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

Jeremy M G Taylor
University of Michigan

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

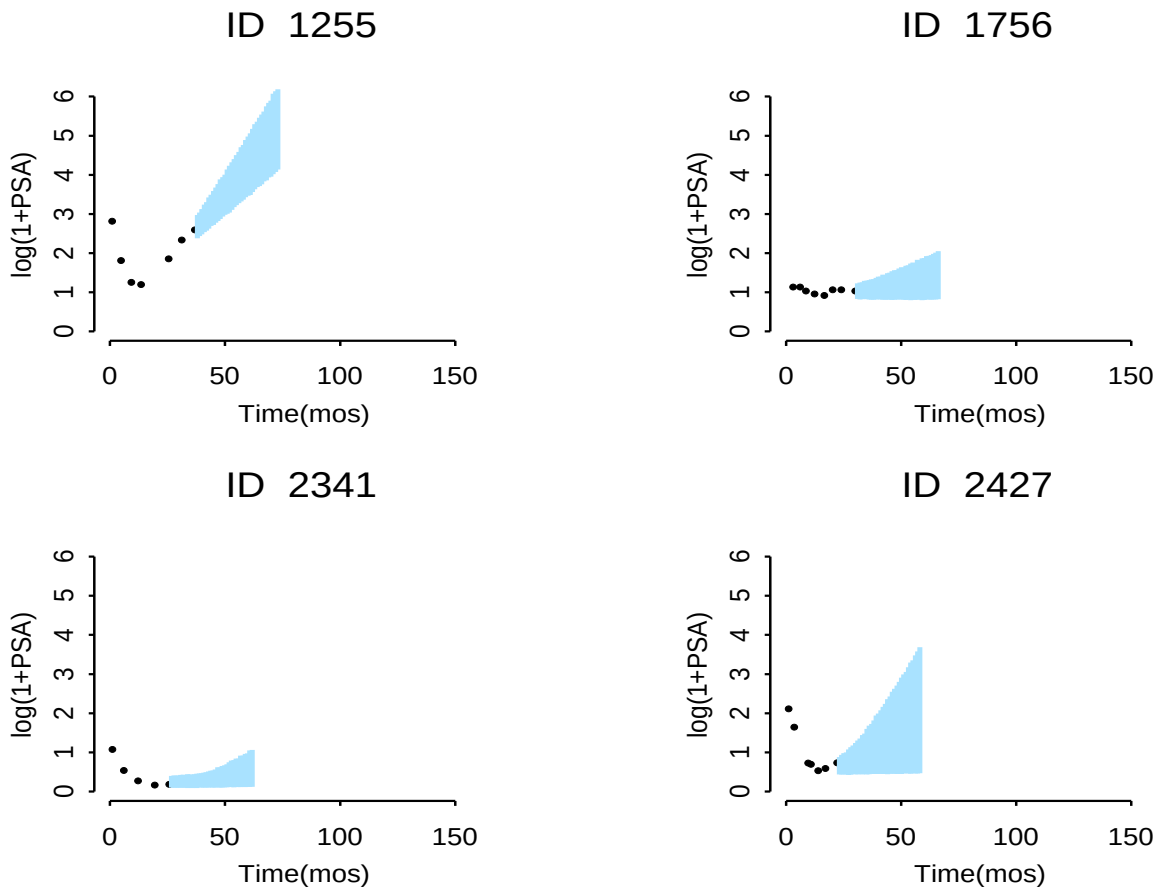
PROSTATE CANCER

- 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



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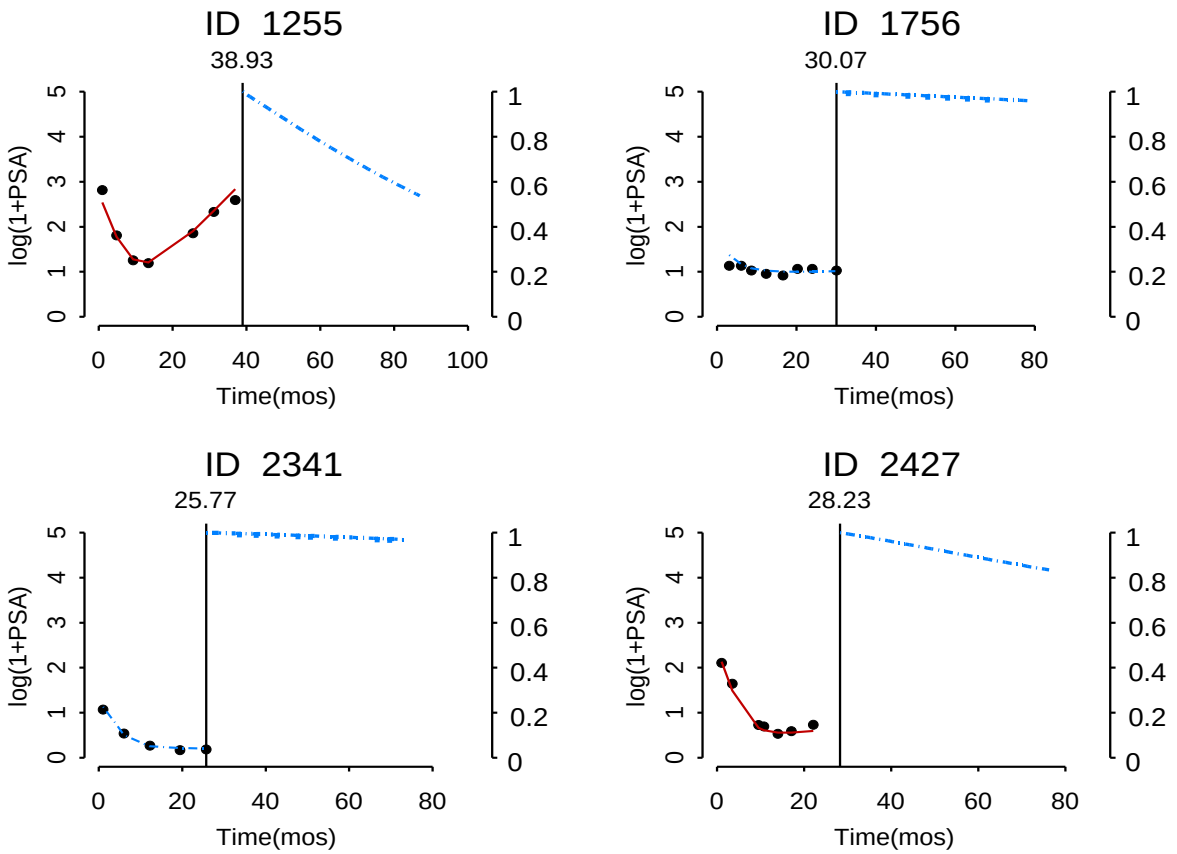
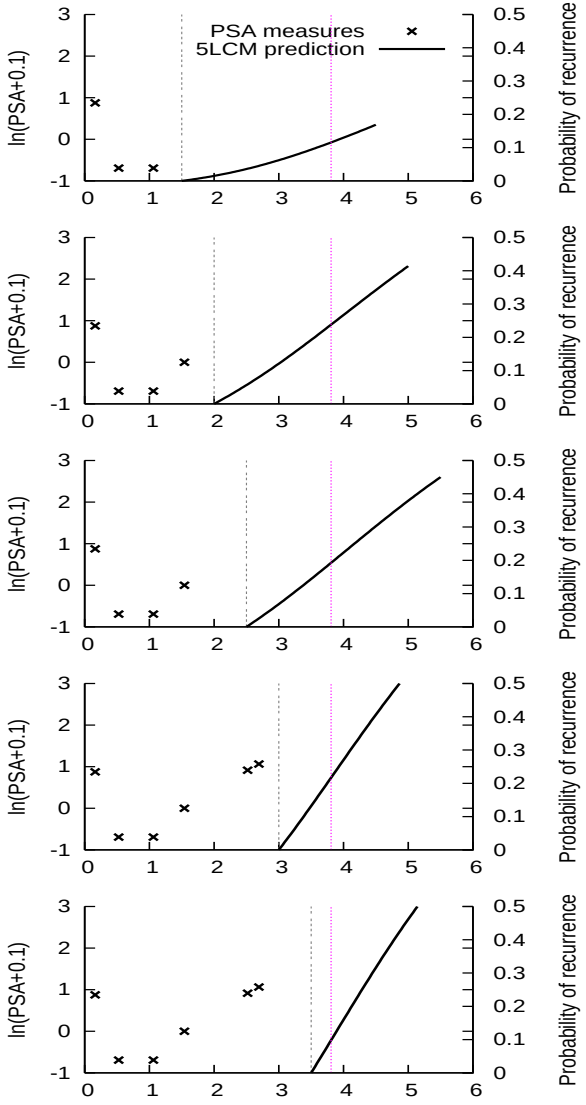


