Analysis of Radiation Interactions and Biological Effects for Boron Neutron Capture Therapy

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ABSTRACT The direct and indirect ionizing radiation sources for boron neutron capture therapy (BNCT) are identified. The mechanisms of physical, chemical and biological radiation interactions for BNCT are systematically described and analyzed. The relationship between the effect of biological radiation and radiation dose are illustrated and analyzed for BNCT. If the DNAs in chromosomes are damaged by ionizing radiations, the instructions that control the cell function and reproduction are also damaged. This radiation damage may be reparable, irreparable, or incorrectly repaired. The irreparable damage can result in cell death at next mitosis while incorrectly repaired damage can result in mutation. Cell death leads to variable degrees of tissue dysfunction, which can affect the whole organism’s functions. Cancer cells cannot live without oxygen and nutrients via the blood supply. A cancer tumor can be shrunk by damaging angiogenic factors and/or capillaries via ionizing radiations to decrease blood supply into the cancer tumor. The collisions between ionizing radiations and the target nuclei and the absorption of the ultraviolet, visible light, infrared and microwaves from bremsstrahlung in the tumor can heat up and damage cancer cells and function as thermotherapy. The cancer cells are more chemically and biologically sensitive at the BNCT-induced higher temperatures since free-radical-induced chemical reactions are more random and vigorous at higher temperatures after irradiation, and consequently the cancer cells are harder to divide or even survive due to more cell DNA damage. BNCT is demonstrated via a recent clinical trial that it is quite effective in treating recurrent nasopharyngeal cancer.

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1. INTRODUCTION

Radiation therapy is a local ionizing-radiation treatment that severely damages cancer cells with as low harm as possible to adjacent normal tissue cells. Cancer cells usually grow and divide much faster than normal tissue cells and are much more sensitive to ionizing radiations. In other words, cancer cells are much more susceptible to damage than adjacent normal tissue cells under ionizing-radiation irradiation.

High-energy X-ray, γ-ray and electron beams have been employed for conventional radiation therapy. This type of radiations have low linear energy transfer (LET) since their energy depositions in tissue as direct radiation interactions (displacements, ionizations, bond-breaks and free–radical formations) and associated indirect interactions (free–radical–induced subsequent chemical reactions and biological responses) are significantly lower than the energy depositions in tissue of high-energy heavier particles such as proton, alpha particle and neutron. Therefore, the radiation absorbed dose and associated biological response, which is characterized by its relative biological effectiveness (RBE), to ionizing radiations depend on the type of radiations.

Boron neutron capture therapy (BNCT) is a therapeutic technique that makes use of energetic alpha particles and back-to-back recoiled \(^7\)Li ions from boron \((^{10}\text{B})\) neutron capture reactions to treat patients with cancer. Both alpha particles and \(^7\)Li ions have a high linear energy transfer and a combined range in tissue of 12–13 µm (comparable with cellular dimensions) and total kinetic energy of 2.33 MeV. BNCT has been used to treat locally invasive malignant tumors such as primary brain tumors and recurrent head and neck cancer.

The BNCT procedure is normally composed of two steps: 1) injection via an intravenous process with a tumor-localizing drug containing \(^{10}\text{B}\) that has a high neutron capture cross section to absorb slow neutrons; and 2) irradiation with epithermal and/or thermal neutrons from either a nuclear reactor or an accelerator. After penetrating through the outer tissue, the neutrons are captured by the \(^{10}\text{B}\) agents in the cancer tumor and the \(^{10}\text{B}\) neutron-capture nuclear reactions subsequently generate high-energy alpha particles and recoiled \(^7\)Li ions to damage cancer cells.

2. DIRECT AND INDIRECT IONIZING RADIATION SOURCES

BNCT utilizes energetic alpha particles and recoiled \(^7\)Li ions from boron \((^{10}\text{B})\) neutron capture reactions for the treatment of cancer patients. Therefore, the direct ionizing radiation source to the boron-treated cancer tumor is a neutron beam.
Two kinds of neutron beams are commonly used in BNCT: 1) a thermal beam for treating surface and shallow cancer tumors; and 2) an epithermal beam for treating deeper (e.g., 8 to 10 cm) cancer tumors. Both kinds of beams include contributions from fast, epithermal and thermal neutrons, as well as gamma rays from the neutron source and from the capture and scattering of neutrons in the beam line structures. Consequently, the direct radiation source includes both neutrons and gamma rays in the neutron beam.

