Evaluation of Viable Dynamic Treatment Regimes in a Sequentially Randomized Trial of Advanced Prostate Cancer

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Dynamic Treatment Regime

Therapy of cancer, and many other diseases typically requires multiple stages.

- Failure of initial treatment to achieve a favorable clinical outcome
- Recurrence, toxicity, etc.
- Therapy consists of a sequence of qualitatively different treatments

Dynamic events may affect future treatment decisions.

- Growing back of solid tumors
- Metastasizing to other body sites following a response of chemotherapy
- Regimen-related toxicity
Dynamic Treatment Practice

- Evaluate the patient’s disease
- Choose a regimen
- Treat the patient

Give more of the same regimen

Evidence of Benefit?

YES

NO

Choose something else

RWSL  R  W  S  L
The AI Prostate Cancer Trial

Thall et al. 2007; Millikan et al. 2008

One of the pioneer trials designed with re-randomization (12/1998 – 01/2006 at MDACC)

4 chemo combinations (CVD, KA/VE, TEE, TEC) → 4x3=12 two-stage dynamic treatment strategies

Binary “Response / No-Response” outcomes, based on drop in PSA, in each course

Also collected survival outcome

This study was a groundbreaking early example of a Sequential Multiple Assignment Randomized Trial (SMART, Murphy 2005).
Per-Course Outcomes: (Each course is 8 weeks)

1\textsuperscript{st} Success = [ >40\% drop in PSA and absence of AD]
Repeat a successful trt, otherwise \textbf{re-randomize} the patient among the other 3 trts (\textit{accidentally SMART} !!! )

2\textsuperscript{nd} Success = [ >80\% drop in PSA and absence of AD]

\textbf{Strategy (a, b)}:

- Treat with $a$ in a course.
  - \textbf{Repeat} the current treatment if \textbf{Success} occurs
  - \textbf{Switch} to $a^*$ if \textbf{Failure} occurs

\rightarrow \textbf{Consecutive S-S} with the same regimen \rightarrow \textbf{Declare victory}
\rightarrow \textbf{A total of 2 courses with Failure} \rightarrow \textbf{Admit defeat}
Possible Courses for Strategy (a, a*)

S : Per-Protocol Success;      S : Per-Protocol Failure.

N=150

S (N=80)

S (N=35)

S (N=10)

S (N=2)

S (N=8)

S (N=39)

S (N=17)

Per-protocol dropout (N=12)

S (N=6)

S (N=5)

Per-protocol dropout (N=22)

S (N=26)

S (N=8)

S (N=7)

Per-protocol dropout (N=7)
Randomize patients fairly among the 4 treatments

1\textsuperscript{st} Success = \{ >40\% drop in PSA and no AD \}
Repeat a successful trt, otherwise re-randomize the patient among the other 3 (adapt trt within the patient)

2\textsuperscript{nd} Success = \{ >80\% drop in PSA and no AD \}
Patient Success = \{ 2 consecutive successful courses \}

Patient Failure = \{ A total of 2 unsuccessful courses, or PD, or TOX \} \rightarrow
Stop therapy (an adaptive within-patient decision)
### RWSL

**Failure**

- **Efficacy**
  - EFF0
  - EFF1
  - EFF2
  - EFF3

- **Toxicity**
  - TOX0
  - TOX1
  - TOX2

or PD, or TOX
Possible Courses for Strategy (a, a*): Viable DTRs

EFF0TOX0 (N=80)

N=150

EFF1TOX0 (N=48)

EFF2TOX0 (N=6)

EFFkTOX1 (N=13)

TOX2 (N=3)

EFF0TOX0 (N=35)

EFF1TOX0 (N=39)

EFF2TOX0 (N=4)

EFFkTOX1 (N=2)

TOX2 (N=0)

EFF0TOX0 (N=10)

EFF1TOX0 (N=17)

EFF2TOX0 (N=0)

EFFkTOX1 (N=1)

TOX2 (N=0)

Drop (N=11)

EFF0TOX0 (N=2)

EFF1TOX0 (N=8)

EFF2TOX0 (N=0)

EFFkTOX1 (N=0)

TOX2 (N=0)

N/A

N/A

N/A

N/A
For each patient, we have the following variables:

- **Treatment Actions**

  \( A_j \) : the chemo received at the start of course \( j \) if the patient actually received one.

