Advancing a radiotherapy predictive model to incorporate probabilistic nanoparticle radiosensitisation in head & neck cancers

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Introduction

Head and neck cancers (HNC) are associated with negative radiotherapy (RT) treatment responses as a result of radioresistance, increased proliferation rates, hypoxia, and proximity to critical structures. Current standard-of-care consists of concurrent chemo-RT; a method frequently associated with high acute grade toxicities. The use of **gold nanoparticles (AuNPs)** as radiosensitisers may offer a new approach to achieve tumoricidal doses without severe side effects (Fig. 1).

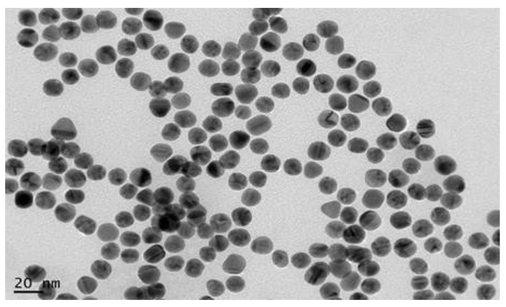

FIG. 1: Transmission electron micrograph of AuNPs (Courtesy of I. Kempson, UniSA).

AuNPs promote localised dose deposition, chemical and biological sensitisation of cells to damage, and disruption of cell cycle and DNA repair; permitting improved local control and/or RT dose reduction and lowered toxicity.

This work aimed to incorporate experimental HNC data into a computational model for theoretically predicting RT and AuNPs injection outcomes in terms of tumour control, based on individual cells.

Methods

The HYP-RT computational model (Dr. Phillips and team) simulates HNC squamous cell carcinoma propagation to provide a radiobiological tool for assessing RT regimens based on the efficiency of tumour cell kill for individual tumour and cell properties (1) (Fig. 2).

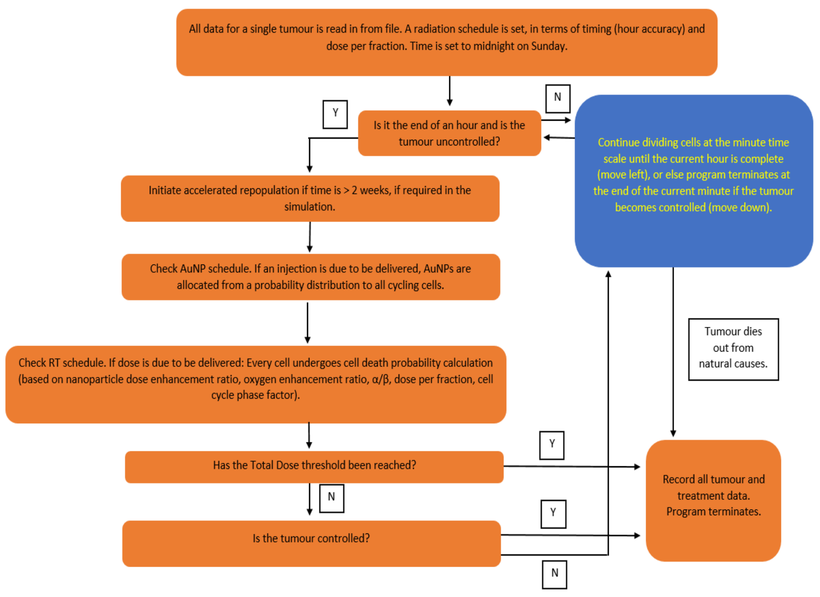

FIG. 2: A flow chart of the HYP-RT model algorithm implementing fractionated radiotherapy treatment and incorporating nanoparticle dose enhancement and continuous tumour cell division.

This project developed the HYP-RT software to incorporate nanoparticle sensitisation, with AuNP uptake randomly assigned from a heterogeneous distribution based on in-vitro data (2). AuNPs were split evenly between dividing cells.

Simulations were run for **5 oxic and 5 hypoxic 10^8 cell tumours** with/without accelerated repopulation (increased proliferation in response to damage; AR) and tumour reoxygenation (due to tumour shrinkage; ROx) per AuNP schedule. RT regimens included 2 Gy/fraction (#) 5 days/wk, 1.2 Gy/# bi-daily 6 days/wk and SABR bi-weekly 12 Gy/#.

Variations in the tumour radiosensitivity (i.e. a/b values) were also investigated. Each change in variables was acquired with 125 simulations, utilising 25 different RT algorithm random seeds.

Total doses required to kill **all clonogenic cells** were obtained from simulations and dose enhancement ratio **(DER)** was calculated as the comparison of the amount of cells killed at a given **RT dose with or without modelled nanoparticles**.

Results

AuNPs diluted rapidly over time but this was mitigated with the use of weekly and bi-weekly injection schedules (Fig 3).

