University of Utah
UNDERGRADUATE RESEARCH JOURNAL

MATHEMATICAL MODELING OF ADAPTIVE THERAPY IN PROSTATE CANCER

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Prostate cancer is a hormonally driven cancer. These cancer cells need androgen, a class of male sex hormone, to survive and grow. Standard treatments for prostate cancer target androgens. This type of therapy is denoted as hormone therapy. Yet, for patients with recurring cancer, hormone therapy is not effective because cancer cells become testosterone independent over time, and consequently, the cells gain resistance and do not respond to therapy. There are studies that suggest therapy administered in intervals [1], as opposed to continuous treatments, could prevent this occurrence. We have analyzed mathematical models of dynamic biological systems for prostate cancer progression [1][2] in order to explore the effect of treatment timing to find the most effective therapy in delaying the inevitable emergence of testosterone resistant cells.

We investigated two interval treatments: adaptive therapy and metronomic therapy. Metronomic therapy is solely based on time. Prior to treatment, time intervals are chosen and the drug is only administered during specified time intervals. Adaptive therapy is dependent on the individual patient's PSA levels. There are predefined upper and lower bounds that are created using the patient's pre-treatment PSA levels. If the PSA levels exceed the upper bounds, the drug is administered. Then, once the PSA drops back to the lower bound, treatment will subside. This happens relatively quickly. In this aspect, it minimizes the patient's exposure to the drug and only given "as needed". It appears that less treatment would give longer time to resistance, and literature has shown that adaptive therapy is the most optimal treatment method in prolonging testosterone immunity. However, we explored these claims and found different variations of metronomic therapy to perform better than variations of adaptive therapy. By manipulating the treatment window to be as short and frequent as needed, we were able to show metronomic therapy can mimic the brevity of adaptive therapy. In addition, we were able to find more optimal PSA bounds that would deliver a longer time to resistance than the initial bounds in the pre-existing models.

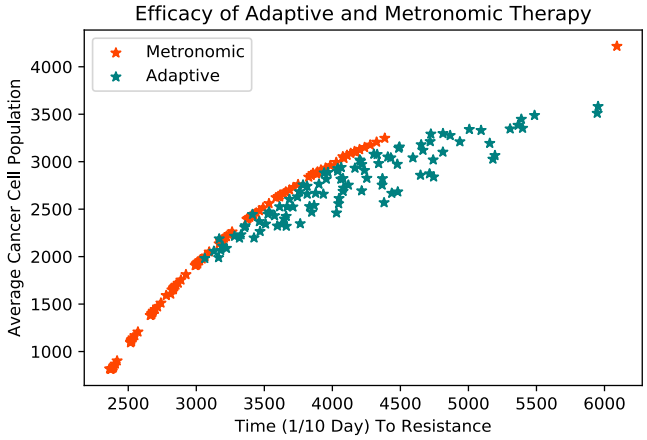

Figure 1:

Scatter plot of both therapies showing the relationship of time to resistance with the average cancer cell population before emergence of resistance.

As shown, adaptive therapy is not always the most effective at prolonging resistance. There are some cases where metronomic therapy outperforms adaptive therapy. In the process of this research, we have found that the current model lacks the flexibility to include realistic mechanisms. We have also developed another mathematical model to give more insight. This will be used to push for an explanation of our current findings and answer the new question posed: Does adaptive therapy succeed only through brevity?

References

[1] Kam, Y., Das, T., Minton, S., & Gatenby, R. A. (2014). Evolutionary strategy for systemic therapy of metastatic breast cancer: balancing response with suppression of resistance. *Women's Health*, *10*(4), 423-430.

[3] Jain, H. V., Clinton, S. K., Bhinder, A., & Friedman, A. (2011). Mathematical modeling of prostate cancer progression in response to androgen ablation therapy. *Proceedings of the National Academy of Sciences*, *108*(49), 19701-19706.

[3] Zhang, J., Cunningham, J. J., Brown, J. S., & Gatenby, R. A. (2017). Integrating evolutionary dynamics into treatment of metastatic castrate-resistant prostate cancer. *Nature communications*, *8*(1), 1816.