



OPEN Cell-cycle dependence on the biological effects of boron neutron capture therapy and its modification by polyvinyl alcohol

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Boron neutron capture therapy (BNCT) is a unique radiotherapy of selectively eradicating tumor cells using boron compounds (e.g., 4-borono-L-phenylalanine [BPA]) that are heterogeneously taken up at the cellular level. Such heterogeneity potentially reduces the curative efficiency. However, the effects of temporospatial heterogeneity on cell killing remain unclear. With the technical combination of radiation track detector and biophysical simulations, this study revealed the cell cycle-dependent heterogeneity of BPA uptake and subsequent biological effects of BNCT on HeLa cells expressing fluorescent ubiquitination-based cell cycle indicators, as well as the modification effects of polyvinyl alcohol (PVA). The results showed that the BPA concentration in the S/G₂/M phase was higher than that in the G₀/S phase and that PVA enhances the biological effects both by improving the uptake and by cancelling the heterogeneity. These findings might contribute to a maximization of therapeutic efficacy when BNCT is combined with PVA and/or cell cycle-specific anticancer agents.

Keywords BNCT, BPA, Cell cycle, CR-39 detector, Heavy ions, PVA

The therapeutic potential of neutron capture was first proposed in 1936, just a few years after neutron's discovery¹. Among the modalities using photons, electrons, and light and heavy ions, boron neutron capture therapy (BNCT) has a unique feature in that it uses short-range heavy ions (such as α -particles and Li ions) emitted by the $^{10}\text{B}(n,\alpha)^7\text{Li}$ reaction, which can selectively eradicate cells that take up tumor-seeking ^{10}B compounds². To date, experimental and clinical studies on BNCT have shown great potential in eradicating several cancers, such as melanoma, head and neck cancers, and brain tumors, while minimizing damage to normal tissues³.

Clinical trials on BNCT began in 1951 for the treatment of malignant glioma^{4,5}; however, in the early days of the study, serious adverse effects such as brain necrosis were reported because of technical limitations. A breakthrough was the development of a tumor-seeking boron compound, 4-borono-L-phenylalanine (BPA), which can be highly taken up in tumors compared with the surrounding normal tissues⁶. Furthermore, the use of BPA clustered by polyvinyl alcohol (PVA-BPA) has shown the potential to enhance the therapeutic effects of BPA⁷. Along with effective ^{10}B delivery techniques, another breakthrough was the development of an accelerator-based (AB) neutron source in clinical facilities, which can generate high-intensity epithermal neutrons ($> 1 \times 10^7$ n/cm²/s) at the beam aperture⁸. Therefore, AB-BNCT with BPA is expected to immediately spread to clinical facilities worldwide⁹.

For AB-BNCT, intravenous injection of BPA is essential¹⁰; however, its ability to deliver drugs to tumors remains a challenge because intracellular BPA concentration varies unevenly in terms of space and time¹¹. Regarding the temporal dynamics of BPA, we previously investigated the time dependencies of ^{10}B distribution in melanoma and found that the effects of cell recovery (DNA lesion repair) during exposure to neutrons are reduced compared with photon beams but still not negligible when delivering high doses to tumors¹². In addition,

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Biological Effects Of Neutron Pro Volume

Rachel Sandford



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