Individual Prediction and Validation Using Joint Longitudinal-Survival Models in Prostate Cancer Studies

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1. INTRODUCTION
   • Prostate Cancer
   • Motivation; Individual Predictions
   • Joint Longitudinal and Survival Models

2. PROSTATE CANCER APPLICATION
   • Datasets, Models and Estimation
   • Individual predictions, longitudinal and survival

3. WEBSITE

4. ESTIMATING SALVAGE HORMONE THERAPY EFFECT

5. MAKING MODEL MORE NON-PARAMETRIC

6. VALIDATION
PROSTATE CANCER

- Common cancer in older men
- Usually growing slowly, most people diagnosed with prostate cancer die of something else
- Treatment for localised disease
  - Radiation therapy (plus or minus hormones)
  - Surgery
- Following radiation PSA rise suggests cancer is regrowing
- Biochemical recurrence
  - Based on PSA
  - Not the real thing
- Clinical recurrence is the real thing
GOAL

- Develop a website for patients and their physicians, psacalc.sph.umich.edu
- The patients were previously treated with radiation therapy for localised prostate cancer
- The patient inputs individual characteristics (stage of disease, treatment dose) and post-treatment measures of health
- The website provides quantitative information about future disease progression
Predictions of PSA for Censored Subjects

ID 1255

ID 1756

ID 2341

ID 2427
Individual Predictions for Censored Subjects

ID 1255

log(1+PSA) vs Time (mos)

ID 1756

log(1+PSA) vs Time (mos)

ID 2341

log(1+PSA) vs Time (mos)

ID 2427

log(1+PSA) vs Time (mos)
Dynamic Predictions of Probability of Recurrence

![Graphs showing PSA measures and SLCM prediction with probability of recurrence on the y-axis and ln(PSA+0.1) on the x-axis.](image-url)
MOCK EXAMPLE

- Patient treated in Oct 2003 for prostate cancer
- Pre-treatment characteristics
  - PSA = 10.3
  - T-stage = 3
  - Gleason grade = 8
  - Treatment dose was 74 Gy
- Patient has not experienced any clinical recurrence of prostate cancer
<table>
<thead>
<tr>
<th>Date</th>
<th>PSA</th>
</tr>
</thead>
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<tr>
<td>29 Feb 2004</td>
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<td>1 May 2004</td>
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<td>4 July 2006</td>
<td>1.3</td>
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<tr>
<td>29 Feb 2008</td>
<td>1.7</td>
</tr>
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<td>1 Jan 2010</td>
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- What is the probability of the prostate cancer coming back within 3 years of today?
• Joint model trained on a large dataset

• Parameter estimates applied to this patient

• $P(\text{prostate cancer recurrence within 3 years}) = 0.22$
Prob(clinical recurrence within 3 years) = 0.22

- What should you do?
  - Intervene with salvage hormone therapy?
  - Order another PSA test for X months in the future?
  - Don’t change the original plan

- This talk
  - How do we get 0.22
  - Attempts to validate the prediction
JOINT MODELS FOR LONGITUDINAL AND SURVIVAL DATA

- Setting: clinical trial or observational study

- Data
  - $(t_i, \delta_i)$, censored event time
  - $X_i$, time-independent covariates
  - $Y_{ij}$, time-dependent covariate, biomarker

- Both $T$ and $Y$ are response variables
• Modelling choices for joint distribution of $T$ and $Y$
  - $[T, Y|X]$
  
  - Factor as $[T|X]$ and $[Y|X, T]$
  
  - Factor as $[Y|X]$ and $[T|Y, X]$
• \([T, Y|X] \sim \text{Multivariate Normal}\)
  
  – deGruttola and Tu (1994), Schluchter (1992)
  
  – \(T\) (or \(\log(T)\)) is censored

• \([T|X]\) and \([Y|X, T]\)
  
  – Pawitan and Self (1993)
  
