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Beyond impaired DNA repair: Exploring the radiosensitizing mechanisms of hyperthermia through mathematical modeling and Monte Carlo simulations

Adriana M. De Mendoza[1], Edwin Munévar[2], Cesar Herreño[2], Jose L. Rodríguez[2], Diego A. Rodríguez[3]

[1]Faculty of Sciences – Physics Department,
Pontificia Universidad Javeriana, Colombia
a.demendoza@javeriana.edu.co

[2]Faculty of Science and Education,
Universidad Distrital – Francisco José de Caldas, Colombia
emunevare@udistrital.edu.co
caherrenof@udistrital.edu.co
jolrodrigueza@correo.udistrital.edu.co

[3]Faculty of Sciences,
Universidad Nacional de Colombia, Colombia
dirodriguezco@unal.edu.co

Hyperthermia therapy (HT) presents significant advantages when compared to other alternatives in the fight against cancer. HT is relatively inexpensive and is among the most effective and least toxic treatments for patients. Heat is a form of energy that does not produce secondary (or higher orders) radiation and does not lead to secondary tumors as part of its side effects [1]. Localized heat, among other effects on the body, has the potential to improve blood perfusion and tumor oxygenation, in addition to stimulating the immune system. Due to these features, HT also works as a powerful sensitizer of other therapeutic modalities such as radiotherapy, reducing the doses, therefore improving the treatment's effectiveness and reducing side effects [2]. The synergy between radiotherapy and hyperthermia is widely documented across *in vitro*, *in vivo*, and clinical studies, offering rich hypotheses for therapeutic benefits.

While HT exhibits promise in enhancing cancer treatment efficacy, it has not yet achieved standard care status due to: (1) Technical Challenges: Achieving precise and uniform heating in the targeted area poses technical difficulties, (2) Ongoing Device Development: HT devices with the required precision are

still in development, and (3) Integration Complexity: Achieving seamless integration with standard cancer treatments poses a challenge, requiring further research for optimal timing, sequencing, and combination of therapies [3]. The development of accurate mathematical models is pivotal for predicting treatment outcomes and facilitating the integration of HT into the clinical workflow [4, 5, 6]. Overcoming these challenges through ongoing research and technological advancements is crucial for establishing hyperthermia as a standard care protocol.

In this study, we develop mathematical models to better understand and predict the effects of heat, especially when combined with ionizing radiation simultaneously or sequentially. To this end, we investigate the causes of thermal enhancement by examining DNA rupture probability. Theoretical calculations reveal that temperature-dependent variations in DNA-ion interactions may affect therapeutic outcomes, and Monte Carlo simulations using the Geant4 toolkit support this hypothesis. Our theoretical calculations and simulations indicate that the radiosensitizing effect of HT depends on the temperature effects on 4 factors: the cellular capacity for DNA repair, the vulnerability of the bonds in the DNA, DNA cross-section, and DNA density. This research thus provides unique insights into multifaceted processes shaping radiosensitization.

Keywords: hyperthermia therapy (HT), radiosensitization, DNA damage, mathematical modeling

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