When to Treat Prostate Cancer Patients Based on their PSA Dynamics

CLARA day on operations research in cancer treatment & operations management

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Outline

- The clinical problem: Prostate Cancer
- Modeling PSA dynamics
- Making the decision:
  When should each patient start his radiation therapy treatment?
- Conclusions
- Future work
Prostate Cancer Summary Statistics

- In 2008:
  - 24,700 Canadian diagnosed with prostate cancer
  - 4,300 died of the disease (Canadian Cancer Society, 2008)
- BCCA responsible for the delivery of all radiotherapy treatment in BC:

![Prostate Cancer Treatment Pie Chart]

- Radical prostatectomy: 28%
- Radical external RT: 29%
- Brachytherapy: 8%
- Palliative RT: 7%
- Other: 28%
Combining Hormone and Radiotherapy

- High risk localized prostate cancer patients are often treated with hormone therapy prior to their radiotherapy treatment
  - Goal: starve tumour cells of testosterone (main fertilizer) resulting in tumour regression
- Patients monitored periodically
  - PSA (blood test) used to predict regression
- “Maximal regression probably occurs when PSA reaches its nadir level” (Gleave, La Bianca and Goldeberg, 2000)
  - Key assumption - The nadir is the ideal time to start RT
- Challenge: Cancers regress at different rates (difficult to predict)
Tumour Regression as a Function of PSA

Tumour Size vs. Time

Tumour

PSA

RT

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Tumour Regression as a Function of PSA
Tradeoffs

Why start RT now?
- Avoid progression
- Risk of cells becoming resistant
- Toxicity of hormone therapy

Why wait?
- Maximum reduction of tumor size under hormone therapy
- More information

Tolerance

Responsiveness

Tolerance Responsiveness Tradeoffs
Start radiation therapy if:
- 8 months of hormone therapy have been received or
- PSA levels start to rise or
- PSA ≥ 1 ng/ml or PSA < 0.05 ng/ml after 4 months
Our Goal

- Improve modeling of PSA kinetics and estimation of future PSA kinetics
- Provide a formal decision making approach and tool to determine when a patient should begin radiation therapy treatment
PSA Kinetics

\[ \ln(PSA) = \alpha + \beta t + \gamma t^2 + \nu \quad \nu \sim N(0, V) \]
Description of the Problem

Population
$N((\alpha, \beta, \gamma), R)$

$\{(\alpha_i, \beta_i, \gamma_i), R_i\}$

$\ln(PSA) = \alpha + \beta t + \gamma t^2 + \nu \quad \nu \sim N(0, V)$
Dynamically Changing Nadir Estimates

\[ \ln(PSA) = \alpha + \beta t + \gamma t^2 + \nu \quad \nu \sim N(0, V) \]
Description of the Problem (Cont.)

Population
$N((\alpha, \beta, \gamma), R)$

Cluster 1
$N((\alpha_1, \beta_1, \gamma_1), R_1)$

Cluster 2
$N((\alpha_2, \beta_2, \gamma_2), R_2)$

Cluster 3
$N((\alpha_3, \beta_3, \gamma_3), R_3)$

$\ln(PSA) = \alpha + \beta t + \gamma t^2 + \nu \quad \nu \sim N(0, V)$
Formulation

Initial Beliefs (based on Population Characteristics) → Observe PSA → Update Curve Parameters

Estimate Nadir
Modeling Initial Beliefs

1. Fit regression curve for each patient
2. Cluster patients
3. Fit regression for each cluster
4. Estimate probability of a patient being in a cluster
163 patients from a prospective randomized trial

All intermediate risk prostate cancer patients (PSA < 40) with no metastasis on staging:
- Either a PSA > 10, or Gleason grade 7, or stage T3a

All received 8 months of hormones before their radiation

All started on luteinizing hormone-releasing hormone with 1 month of nonsteroidal antiandrogen

All had PSA and testosterone readings every 2 months before radiotherapy
Tumor Kinetics

- $X(t) = \text{number of androgen dependent cells}$
- $Y(t) = \text{number of androgen independent cells}$
- $N(t) = \text{total number of cells} = X(t) + Y(t)$

