Optimal Strategies for Active Surveillance of Men With Prostate Cancer

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Prostate Cancer (PCa)

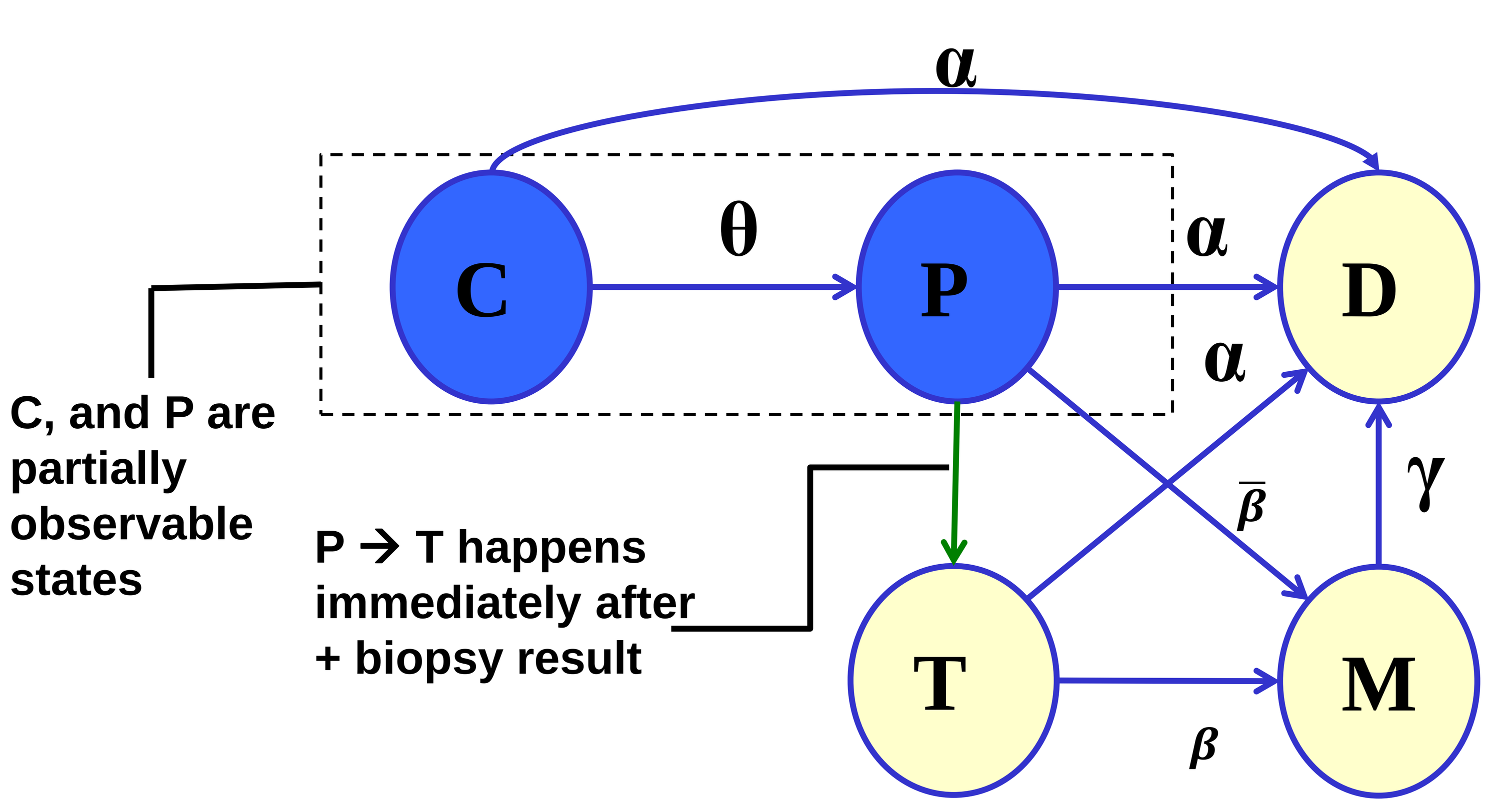
- PCa is the 2nd most common cancer in American men
- American Cancer Society estimates about 29,430 deaths from PCa in 2018
- Early detection and treatment can mitigate the deterioration of patients' health and improve survival rate
- Common treatments include radial prostatectomy, radiation therapy, and active surveillance
- Active surveillance is suited for low-risk cancer because it:
  - Has comparable survival rate with other treatments
  - Avoids treatment with significant side-effects