Dynamic Predictions of Probability of Recurrence



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 1: Post treatment PSA measurements

Date	PSA
29 Feb 2004	2.1
1 May 2004	1.5
25 Dec 2004	1.1
4 July 2006	1.3
29 Feb 2008	1.7
1 Jan 2010	2.1

- 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(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, δ_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 $[T|Y, X]$

- $[T, Y|X] \sim$ 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

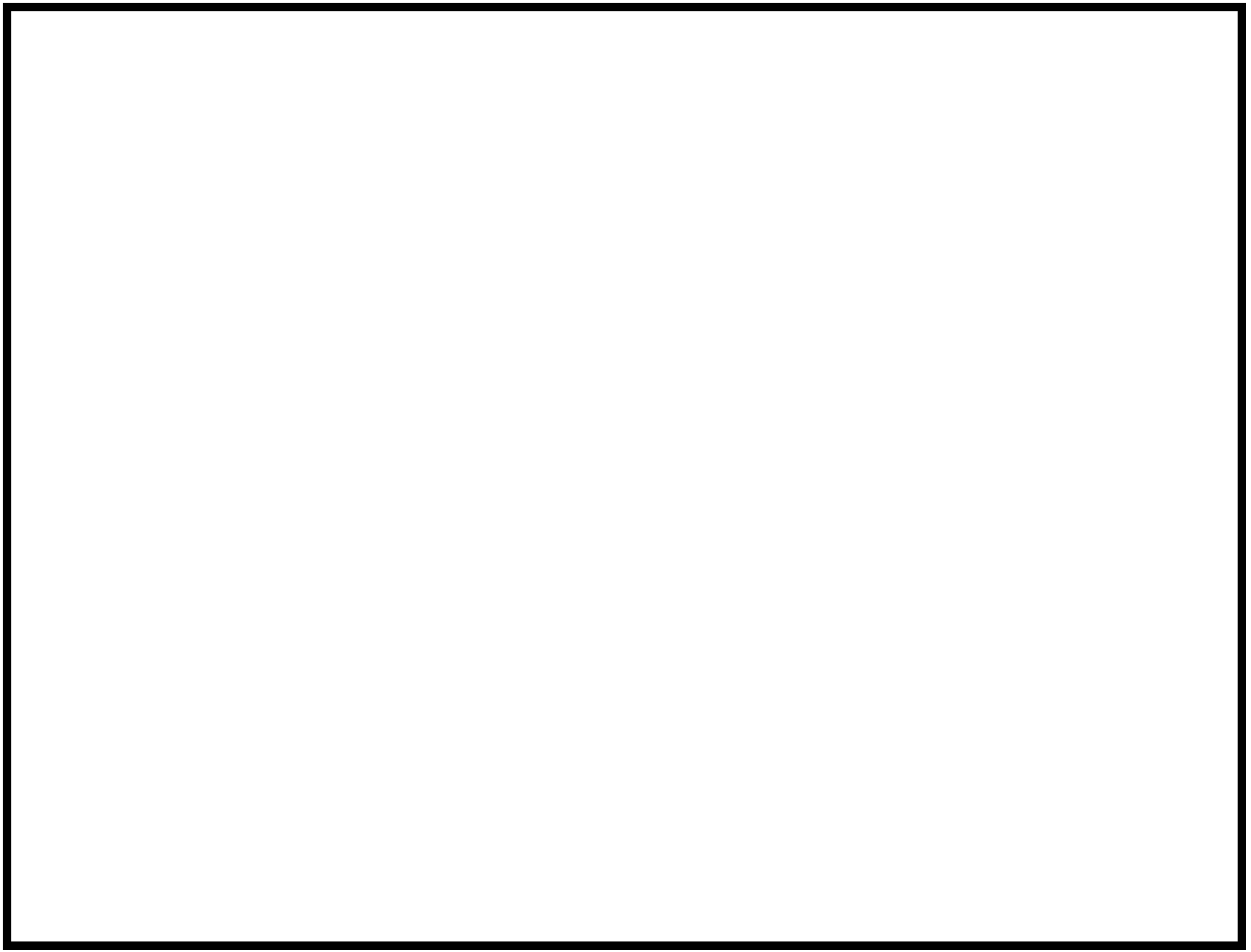
- Prostate cancer patients treated with radiation therapy.
- Training data
  - RTOG, n=615
  - Detroit, n=1268
  - Univ Michigan, n=503
- Testing data
  - Melbourne, n=395
  - Vancouver, n=846

Longitudinal Data (Y). Post-treatment PSA

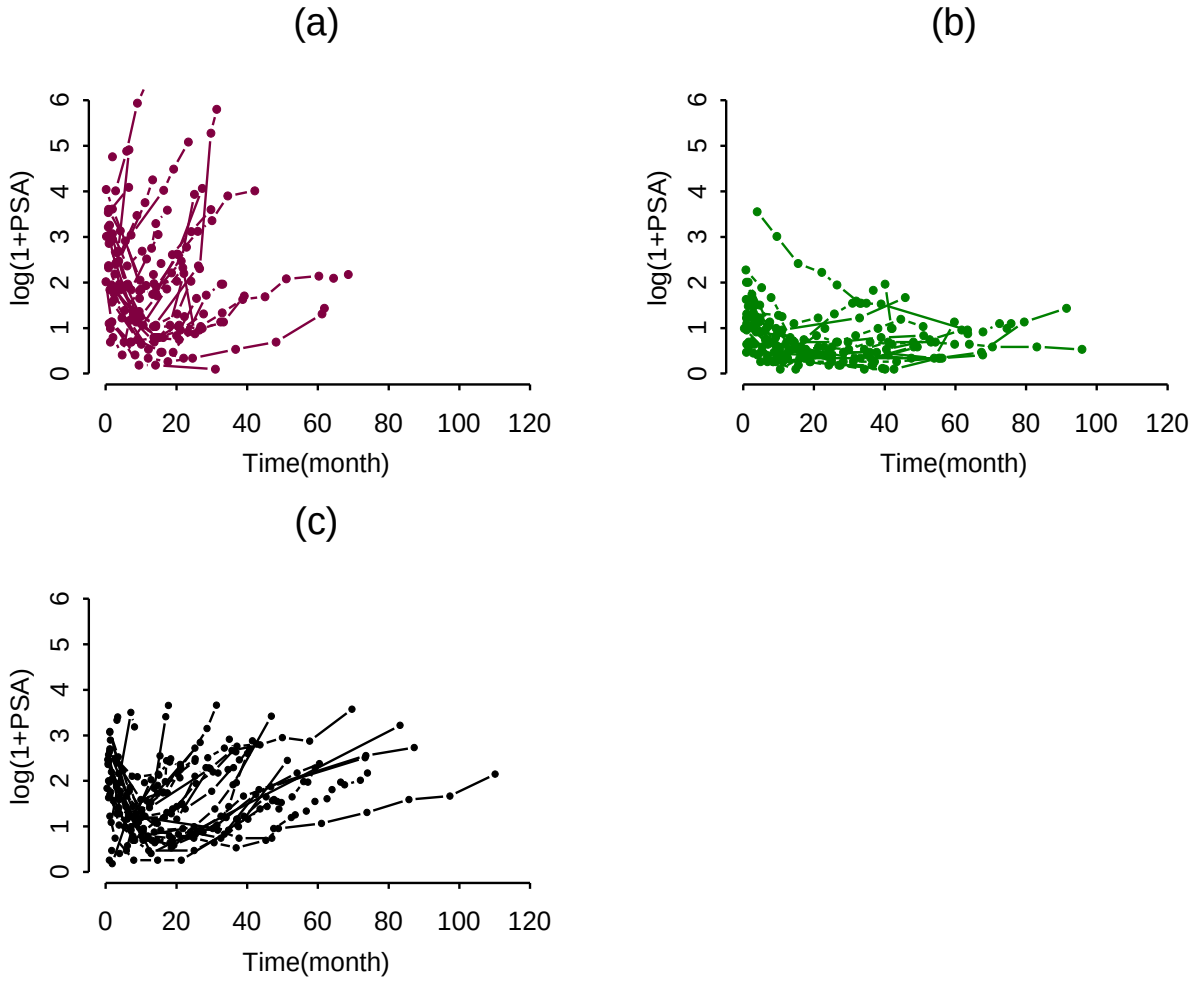
- measured approximately every 6 months
- a total of 46,000 post-treatment PSA values
- median no. of PSA per patient is 8
- 10 year follow-up

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.

