A Mechanistic-Statistical QSP framework Integrating Clonal Competition and Survival Models to Optimize Androgen Deprivation Therapy in Prostate Cancer

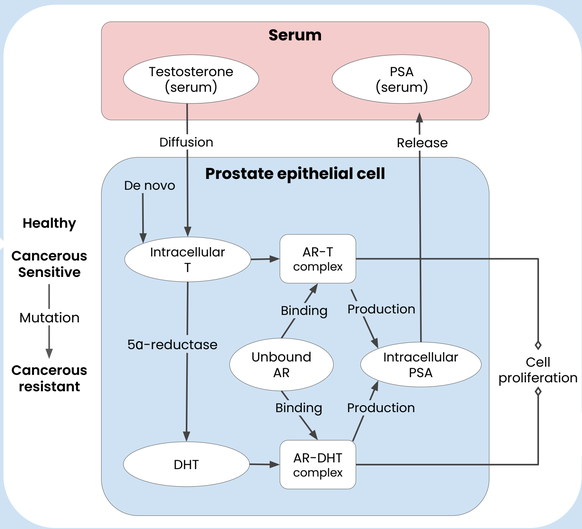
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Combining **QSP with survival models** supports the hypothesis that **intermittent therapy initially delays prostate cancer** progression through cellular competition, but **continuous suppression provides superior long-term survival**

