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Synchrotron activation radiotherapy: Effects of dose-rate and energy spectra to tantalum oxide nanoparticles selective tumour cell radiosensitization enhancement

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Abstract

Synchrotron radiation is unique in its ability to deliver dose at high dose rates using kiloelectronvolt photons. We are investigating the use of Tantalum pentoxide (Ta2O5) nano-structured particles (NSPs) that are to date unexplored in synchrotron radiation fields as they have high atomic number (Z=73) are biocompatible and are therefore potential radio sensitizers. We exposed cell culture flasks containing 9L gliosarcoma tumour cells or Madin-Darby Canine Kidney (MDCK) non-tumour cells to the NSPs and treated the cells using a broad synchrotron beam (140 keV median energy; average dose rate of 50 Gy/s) at the Australian Synchrotron. We compare the results with those from similar cells treated using a conventional 150 kVp orthovoltage field (dose rate of 0.0127 Gy/s). The results reveal that the high dose-rate synchrotron irradiation is more effective at killing the 9L cells relative to the MDCK cells than the orthovoltage irradiation. On the other hand, the NSPs are more effective at radiosensitizing the 9L cells compared to the MDCK cells in the orthovoltage radiation field, which is due to the NSP energy dependence in the kilovoltage energy range. Both the dose rate and energy spectrum need to be considered in future studies with synchrotron activation radiotherapy (SART).

Keywords

oxide, synchrotron, nanoparticles, enhancement, selective, tumour, cell, activation, radiotherapy:, effects, radiosensitization, dose-rate, energy, spectra, tantalum

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Synchrotron activation radiotherapy: Effects of dose-rate and energy spectra to tantalum oxide nanoparticles selective tumour cell radiosensitization enhancement

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Abstract. Synchrotron radiation is unique in its ability to deliver dose at high dose rates using kiloelectronvolt photons. We are investigating the use of Tantalum pentoxide (Ta_2O_5) nano-structured particles (NSPs) that are to date unexplored in synchrotron radiation fields as they have high atomic number (Z=73) are biocompatible and are therefore potential radio sensitizers. We exposed cell culture flasks containing 9L gliosarcoma tumour cells or Madin-Darby Canine Kidney (MDCK) non-tumour cells to the NSPs and treated the cells using a broad synchrotron beam (140 keV median energy; average dose rate of 50 Gy/s) at the Australian Synchrotron. We compare the results with those from similar cells treated using a conventional 150 kV_p orthovoltage field (dose rate of 0.0127 Gy/s). The results reveal that the high dose-rate synchrotron irradiation is more effective at killing the 9L cells relative to the MDCK cells than the orthovoltage irradiation. On the other hand, the NSPs are more effective at radiosensitizing the 9L cells compared to the MDCK cells in the orthovoltage radiation field, which is due to the NSP energy dependence in the kilovoltage energy range. Both the dose rate and energy spectrum need to be considered in future studies with synchrotron activation radiotherapy (SART).

1. Introduction

High-Z nanoparticles (NPs) have been shown to improve the effectiveness of dose conformity to tumour tissue, particularly with macroscopic (broad beam) kilovoltage x-rays [1, 2]. The advantages of NPs, besides the primary benefit of enhancing local tumour radio-sensitivity, often include biocompatibility, permeability to cell membranes due to their nano-scale dimensions, and engineered abilities to specifically target certain tumours when coated.

Tantalum pentoxide (Ta_2O_5) nano-structured ceramic particles (TaNSPs) were first reported as radio-sensitizers by Brown *et al.* 2014 [2]. Nano-structured ceramic particles (NSPs) have different characteristics and furthermore, aggregation properties than inert metal NPs. TaNSPs have a high atomic number (Z=73), are biocompatible, and its oxide component may provide a useful target for drug attachment.