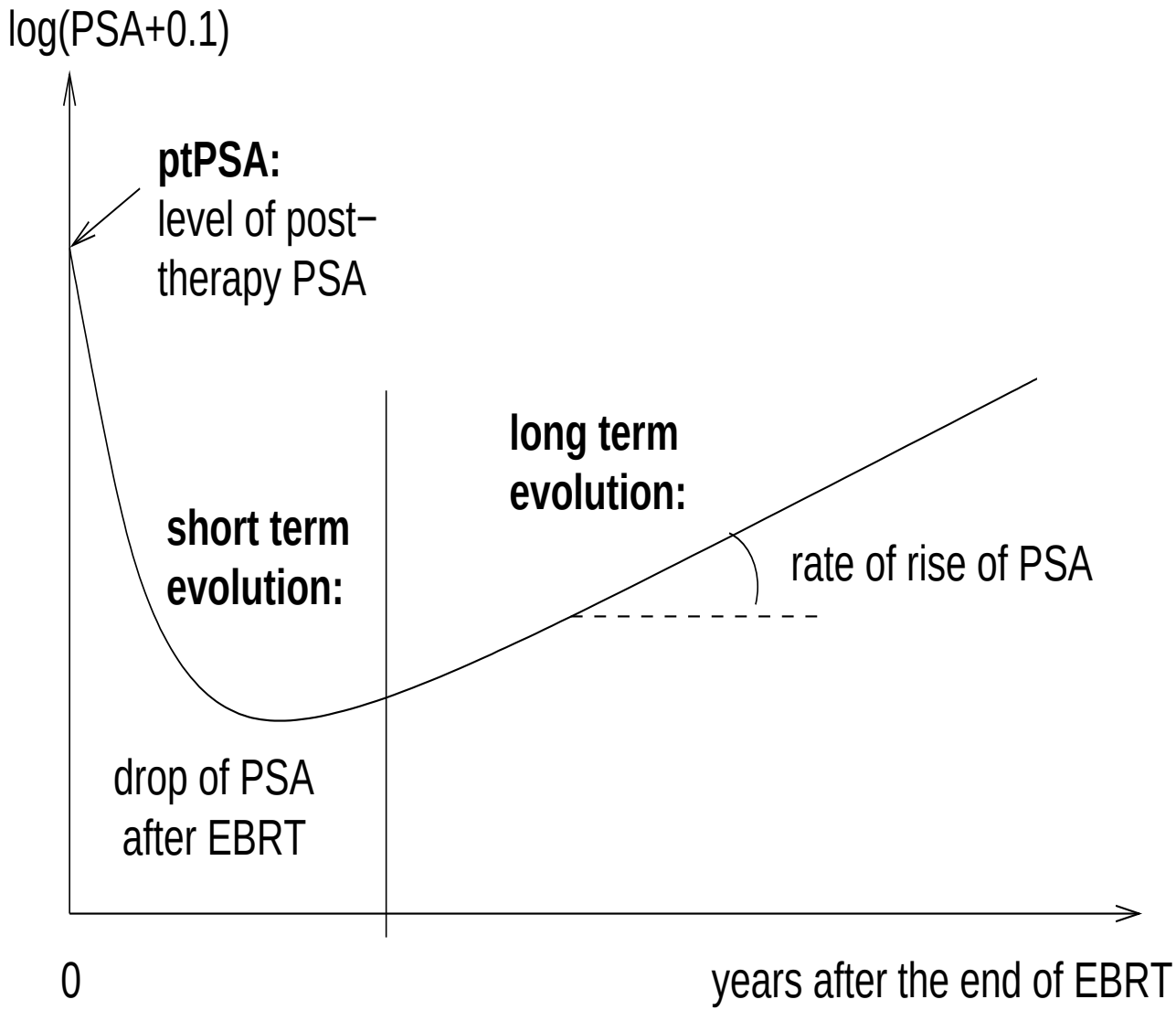


Statistical Model

Notation

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

Longitudinal model



Longitudinal. Non-linear random effects models.

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

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

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.

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

$$X_i \;\; = \;\; (bPSA_i, Tstage_i, Gleason_i)$$

Hazard model. Time-dependent proportional hazards.

$$\lambda_i(t \mid X_i, Z_i, sl_i, HT_i)$$

$$= \lambda_0(t)$$

$$\exp[\eta g(Z_i(t)) + \omega sl_i(t) + \gamma X_i + \phi HT_i(t)]$$

$sl_i(t) =$ slope of $Z_i(t)$

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

$\lambda_0(t)$ is a step function.

- Estimation via MCMC
  - parameters θ
  - latent variables R_i
  - draws of θ, R_i, save for later use
  - over 12 hours of computing to obtain estimates
- Likelihood
  $\prod_i \int [\prod_j P(Y_{ij}|\theta, X_i, R_i)] P(T_i, \delta_i|\theta, X_i, R_i) f(R_i) dR_i$

PREDICT FUTURE PSA VALUES.

From model

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

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

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
- $$P[T < t_i + a \,|\, T > t_i, Y_i, X_i]$$
$$= (1/K) \sum_k P[T < t_i + a \,|\, T > t_i, X_i, \theta^k, R_i^k]$$

  where θ^k, R_i^k are draws from the posterior distribution

Residual time distribution

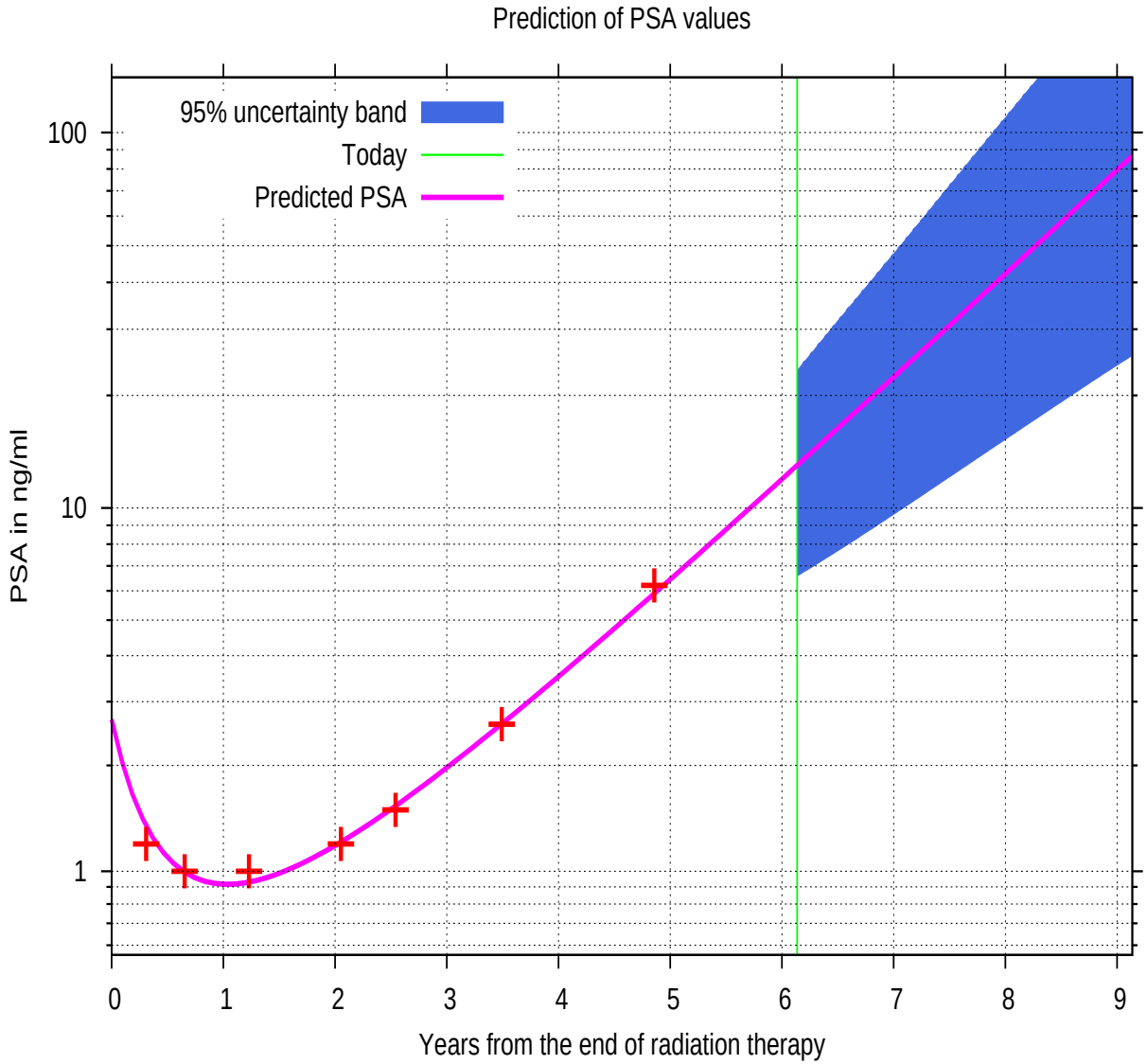
$$P[\,T > t_i + a \,|\, T > t_i, X_i, \theta, R_i]$$