Active surveillance (AS) of PCa

- AS: periodically monitoring cancer using PSA or biopsy tests until it has progressed
- Testing infrequently could cause missed detection, but testing too frequently could cause significant harm from biopsies
- Research questions:
  - *What is the optimal policy for when to biopsy?*
  - *When should biopsy be deferred for patients with low-risk PCa?*

Partially Observable Markov Decision Process (POMDP) Model

- 5 states: C = low-risk cancer, P = progressed cancer, T = treatment, M = metastasized cancer, D = death
- Belief vector represent partially observable states of C and P:
  - $\pi_n = \mathbb{P}(P)$, the probability patient has progressed cancer in period n
  - π_n is updated using Bayesian updating based on the observation in the current period
- Actions: wait (a_n = W), and biopsy (a_n = B)
- Objective: maximize Quality Adjusted Life Years (QALY)
- We consider the following transition probabilities:



- Optimality equations:
  - Patient continues on to next period if the decision is to wait, or (–) biopsy result
  - Patient enters treatment immediately following a (+) biopsy

$$v_n(\pi_n) = \max \begin{cases} r_n(\pi_n, W) + \lambda[\alpha_n \bar{R}_{n+1}(D) + (1-\alpha_n)\bar{\beta}_n \hat{\pi}_n^o(P)\bar{R}_{n+1}(M) \\ +(1-\alpha_n)(1-\bar{\beta}_n \hat{\pi}_n^o(P))v_{n+1}(\pi_{n+1}^o)], & a_n = W \\ r_n(\pi_n, B) + \lambda[\mathbb{P}(+ \mid \pi_n, B)(\alpha_n \bar{R}_{n+1}(D) + (1-\alpha_n)\beta_n \hat{\pi}_n^+(P)\bar{R}_{n+1}(M) \\ +(1-\alpha_n)(1-\beta_n)\bar{R}_{n+1}(T) - \kappa) + \\ \mathbb{P}(- \mid \pi_n, B)(\alpha_n \bar{R}_{n+1}(D) + (1-\alpha_n)\bar{\beta}_n \hat{\pi}_n^-(P)\bar{R}_{n+1}(M) \\ +(1-\alpha_n)(1-\bar{\beta}_n \hat{\pi}_n^-(P))v_{n+1}(\pi_{n+1}^-)], & a_n = B. \end{cases}$$

- $\bar{R}(T), \bar{R}(M)$, and $\bar{R}(D)$ are remaining expected QALY rewards in state T, M D, respectively
- r_n is the immediate reward associated with a given action
- v_n is the total remaining QALY

Results

- Used backward induction to generate values for optimality equation at every time period
- Create policy that will indicate whether it is optimal to wait or to biopsy for given belief vector at a given time period
- Figure 1 shows a graphical representation of reward function with respect to π_n, for n = 80

Figure 1: Reward Function (age = 80)