Polychromatic synchrotron radiation has significantly high dose rates, of order of tens to hundreds of Gy per second. The effect of these beams on tumour tissue are not yet well documented, however it

is known that the inclusion of a high-Z targeting agents, such as platinum, gold, and iodine, can improve the treatment efficiency of synchrotron treatments, in their lower dose-rate monochromatic mode [3].

We aim to provide preliminary evidence of increased tumour response to high dose rates when compared to normal cells and characterise the ability of high-Z particles to selectively enhance synchrotron therapies, determining their efficacy toward Synchrotron Activation Radiotherapy (SART).

2. Methods

Tantalum pentoxide NSPs were synthesized according to the method detailed by Brown *et al.* [2] with sonication in an ultrasonic water bath, whilst suspended in PBS (phosphate buffered saline), for 2 hrs and mixed at 30 min intervals to promote the formation of smaller aggregates.

The NSPs were added to T12.5cm^2 cell culture flasks containing monolayers of 9L gliosarcoma cancer cells (derived from rodent brain cells) or MDCK (Madin-Darby Canine Kidney) cells 24 hours before 90-100% confluence. Each cell culture was grown with complete Dulbecco's modified eagle medium (c-DMEM) (DMEM supplemented with 10% fetal bovine serum (FBS) and 1% penicillin and streptomycin) and incubated at 37 °C and 5% (v/v) CO_2. NSP concentrations ranging from 50-500 µg/mL were added into flasks containing 5 mL DMEM.

Following 24 hrs of incubation with the NSPs, the cells were subcultured into 100 mm diameter petri dishes with 10 mL c-DMEM to evaluate NSP toxicity. Following 15 cell doubling times the cells were washed with 5 mL PBS (with calcium and magnesium ions) and fixed and stained with 5 mL of a (25% crystal violet and 75% ethanol) solution. Colonies consisting of no less than 50 cells were counted as surviving. The plating efficiency was evaluated as the ratio between the number of colonies present to the original cell seeding number. In this way, the impact of the irradiation or NSP toxicity was evaluated by comparing the plating efficiency of these treatments directly to the control plating efficiency and expressing this ratio as a normalized survival fraction.

For all experiments the flasks were irradiated when embedded in a 20 cm x 20 cm x 12 cm solid water phantom (RMI-457) with the cells at 2.5 cm depth. The irradiation field size was large enough to cover the whole flask in the case of the orthovoltage irradiations. For the synchrotron irradiations a step and shoot technique was utilized to create the irradiation field from the 1 mm x 12 mm intrinsic radiation field. The uniformity of the irradiation field was checked using EBT-3 film. The total dose was confirmed via a PTW Pinpoint^{TM} ion chamber (model 31014).

Flasks with or without 50 µg/mL of NSPs were irradiated in a vertical orientation at hutch 1B on the Imaging and Medical Beamline (IMBL) at the Australian Synchrotron, with a single dose (2 Gy), at 50 Gy/sec, using a pink beam (4.65 mm Cu ex vacuo filtration). These results were compared with 2 Gy low dose-rate (LDR) 150 kVp orthovoltage X-ray beam from a Nucletron Oldelft Therapax DXT 300 Series 3 Orthovoltage unit at 0.76 Gy/min.

The differences in energy spectra of these beams is shown in Figure 1.

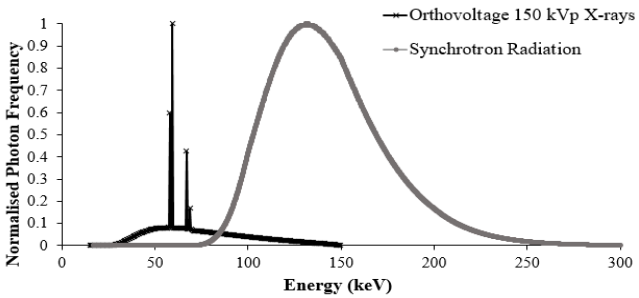

Figure 1. Photon beam energy spectra of 150 kVp orthovoltage X-rays (66 keV effective energy) and synchrotron pink beam (137 keV weighted average energy).