$$= exp[-\int_{u=t}^{t+a} \lambda_i(u|X_i, \theta, Z_i(u), sl_i(u))du]$$

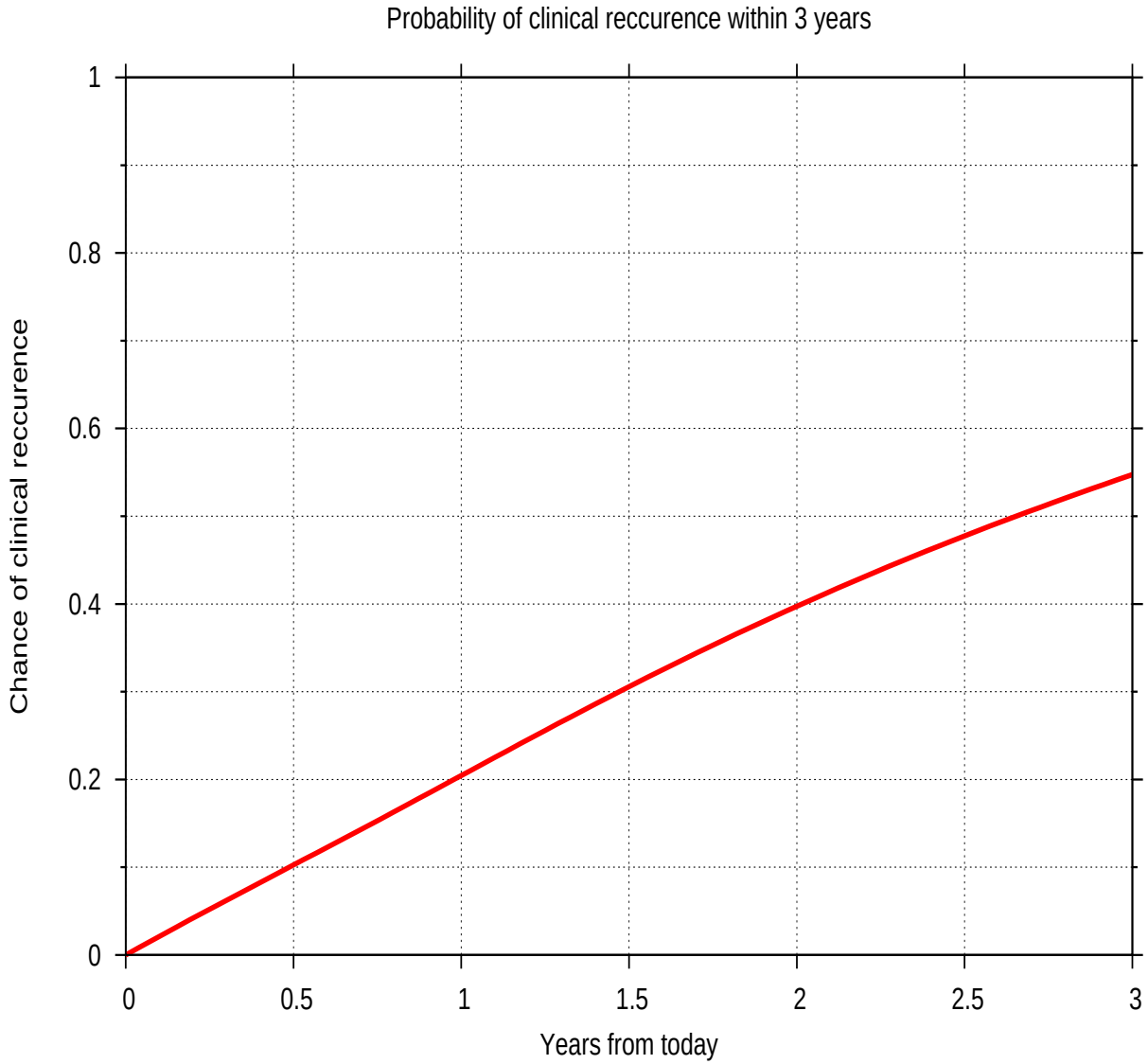
$$\lambda_i(u \mid X_i, \theta, Z_i(u), sl_i(u))$$

