source. I_1 , infiltrations in the left temporal lobe; I_2 , infiltrations in the right temporal lobe.

prescribed dose was assumed at the right balloon surface at 2.15 cm from the source. In the Cf-BNCT-HWB protocol, the doses in the infiltrations were approximately 60 times larger than those in the Cf-BNCT, whereas in the Cf-BNCT-LWB protocol, the doses in I_1 and I_2 were, respectively, 79 and 39 times larger than those in the Cf-BNCT protocol.

Table 3 presents the estimated values of dose components followed by achievable total biologically weighted dose in the brain and tumour in the Cf-BNCT-LWB and Cf-BNCT-HWB protocols and similar estimated values at Massachusetts Institute of Technology (MIT)^{9,29} and Petten³⁰ institutions were taken from BNCT facilities, considering an irradiation field directed towards the tumour at the same depth (d) as infiltrations I_1 (6.95–7.55 cm) and I_2 (11.15–12.35 cm). Boron concentrations in tumour and brain tissue were found in the literature.^{9,29,30}

Dose values in Table 3 were found by the M67 epithermal neutron beam at the MIT Nuclear Reactor Laboratory in a basement

medical treatment room. We measured physical dose rates in an ellipsoidal phantom assuming 1.84% nitrogen by mass, $15 \mu\text{g g}^{-1}$ boron in the brain and a reactor power of 5 MW. We used units of centigray per minute and scaled using weighting factors.⁹ In the fission converter facility, a weighted dose depth profile with a 160-mm diameter filled size with fission converter operating at 83 kW was used, assuming boron concentrations typical for boronophenylalanine (BPA) of 65 and $18 \mu\text{g g}^{-1}$ for tumour and normal brain tissue, respectively (1.0 for photon, 3.2 for neutrons; 1.35 for boron in brain and 3.8 in tumour), in the ellipsoidal water phantom and BPA uptake. In this case, in I_1 , dose components were estimated by percentage values for D_B of 49%; D_γ (n, γ), 34%; D_G (source), 4%; D_n , 2%; and D_N , 13%.²⁹

Dose values from Petten (Table 3) were estimated from MCNP depth dose calculations represented by the four dose component curves in which a single BNCT beam towards a patient head was applied [irradiation time of 74.77 min; ^{10}B -blood concentration (c_b) of 30 ppm], evaluated by the Idaho National Engineering and Environmental Laboratory treatment planning software (D_B , boron absorbed dose by ^7Li and ^4He particles; D_γ , γ -ray absorbed dose; D_n , fast neutron absorbed dose; and D_N , nitrogen absorbed dose).³⁰

In the Cf-BNCT-HWB and Cf-BNCT-LWB protocols, the emission of 10^9 p s^{-1} was considered, in which p was evaluated per neutron emitted by source. The prompt spectral γ -ray yield from the reaction $^{252}\text{Cf(sf)}$ was adopted as 8.30.³¹ The average number of neutrons for ^{252}Cf was 3.7509 neutrons per fission.³² Therefore, the ratio of γ -ray and neutron emitting was 2.2128. Thus, the dose produced per γ -ray particle emitted by the source was previously multiplied by 2.2128 to be added to the dose values normalized by neutron particles emitted by ^{252}Cf . A neutron was considered to emit $2.31434 \times 10^{12} \text{ n s}^{-1} \text{ g}^{-1}$ per ^{252}Cf mass. Thus, in the Cf-BNCT-LWB and Cf-BNCT-HWB in

Figure 7. Normalized thermal and fast neutron fluency in function of depth from right balloon surface starting at 6.25 cm depth. Infiltrations I_1 and I_2 are at 6.8–7.7 cm depth and 11.0–12.5 cm depth, respectively. Cf, californium-252; Cf-BNCT, Cf brachytherapy combined with boron neutron capture therapy; Cf-BNCT-HWB, Cf-BNCT combined with a moderator balloon filled with heavy water; Cf-BNCT-LWB, Cf-BNCT with balloon filled with light water.

