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Background Effective immunotherapy requires optimal combination of immunotherapeutic agents to build a robust immune response against cancer. In this framework, radiotherapy has proven its ability to induce immunogenic cell death (ICD), showing a promising potential for successful combination. Hafnium oxide (HfO2) nanoparticles, undergoing clinical trials for enhancing radiotherapy, was designed as high electron density material at the nanoscale, to enhance the absorption of radiation delivered within tumors. The nanoparticles are taken up by cancer cells and, when exposed to radiotherapy, locally increase the radiation dose deposit, triggering more cancer cells death when compared to radiotherapy alone (Figure 1). Methods Generation of ICD components – namely calreticulin (CALR) surface exposure, release of high mobility group box 1 (HMGB1) protein and liberation of adenosine-5’-triphosphate (ATP) – were examined on human cancer cell lines across human cancer types, 24- to 96-hrs post-treatment with HfO2nanoparticles and exposure to irradiation (from 4Gy to 15 Gy).CT 26 (murine colorectal cancer cells) treated with or without HfO2 nanoparticles were exposed to irradiation (6Gy). Irradiated cells (1.106) were inoculated subcutaneously into the flank of BALB/c mice (vaccination phase). Seven days after, mice were challenged with live CT 26 tumor cells (3.105) (challenge phase).  The host immune response against these cells was evaluated by the apparition of at least one tumor (vaccination or challenge site).Results *In vitro*, human cancer cell lines treated with HfO2 nanoparticles exposed to irradiation enhanced the quantity of ICD (more than 25%) when compared to irradiation alone. Interestingly, in tested human cell lines HCT116 (radiosensitive colorectal cancer) and 42MGBA (radioresistant glioblastoma), the generation of HMGB1 from cells treated with HfO2 nanoparticles and exposed to 4Gy and 10Gy respectively, was superior to the generation of ICD from cells treated with 6Gy and 15Gy alone respectively.*In vivo*, the percentage of mice protected against live CT 26 challenge was markedly increased for mice vaccinated with cells treated with HfO2nanoparticles exposed to 6Gy versus 6Gy alone (66% vs 33% respectively).    ConclusionsHfO2 nanoparticles exposed to irradiation enhanced cancer cells destruction and ICD compared to irradiation alone, suggesting a strong potential for transforming tumor into an effective in situ vaccine. They may contribute to transform “cold” tumor into “hot” tumor and effectively be combined with most of the immunotherapeutic agents across oncology.  Acknowledgements Trial Registration References Consent Uploaded File(s)Supporting Tables, Figures and Imageshttps://www.conferenceabstracts.com/uploads/cfp2/attachments/AABGHGNQ/AABGHGNQ--214573-1-ANY.pngHfO2 nanoparticles: same mode of action than radiotherapy, but amplified |

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