$$= \lambda_0(t) \exp[\eta g(Z_i(u)) + \omega sl_i(u) + \gamma X_i]$$

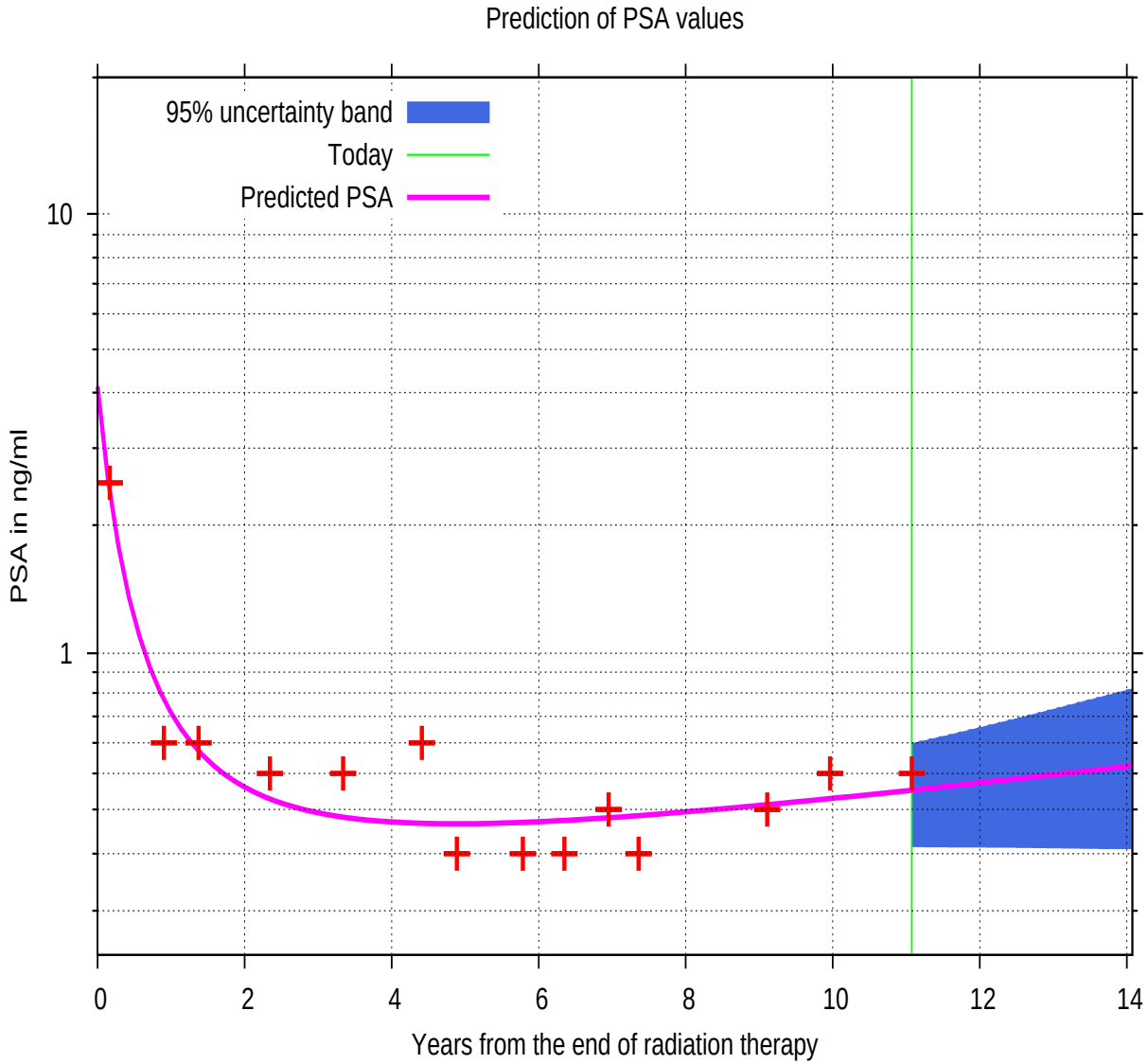
Predictions of PSA for Censored Subject



Residual Time Distribution for Censored Subject



Predictions of PSA for Censored Subjects



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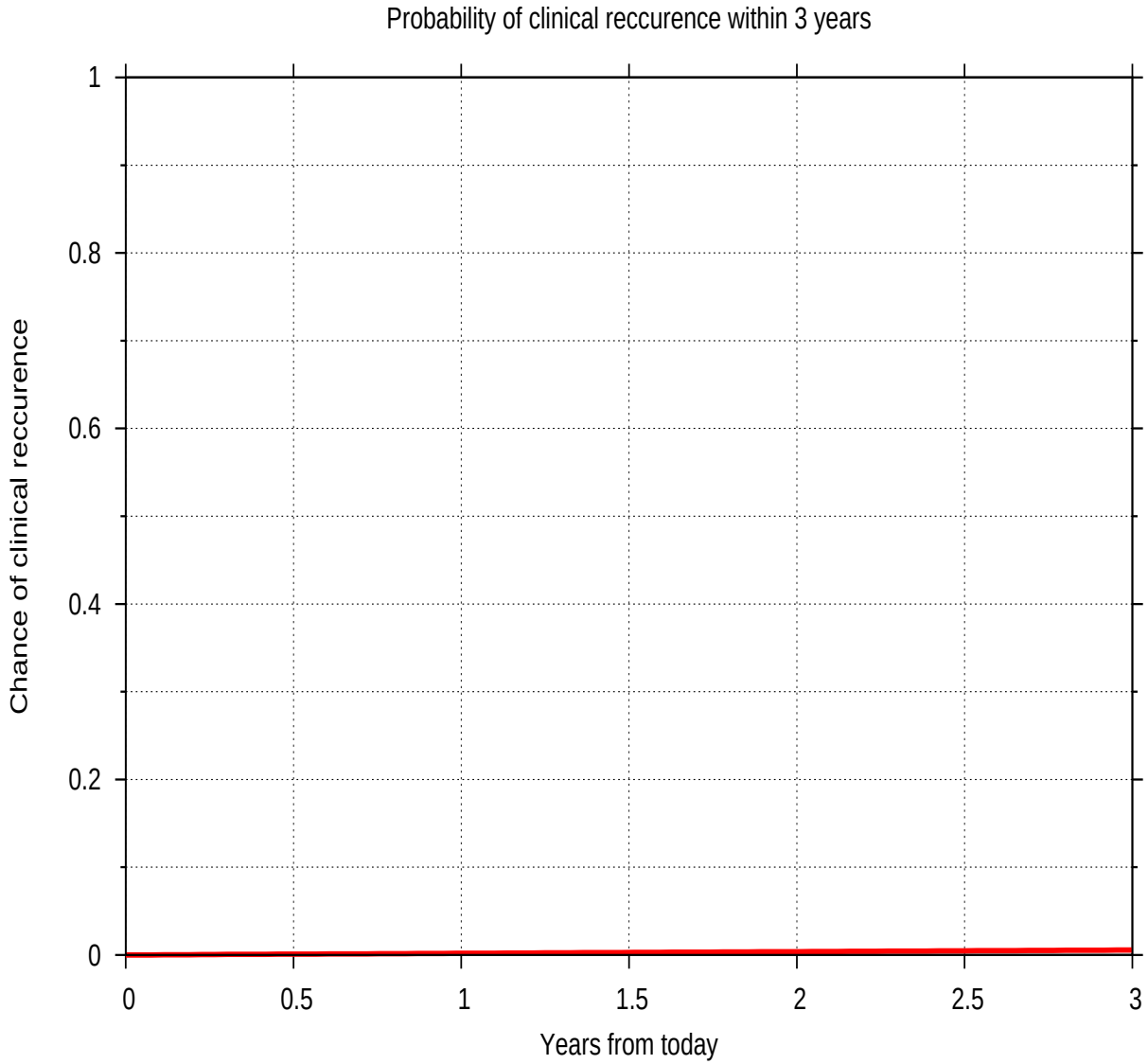
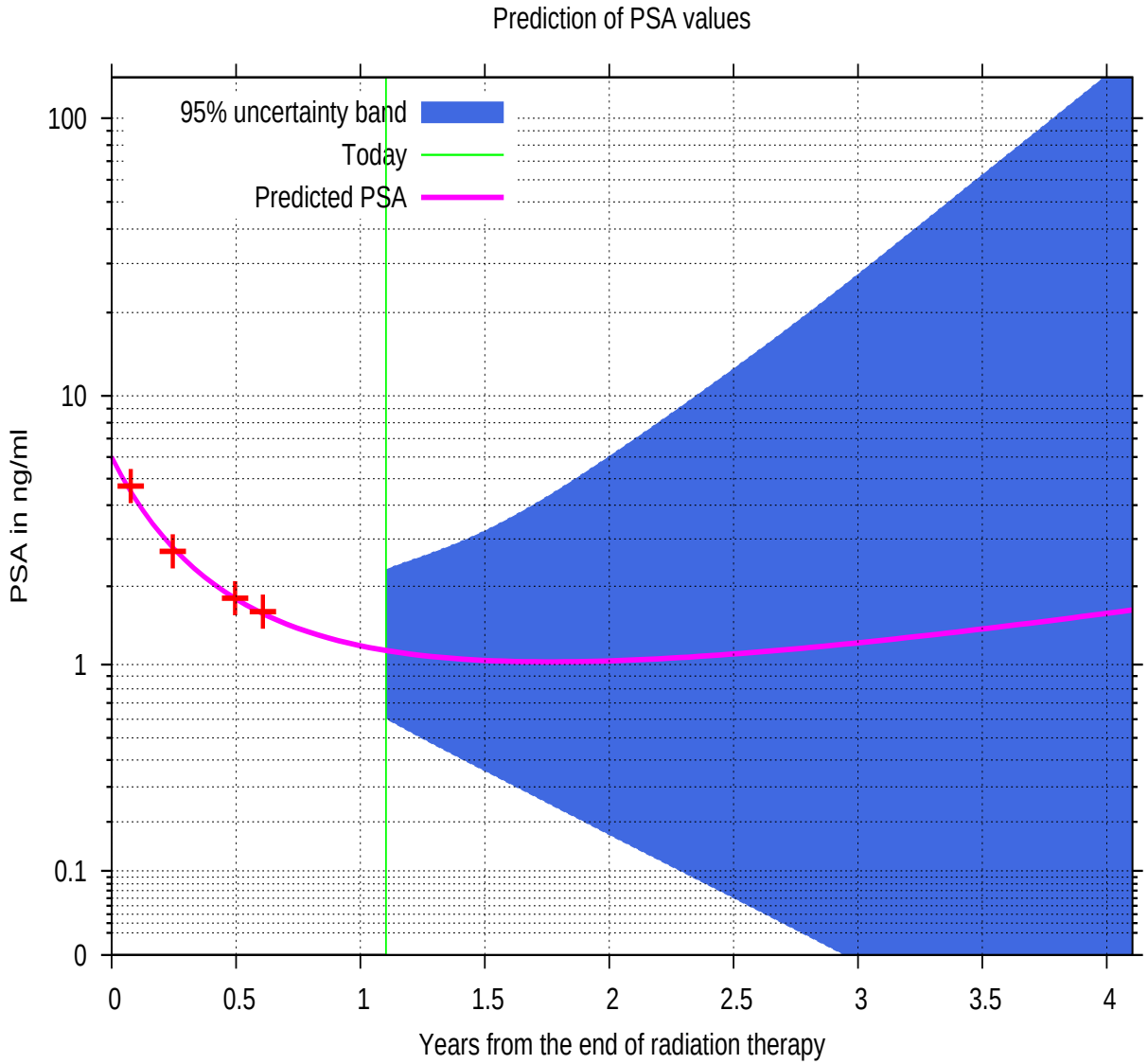