  – \([Y|X, T]\) does not match time sequence of data collection
• \([Y|X]\) and \([T|Y,X]\)
  - Faucett and Thomas (1996), Wulfsohn and Tsiatis (1997), and others
  - Most popular
  - Usually involves latent variables, \(R_i\)
  - \([Y_{ij}|X_i, R_i]\)
  - \([T_i|Y_i, X_i, R_i] = [T_i|X_i, R_i]\)
• Factor \([T, Y \mid X]\) as \([Y \mid X][T \mid Y, X]\)

• \([Y \mid X]\), longitudinal model
  – longitudinal random effects model

• \([T \mid Y, X]\)
  – time-dependent proportional hazards model

• Use joint model for prediction of future longitudinal and event times for individual patients
PROSTATE CANCER DATASETS

• Prostate cancer patients treated with radiation therapy.

• Training data
  – RTOG, n=615
  – Detroit, n=1268
  – Univ Michigan, n=503

• Testing data
  – Melbourne, n=395
  – Vancouver, n=846
Longitudinal Data (Y). Post-treatment PSA

- measured approximately every 6 months

- a total of 46,000 post-treatment PSA values

- median no. of PSA per patient is 8

- 10 year follow-up
Endpoints and Censoring (T)

- 15% events: local/regional recurrence, distant metastasis
- 85% censored patients:
  - 20% are dead not from prostate cancer.
  - 65% are lost to follow-up or censored by the end of the study
- 10% of patients received salvage hormone therapy (HT) prior to recurrence (because of rising PSA).
PSA profiles for 3 groups.
(a) Events, (b) Censored, (c) Hormonal Therapy.
**Statistical Model**

**Notation**

- \( X_i \) - baseline covariates.
- \( Y_i(t) = PSA_i(t) \) - longitudinal PSA data
- \( T_i \) - time of recurrence.
- \( R_i \) - random effects.
- Assumption - \( Y_i \) and \( T_i \) conditionally independent given \( R_i \) and \( X_i \).
Longitudinal model

log(PSA+0.1)

ptPSA: level of post-therapy PSA

short term evolution:
drop of PSA after EBRT

long term evolution:
rate of rise of PSA

years after the end of EBRT
Longitudinal. Non-linear random effects models.

\[ \log \left[ PSA_i(t) + 0.1 \right] = Z_i(t) + \epsilon_{it} \]

\[ Z_i(t) = r_i0 + r_i1 f(t) + r_i2 t \]

where \( f(t) = ((1 + t)^{-1.5} - 1) \), \( \epsilon_{it} \sim t\)-distribution and \( R_i = (r_{i0}, r_{i1}, r_{i2}) \) are random effects for subject \( i \).

\[ [R_i \mid X_i] \sim N(\mu X_i, \Sigma) \]

\[ X_i = (bPSA_i, Tstage_i, Gleason_i) \]
Hazard model. Time-dependent proportional hazards.

\[ \lambda_i(t \mid X_i, Z_i, s_{li}, HT_i) \]

\[ = \lambda_0(t) \exp[\eta g(Z_i(t)) + \omega s_{li}(t) + \gamma X_i + \phi HT_i(t)] \]

\[ s_{li}(t) = \text{slope of } Z_i(t) \]

\[ HT_i(t) = \begin{cases} 
0 & \text{if } t < S_i \\
1 & \text{if } t > S_i 
\end{cases} \]

\[ \lambda_0(t) \text{ is a step function.} \]
• Estimation via MCMC
  – parameters $\theta$
  – latent variables $R_i$
  – draws of $\theta, R_i$, save for later use
  – over 12 hours of computing to obtain estimates

• Likelihood
  \[ \prod_i \int \left[ \prod_j P(Y_{ij} | \theta, X_i, R_i) \right] \cdot P(T_i, \delta_i | \theta, X_i, R_i) \cdot f(R_i) \, dR_i \]
PREDICT FUTURE PSA VALUES.