3. Results

Preliminary observations of TaNSPs with a light microscope, show they are distributed quite homogeneously amongst MDCK flask, except for some aggregation outside the cells over time (Figure 2). However, the TaNSPs tend to form clusters around the cell nucleus in the 9L gliosarcoma cells (Figure 3) due to the entrance of the TaNSPs into the cell and subsequent aggregation.

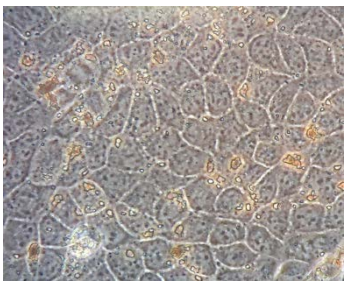

Figure 2. Ta_2O_5 NSPs (black-brown) in MDCK.

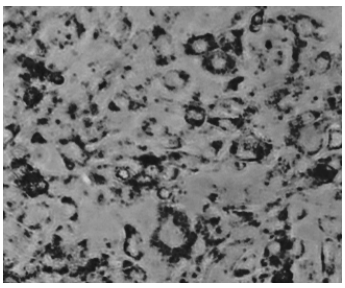

Figure 3. Ta_2O_5 NSPs (black) in 9L cells.

Toxicity of the Ta_2O_5 NSPs produce population survivals of 80-100%, in both cell lines without discrimination toward either cell line, as shown in Figure 4 for a range of NP concentrations.

In the case of 9L cells, the results are very consistent with previously published data from a different production batch and indicates the excellent reproducibility of the production technique.

This indicates that with TaNSPs, no toxic effect is acting on either cell line, and the cell survival following irradiation is purely dependent on the efficacy of the treatment itself.

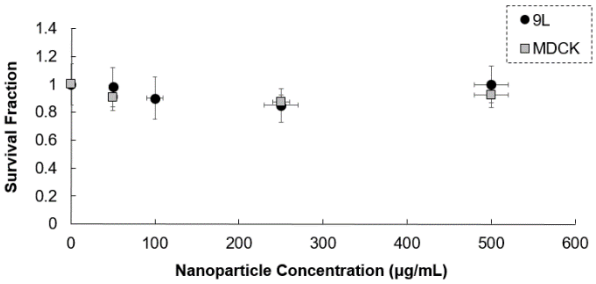

Figure 4. Intrinsic toxicity of Ta_2O_5 NSPs for 9L and MDCK cell lines.

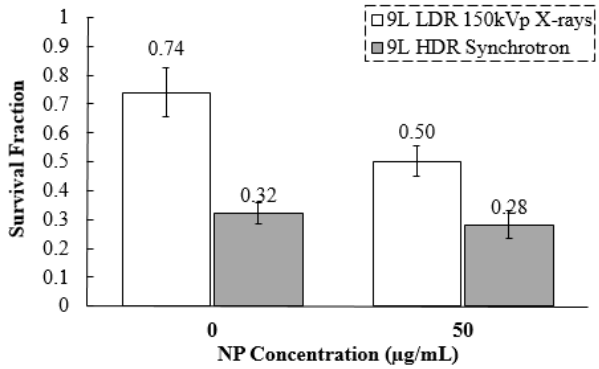

Figure 5. 9L cell survival following orthovoltage or synchrotron broad beam irradiation, with and without NSPs.

