A model of natural selection predicts treatment resistance in prostate cancer

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Standard of care treatment for recurrent and advanced prostate cancer includes chemical castration. Inevitably, however, such treatment results in hormone-refractory tumors with dire prognosis. Clearly, a predictive mathematical model of this process would greatly improve our understanding and ability to mitigate castration resistance in this tumor. Here I develop an adaptive dynamics model of androgen-ablation therapy and show that it predicts progression of treatment resistance in a significant subset of prostate cancer patients. The model assumes that castration resistance evolves due to natural selection on androgen receptor (AR) expression. Formulation and parameterization of the model was completed based on a sample of 25 patients treated with intermittent androgen ablation therapy. The model was then used to predict PSA dynamics in an independent set of 30 patients from the same clinical study. Predictions were reasonably accurate typically for one cycle, and for some patients up to 4 cycles. However, there were significant exceptions in some cases the model exhibited no predictive power. These observations are consistent with the conclusion that the model accurately reflects castration resistance arising via natural selection acting on AR expression, but fails for cases in which resistance is caused by a different mechanism, like “outlaw" or AR bypass pathways. This modeling approach therefore may provide a noninvasive method to identify emerging resistance mechanisms in nascent hormone-refractory tumors and to plan treatment to delay development of castration resistance.