From model

$$\log\left[ PSA_i(t) + 0.1 \right] = Z_i(t) + \epsilon_{it}$$

$$Z_i^k(t) = r_{i0}^k + r_{i1}^k f(t) + r_{i2}^k t$$

where $k$ denotes $k^{th}$ draw from posterior distribution (MCMC)
PREDICT RECURRENCE FOR CENSORED PATIENTS IN DATASET

- For patient $i$, the conditional probability of recurrence within $a$ months

$$P[T < t_i + a \mid T > t_i, Y_i, X_i] = \frac{1}{K} \sum_{k} P[T < t_i + a \mid T > t_i, X_i, \theta^k, R^k_i]$$

where $\theta^k, R^k_i$ are draws from the posterior distribution
Residual time distribution

\[
P[T > t_i + a | T > t_i, X_i, \theta, R_i] = \exp \left[ - \int_{u=t}^{t+a} \lambda_i(u | X_i, \theta, Z_i(u), sl_i(u)) \, du \right]
\]

\[
\lambda_i(u | X_i, \theta, Z_i(u), sl_i(u)) = \lambda_0(t) \exp[\eta g(Z_i(u)) + \omega sl_i(u) + \gamma X_i]
\]
Predictions of PSA for Censored Subject

Prediction of PSA values

95% uncertainty band
Today
Predicted PSA

PSA in ng/ml

Years from the end of radiation therapy
Residual Time Distribution for Censored Subject

Probability of clinical recurrence within 3 years

Chance of clinical recurrence

Years from today

0 0.5 1 1.5 2 2.5 3

0 0.2 0.4 0.6 0.8 1
Predictions of PSA for Censored Subjects

Years from the end of radiation therapy

PSA in ng/ml

95% uncertainty band
Today
Predicted PSA

Today
Predicted PSA

1
10
0
2
4
6
8
10
12
14

PSA in ng/ml

Years from the end of radiation therapy
Residual Time Distribution for Censored Subject

Probability of clinical recurrence within 3 years

Years from today

Chance of clinical recurrence

0
0.2
0.4
0.6
0.8
1
1.5
2
2.5
3
Predictions of PSA for Censored Subjects

Years from the end of radiation therapy

PSA in ng/ml

95% uncertainty band
Today
Predicted PSA

0
0.1
1
10
0
0.5
1
1.5
2
2.5
3
3.5
4

Today
0
0.5
1
1.5
2
2.5
3
3.5
4

Predicted PSA
0
0.1
1
10
Predict Recurrence for New Censored Patient \((m)\)

- Want \(P[T < t_m + a \mid T > t_m, Y_m, X_m]\)
- Obtain by averaging
  \[
P[T < t_m + a \mid T > t_m, X_m, \theta^k, R^k_m]\]
- Don’t want to add new subject to dataset
- Have draws of \(\theta\) from converged chain, needs draws of \(R_m\)
- For each \(\theta^k\) run quick MCMC to get a draw of \(R^k_m\).
- Draw \(R_m\) from \(P(R_m \mid \theta^k, T_m > t_m, Y_m, X_m)\)
- Use likelihood contribution from subject \(m\)
  \[
P(Y_m \mid \theta^k, X_m, R_m)P(T_m, \delta_m = 0 \mid \theta^k, X_m, R_m)\]
Website for the public to use

psacalc.sph.umich.edu.

Public = cancer patients and their doctors
Issues

- What to present?
- How to present it?
- A lot of clinical information is required as input
- Needs to run fast
- Aid in clinical decision making
- Could present predictions if salvage HT is started
- How to publicize it
- How much validation needs to be done and shown
Possible uses

• Individual patient monitoring

• Definition of an endpoint
  – Taylor definition:
    1st time $\Pr(\text{Clinical Recurrence within 3 years}) > 0.1$

• Entry criteria for clinical study
  – eg $\Pr(\text{Clinical Recurrence within 3 years}) > 0.1$
ISSUES IN VALIDATION

- Training data, External validation data
- Prediction at time $t$ about an event in $(t, t + a)$
- Prediction is a distribution function, data is censored
SIMPLE GRAPHICAL APPROACH FOR BINARY Y
(Hosmer-Lemeshow)

- $\hat{P}_i = \hat{P}(X_i) = \text{predicted probability } P(Y = 1|X_i)$
- Create homogeneous groups of people with similar $\hat{P}_i$
- Estimate proportion for people in group $g$, $\hat{P}_g$
- Compare $\hat{P}_i$ with $\hat{P}_g$
ALTERNATIVE APPROACHES WHEN Y IS BINARY