During neutron penetration through a boron-treated cancer tumor, the following indirect ionizing radiation sources are generated:

1. Alpha particles and recoiled $^7$Li ions from boron ($^{10}$B) neutron capture reactions;
2. Protons from nitrogen neutron capture reactions;
3. Gamma rays from hydrogen neutron capture reactions;
4. Recoiled protons and other recoiled target nuclei from fast neutron collisions;
5. Compton electrons and photoelectrons from gamma-ray Compton scattering and photoelectric effect;
6. Electron-positron pair production by the incident gamma ray energy greater than 1.02 MeV;
7. Bremsstrahlung from deceleration of charged particles;
8. Secondary electrons from charged-particles and target nuclei Coulomb interactions.

**3. MECHANISM OF PHYSICAL AND CHEMICAL RADIATION INTERACTIONS**

Radiation physical interactions occur very rapidly (up to $10^{-15}$ sec) and the associated chemical reactions occur less rapidly (up to $10^{-6}$ sec), whereas the subsequent biological responses occur rather slowly (in days up to months). The direct ionizing radiation source to boron-treated cancer tumor is neutron beam. Neutrons have no charge and thus are indirectly ionizing. Neutrons can be divided into three energy groups: fast (energy above 5.53 keV), epithermal (energy between 5.53 keV and 0.6825 eV), and thermal (energy below 0.6825 eV) groups. Fast neutrons bombardment can cause displacements and recoils of nuclei in tissue cells during the slowing down process. Epithermal and thermal neutrons are easily captured by odd-neutron-number nuclides such as $^5$B$^{10}$. The range of a neutron depends on its kinetic energy; therefore, a thermal neutron beam is used for surface and shallow cancer treatment and an epithermal beam is used for deeper cancer treatment. Typical thermal and epithermal neutron beam ranges are shown in Figure 1 (IAEA 2001).

A neutron beam often also contains gamma rays. In addition to the incident neutron beam, additional ionizing radiations are produced within the body in the form of boron disintegration products, protons from nitrogen neutron capture reactions, gamma rays from hydrogen neutron capture reactions, Compton electrons and photoelectrons from gamma-ray Compton scattering and photoelectric effect, bremsstrahlung from deceleration of charged particles, secondary electrons from charged-particles and target nuclei Coulomb interactions, etc.

The basic interaction of a moving charged particle in the body is the Coulomb interaction between the charged particle and the bound electrons in tissue cells. A charged particle traversing tissue loses energy primarily through ionization and excitation of atoms and/or molecules. A moving charged particle exerts electromagnetic forces on tissue–cell molecular electrons and imparts energy to them. Energy transferred may be sufficient to ionize an electron or excite atoms into an excited state. A heavy charged particle can transfer a small fraction of its energy in a single electronic collision and travel essentially straight paths in tissue.

The rate of energy loss along an alpha particle track is shown in Figure 2 (Attix 1986), and the range of the alpha particle track from boron-neutron capture is about 9 µm in body tissue.

All forms of ionizing radiations eventually result in a distribution of low-energy ionized electrons. The interactions of ionized electrons within cancer tumors are very important in radiation chemistry and biology. A large difference in mass between electrons and heavy charged particles has important consequences for interactions. Charged particles deposit energy through two mechanisms—collisional and radiative losses. The collisional loss is the energy loss via Coulomb interactions with orbital electrons in tissue, which results in ionization and excitation, and the radiative loss is via bremsstrahlung. Delta ray is a secondary electron generated by incident fast electron or charged particle via ionization. The life history of a fast electron is shown in Figure 3 (Attix 1986).

High energy photons travel considerable distances before undergoing interaction leading to energy transfer to electrons ultimately depositing their energies into tissue. Photons are far more penetrating than charged particles of
similar energy. There are three photon energy loss mechanisms after interactions: pair production, Compton scattering and photoelectric effect.

Ionizing radiations produce a large amount of secondary electrons that rapidly slow down to energies below 7.4 eV, threshold to produce electronic transitions, in body blood and tissue. Depending on the amount of energy transferred to the bound electrons, the tissue cell molecules can undergo:

- Ionization (threshold in water ~ 13 eV);
- Excitation (threshold in water ~ 7.4 eV);
- H–H Bond broken: 4.51 eV (H₂ → H⁺ + H⁻);
- Hydrogen bond broken ~ 0.4 eV;
- Average Dipole-dipole bond broken ~ 0.2 eV.