- **Without hormone treatment:**

$$\frac{dN(t)}{dt} = (g - a)N(t) \quad \Rightarrow \quad N(t) = Ce^{(g-a)t}$$

- **With hormone treatment:**

$$\frac{dN(t)}{dt} = gtN(t) -aN(t) \quad \Rightarrow \quad N(t) = Ce^{(1/2)gt^2-at}$$

$PSA \propto N(t)$

$$\ln(PSA) \approx \alpha + \beta t + \gamma t^2$$
Modeling Initial Beliefs

\[ \ln(PSA) = \alpha + \beta t + \gamma t^2 \]

\( t_{\text{nadir}} \)
Modeling Initial Beliefs

- Clustered based on min PSA and $t_{nadir}$
- 3 groups:

<table>
<thead>
<tr>
<th></th>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>$t_{nadir}$ (days)</td>
<td>171</td>
<td>242</td>
<td>&gt;&gt;240</td>
</tr>
<tr>
<td>min PSA</td>
<td>.21</td>
<td>.98</td>
<td>.26</td>
</tr>
<tr>
<td>Probability</td>
<td>72%</td>
<td>20%</td>
<td>8%</td>
</tr>
</tbody>
</table>

Fit regression curve for each patient
Cluster patients
Fit regression for each cluster
Estimate probability of a patient being in a cluster

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Modeling Initial Beliefs

- Weighting regression parameters
- Measurement error

Cluster patients
- Fit regression curve for each patient
- Estimate probability of a patient being in a cluster

Graphs showing PSA vs Time for Group 1, Group 2, and Group 3.
Modeling Initial Beliefs

Logistic regression:

- **Probability in Group 1:**
  \[
  \text{EXP}(2.3 - 0.16 \times \text{iPSA})
  = \frac{1}{1 + \text{EXP}(1.16 - 0.06 \times \text{iPSA}) + \text{EXP}(2.3 - 0.16 \times \text{iPSA})}
  \]

- **Probability in Group 2:**
  \[
  \text{EXP}(1.16 - 0.06 \times \text{iPSA})
  = \frac{1}{1 + \text{EXP}(1.16 - 0.06 \times \text{iPSA}) + \text{EXP}(2.3 - 0.16 \times \text{iPSA})}
  \]

- **Probability in Group 3:**
  \[
  1 - (\text{Probability in Group 1}) - (\text{Probability in Group 2})
  \]
Formulation

1. **Initial Beliefs** (based on Population Characteristics)
2. Observe PSA
3. Update Curve Parameters
4. Estimate Nadir

Flowchart with steps:
- Initial Beliefs (based on Population Characteristics) → Observe PSA → Update Curve Parameters → Estimate Nadir
Timeline

- Observe PSA_t
- Update curve parameters_t

Don't Start

- Receive treatment
- Observe PSA_{t+1}
- Update curve parameters_{t+1}

State Updating (Kalman Filtering)

P(treating at the “right” time)
Model Assumptions

- Disturbances and initial state vector are normally distributed
- Model is time-homogeneous
- Errors are temporally and mutually independent
Curve Update

- **Observation Equation:**
  \[ Y_t = F_t' \theta_{t,i} + \nu_{t,i} \quad \nu_{t,i} \sim N(0, V_{t,i}) \]
  \[ Y_t = \ln(PSA_t) = \alpha_{t,i} + \beta_{t,i} t + \gamma_{t,i} t^2 + \nu_{t,i} \]

- **State Equation:**
  \[ \theta_{t,i} = \theta_{t-1,i} + w_{t,i} \quad w_{t,i} \sim N(0, W_{t,i}); W_{t,i} = 0 \]

- **Updating Equations:**
  \[ \theta_{t,i} = \theta_{t-1,i} + R_{t-1,i} F_t Q_{t,i}^{-1} [Y_t - F_t' \theta_{t-1,i}] \]
  \[ R_{t,i} = R_{t-1,i} - R_{t-1,i} F_t Q_{t,i}^{-1} F_t' R_{t-1,i} \]
  \[ Q_{t,i} = F_t' R_{t-1,i} F_t + V_{t,i} \]
  \[ P(i)_{t+1} = \frac{\sum_{k=1}^{3} P(k)_t \ast \int f(F_{t+1}' \theta_{t,i} ; Q_{t+1,k}) dy}{\int f(F_{t+1}' \theta_{t,i} ; PSA_{t+1}) dy} \]