- ROC curves, AUC
  - Popular and familiar
  - Change $\hat{P}_i$ to $\hat{P}_i/2$ would give same ROC curve.
SIMPLE GRAPHICAL APPROACH FOR SURVIVAL DATA (like Hosmer-Lemeshow)

- Create homogeneous groups with “similar”
  \( \hat{S}(t + a | T_i > t, H_i) \)

- Estimate empirical survival distribution for people in group \( g \), \( \hat{S}_g(a) \)

- Compare \( \hat{S}(t + a | T_i > t, H_i) \) with \( \hat{S}_g(a) \)
  - Calibration
1. Estimation on training data (3 cohort of patients):
   . 2386 patients

2. Predict on training data

3. Prediction on 2 independent cohorts:
   . 846 patients from Vancouver cohort
   . 395 patients from Melbourne
Graphical validation

- 4 groups based on $\hat{S}(3 + a|T_i > 3, H_i(t))$
  - $\hat{S} \in (1.0, 0.975)$
  - $\hat{S} \in (0.9, 0.975)$
  - $\hat{S} \in (0.7, 0.9)$
  - $\hat{S} \in (0.0, 0.7)$

- Make predictions for everyone in testing datasets who are at risk at 3 years based on their PSA data prior to 3 years

- Place person into group

- Kaplan-Meier curve of what happened to them after 3 years
Survival Probability

Time since radio-therapy

- $P(3 \text{ years}) \in [0,0.025]$
- $P(3 \text{ years}) \in (0.025,0.1]$
- $P(3 \text{ years}) \in (0.1,0.3]$
- $P(3 \text{ years}) \in (0.3,1]$
Survival Probability

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- $P(3 \text{ years}) \in (0.3, 1]$
A complication with Kaplan-Meier estimate, dependent censoring

- people are given salvage hormone therapy (HT) prior to an event, because of rising PSA

- Options
  - censor at time of HT
  - call HT an event
  - ignore HT
  - something fancier
Survival Probability

Time since radio−therapy

Survival Probability

Time since radio−therapy

P(3 years) ∈ [0, 0.025]
P(3 years) ∈ (0.025, 0.1]
P(3 years) ∈ (0.1, 0.3]
P(3 years) ∈ (0.3, 1]
Survival Probability

Time since radio-therapy

- $P(3 \text{ years}) \in [0, 0.025]$
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Survival Probability

Time since radio-therapy

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- \( P(3 \text{ years}) \in (0.025, 0.1] \)
- \( P(3 \text{ years}) \in (0.1, 0.3] \)
- \( P(3 \text{ years}) \in (0.3, 1] \)
Is this worth all the trouble? Simpler approaches:

- Cox model (PHM) with baseline variables:
  \[ P(T_i \leq t + a | T_i \geq t, X_i; \hat{\theta}_0) \]

- PHM with baseline variables & the last PSA (landmark analysis)
  \[ P(T_i \leq t + a | T_i \geq t, Y_i(t); \hat{\theta}_t) \]
References

- Yu et al, 2004, Statistica Sinica
- Taylor et al, 2005, J Clin Oncol
- Yu et al, 2007, JASA
- Pauler and Finkelstein, 2002, Stat in Med
- Proust-Lima et al, 2009, Biostatistics
Collaborators and funding

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Hormonal therapy and dependent censoring

• Salvage hormonal therapy (HT) is sometimes given when a patient exhibits a rising trend in PSA, before a clinical event.

• HT delays occurrence of the clinical event

• HT is a nuisance factor present in the data.

