Modelling the effect of Radiotherapy on tumour growth inhibition: the head and neck tumour case

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Physiomics' Virtual Tumour™ technology

Physiomics' key technology is Virtual Tumour, which provides a platform for identifying, ranking and optimizing anti-cancer treatments, and in particular combination regimens [1,2]. Virtual Tumour (Figure 1) is a computer model that simulates tumour cell division and the effect of antineoplastic agents, taking into consideration the differences between proliferative cells and those that are part of the necrotic core. The complexity of the model is deliberately constrained so that it can be parameterized with data that are usually produced during drug development. These data include PK data for the drug, biomarkers showing the cell population response, and growth measurements showing how tumour growth is affected. This technology provides a rationale for designing an appropriate schedule, and allows our partners to prioritize the most effective drug combinations.

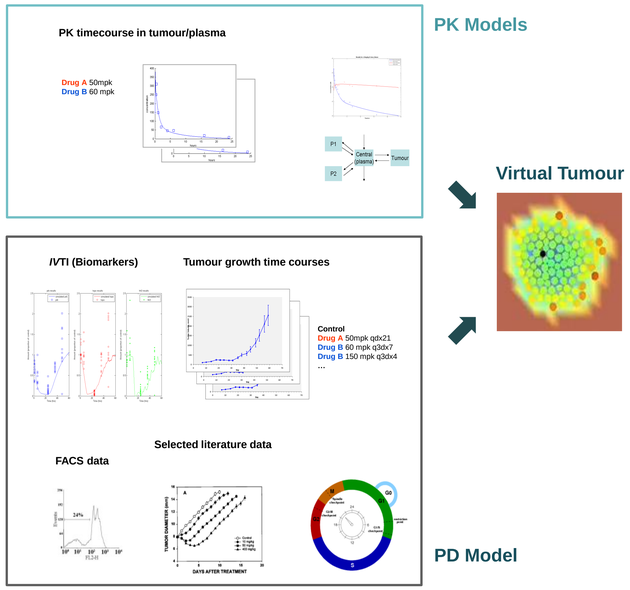

Figure 1. Physiomics' Virtual Tumour simulation platform is a computer simulation of a growing tumour, which integrates the cell division dynamic with the effect of antineoplastic agents. The platform is composed of PK models of the drugs of interest, as well as a pharmacodynamic model of cell-cycle progression. Drug effect can be calibrated by using various data sources: *in vivo* target inhibition (*IVTI*), xenograft growth time courses, flow cytometry and public literature data.

Aims and objectives

We have previously developed models that replicate and predict the effect that radiation (RT) has on tumour growth inhibition in several preclinical studies. These studies involve different RT doses and regimes as well as combinations with therapeutic agents with disparate mechanism of action. These encouraging results in the preclinical space led us to develop an enhanced strategy for modelling RT treatments using a tumour model that can predict tumour shrinkage and long-term regrowth in clinical setting (squamous cell carcinoma of the head and neck).

Data sets

- Phase 3 randomized trial of concomitant radiation and cisplatin in patients with advanced head and neck cancer. A dose of 70 Gy in 35 fractions over 7 weeks was delivered. Cisplatin (100 mg/m^2) was administered over 1 hour on day 1 of weeks 1, 4 and 7. (ClinicalTrials.gov Identifier: NCT00094081) [3]
- Phase 3 randomized study of cisplatin in patients with recurrent or metastatic head and neck cancer. A dose of cisplatin (75 mg/m^2) was administered on day 1 every 21. (ClinicalTrials.gov Identifier: NCT00415194) [4]

Characterisation of clinical head and neck tumour dynamics

- The initial rate of SLD (sum of longest diameter) shrinkage depends on the SLD before treatment. The tumour with the largest initial SLD shows the fastest initial tumour shrinkage rate (Figure 2 and 3).
- The magnitude of the tumour shrinkage can not be explained only by depletion of proliferative layer of the tumour.
- Many tumours remained suppressed for several years and a wide range of times to regrowth were observed (Figure 3).

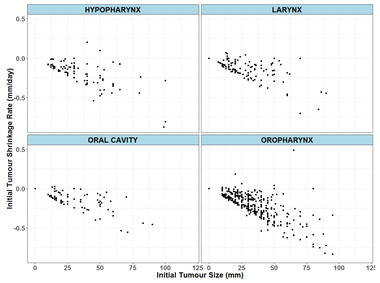

Figure 2: Initial shrinkage rate vs Initial tumour size.

Initial rate = (SLDt1 - SLDo)/(t1 - to) where t1 = time of the first observation after treatment, to is the time 0 and the subscripts on SLD correspond at the time of measurement.

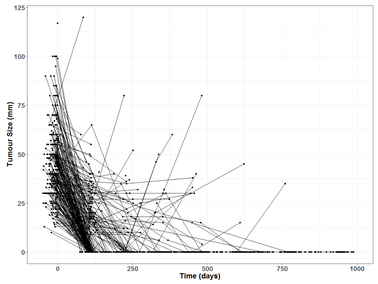

Figure 3: Change in the primary site lesion size over time.

Implementation of tumour growth model

We adapted our Virtual Tumour™ model to enable it to capture the experimental findings noted above.