- **At baseline**

  \( P_1 \) : PSA at baseline.

  \( V_1 \) : indicator of high (versus low) disease volume at baseline.

- **At the end of course \( j - 1 \) and just prior to \( A_j \) for \( j = 2, \ldots, 5 \)**

  \( P_j \) : PSA

  \( T_j \) : Toxicity

  \( E_j \) : compound measure of efficacy

- **Final Survival outcome: \( X \)**
Formally Define Viable DTRs:

\[ L_1 = (P_1, V_1) \quad L_j = (P_j, T_j, E_j, I_{(2(j-1), \infty)}(X)) , \quad j = 2, \ldots, 5. \]

\[ S_j = I_{\{(\text{TOX0, EFF0})\}}[(T_j, E_j)] \quad \text{and} \quad F_j = I_{\{(\text{TOX0, EFF1})\}}[(T_j, E_j)] \]

\[
\begin{align*}
g_{a,a^*,1}(L_1) &= a, \\
g_{a,a^*,2}(L_2) &= \begin{cases} 
  a & \text{if } S_2 = 1 \\
  a^* & \text{if } F_2 = 1 \\
  \text{OFF} & \text{if } S_2 \neq 1, F_2 \neq 1, X > 2
\end{cases}
\end{align*}
\]

\[
\begin{align*}
g_{a,a^*,3}(L_3) &= \begin{cases} 
  a^* & \text{if } S_2F_3 = 1 \text{ or } F_2S_3 = 1 \\
  \text{OFF} & \text{if } S_2F_3 \neq 1, F_2S_3 \neq 1 \text{ and } X > 4
\end{cases}
\end{align*}
\]

\[
\begin{align*}
g_{a,a^*,4}(L_4) &= \begin{cases} 
  a^* & \text{if } S_2F_3S_4 = 1 \\
  \text{OFF} & \text{if } S_2F_3S_4 \neq 1 \text{ and } X > 6
\end{cases}
\end{align*}
\]
\[ Y^{\text{bin}} = y^{\text{bin}}(L) = \begin{cases} 
1 & \text{if } \tilde{S}_j \tilde{S}_{j+1} = 1 \quad \text{for } j = 2, 3 \text{ or } 4 \\
0 & \text{otherwise} 
\end{cases} \]

\[ \tilde{S}_j = I_{\{(\text{TOX}_0, \text{EFF}_0), (\text{TOX}_1, \text{EFF}_0)\}}[(T_j, E_j)] \]

\[ Y^{\text{ord}} = y^{\text{ord}}(L) = \begin{cases} 
1 & \text{if } \tilde{S}_j \tilde{S}_{j+1} = 1 \text{ for } j = 2, 3 \text{ or } 4 \\
0.5 & \text{if } \tilde{S}_2(1 - \tilde{S}_3)(1 - \tilde{S}_5) = 1 \text{ or } (1 - \tilde{S}_2)\tilde{S}_3(1 - \tilde{S}_4) = 1 \\
0 & \text{otherwise} 
\end{cases} \]
\[
C_j = c(E_j, T_j) \\
E_j = \text{Efficacy outcome} \\
\begin{array}{lcccl}
T_j = & \text{TOX0} & 1.0 & 0.5 & 0.1 & X \\
\text{Toxicity} & \text{TOX1} & 0.8 & 0.3 & 0 & X \\
\text{outcome} & \text{TOX2} & X & X & X & 0 \\
\end{array}
\]

\[
Y^{\text{expert}} = y^{\text{expert}}(L) = \frac{\sum_{j=2}^{5} \{1 - I_{\{\text{OFF,N/A}\}}[A_{j-1}]\} C_j}{\sum_{j=2}^{5} \{1 - I_{\{\text{OFF,N/A}\}}[A_{j-1}]\}}
\]
For each switch rule \( g_{a,a^*} \),

\[
\overline{L}_{(a,a^*)} : \text{denote the hypothetical outcome}
\]

\[
Y_{(a,a^*)} = y \left( \overline{L}_{(a,a^*)} \right) : \text{counterfactual endpoint}
\]

\[
(a_{opt}, a^*_{opt}) = \text{arg} \max_{(a,a^*)} E \left[ Y_{(a,a^*)} \right]
\]
Saturated Marginal Structural Mean Model

\[ E \left[ Y_{(a,a^*)} \right] = \sum_{a_1 \in A} \sum_{a_2 \in A - \{a_1\}} \beta_{a_1,a_2} I\{(a_1,a_2)\} \{(a,a^*)\} \]