• A different problem would be estimating the effect of HT.
\[ \lambda_i(t \mid X_i, Z_i, sl_i, HT_i) = \lambda_0(t) \exp[\eta g(Z_i(t)) + \omega sl_i(t) + \gamma X_i + \phi HT_i(t)] \]

\[ sl_i(t) = \text{slope of } Z_i(t) \]

\[ HT_i(t) = \begin{cases} 
0 & \text{if } t < S_i \\
1 & \text{if } t > S_i 
\end{cases} \]

Sensitivity analyses suggests estimates of \( \eta, \omega, \gamma \) are stable.
Using model to estimate effect of salvage hormonal therapy

- When PSA starts to rise some patients receive an intervention, which is thought to delay recurrence
- Level and slope of PSA are the important factors associated with the decision to initiate salvage therapy
- Of all patients about 10% receive salvage therapy prior to any recurrence
- Of all recurrences about 75% are before salvage therapy and 25% are after salvage therapy
Years After EBRT

log(PSA+0.1)

EBRT
Salvage ADT
Recurrence

Years After EBRT
“Casual” model

- $\lambda_i^{(0)}(t)$ is the natural or counterfactual hazard for patient $i$, assuming he will never be given salvage therapy
- $\lambda_i^{(0)}(t)$ is a subject specific curve (a latent curve)
- Patient $i$ gets salvage therapy at time $S_i$
- $\lambda_i^{(0)}(t) exp(\phi I(t > S_i))$ is the hazard for patient $i$
- $exp(\phi)$ is relative hazard
  - Mechanistic interpretation
  - Subject specific interpretation
  - Effect of salvage therapy on the individual
  - $\phi$ could depend on covariates
- Approach, estimate jointly $\phi$ and $\lambda_i^{(0)}(t)$
Model for $\lambda_i^{(0)}(t)$

- Think of $\lambda_i^{(0)}(t)$ as a "latent curve" for patient $i$

- $\lambda_i^{(0)}(t) = \lambda_0(t) \exp[\eta g(Z_i(t)) + \omega s_l_i(t) + \gamma X_i]$

- $Z_i(t)$ and $s_l_i(t)$ are deterministic, defined by random effects and parameters

- Note $Z_i(t)$ and $s_l_i(t)$ in this model are values as if salvage therapy is not given

- Involves values of $Z_i(t)$ and $s_l_i(t)$ after $S_i$
Years After EBRT

$\log(\text{PSA} + 0.1)$

- EBRT
- Salvage ADT
- Recurrence

Years After EBRT
Years After EBRT

log(PSA+0.1)
• Fit joint model
  – Longitudinal model for PSA in absence of hormone therapy (delete PSA data after $S_i$)
    $\lambda_0(t) \exp[\eta g(Z_i(t)) + \omega s l_i(t) + \gamma X_i + \phi I(t > S_i)]$
  
• Note, $Z_i$ and $s l_i$ are the factors that “drive” the decision to initiate salvage therapy
Key assumption

- Let $T_i^{(0)} \sim \lambda_i^{(0)}(t)$
- Let $S_i$ be time of salvage HT
- $R_i$ are subject-specific parameters for person $i$
- $X_i$ are baseline covariates for person $i$
- $T_i^{(0)}$ conditionally independent of $S_i$ given $R_i$ and $X_i$
- Assumption can be weakened
Results

• Data,
  – 2781 patients
  – 305 got salvage therapy
  – 338 recurrences

• Estimation, two-stage, longitudinal then survival

• $exp(\hat{\phi}) = 0.24$, 95% CI = (0.17, 0.33)

• Other approaches,
  – sequential propensity score matching (sequential stratification),
    $exp(\hat{\phi}) = 0.29$, 95% CI = (0.21, 0.40)
  – estimating equations, IPW, MSM
Sequential Stratification

- Idea, for each of the 305 people who got salvage HT conceptualize that they were randomly chosen from a group of people to get hormone therapy

- Index cases are the people who got Salvage HT, set $C_{j0} = 1, j=1,\ldots,305$

- For each index case find ”similar” people who are still at risk, $C_{jk} = 0, k = 1,\ldots,n_j$
• Do within-strata comparison of future events of index case versus controls

• Fit stratified Cox model \( \lambda_j(t) \exp(\phi C_{jk} + \omega X_{jk}) \),
  
  – SE from sandwich estimator
• Define ”similar” based on model for probability of starting salvage HT
  – Matched on $Z_i(t)$ and $s_l_i(t)$
  – We used matched sets of size 10
Marginal Structural Models