1 QSP MODEL

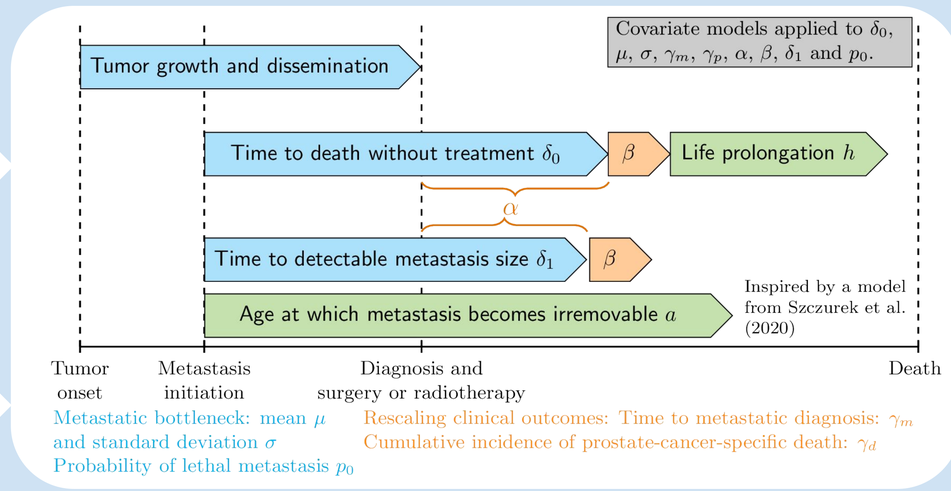
Preclinical and Clinical data



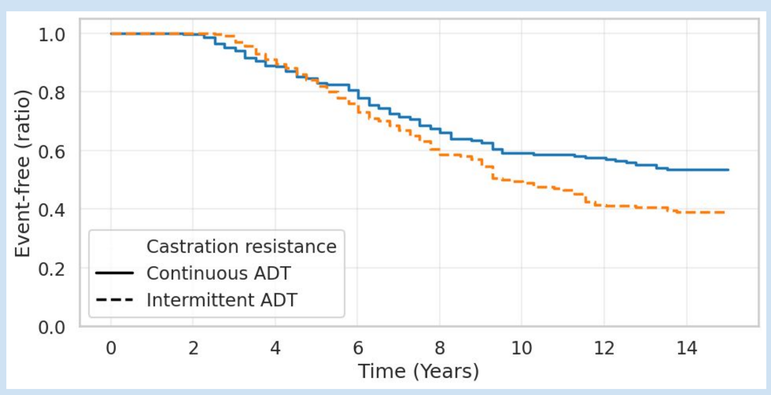
PSA projections

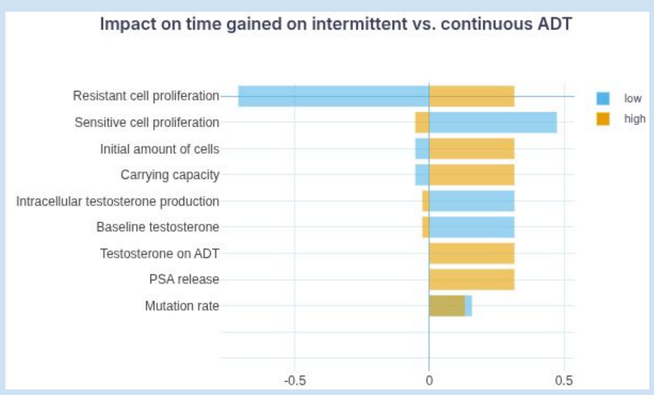
2 STATISTICAL MODEL

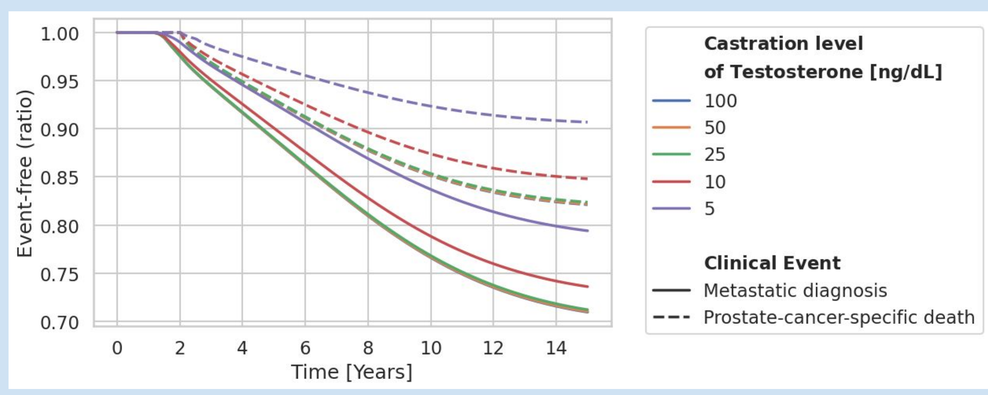
Clinical trial data & SEER database



3 SIMULATION RESULTS







OBJECTIVE

This work develops a QSP mechanistic-statistical framework to evaluate how androgen deprivation therapy (ADT) schedules drive progression from hormone-sensitive to metastatic castration-resistant prostate cancer. By integrating intra-tumoral cellular dynamics with statistical survival models, the framework predicts time to metastasis and prostate-cancer-specific mortality while evaluating competitive dynamics between hormone-sensitive and resistant cell populations to optimize ADT.

METHODS

1. Mechanistic QSP Model & Clonal Competition

- **Cell Proliferation & Biomarkers:** Modeled prostate-specific antigen (PSA) production, androgen receptor (AR) signaling, and cellular proliferation as functions of serum testosterone and intratumoral dihydrotestosterone (DHT) (adapted from Jain et al.).
- **Clonal Dynamics:** Incorporated three cell populations: healthy, hormone-sensitive, and hormone-resistant. This allows to capture the adaptive transition to castration resistance under treatment pressure.
- **Calibration:** Calibrated using preclinical animal PD data and longitudinal clinical trials evaluating continuous vs. intermittent ADT.

2. Statistical Survival Bottleneck Framework

- **Time-to-Event Modeling:** Coupled QSP-simulated tumor/PSA dynamics to a stochastic bottleneck model for metastatic initiation and cancer-specific mortality (adapted from Szczurek et al.).
- **Patient Covariates:** Integrated baseline PSA, age, Gleason score, and first-line treatment as prognostic covariates.
- **Data Calibration:** Parametrized via individual-level SEER database cohorts and summary survival outcomes from ADT clinical trials (Naik et al.).

RESULTS

Long-Term Efficacy & Castration Depth

- Continuous ADT is consistently superior to intermittent ADT for long-term metastasis-free and prostate-cancer-specific survival, in agreement with clinical evidence.
- Deep testosterone suppression (castration levels < 20 ng/mL) significantly delayed progression to metastasis and extended survival relative to partial suppression.

Emergent Short-Term Dynamics: Competitive Release

- Intermittent ADT provided transiently better tumor burden control in high-grade / aggressive disease during early treatment cycles.
- Mechanism: Off-cycle testosterone recovery allowed hormone-sensitive clones to suppress the rapid growth of aggressive, hormone-resistant clones via microenvironmental resource competition, consistent with previously reported results (Brady-Nicholls et al.)
- Transition: The competitive benefit is temporary; resistant clones eventually dominate, confirming long-term superiority of continuous suppression.

CONCLUSION

- **Translational Bridge:** Successfully links preclinical androgen receptor biology and clonal competition to clinical population survival outcomes.
- **Mechanistic Insight:** Demonstrates that short-term transient advantages of intermittent ADT stem from clonal competition, offering a rationale for adaptive dosing strategies based on initial tumor aggressiveness.
- **Early Evaluation:** Enables in silico exploration of novel investigational therapies on long-term clinical endpoints prior to phase 3 trials.

REFERENCES

[1] Jain et al., 2011 [2] Szczurek et al., 2020 [3] Surveillance, Epidemiology, and End Results (SEER) Program [4] Naik et al., 2016 [5] Brady-Nicholls et al., 2020