Inverse Probability Weighted Estimator

\[ \frac{\sum_{i=1}^{n} \Delta_{a,a^+,i} \omega_i Y_i}{\sum_{i=1}^{n} \Delta_{a,a^+,i} \omega_i}, \text{ where} \]

the weights come from two sources:

\[ P \left( A_j = a_j | A_{j-1} = \bar{a}_{j-1}, \bar{L}_j, \mathcal{L} \right) = P \left( A_j = a_j | A_j \neq N/A, \bar{A}_{j-1} = \bar{a}_{j-1}, \bar{L}_j, \mathcal{L} \right) \times P \left( A_j \neq N/A | \bar{A}_{j-1} = \bar{a}_{j-1}, \bar{L}_j, \mathcal{L} \right), \]

For Treatment Assignment

For Patient Drop-out
Inverse Probability of Treatment Weights

Estimate the weights to improve estimation efficiency.

We further considered Inverse Probability of Missing.

<table>
<thead>
<tr>
<th>Group</th>
<th>$A_1$</th>
<th>$A_2$</th>
<th>$A_3$</th>
<th>$A_4$</th>
<th>$\omega_1$</th>
<th>$\omega_2$</th>
<th>$\omega_3$</th>
<th>$\omega_4$</th>
<th>$\omega$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>$a$</td>
<td>OFF</td>
<td>OFF</td>
<td>OFF</td>
<td>4</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
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<tr>
<td>2</td>
<td>$a$</td>
<td>$a$</td>
<td>OFF</td>
<td>OFF</td>
<td>4</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>3</td>
<td>$a$</td>
<td>$a^*$</td>
<td>OFF</td>
<td>OFF</td>
<td>4</td>
<td>3</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>4</td>
<td>$a$</td>
<td>$a^*$</td>
<td>$a^*$</td>
<td>OFF</td>
<td>4</td>
<td>3</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>5</td>
<td>$a$</td>
<td>$a$</td>
<td>$a^*$</td>
<td>OFF</td>
<td>4</td>
<td>1</td>
<td>3</td>
<td>1</td>
<td>1</td>
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<tr>
<td>6</td>
<td>$a$</td>
<td>$a$</td>
<td>$a^*$</td>
<td>$a^*$</td>
<td>4</td>
<td>1</td>
<td>3</td>
<td>1</td>
<td>1</td>
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<tr>
<td></td>
<td>Expert Score&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Expert Score&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Log Survival&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Log Survival&lt;sup&gt;d&lt;/sup&gt;</td>
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<tr>
<td>(CVD, KA/VE)</td>
<td>0.62 (0.47, 0.77)</td>
<td>0.62 (0.47, 0.77)</td>
<td>2.93 (2.59, 3.26)</td>
<td>2.92 (2.58, 3.26)</td>
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<tr>
<td>(CVD, TEC)</td>
<td>0.63 (0.49, 0.77)</td>
<td>0.63 (0.48, 0.78)</td>
<td>3.28 (2.88, 3.67)</td>
<td>3.27 (2.85, 3.68)</td>
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<tr>
<td>(CVD, TEE)</td>
<td>0.57 (0.43, 0.71)</td>
<td>0.57 (0.43, 0.71)</td>
<td>2.93 (2.32, 3.54)</td>
<td>2.92 (2.31, 3.53)</td>
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<tr>
<td>(KA/VE, CVD)</td>
<td>0.65 (0.52, 0.77)</td>
<td>0.67 (0.55, 0.80)</td>
<td>3.20 (2.65, 3.76)</td>
<td>3.20 (2.64, 3.77)</td>
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<tr>
<td>(KA/VE, TEC)</td>
<td>0.70 (0.59, 0.81)</td>
<td>0.73 (0.62, 0.84)</td>
<td>3.05 (2.69, 3.41)</td>
<td>3.05 (2.68, 3.42)</td>
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<tr>
<td>(KA/VE, TEE)</td>
<td>0.62 (0.47, 0.77)</td>
<td>0.65 (0.50, 0.80)</td>
<td>3.00 (2.54, 3.46)</td>
<td>3.00 (2.53, 3.47)</td>
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<tr>
<td>(TEC, CVD)</td>
<td>0.77 (0.65, 0.89)</td>
<td>0.77 (0.65, 0.89)</td>
<td>3.02 (2.68, 3.36)</td>
<td>3.18 (2.89, 3.47)</td>
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<tr>
<td>(TEC, KA/VE)</td>
<td>0.72 (0.56, 0.87)</td>
<td>0.72 (0.56, 0.88)</td>
<td>3.13 (2.60, 3.67)</td>
<td>3.31 (2.80, 3.82)</td>
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<tr>
<td>(TEC, TEE)</td>
<td>0.73 (0.62, 0.83)</td>
<td>0.73 (0.62, 0.83)</td>
<td>3.03 (2.63, 3.42)</td>
<td>3.17 (2.83, 3.50)</td>
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</tr>
<tr>
<td>(TEE, CVD)</td>
<td>0.65 (0.50, 0.80)</td>
<td>0.68 (0.54, 0.83)</td>
<td>3.06 (2.43, 3.69)</td>
<td>3.02 (2.42, 3.63)</td>
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</tr>
<tr>
<td>(TEE, KA/VE)</td>
<td>0.63 (0.50, 0.75)</td>
<td>0.66 (0.53, 0.79)</td>
<td>2.83 (2.38, 3.28)</td>
<td>2.79 (2.36, 3.23)</td>
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</tr>
<tr>
<td>(TEE, TEC)</td>
<td>0.67 (0.53, 0.81)</td>
<td>0.71 (0.57, 0.84)</td>
<td>2.87 (2.42, 3.31)</td>
<td>2.83 (2.39, 3.27)</td>
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</tbody>
</table>