Table 2. Dose vs exposure time to achieve a prescribed biologically weighted dose of 60 Gy in the tumour (T) and balloon adjacent tumour bed tissue (TB) and normal tissue (N), with 72 µg of californium mass

Therapy ²⁵² Cf plus	Time (h)	Dose (Gy) (relative biological effectiveness)				
		T	TB	I ₁	I ₂	N ^a
		0.25 ^b	2.15	2.65	6.85	
BNCT ^c	1.0	60 ^d	6.5	1.6	0.5	2.4
BNCT ^c HWB	54.0	^e	60	91.5	30.0	20.7
BNCT ^c LWB	68.2	^e	60	126.8	19.3	23.0

BNCT, boron neutron capture therapy; Cf, californium-252 brachytherapy; HWB, balloon catheter filled with heavy water; LWB, balloon catheter filled with light water.

^aHigher dose at normal tissue at a relative distance referent to 1.65 cm depth (surface balloon) in case of HWB and LWB, and 5.85 cm right to Cf-BNCT.

^bRelative distance between the centre of the Cf source and the voxel position in which the dose was evaluated, in centimetres.

^cBoron concentrations of 52.5 µg g⁻¹ in the tumour and infiltrations, and 15 µg g⁻¹ in the adjacent normal tissue (concentration ratio of 1:3.5).

^dValue taken at a voxel near the surface of the californium-252 source placed at a non-resectable tumour represented on the model.

^eResected tumour; volume filled with moderator balloon.

Table 3, a source mass of 432 µg of ²⁵²Cf was assumed to generate 10⁹ n s⁻¹.

DISCUSSION

GBM presents a high degree of malignancy and tends to spread quickly, invading the surrounding normal brain tissue. Investments in new technologies have continuously occurred with the

purpose of maximizing tumour control and minimizing their side effects.^{5,16,33} However, the cure for glioblastoma still represents a challenge and involves the overall elimination of neoplastic cellular residues and infiltrations in the periphery of the resection region at the tumour bed.^{34–36} Currently, the standard protocol for early diagnosed glioblastoma comprises tumour resection, followed by radiotherapy with concomitant or adjuvant chemotherapy,

Table 3. Typical estimated values of biologically weighted dose components and their achievable total values for californium-252 (²⁵²Cf) brachytherapy combined with boron neutron capture therapy (Cf-BNCT) with a balloon catheter filled with light water (LWB) and Cf-BNCT with a balloon catheter filled with heavy water (HWB) to a 432-µg ²⁵²Cf, and for conventional boron neutron capture therapy (BNCT) at MIT, Petten institutions taken on BNCT facilities, considering an irradiation field directed towards the tumour at the same depth (*d*) referent to infiltrations *I*₁ and *I*₂ positions, boron concentration on tumour (*C*_B^T) and brain (*C*_B^B)

BNCT type	d	C_B^T/C_B^b (ppm)	Biologically weighted dose components (Gy) and weighting factors					Biologically weighted total dose (Gy)		Exposure time (min)
			D_B		$D_\gamma w_F$; $D_G w_F = 0.5$	$D_n w_n$ 3.2	$D_N w_N$ 3.2	Brain	Tumour	
			w_B^b 1.3	w_B^T 3.8						
M67-MIT ^a	I_1	−/15	0.5		1.8	0.25	0.1	2.65		100
	I_2		0.15		1.2	0.15	0.03	1.53		
MIT ^b	I_1	65/18	0.8	4.2	0.55; 0.06	0.03	0.21	1.65	5.05	1
	I_2		—	—	—	—	—	—	—	
Petten ^c	I_1	30 (blood)	2.9		3.15	0.12	0.1	6.27		74.77
	I_2		0.6		1.8	0.05	0.05	2.50		
Cf-LWB ^d	I_1	52.5/15	0.54	7.04	0.09; 0.11 ^e	1.73	0.49	2.96	9.45	60
	I_2		0.22	1.04	0.02; 0.01 ^e	0.20	0.07	0.52	1.34	
Cf-HWB ^f	I_1	52.5/15	0.54	5.96	0.04; 0.10 ^e	2.86	0.41	4.21	9.63	60
	I_2		0.22	2.18	0.02; 0.01 ^e	0.42	0.15	0.84	2.80	

Cf, ²⁵²Cf brachytherapy.