Predictions of PSA for Censored Subjects



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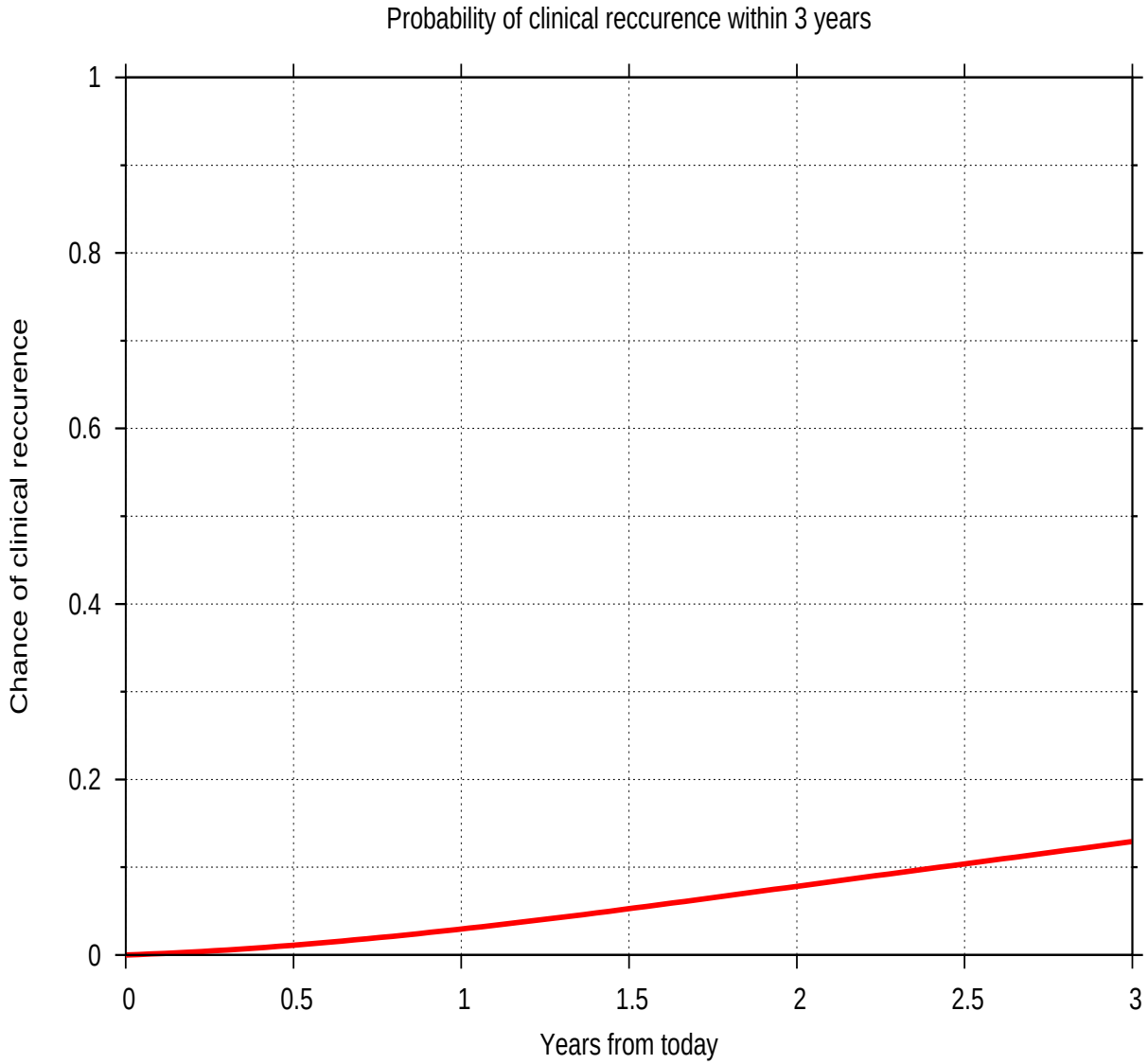


Predict Recurrence for New Censored Patient (m)

- Want $P[\,T < t_m + a \,|\, T > t_m, Y_m, X_m]$
- Obtain by averaging

$$P[\,T < t_m + a \,|\, T > t_m, X_m, \theta^k, R_m^k]$$

- Don't want to add new subject to dataset
- Have draws of θ from converged chain, needs draws of R_m
- For each θ^k run quick MCMC to get a draw of R_m^k.
- Draw R_m from $P(R_m|\theta^k, T_m > t_m, Y_m, X_m)$
- Use likelihood contribution from subject m
  $P(Y_m|\theta^k, X_m, R_m)P(T_m, \delta_m = 0|\theta^k, X_m, R_m)$

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(Clinical Recurrence within 3 years) > 0.1
- Entry criteria for clinical study
  - eg Pr(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)

- $\hat{P}_i = \hat{P}(X_i) =$ 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.

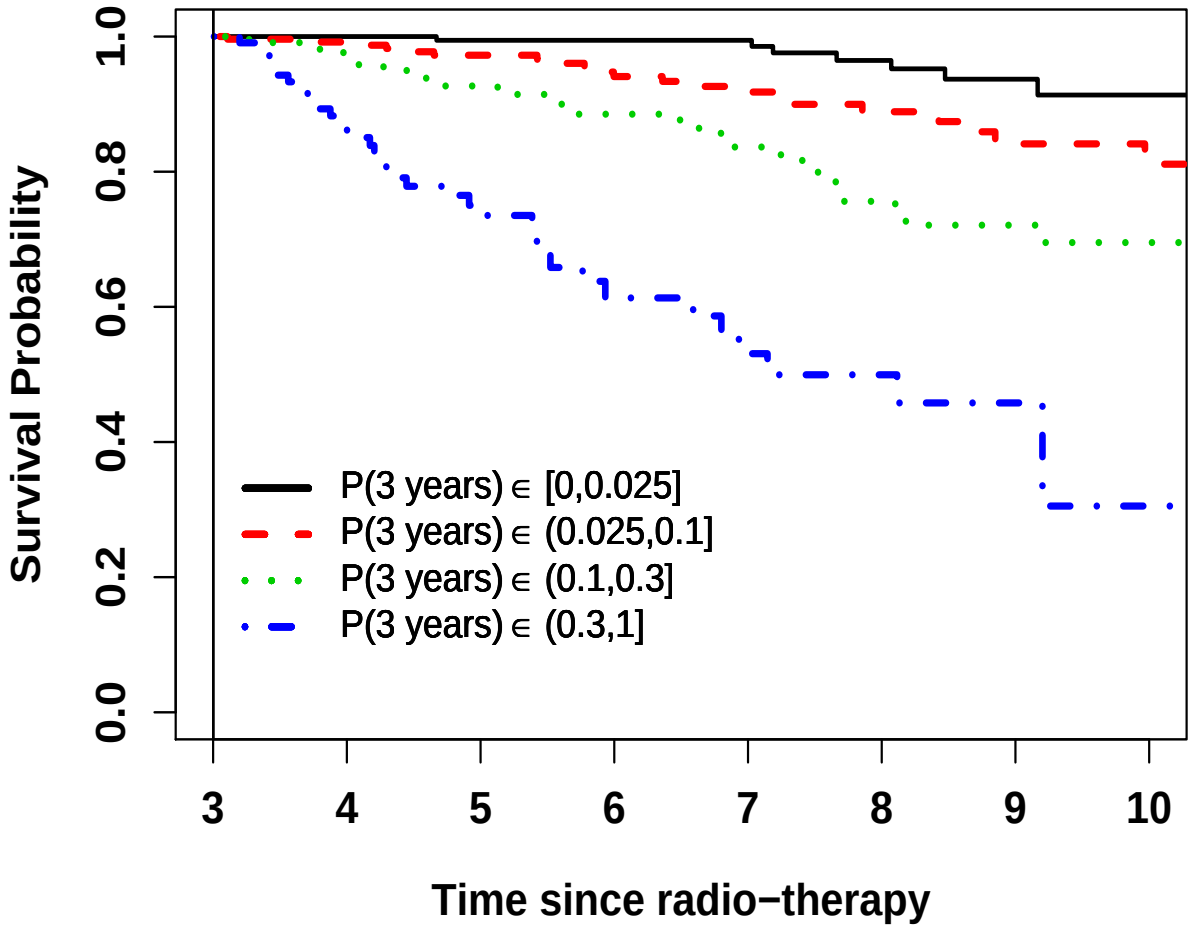
SIMPLE GRAPHICAL APPROACH FOR SURVIVAL DATA (like Hosmer-Lemeshow)