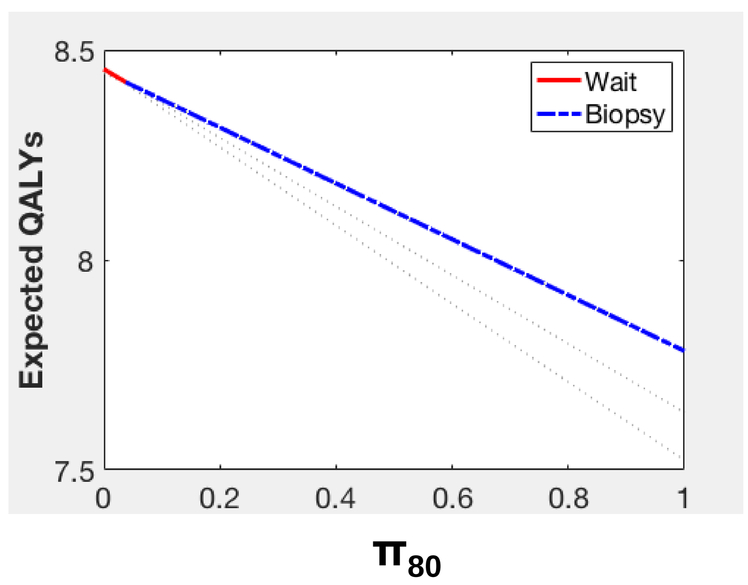
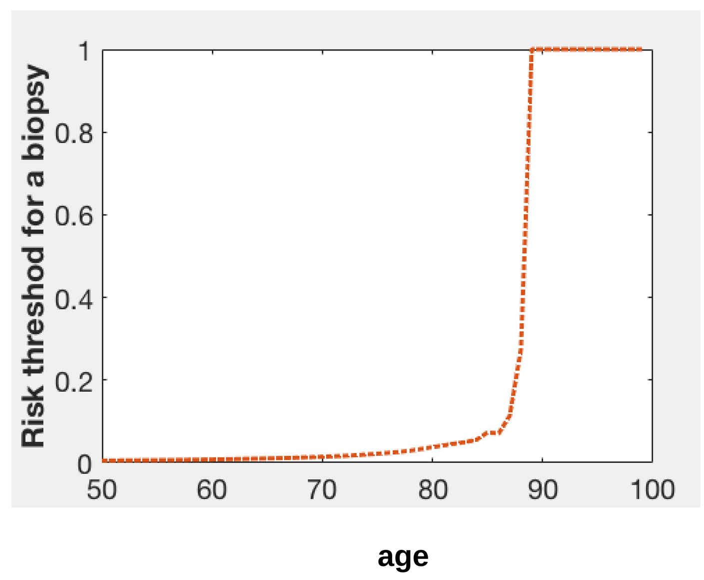


Figure 2: Risk Threshold



- Another property of interest is the *threshold policy*:
  - A threshold policy exists if there is a probability π*, such that if the probability of having progressed cancer is above π*, then the optimal decision is to biopsy; otherwise, waiting is optimal
- Figure 2 shows the threshold with respect to age

Sensitivity Analysis

- One-way sensitivity analysis for certain parameters to vary between their lower and upper bound (Figure 3a-d)
- Test the base case, lower bound, and upper bound for each parameter to see how they affect threshold with respect to time
- Top 4 influential factors: annual QALY for living in treatment (q_T), annual QALY for living with metastasized cancer (q_M), transition probability from P to M ($\bar{\beta}$), and immediate QALY disutility for treatment (κ)

Figure 3a: q_T = [0, 0.05, 0.07]

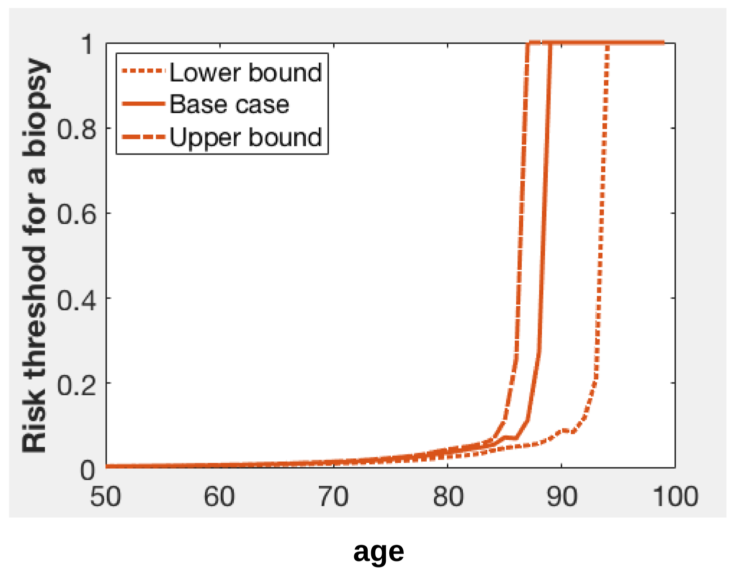


Figure 3b: q_M = [0.14,0.40,0.76]