^aM67 epithermal neutron beam at BNCT facilities in MIT Nuclear Reactor Laboratory (MITR-II) in Boston, MA.⁹

^bMIT fission converter operating at 83 kW.²⁹

^cPetten, calculated with the Idaho National Engineering and Environmental Laboratory treatment planning software.³⁰

^dWeighted dose from Cf-BNCT-HWB; emitting 10⁹ p s⁻¹ evaluated per neutron emitted by source.

^eAdjusted by the difference of gamma and neutron emitting.

^fWeighted dose from Cf-BNCT-LWB; emitting 10⁹ p s⁻¹ evaluated per neutron emitted by source.

mainly with the chemotherapeutic agent known as temozolomide (TMZ). Nevertheless, recurrence is observed in most cases.^{2,4}

Brachytherapy is often prescribed following external beam radiation, especially in cases of recurrence. However, recent studies have investigated the use of brachytherapy as an initial treatment at the time of diagnosis.^{37,38,39} Usually, ¹²⁵I and ¹⁹²Ir are the isotopes employed in brachytherapy for brain tumour treatment,^{40,41} but ²⁵²Cf has also been used in brain tumour therapy with some hopeful results.^{18,37,41}

During the past few years, the ¹²⁵I-brachytherapy modality has been developed. It consists of a device that includes a balloon and a catheter for infusing a radioactive fluid. During the irradiation period, the balloon is filled with ¹²⁵I radioactive solution, emitting photons with an average energy of 28 keV.^{4,42} The device is inserted into the patient during the surgical procedure for tumour resection so that the space originally occupied by the tumour is filled by the balloon.^{33,42} Early investigations^{42,43} showed that the mean survival of patients treated with such a technique was 4.6–14 months and 13.7 months, respectively. ²⁵²Cf brachytherapy combined with BNCT delivered a selective irradiation to the target tumour and to infiltration zones, whereas intracavitary balloon catheter brachytherapy with ¹²⁵I delivered negligible doses in the tumour infiltration zones. However, this modality was addressed because ¹²⁵I-brachytherapy uses a tumour resectable cavity and a catheter in which its tip has a balloon that can be inflated.

The cavity formation owing to the excised tumour in the brain may also be explored to improve BNCT. In the 1980s and 1990s, the Japanese had often performed a craniotomy on the patient and explored an air-empty cavity to overcome the thermal neutron depth dose deficit in BNCT.⁴⁴ Sakurai et al²⁵ investigated the effect of a cavity filled with air on the depth-dose distribution in BNCT for malignant brain tumours. According to Sakurai et al, the cerebrospinal fluid in the tumour-resectable cavity was drained out, and air was infused to the space providing a void in the brain. This air space improves the epithermal and thermal external neutron beam penetrations to the brain. Indeed, the thermal neutron flux at a particular depth increases with this technique.⁴⁵ The present Cf-BNCT-LWB and Cf-BNCT-HWB modalities also explore cavity formation owing to tumour resection; we introduced a water-inflated balloon with the goal of improving the slowing of fast neutrons provided by a segment of ²⁵²Cf-fission source placed at the balloon centre. Although spatial distribution of neutrons is quite different because one is provided by a teletherapy and the other by brachytherapy, both techniques may improve thermal neutrons at the tumour bed. However, the reduction in fast neutrons by a slow-down moderator is only possible in a water-filled cavity, such as in the Cf-BNCT-LWB or Cf-BNCT-HWB modalities.