- 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
0.0
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0.4
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Time since radio−therapy
P(3 years) ∈ [0,0.025]
P(3 years) ∈ (0.025,0.1]
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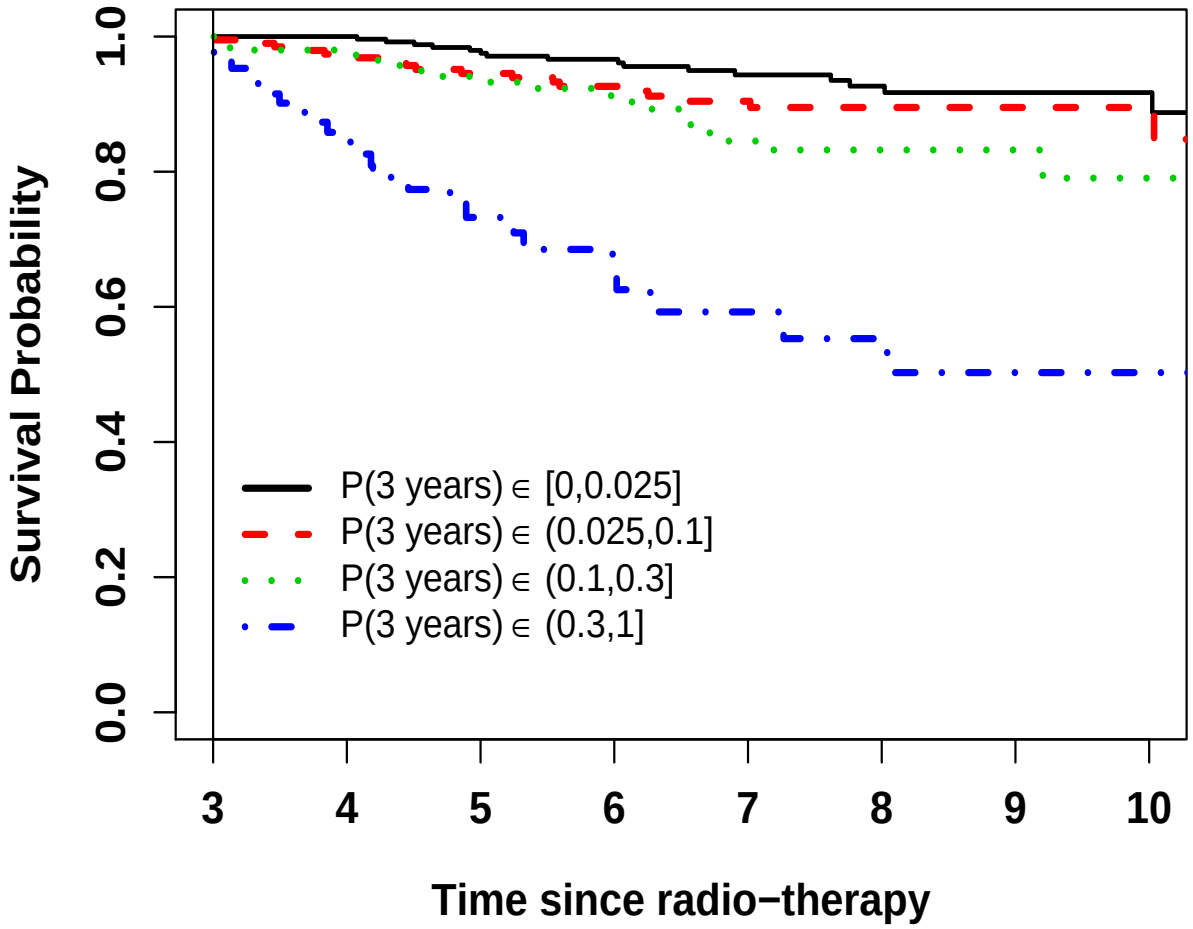
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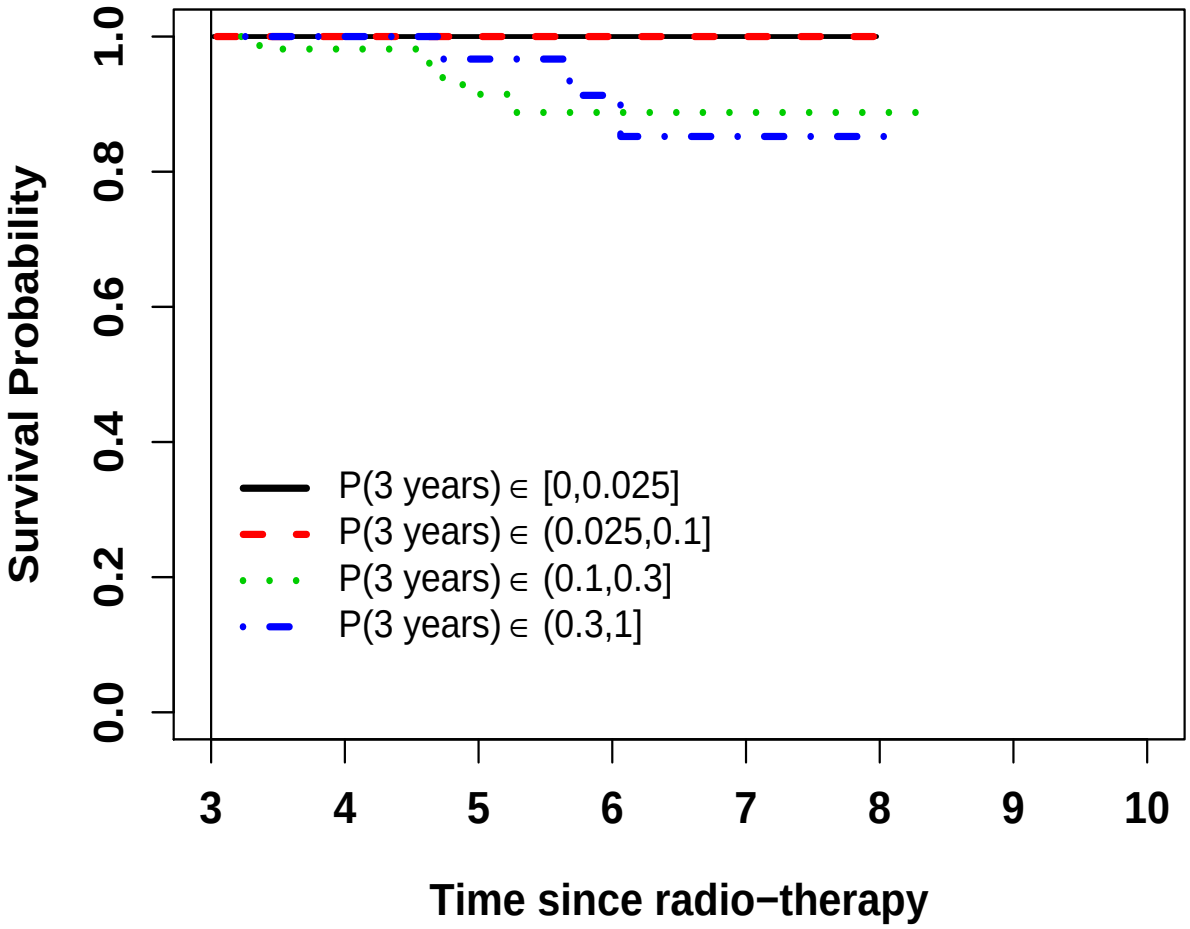
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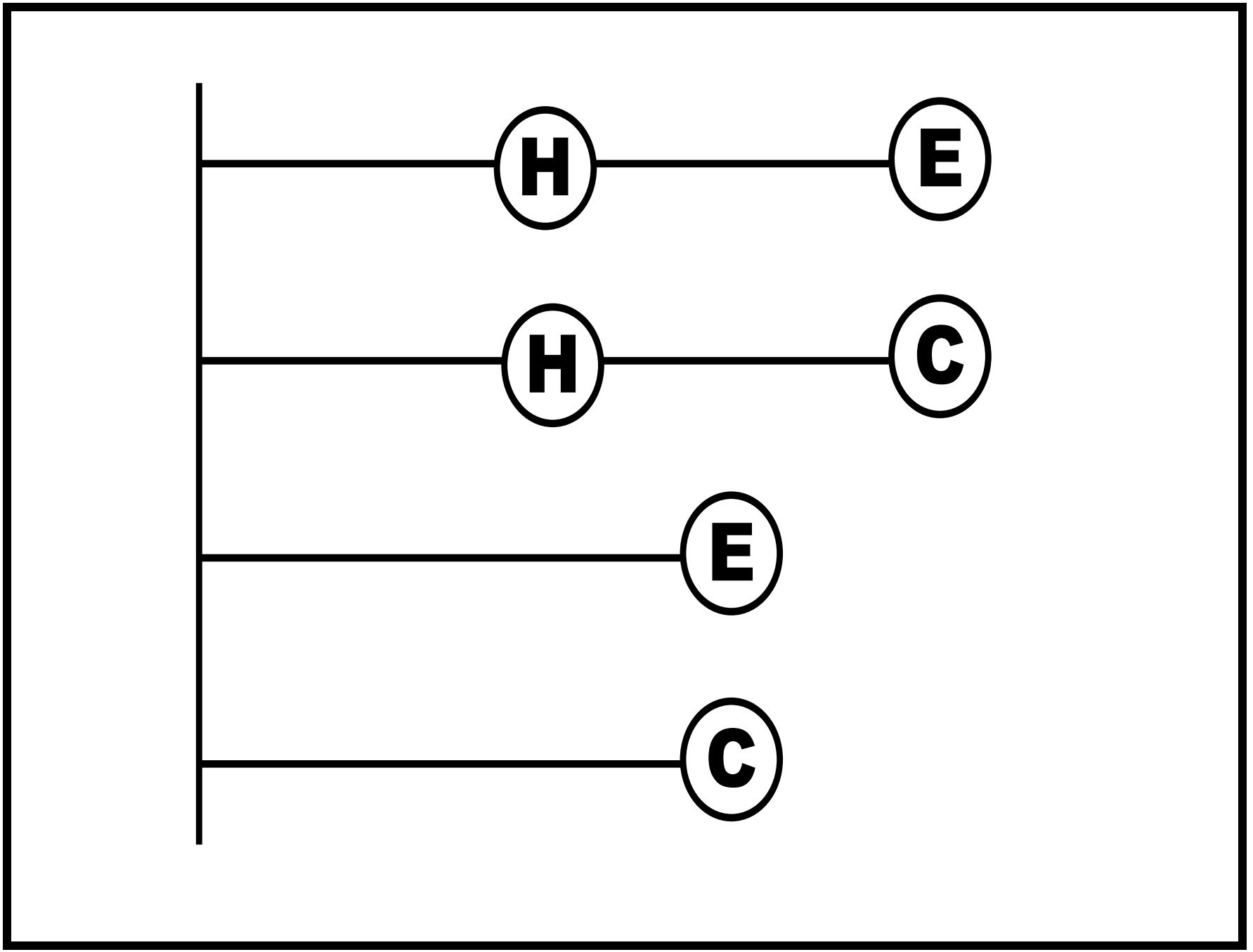
A complication with Kaplan-Meier estimate, dependent censoring

