

**Deterministic modelling of kinetics and
radiobiology of radiation-cisplatin
interaction in the treatment of
head and neck cancers**

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Abstract

One of the main objectives of combining radiation treatment and chemotherapy is to obtain a therapeutic gain by an improved tumour control with less or no enhancement of normal tissue toxicity. The optimal schedule for the combined treatment of cisplatin-radiation is still under investigation. Neither the optimal time interval, nor the most adequate sequence of administration of cisplatin and radiation are known. The results of the trials are also inconclusive. Some trials showed a supra-additive effect from the administration of cisplatin before radiotherapy, others, on contrary, from the injection of drug after radiotherapy.

The present work encompasses the major challenges brought by the combined modality treatment: cisplatin-radiotherapy. The major goal of this work was to investigate the optimal treatment sequencing between cisplatin and radiotherapy and also the optimal schedule for head and neck carcinomas. Therefore, a computer-based tumour model with literature-given biological parameters has been developed which has allowed the simulation of treatment with radiation and chemotherapy. Radiotherapy has been simulated on the virtual tumour and the effects of radiotherapy on tumour regression and regrowth have been analyzed. Also, the mechanisms of cisplatin's action on tumour have been implemented, and the phenomena of drug resistance and tumour repopulation during chemotherapy studied. Finally, the combined modality treatment has been simulated, and the effect of drug-radiation interaction on tumour behaviour evaluated.

The current investigation has shown that cisplatin administered immediately before radiation gives similar tumour control to the post-radiation sequencing of the drug. Furthermore, the killing effect of the combined modality treatment on tumour increases with the increase in cell recruitment. The individual cell kill produced by cisplatin and radiation leads to an additive-only tumour response when the treatments are given concurrently, and for a synergistic effect cisplatin must potentiate the effect of radiation. The final conclusion, by which cisplatin

administered on a daily basis leads to a better tumour control than cisplatin administered weekly, is in accordance with the latest trial results on head and neck cancers. Therefore, treatment regimens that correlate better with the pharmacokinetics and the radiobiological properties of the therapeutic agents result in better outcomes.

Thesis Statement

This work contains no material which has been accepted for the award of any other degree or diploma in any university or other institution and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text.

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Adelaide

13th of September 2004

Publications and presentations

Publications in refereed journals

L. Marcu, E. Bezak, I. Olver, T van Doorn, Tumour resistance to cisplatin: a modelling approach, *Physics in Medicine and Biology* 2005; 50:93-102.

L. Marcu, AB Lyons, E. Bezak, T van Doorn, The mechanisms and the onset of accelerated repopulation of radiotherapy stimulated squamous cell carcinoma, *Austral-Asian Journal of Cancer* 2004; 3:167-171.

L. Marcu, T van Doorn, I. Olver, Modelling of post irradiation accelerated repopulation in squamous cell carcinomas, *Physics in Medicine and Biology* 2004; 49:3767-3779.

L. Marcu, T van Doorn, I. Olver, Cisplatin and radiotherapy in the treatment of locally advanced head and neck cancer: a review of their cooperation, *Acta Oncologica* 2003; 42:315-325.

L. Marcu, T van Doorn, I. Olver, S. Zavgorodni, Growth of a virtual tumour using probabilistic methods of cell generation, *Australasian Physical and Engineering Sciences in Medicine* 2002; 25:155-161.

Submitted papers in refereed journals

L. Marcu, T van Doorn, E. Bezak, Determination of cell cycle phase-specific α parameters for squamous cell carcinomas of the head and neck, *International Journal of Radiation Oncology Biology Physics*, 2004.

L. Marcu, E. Bezak, I. Olver, T van Doorn, Scheduling cisplatin and radiotherapy in the treatment of squamous cell carcinomas of the head and neck: a modelling approach, *International Journal of Radiation Biology*, 2004.

Conference presentations

L. Marcu, T van Doorn, E. Bezak, I. Olver, Tumour resistance to cisplatin: a modelling approach, *MOT Meeting, Adelaide*, May 2004.

L. Marcu, AB Lyons, T van Doorn, E. Bezak, The mechanisms and the onset of accelerated repopulation of radiotherapy stimulated squamous cell carcinoma, *MOT Meeting, Adelaide*, May 2004.

L. Marcu, T van Doorn, I. Olver, Cell recruitment in tumour regrowth during radiotherapy: a modelling approach, *WC2003, Sydney*, August 2003.

T van Doorn, **L. Marcu**, I. Olver, S. Zavgorodni, Inter-relation of biological parameters in the computer simulation of the temporal development of a head and neck tumour, *ICTR, Lugano*, Switzerland, March 2003.

L. Marcu, T van Doorn, I. Olver, S. Zavgorodni, Recruitment and stem cell cycle duration in accelerated repopulation of radiotherapy stimulated squamous cell carcinoma, *ICTR, Lugano*, Switzerland, March 2003.

L. Marcu, T van Doorn, I. Olver, S. Zavgorodni, Monte Carlo simulation of the radiotherapy of a virtual head and neck tumour, *EPSM, Rotorua*, New Zealand, November 2002.

L. Marcu, T van Doorn, I. Olver, S. Zavgorodni, Computer simulation of tumour growth and cellular phase distribution prior to chemoradiotherapy, *EPSM, Fremantle*, September-October 2001.

L. Marcu, T van Doorn, I. Olver, Daily versus weekly administration of cisplatin in combined chemoradiotherapy, *AIP Conference, Adelaide*, December 2000.

Other presentations

L. Marcu, Accelerated repopulation of radiotherapy stimulated squamous cell carcinoma, *ACPSEM student night*, October 2003.

“First prize for the best postgraduate paper presentation”

L. Marcu, Radiotherapy treatment of a virtual head and neck tumour by Monte Carlo simulation, *ACPSEM student night*, October 2002.

“Second prize for the best postgraduate paper presentation”

L. Marcu, Computer simulation of tumour growth and cellular phase distribution prior to chemoradiotherapy, *ACPSEM student night*, September 2001.

“First prize for the best postgraduate paper presentation”

In memory of my Father