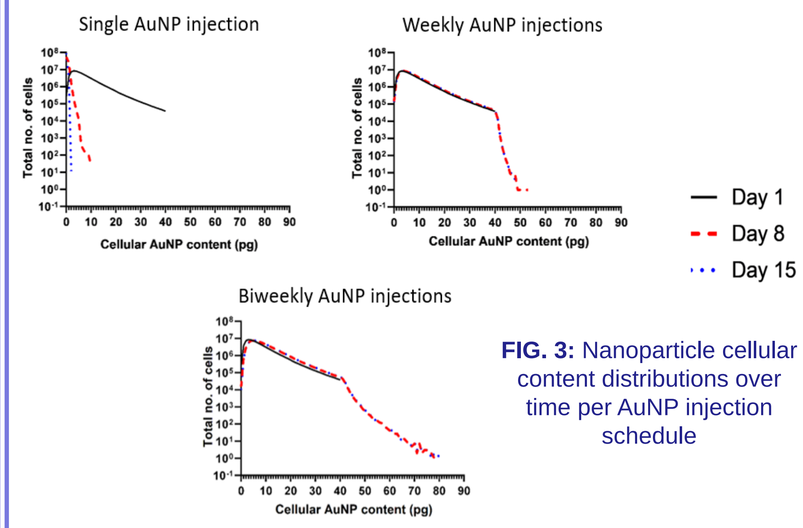

FIG. 3: Nanoparticle cellular content distributions over time per AuNP injection schedule

Total radiation doses required for tumour control were significantly reduced when AuNPs were used ($p < 0.05$) (Fig. 4-6). The exception was the total dose for hypoxic tumours with AR applied receiving 2 Gy/# RT, as tumour control was not achieved even with AuNPs (Fig. 5).

Tumour control was achieved for lower doses in oxic and hypoxic tumours with AuNPs present, with the lowest total dose outcomes associated with bi-weekly AuNP injections (Fig 4-6).

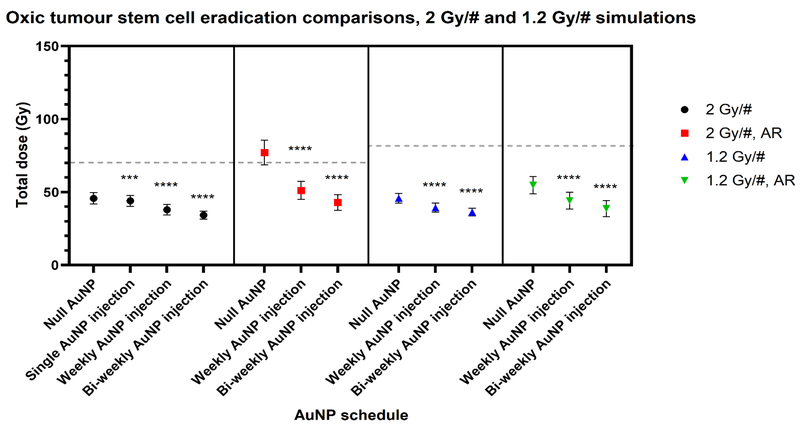

FIG. 4: Total dose mean and standard deviations resulting in 0 surviving stem cells for oxic tumours receiving 2 Gy/# and 1.2 Gy/# RT. (Clinically reported total dose lines for 2 Gy/# (3-5) and 1.2 Gy/# (6) at 70 Gy and 81.6 Gy respectively included, $p \leq 0.001$ = ***, $p \leq 0.0001$ = ****)

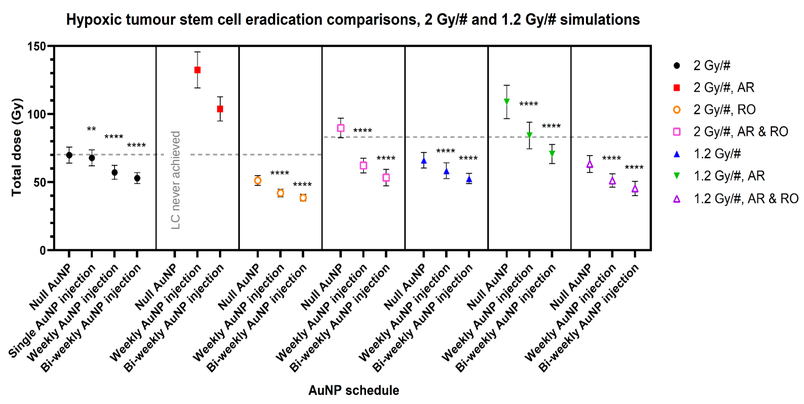

FIG. 5: Total dose mean and standard deviations resulting in 0 surviving stem cells for hypoxic for varying AuNP injections, with the delivery of 2 Gy/# and 1.2 Gy/# RT. (Clinically reported total dose lines for 2 Gy/# (3-5) and 1.2 Gy/# (6) at 70 Gy and 81.6 Gy respectively included, $p \leq 0.01$ = **, $p \leq 0.0001$ = ****).