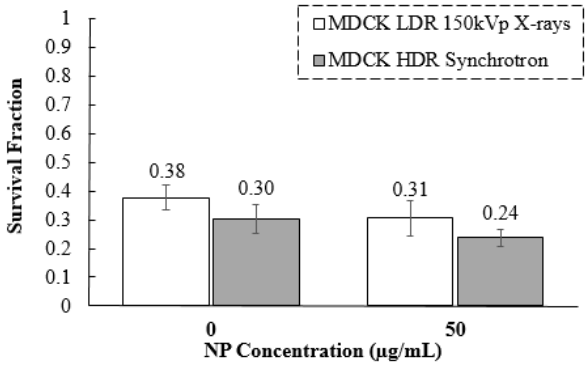

Figure 6. MDCK cell survival following orthovoltage or synchrotron broad beam irradiation, with and without NSPs.

Figures 5 and 6 highlight the effects of the different dose-rates on the cancer and normal cell lines respectively. Conventional 150 kVp orthovoltage treatment at 2 Gy LDR (low dose-rate) is compared with a synchrotron HDR (high dose-rate) broad beam.

Radioresistant 9L gliosarcoma cells appear to be more affected by the high dose rate than the MDCK cells. The orthovoltage treatment in comparison produces much greater 9L survival at 2 Gy than the synchrotron radiation. Radiosensitive MDCK in contrast, shows that there is insignificant difference between the orthovoltage treatment and HDR synchrotron treatment.

The addition of NSPs however, do not appear to significantly enhance the treatment of the 9L cells using synchrotron radiation. In contrast, the orthovoltage treatment does see a noticeable dose

enhancement expressed through an increase in cell death in the tumour cells. In the normal cells however, there is no therapy enhancement in either LDR or HDR treatment. We believe this is due to the difference in the nanoparticle uptake by the tumour line (more nanoparticles closer to the nucleus).

These results highlight the importance of considering the kV beam energy used for SART. NP dose enhancement is indeed highly energy dependent in the kilovoltage range.

Figure 7 shows that the 150 kVp X-rays was precisely chosen to more directly target the photon absorption of the TaNPs relative to water and therefore optimize cell sensitization enhancement. The broad beam synchrotron radiation spectra would need further optimization and be lowered in energy to fully take advantage of dose enhancement by photoelectric effect on TaNSPs.

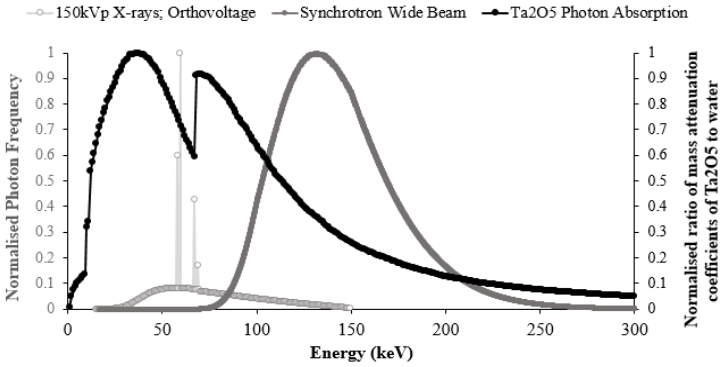

Figure 7. Comparison of beam energy spectra (grey) and ratio of total mass energy absorption coefficients of Ta_2O_5 to water (black) [4].

4. Conclusion

The inclusion of tantalum (V) oxide NSPs in kV beams is shown to improve tumour selectivity of the therapy. We believe the improvement is related to the preferential uptake of the NSPs by the 9L gliosarcoma cells compared to the MDCK kidney cells, which seems to naturally occur. The selective uptake leads to a higher concentration of NSPs in the 9L cells compared to the MDCK cells. The higher concentration also leads to selective dose enhancement in 9L cells due to the high-Z nature of the NSPs acting to significantly increase the interaction cross section of the cells at low photon energies (40-100 keV). Furthermore, the high dose rate of the synchrotron broad beam tends to produce greater effect on 9L radioresistant tumorous cells. However, NSPs are less effective in the synchrotron broad field for either cell line in this case, due to the beam energy spectrum requiring further optimization to maximize the radiosensitization of the TaNSPs.

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