Free radicals, especially highly reactive HO⁻ and H⁺, form in irradiated body blood and tissue cells as follows (Equation 1):

\[
\text{Irradiated } H_2O \rightarrow e^-_{aq} + HO^- + H^+ + H_2 + H_2O_2 + H_3O^+ \tag{1}
\]

Typical yields produced by absorption of 100 eV x-ray or electron are shown in Table 1 (Attix 1986).

Various free radical species then proceed to react with each other or with other molecules in their vicinity. The chemical reactions between/among the radical species and adjacent molecules lead to the subsequent biological changes observed after cancer tumor irradiation.

### 4. MECHANISM OF BIOLOGICAL RADIATION INTERACTIONS

Chromosomes (microscopic bodies inside the nucleus of each cell) are organized in pairs and are responsible for the function and reproduction of each cell in a living organism. When a cell divides to reproduce, an exact copy of the cell chromosomes are created for the new cell. If the DNAs in the chromosomes are damaged by ionizing radiations, the instructions that control the cell function and reproduction are also damaged. This radiation damage may be: 1) repairable, 2) irreparable, or 3) incorrectly repaired. The irreparable damage can result in cell death at next mitosis, and the incorrectly repaired damage can result in mutation. Cell death leads to variable degrees of tissue dysfunction, which can affect the functions of the whole organism.

Typical damage of ionizing radiations on DNA by alpha (α), beta (β) and γ or x-ray is shown in Figure 4. An alpha particle, which is a heavy charged particle, has a greater probability of causing damage compared to a beta (β) and γ or x-ray.

Cancer cells cannot live without oxygen and nutrients via the blood supply. Cancer cells often send out signals, called angiogenic factors, that encourage the development of new blood vessels (which is called angiogenesis), which enables the further growth of the cancer tumor. A cancer tumor can be shrunk by damaging angiogenic factors and/or micro blood vessels (capillaries) via ionizing radiations to decrease blood supply into the cancer tumor.

In addition to preceding direct radiation damage on cancer cells, the collisions between ionizing radiations and target nuclei and the absorption of the ultraviolet, visible light, infrared and microwaves from bremsstrahlung in tumor can heat up and damage cancer cells and functions as thermotherapy (namely, hyperthermia). The cancer cells are more chemical and biological sensitive at the BNCT-induced higher temperatures since free-radical-induced chemical reactions are more randomly and vigorously at higher temperatures after irradiation, and consequently the cancer cells are harder to divide or even survive due to more cell DNA damage. When the ambient temperature is above 45°C for a long period, a cancer cell is often difficult to survive.

### 5. RELATIONSHIP BETWEEN BIOLOGICAL RADIATION EFFECT AND RADIATION DOSE

The biological radiation effect is closely related to the biological radiation dose. The physical radiation dose is a measure of the amount of energy from all ionizing radiations deposited in irradiated material such as irradiated tumor cells. However, the biological radiation dose must account for the relative biological effectiveness (RBE), defined as the ratio of the doses required by two radiations to cause the same level of biological effect, among different ionizing radiations. Consequently, the biological radiation dose in tissue (HT) is defined as the sum of the products of all individual physical radiation doses in tissue (DTRi) and their associated individual RBE weighting factors (wRi), as shown in Equation 2.

\[
H_T = \sum_{R_i} w_{R_i} D_{T,R_i} \tag{2}
\]
The biological radiation dose evaluation for BNCT requires careful evaluation on different components of the radiation field, which includes the boron-capture-derivative dose, the fast neutron dose, the nitrogen-capture proton dose, and the sum of the gamma doses. The standard RBE weighting factors for various ionizing radiations are provided in International Commission on Radiation Units and Measurement, Report 60 (Allisy et al. 1998).

Typical BNCT depth-dependent dose curves including total and various components are shown in Figure 5 (IAEA 2001), where the RBE values represent the RBE weighting factors.

A recent BNCT clinical trial case is illustrated in Figure 6 (Wang et al. 2016), which shows a set of two F<sup>18</sup>-labeled-fluorodeoxy-glucose positron emission tomography/computed tomography images of a recurrent nasopharyngeal cancer (indicated by arrows) before BNCT and the other set of cancer-disappeared images three months after BNCT. Two-fraction BNCT with intravenous L-boronophenylalanine (L-BPA, 400 mg/kg) was administered at a 28-d interval. The drug was infused at the rate of 180 mg/kg/h for two hours before neutron irradiation in the first phase, and at the rate of 1.5 mg/kg/min in the second phase, concurrent with neutron irradiation and stopped when the neutron beam was off (Wang et al. 2016).