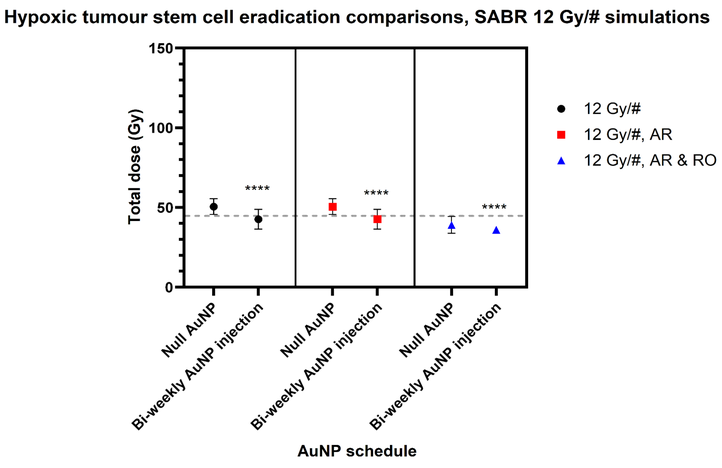

FIG. 6: Total dose mean and standard deviations resulting in 0 surviving stem cells for hypoxic tumours with/without AuNP, for simulations delivering SABR 12 Gy/# RT with/without AR and/or ROx. (Clinically reported total dose line for HNC SABR treatments at 44 Gy included (7), $p \leq 0.0001$ = ****).

Simulated 1.2 Gy/# and 12 Gy/# RT regimens were associated with reduced total radiation dose outcomes compared to 2 Gy/# RT simulations, as expected. The application of AR was associated with increases in required total doses, whilst ROx was associated with reductions in required total doses.

Increasing tumour α/β values resulted in an increase in required total doses, both with and without AuNPs injections applied for a 2 Gy/# RT regimen (Fig. 7).

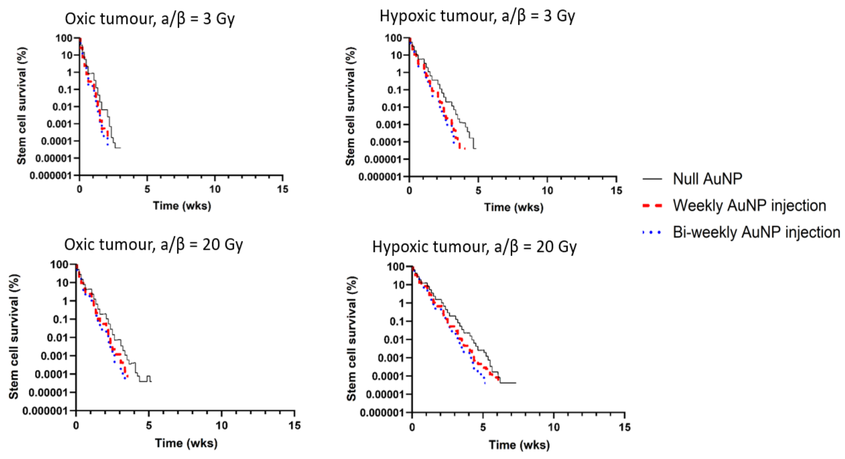

FIG. 7: Stem cell survival in oxic and hypoxic tumours for different tumour fractionation radiosensitivities

Discussion

Single AuNP injections had minimal (yet significant) impact on reducing the total dose for 100% tumour control due to the dilution of effects from cellular division and cell kill (Fig. 4-7).

AuNP injections on a weekly and bi-weekly basis resulted in **significantly reduced total radiation doses required to achieve tumour control**, with bi-weekly injections associated with greater reductions due to increasingly larger concentrations of AuNPs. In most simulations where the absence of AuNPs required RT doses above standard prescriptions, the addition of AuNPs allowed for reductions below these doses (i.e. control without dose escalation or increased toxicity).

1.2 Gy/# and 12 Gy/# treatments resulted in reduced total dose outcomes. An increase in α/β tumour values correlated to increased required total doses for tumour control. These outcomes show support for the use of AuNPs for tumours across a spectrum of α/β values, and the potential for effective >10Gy α/β value HNC tumour control, particularly in hypoxic (radioresistant) conditions.

Summary

AuNPs offers a method through which radioresistant tumours may be treated effectively.

However, results suggest the need for regular administrations, of AuNPs for effective radiosensitisation to occur.

The use of AuNPs was shown theoretically to be an effective method of enhancing radiosensitivity to achieve effective tumour control, permitting the potential reduction of delivered doses and normal tissue complications, alongside effective treatment of radioresistant (hypoxic or rapidly re-growing) tumours that may be otherwise uncontrollable with RT.

ACKNOWLEDGEMENTS:

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