<sup>a</sup> 1 imputed for the dropouts with CVD in the 1st course, and 0 imputed for all other dropouts.

<sup>b</sup> 0 imputed for the dropouts with TEC in the 1st course, and 1 imputed for all other dropouts.

<sup>c</sup> Maximum of the survival time in reference group imputed for dropouts with KA/VE in the 1st course and 1/2 of the minimum remaining survival time imputed for all other dropouts

<sup>d</sup> 1/2 of the minimum remaining survival time in reference group imputed for dropouts with CVD or TEE in the 1st course and Maximum of the survival time time imputed for all other dropouts
1. Re-randomization design using “repeat a winner” and “switch-away from a loser” rules is a good idea.

2. Limitations of this study
   - Moderate sample size
   - Conservative simultaneous confidence intervals

3. Make sure you define patient outcome carefully. It is seldom binary or simple, and it should reflect actual clinical practice.

4. Cute DTR and IPW methodologies are the right thing to do, but they are of little use without intelligent medical collaborators.
Prostate Cancer Recurrence Management

- Prostate cancer recurrence need to be managed after initial treatment (EBRT).
- PSA is measured over time as an indicator for increasing risk of recurrence.
- Salvage treatment decision need to be made dynamically to prolong the recurrence free survival

When would be the best time to initiate salvage treatment?
The proposed method provides reasonable amount of robustness for the problem

- Random Forest to provide more robustness and flexibility model for weight estimation.
- Non-parametric survival estimation without any assumption like proportional hazard.

Random Survival Forest (Bou-Hamad, 2011) could be more reasonable estimation for the weights

- More efficient maximization method is needed for higher dimension $b$, e.g. Adaptive grid approach (Leary, 2001)
Ultimate Goals:
Eyeball Test
Empirical Data + Novel Statistical Methodology

Better Prognostic Tools

• Patient satisfaction and personalized care
• Allocation of scarce and expensive resources (e.g. liver transplantation and HCV treatment)
• Survival improvement
• Guidance on adaptive treatment strategies for patients
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