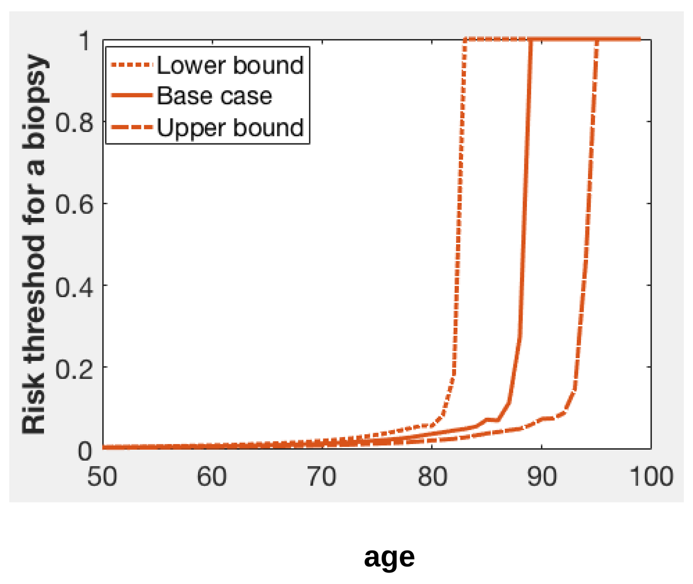


Figure 3c: $\bar{\beta}$ = [0.0552, 0.069, 0.0828]

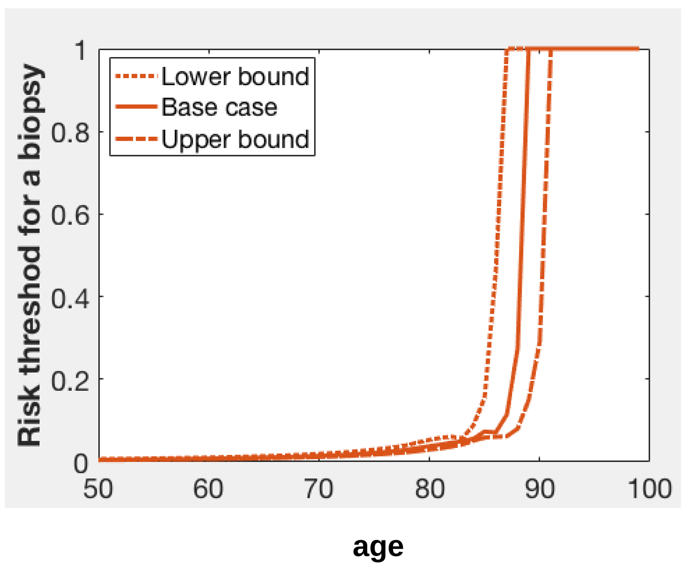
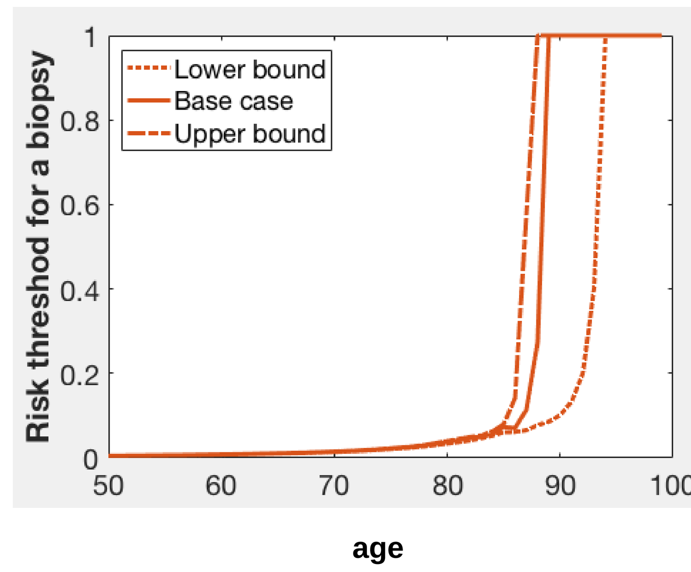


Figure 3d: κ = [0.0917, 0.24667, 0.323]



Conclusions

- There exists a Threshold Policy (π*) at every time period, and this threshold increases with respect to age
- Patients over age 88 are suggested to discontinue surveillance because there is no benefit from treatment due to other cause mortality
- Threshold vs. time is most sensitive to q_M, q_T, $\bar{\beta}$, and κ, and robust to the other values tested (β, f, γ, and θ)

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