THE INFLUENCE OF REPOPULATION MECHANISMS ON TREATMENT GAP TIMING IN HEAD AND NECK CANCER RADIOTHERAPY

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BACKGROUND

In head and neck cancers tumour repopulation and hypoxia are the leading cause of treatment failure. Various mechanisms behind repopulation have been identified: recruitment of quiescent cells, accelerated stem cell division, loss of asymmetrical division of stem cells and abortive division (see table 1) [1]. The latter mechanism refers to the proliferation of differentiated cells rather than stem cells, however, it can still contribute towards overall repopulation. Advanced head and neck cancers are often managed with altered fractionation schedules, such as accelerated radiotherapy, in order to overcome malignant repopulation. Treatment breaks can be employed to allow normal tissue recovery.
The aim of the present work is to illustrate the influence of repopulation due to both stem and differentiated cells on treatment break timing during accelerated radiotherapy in head and neck carcinomas.

Table 1. Repopulation mechanisms in head and neck carcinomas and their corresponding definitions

Repopulation mechanism	Effect / definition	Type of cells affected
Cell recruitment	Recycling the quiescent cells into the cell cycle	Quiescent cells
Accelerated repopulation	Shortening of cell cycle time	Proliferating stem cells
Loss of asymmetrical division	Symmetrical division of stem cells in mitosis (i.e. two daughter stem cells)	Proliferating stem cells
Abortive division	Limited number of proliferations after which the cell becomes sterile	Proliferating differentiated cells (finitely proliferating cells or doomed cells)

METHODS

A Monte Carlo computational method has been employed to simulate the growth of a head and neck carcinoma, with biologically realistic parameters [2]. In the model, stem and differentiated cells represent about 16% of the tumour population and have a mean cell cycle time of 33h.
The aim of the simulation was to follow the behaviour of the virtual tumour on a temporal scale and to analyse tumour response to altered fractionation radiotherapy when all the mechanisms responsible for repopulation are activated. Based on the RTOG-9030 schedule [3] (1.6 Gy/fraction, twice daily, 6 hours apart, 5 days a week and a total number of 42 fractions), three different timings for treatment interruptions have been simulated using the Linear Quadratic model: after 20, 24 and 28 fractions, respectively. Both stem and differentiated cells have been monitored and their contribution towards tumour growth analysed and discussed.

RESULTS

Due to the activation of repopulation mechanisms during radiotherapy, there is a large increase in the percentage of stem and also differentiated cells that contribute to tumour development. While before radiotherapy the tumour consisted of 6% stem cells and 10% differentiated cells, during accelerated radiotherapy, both percentages increased drastically, depending also on the timing of treatment breaks. Therefore, the average percent of stem cells varied from 41.3% (break after 20 fractions) to 36.6% (break after 28 fractions), while the average percent of differentiated cells varied from 30.5% (break after 20 fractions) to 33.7% (break after 28 fractions).

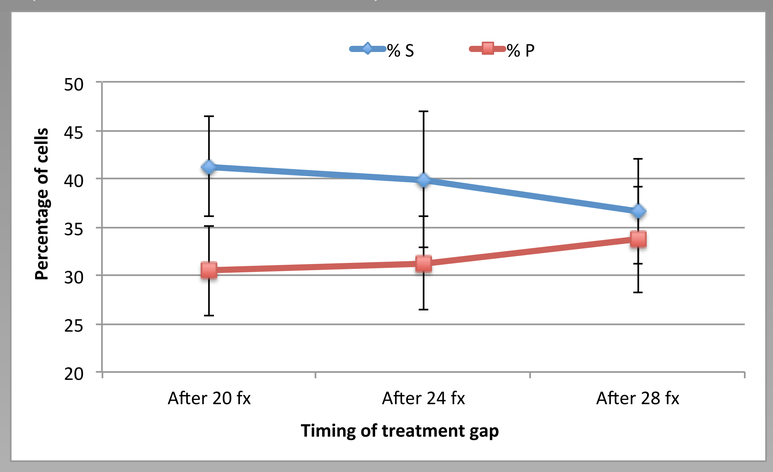

Figure 1. The influence of treatment gap timing on percentage of cell type

An interesting observation is the fact that the percentage of stem cells decreases with the delay of treatment gap (figure 1). This is because early breaks (after 20 fractions) do not allow sufficient cell kill among the continuously proliferating stem cells to control the tumour (figures 2 and 3 – enlarged graph for small number of cells). The behaviour of differentiated cells is just the opposite, to keep a constant cell kill along the treatment.

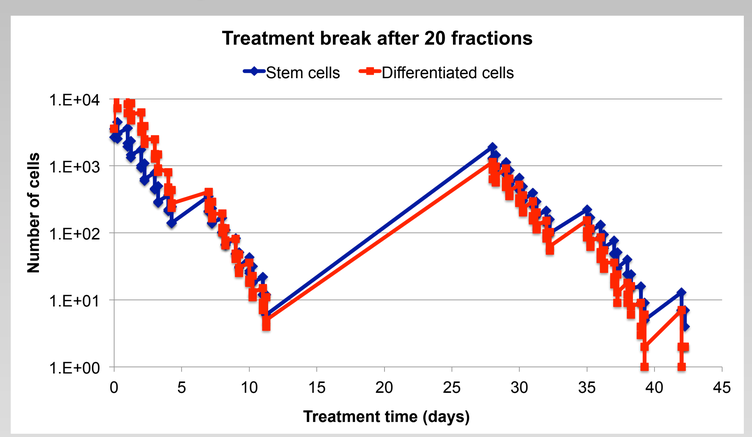

Figure 2. Surviving curves of stem and differentiated cells under accelerated RT with treatment gap after 20 fractions

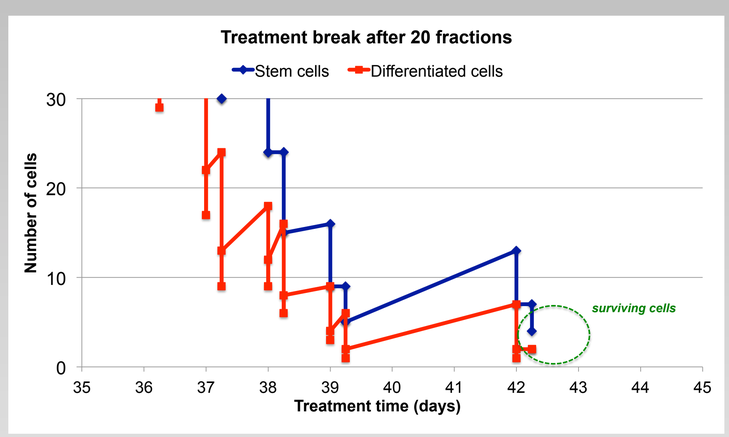

Figure 3. Enlarged representation of the end part of surviving curve from Figure 2

CONCLUSIONS

The model has shown that the timing of treatment breaks is an important factor influencing tumour control in rapidly proliferating tissues.
Not only stem cells but also differentiated cells, via abortive division, can contribute to malignant cell repopulation during treatment.
Differentiated cells undergoing abortive division are 'doomed' cells as they eventually cease creating new cells and die out.
On the other hand, stem cells are able to regrow the tumour, thus for their eradication there is need for fine adjustments of treatment parameters.

ACKNOWLEDGEMENT

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