- We assumed that the mechanism of action of RT and cisplatin at the cell cycle level in the clinical model is similar to the previously developed preclinical model.
- We hypothesized that the proliferative layer status plays a role protecting the physical integrity of the necrotic core and preventing it from being degraded by biological or physical processes. Reducing the growing layer width by depleting the number of viable cells therefore contributes to the tumour size shrinkage via necrotic core material leakage.
- As it has been shown that cell cycle doubling time was a strong prognostic factor for RT response, we estimated the tumour cell doubling times by calibrating the tumour regrowth to match locoregional control probability curves [5,6].

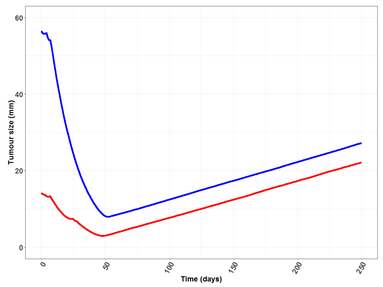

Figure 4: Effect of different Initial tumour size on tumour shrinkage over time. Treatment: 3Gy (5 days On/2 days Off) for 2weeks. 30 Gy total.

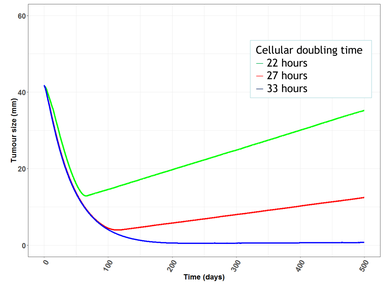

Figure 5: Effect of different cellular doubling time on tumour shrinkage over time for three different doubling time. Treatment: 2Gy (5 days On/2 days Off) for 6weeks. 60 Gy total

Virtual Tumour clinical model for cisplatin

Cisplatin mode of action. It damages DNA during S and G2 phases. It also delays G2 phase.

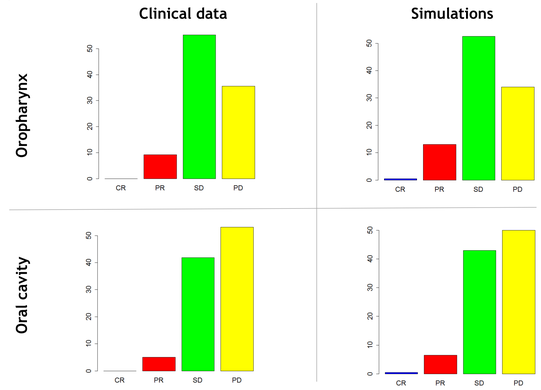

Figure 6: Complete response (CR), partial response (PR), stable disease (SD) and progressive disease (PD) rates by tumour location (clinical vs simulated)

Virtual Tumour clinical model for RT & cisplatin

Radiation (RT) mode of action. It damages DNA in all phases.

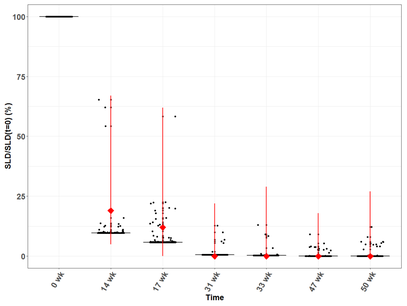

Figure 7: Percentage tumour shrinkage over time with respect to the tumour size before treatment. The red dots show the median of the clinical data. Black dots indicate individual simulation and back lines are simulated median.

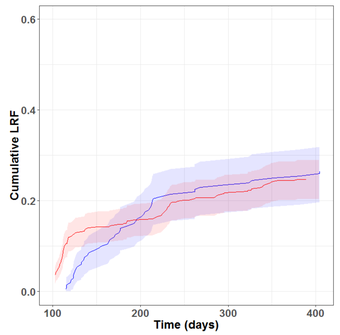

Figure 8: Cumulative locoregional failure/ regrowth rate vs time. Clinical results in red and simulated in blue.

Conclusions

Starting with a model that explained and predicted the effect of cisplatin/radiotherapy on tumour growth inhibition in the preclinical space we were able to extend it to one that describes both tumour growth inhibition and regrowth in the clinical space. Thus, we have developed a platform for head and neck cancer that could be used to predict the effects of radiotherapy alone or in combination with other procedures on tumour shrinkage and locoregional control. This approach can also be implemented to model other tumour types.

References:
[1] Fernandez, *et al.* (2011) Modeling the sequence-sensitive gemcitabine-docetaxel combination using the Virtual Tumour. AACR 102nd Annual Meeting, Orlando, FL, April 2-6, 2011. [2] Fernandez, E. et al. Modelling and translating head and neck radiation therapy on all three levels: in vitro, in vivo and clinical. PAGE Meeting, Lisbon, Portugal (2016). [3]: https://clinicaltrials.gov/ct2/show/NCT00094081 [4]: https://clinicaltrials.gov/ct2/show/NCT00415194 [5]: Corvo, R et al. Potential doubling time in head and neck tumors treated by primary radiotherapy: Preliminary evidence for a prognostic significance in local control. International Journal of Radiation Oncology Biology Physics , Volume 27 , Issue 5 , 1165 - 1172 [6]: Kotelnikov, VM et al. Cell kinetics of head and neck cancers. Clin Cancer Res May 1 1995 (1) (5) 527-537