The epithermal and thermal neutron fluxes at the TRIGA reactor neutron beam outlet were on the order of 10<sup>8</sup> neutrons/cm<sup>2</sup>-sec for BNCT. The prescription dose (D80) of 20 Gy-Eq per fraction was selected to cover 80% of the gross tumor volume (Wang et al. 2016).

BNCT may cause specific side radiation effects on various body parts. Getting radiation therapy on the head and neck can cause tooth decay, a stiff jaw, gum sores and difficulty swallowing. Chest radiation treatment can cause shortness of breath, cough and lung inflammation. Exposing the abdomen or stomach to radiation may cause diarrhea, nausea or vomiting. Consequently, BNCT must be carried out very carefully with the radiation dose in tumor-adjacent tissue as low as practicable.

6. CONCLUSIONS

The direct and indirect ionizing radiation sources for BNCT have been identified. The direct ionizing radiation source is neutron beam, which contains neutrons and associated gamma rays from a nuclear reactor or an accelerator. The indirect ionizing radiation sources include:

1. Alpha particles and recoiled $^7$Li ions from boron ($^{10}$B) neutron capture reactions;
2. Protons from nitrogen neutron capture reactions;
3. Gamma rays from hydrogen neutron capture reactions;
4. Recoiled protons and other recoiled target nuclei from fast neutron collisions;
5. Compton electrons and photoelectrons from gamma-ray Compton scattering and photoelectric effect;
6. Bremsstrahlung from deceleration of charged particles;
7. Secondary electrons from charged-particles and target nuclei Coulomb interactions.

Fast neutrons bombardment can cause displacements and recoils of nuclei in tissue cells during the slowing down process. Epithermal and thermal neutrons are easily captured by odd-neutron-number nuclides such as $^5$B, $^{10}$B. The thermal neutron beam is used for surface and shallow cancer treatment and the epithermal beam is used for deeper cancer treatment since thermal neutrons have a shorter range.

All forms of ionizing radiations eventually result in a distribution of low-energy ionized electrons. Interactions of ionized electrons within cancer tumor are very important in radiation chemistry and biology. Large difference in mass between electrons and heavy charged particles has important consequences for interactions. Charged particles deposit energy via two mechanisms—collisional and radiative losses. The collisional loss is the energy loss via two mechanisms—collisional and radiative losses. The collisional loss is the energy loss via Coulomb interactions with orbital electrons in tissue, which results into ionization and excitation, and the radiative loss is via bremsstrahlung. Delta ray is a secondary electron generated by incident fast electron or charged particle via ionization.

High energy photons travel considerable distance before undergoing interaction leading to energy transfer to electrons ultimately depositing their energies in tissue. Photons are far more penetrating than charged particles of similar energy. There are three photon energy loss mechanisms after interactions: pair production, Compton scattering and photoelectric effect.
Ionizing radiations produce plenty of secondary electrons that rapidly slow down to energies below 7.4 eV, the threshold to produce electronic transitions, in body blood and tissue. Free radicals, especially highly reactive HO$^-$ and H$, form in irradiated body blood and tissue cells. Various free radical species then proceed to react with each other and/or with other molecules in their vicinity. The chemical reactions between/among the radical species and adjacent molecules lead to the subsequent biological changes observed after cancer tumor irradiation.

If the DNAs in the chromosomes are damaged by ionizing radiations, the instructions that control the cell function and reproduction are also damaged. This radiation damage may be: 1) repairable, 2) irreparable, or 3) incorrectly repaired. The irreparable damage can result in cell death at next mitosis while the incorrectly repaired damage can result in mutation. Cell death leads to variable degrees of tissue dysfunction, which can in turn affect the whole organism’s functions.

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The biological radiation effect is closely related to the biological radiation dose. The biological radiation dose in tissue is calculated as the sum of the products of all individual physical radiation doses in tissue and their associated individual RBE weighting factors. The biological radiation dose evaluation for BNCT requires careful evaluation on different components of the radiation field, which includes the boron-capture-derivative dose, the fast neutron dose, the nitrogen-neutron-capture proton dose, and the sum of the gamma-induced doses. BNCT has been demonstrated via a recent clinical trial that it is quite effective to treat the recurrent nasopharyngeal cancer.

REFERENCES