- The standard MSM is estimating a different quantity than $\phi$
- Estimating a population averaged or marginal quantity
- Estimating the marginal treatment effect from a randomized trial if 1/2 the people got HT at time zero and the other 1/2 did not get HT
Comparison of Results

- Two-stage
  \[ \exp(\hat{\phi}) = 0.24, \quad 95\% \ CI = (0.17, 0.33) \]

- Sequential stratification,
  \[ \exp(\hat{\phi}) = 0.29, \quad 95\% \ CI = (0.21, 0.40) \]

- MSM,
  \[ \exp(\hat{\phi}) = 0.16, \quad 95\% \ CI = (0.04, 0.67) \]
Simulation study

- Simulate PSA and event time data from subject specific model
- Impose Salvage HT in a realistic way
- Parameter values chosen so that simulated data “looks like” the real data.
- Estimate $\phi$ using 3 methods
Table 2: True $\phi=-1.5$

<table>
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<tr>
<th>Method</th>
<th>estimate</th>
<th>Emp.SD</th>
<th>Ave.SE</th>
<th>Coverage</th>
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<tr>
<td>Two-stage</td>
<td>-1.464</td>
<td>0.149</td>
<td>0.146</td>
<td>94.0%</td>
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<td>Sequential Strat</td>
<td>-1.386</td>
<td>0.182</td>
<td>0.145</td>
<td>81.5%</td>
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<tr>
<td>MSM</td>
<td>-0.690</td>
<td>0.377</td>
<td>0.144</td>
<td>12.5%</td>
</tr>
</tbody>
</table>
Make model more non-parametric

- Replace $Z_i(t) = r_{i0} + r_{i1} f(t) + r_{i2} t$
  by
  $Z_i(t) = \mu(t) + W_i(t)$
  where $\mu(t)$ and $W_i(t)$ are smooth
Adapt mixed model representation of smoothing splines

- \( Z_i(t) = \sum_{k=1}^{K} \eta_k B_k(t) + \sum_{k=1}^{K} b_{ik} B_k(t) \)
  - \( B_k(t) \) are B-splines
  - \( \eta_k \) has dimension \( K \)
  - \( b_i \sim MVN_K(0, \Sigma) \)
  - \( \Sigma = Cov(b_i) \) will have lots of parameters
    \( (K(K+1)/2) \)
  - Number of parameters = \( K + K(K+1)/2 \)
• Reparametrize $\eta$ and $b_i$ into linear ($l$) and non-linear ($nl$) parts to reduce dimension

$$\eta = \Phi^l \eta^l + \Phi^{nl} \eta^{nl}$$

$$b_i = \Phi^l b_i^l + \Phi^{nl} b_i^{nl}$$

- $\eta^l$ and $b_i^l$ have dimension 2
- $\eta^{nl}$ and $b_i^{nl}$ have dimension $K-2$
- $\eta_k^{nl} \sim N(0, \sigma^2_\eta)$, $b_{ik}^{nl} \sim i.i.d. N(0, \sigma^2_b)$, $b_i^l \sim N_2(0, \Omega)$
- Number of parameters = 7 (2 fixed, 5 random effects)
• $M = D'D$ where $D$ is second order difference matrix
• $\Phi^l$ is $K \times 2$ matrix, contains basis of the null space of $M$, columns are 1 and $t$.
• $\Phi^{nl}$ is $K \times (K - 2)$ matrix
• $\Phi^{nl} = D'(DD')^{-1}$
Dataset.

- Patients Initially Treated with Radiation Therapy plus Hormonal Therapy
  - n=2434
  - Heterogeneous pattern of PSA
\[ TG = 0, \ GS = 0, \ bpsa = 3.666, \ death = 0 \]
TG = 0, GS = 0, bpsa = 3.666, death = 0
TG = 0, GS = 0, bpsa = 3.666, death = 0

TG = 0, GS = 1, bpsa = 2.485, death = 0

TG = 1, GS = 1, bpsa = 2.208, death = 0

TG = 0, GS = 1, bpsa = 3.329, death = 0