Probability function of a normal distribution
Distribution of Time of Nadir

\[ t_{\text{nadir}} = -\beta/2\gamma \]

where \((\beta, \gamma) \sim N \left( \left( \beta_{t,i}, \gamma_{t,i} \right); \begin{pmatrix} r_{22_{t,i}} & r_{23_{t,i}} \\ r_{32_{t,i}} & r_{33_{t,i}} \end{pmatrix} \right) \]

As \(P(\gamma > 0) \to 1\),

\[ F(t_{\text{nadir}}) = \int_{-\infty}^{t_{\text{nadir}}} e^{-\frac{1}{2}u^{2}} \frac{1}{\sqrt{2\pi}} \, du \]

(Hinkley, 1969)
Clinically Implementable Policies

- Current policy

- Start RT when the cumulative probability of having reached the nadir is greater than a threshold.

- Start RT when the probability of treating at the nadir is greater than a threshold.
Cumulative Percentage of Patients who Would Have Started RT under Different Decision Rules

- Start RT when the probability of treating at the nadir is maximized

Days from Hormone Therapy Start vs. Cumulative Percentage of Patients
## The Tool

**Patient**: Peter Parker  
**Patient ID**: 129380  
**LHRH hormone start date**: 27/11/08  
**Gleason 1**: 4  
**Gleason 2**: 4

### Estimated time of the nadir (dd/mm/yyyy)
- **25/05/2009**

### Probability of reaching the nadir in the next 60 days
- **0.8%**

### Probability of having reached the nadir
- **0.94%**
The Tool
Current Research

- Develop MDP models to determine
  - “optimal” start time
  - when to take the next reading
  - when to change hormone therapy drug
- Validate model at other sites and with other data
- Undertake a clinical trial to measure benefits of proposed patient adapted protocol
Summary

- Used clustering techniques to capture different types of PSA progressions

- Developed an iterative way to update the estimates of the distribution of the nadir

- By using a threshold to decide whether to start RT, we were able to identify earlier when the nadir is reached
The Big Picture...
Thank you!
MDP Model

- Discrete time, finite horizon MDP
- Action: \( \begin{cases} \text{Start radiation therapy} \\ \text{Don’t start radiation therapy} \end{cases} \)
- State: \( \theta_t = \begin{pmatrix} \alpha_t \\ \beta_t \\ \gamma_t \end{pmatrix} \); \( R_t \)
  - Parameter means
  - Parameter covariances
MDP Model – Maximize Probability of Treating within $\zeta$ of the Nadir

$$\nu_t(\theta_t, R_t) = \max \left\{ \begin{array}{l}
\int \nu_{t+1}(\theta_t + R_t F_{t+1} Q_{t+1}^{-1} Y_{t+1} - F_{t+1}' \theta_t | Y_{t+1}, R_t - R_t F_{t+1} Q_{t+1}^{-1} F_{t+1}' R_t) \\
dP(Y_{t+1} | \theta_t, R_t)
\end{array} \right. $$

Don't Start RT

$$Y_{t+1} \sim N(F_{t+1}' \theta_t, Q_{t+1})$$

$$Q_{t+1} = n_{1t} + 2(t+1)n_{2t} + (t+1)^2(2n_{3t} + r_{22t}) + 2(t+1)^3 r_{23t} + (t+1)^4 r_{33t} + V_t$$

$$F_{t+1} = \begin{pmatrix} 1 \\ t+1 \\ (t+1)^2 \end{pmatrix}$$

$$\theta_t = \begin{pmatrix} \alpha_t \\ \beta_t \\ \gamma_t \end{pmatrix}$$

$$R_t = \begin{pmatrix} r_{1t} & n_{1t} & n_{1t} \\ r_{21t} & r_{22t} & r_{23t} \\ r_{31t} & r_{32t} & r_{33t} \end{pmatrix}$$
Issues Involved in Solving the MDP

- Continuous state space
- Partially observable state space
- Reward function: ratio of correlated Normal random variables