BNCT is a technique that is being continuously developed and presents encouraging results. Clinical results have shown a median survival from 7 to 21.9 months in a total of 190 patients with glioblastoma treated with BNCT between the years 1994 and 2008.⁶ Among these 53 patients, only 9.4% achieved a 2-year survival. Recently, the treatment of 23 patients with

BNCT has been reported with a median survival of 19.5 months and 26.1%, 17.4% and 5.8% of patients had a 2-, 3- and 5-year survival, respectively.⁴⁶ Kageji et al⁴⁶ also suggested that the combination of BNCT with TMZ could produce better results.

A boron carrier to the tumour is still a challenge for the success of the BNCT technique. Currently, the only compounds in clinical use are BPA and sodium borocaptate, but none is considered ideal in relation to its uptake by the tumour and concentration ratio of tumour:normal tissue.^{6,13,47} Recently, several studies have addressed boron incorporation into the tumour-targeting molecules, such as peptides, proteins, antibodies, nucleosides, sugars, porphyrins, liposomes and nanoparticles, showing promising results in animal models and *in vitro*.⁶ Another drawback in BNCT application is related to the complexity and the high cost of a reactor as a neutron source for tumour irradiation, as previously mentioned. However, reports on clinical attempts based on reactor technology have been continuously published in the past two decades, with encouraging results.^{5,12,48,49}

This article proposed a combination of ²⁵²Cf brachytherapy, BNCT and an intracavitary balloon catheter, filled with a solution that slowed the neutrons emitted by a sealed source for the treatment of GBM. The results showed a dosimetric advantage in Cf-BNCT-HWB compared with Cf-BNCT because the dose in the infiltrations was approximately 60 times larger with HWB. Infiltration at 3.0 up to 7.0 cm from the balloon surface receives a higher dose in Cf-BNCT-HWB than that of LWB; however, a better dose is observed in the LWB protocol in infiltrations up to 2.0 cm from the balloon surface. However, overall normal tissue received lower doses in the Cf-BNCT-LWB protocol.

²⁵²Cf neutron brachytherapy is a fast neutron therapy in the entire brain. In a previous study that coupled this modality with BNCT (Cf-BNCT),²² there was a small advantage at infiltrations *I*₁ and *I*₂ owing to a larger contribution to the boron component to the total biologically weighted dose in relation to the fast neutron component at 4 and 7 cm from the ²⁵²Cf source. At the distance of 0–4 cm, the fast neutron dose was superior to other components. It was also shown that the dependence of the boron ratio on tumour and normal brain dictates the success of Cf-BNCT, which depends on the development of new drugs with higher boron ratios, such as 1:10. Additionally, fast neutron fluency in Cf-BNCT near the source is larger than thermal fluency. Thus, the Cf-BNCT modality could be a fast neutron brachytherapy, and its weight dose component may be large with few exceptions only at positions with a larger boron ratio close to 1:10.

In the Cf-BNCT-HWB or Cf-BNCT-LWB protocols, the normalized thermal and fast neutron fluencies in relation to depth, from the right side of the balloon starting at its surface, are shown in Figure 7. The starting evaluated position was 6.25 cm, whereas the Cf source was at 4.3 cm inside the water balloon. The results show that the fast neutron fluency was lower than the thermal fluency past 6.5 cm from the balloon surface. Indeed, the boron component was higher at *I*₁ and *I*₂ than the scattering neutron component values. Therefore, the biological weighted dose components generated by the thermal fluency was higher than the component generated by the fast neutron fluency. Thus,

Cf-BNCT-HWB and Cf-BNCT-LWB are not fast brachytherapies. Figure 4 presents an inversion of the total biologically weighted dose from Cf-BNCT-LWB and Cf-BNCT-HWB in relation to the values from Cf-BNCT at the infiltration positions, demonstrating suitable dose selectivity in the regions in which boron concentration ratios were equal to or higher than 1:3.5 owing to the presence of differential uptake of cancerous cells.

