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

M. Huynh1, W. Phillips2,4, I. Kempson3, E. Bezak1,4

1Cancer Research Institute and School of Health Sciences, University of South Australia, Adelaide, Australia
2Department of Medical Physics, Royal Adelaide Hospital Cancer Centre, Australia
3Future Industries Institute, University of South Australia, Mawson Lakes Campus, Adelaide, Australia
4School of Physical Sciences, University of Adelaide, North Terrace, Australia

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).

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 radiotherapeutic tool for assessing RT regimens based on the efficiency of tumour cell kill for individual tumour and cell properties (1) (Fig. 2).

This project developed the HYP-RT software to incorporate nanoparticle sensitisation, with AuNPs 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 10^6 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/2.

Variations in the tumour radiosensitivity (i.e. α/β 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).

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 doses outcomes associated with bi-weekly AuNP injections (Fig. 4-6).

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 resulted in required total 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 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.

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References