Table 3 presents a dosimetric comparison of reputable centres that perform conventional BNCT and Cf-BNCT-LWB and Cf-BNCT-HWB. This comparison is not absolute because the parameters from conventional BNCT were not equal to our Cf-BNCT-balloon simulations, but they were representative of a clinical or a calibration situation described in the literature.^{9,29,30} Additionally, it was limited to the I_1 and I_2 infiltration positions. However, it was shown that, by applying a $432\text{-}\mu\text{g }^{252}\text{Cf}$ source, the total biological dose at Cf-HWB and Cf-LWB, found in I_1 and I_2 , were similar to those in conventional BNCT. Additionally, the exposure time with a larger mass source of ^{252}Cf may be clinically acceptable and in the same order of magnitude of those addressed by Petten and M67-MIT.

The Cf-BNCT-HWB, with a smaller activity with a $72\text{-}\mu\text{g }^{252}\text{Cf}$ source, required 54.0 h to reach a biologically weighted dose of 60 Gy in the adjacent tissue to the balloon. If 60 Gy was assumed in the infiltration I_1 , the achievable dose in the adjacent normal tissue to the balloon would be 39.4 Gy. In this case, the total irradiation time would be reduced to 35.4 h, which means six fractions of 5 h 54 min. It is relevant to mention that the dose in the infiltration I_1 was 52% higher than in the adjacent tissue to the balloon, although it was near the ^{252}Cf source.

The protocol for Cf-BNCT-HWB or Cf-BNCT-LWB may consist of a daily fractionate exposure with a $72\text{-}\mu\text{g }^{252}\text{Cf}$ source, as described in Table 2, in which the source is inserted, positioned and inflated by an automated brachytherapy device. Considering a prescribed biologically weighted dose of 60 Gy in the adjacent tissue to the balloon and a ^{252}Cf source of 72 μg mass, the treatment could be performed in 9 fractions of 6 h or in 18 fractions of 3 h of exposure in the Cf-BNCT-HWB protocol. In the Cf-BNCT-LWB protocol, the treatment could

be performed in 9 fractions of 7 h 35 min or in 18 fractions of 3 h 47 min of exposure. These exposure times could be further reduced by employing a ^{252}Cf source with a larger ^{252}Cf mass. Compared with teletherapy, in which the patient is irradiated with a dose of 2.0 Gy in 30 fractions, there is significant time saving, regardless of the advantages in the spatial dose distribution.

Although it is not possible to identify small infiltrations at the time of the diagnosis, or if there are multiple metastases developing in the brain, or even if there are infiltrations remaining after tumour resection, these residual cells may be capable of taking up boron compounds in large concentrations, which differentiates them from normal cells. Thus, the therapy could address these regions without previous identification.

Furthermore, progress in selective boron carriers would improve the present proposed technique's selectivity for neoplasia dissemination. Additionally, the ^{252}Cf source is affordable, and this type of neutron source is independent of reactor systems. ^{252}Cf brachytherapy in association with BNCT, improved by a moderator balloon, may represent an alternative method for establishing a BNCT protocol in various radiotherapy centres around the world. The side effects produced by Cf-BNCT-LWB or Cf-BNCT-HWB should be evaluated, primarily through experimental studies in animals and then in clinical trials. New boron drugs that bring higher cancerous cell capitation will make the present study's protocols more attractive in radiation therapy.

CONCLUSION

Considering the highly infiltrative feature of glioblastoma, Cf-BNCT-HWB and Cf-BNCT-LWB protocols provide a selective dose for brain tumour and infiltrations, far from the ^{252}Cf source, sparing the surrounding normal brain tissue. Cf-BNCT-HWB demonstrated better dosimetric advantages than Cf-BNCT-LWB and Cf-BNCT at infiltrations from 2.0 to 5.0 cm from the balloon surface. Moreover, Cf-BNCT-LWB provides dosimetric advantages up to 2.0 cm near balloon surface compared with the other protocols.

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