- 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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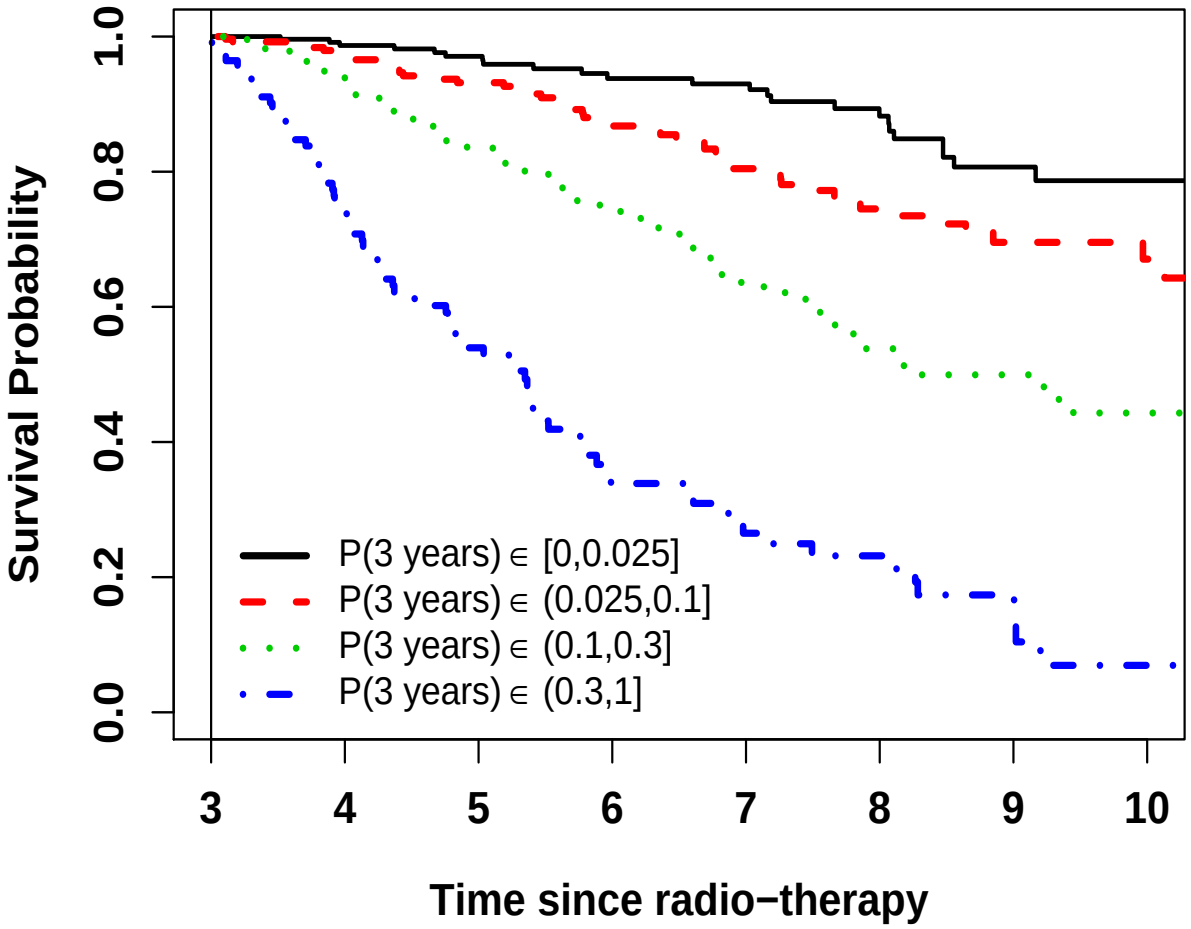
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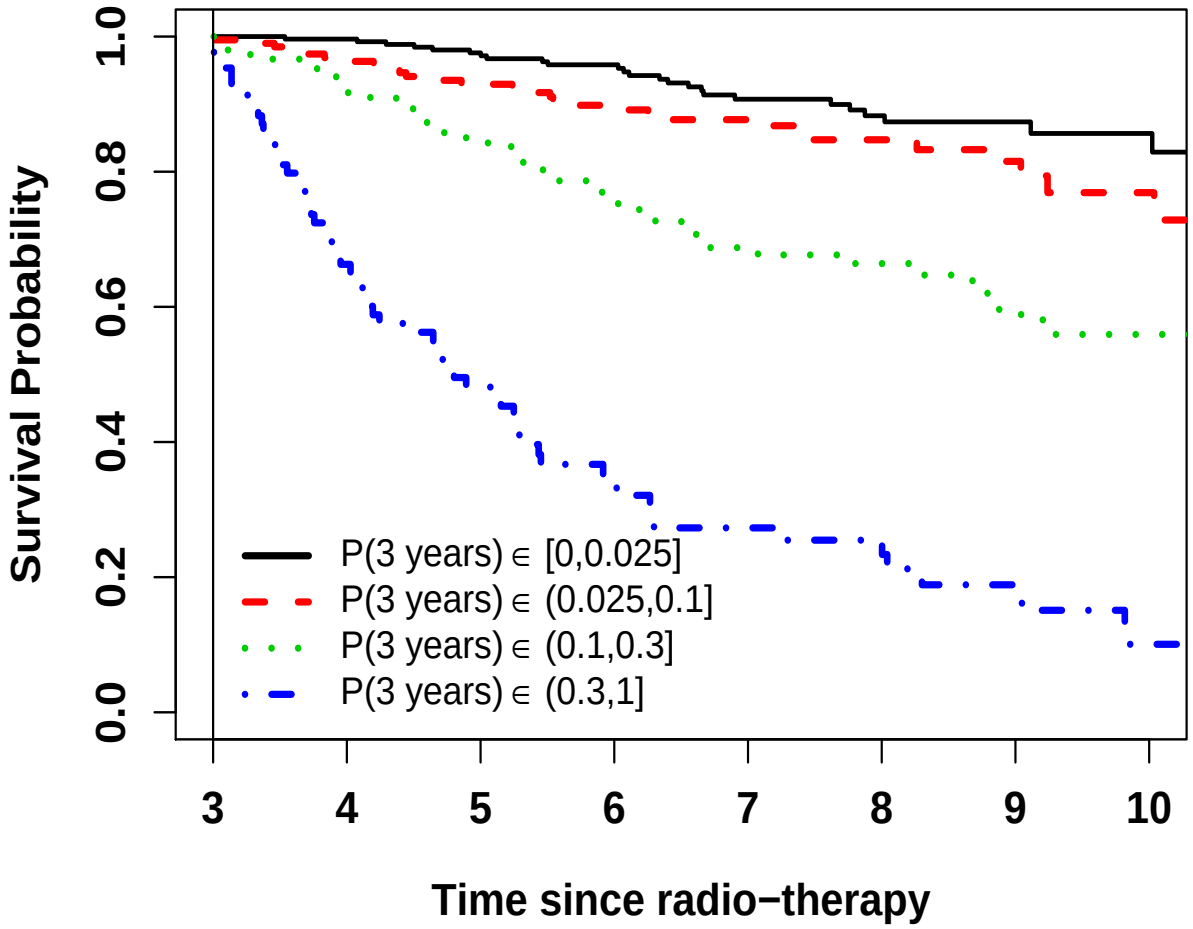
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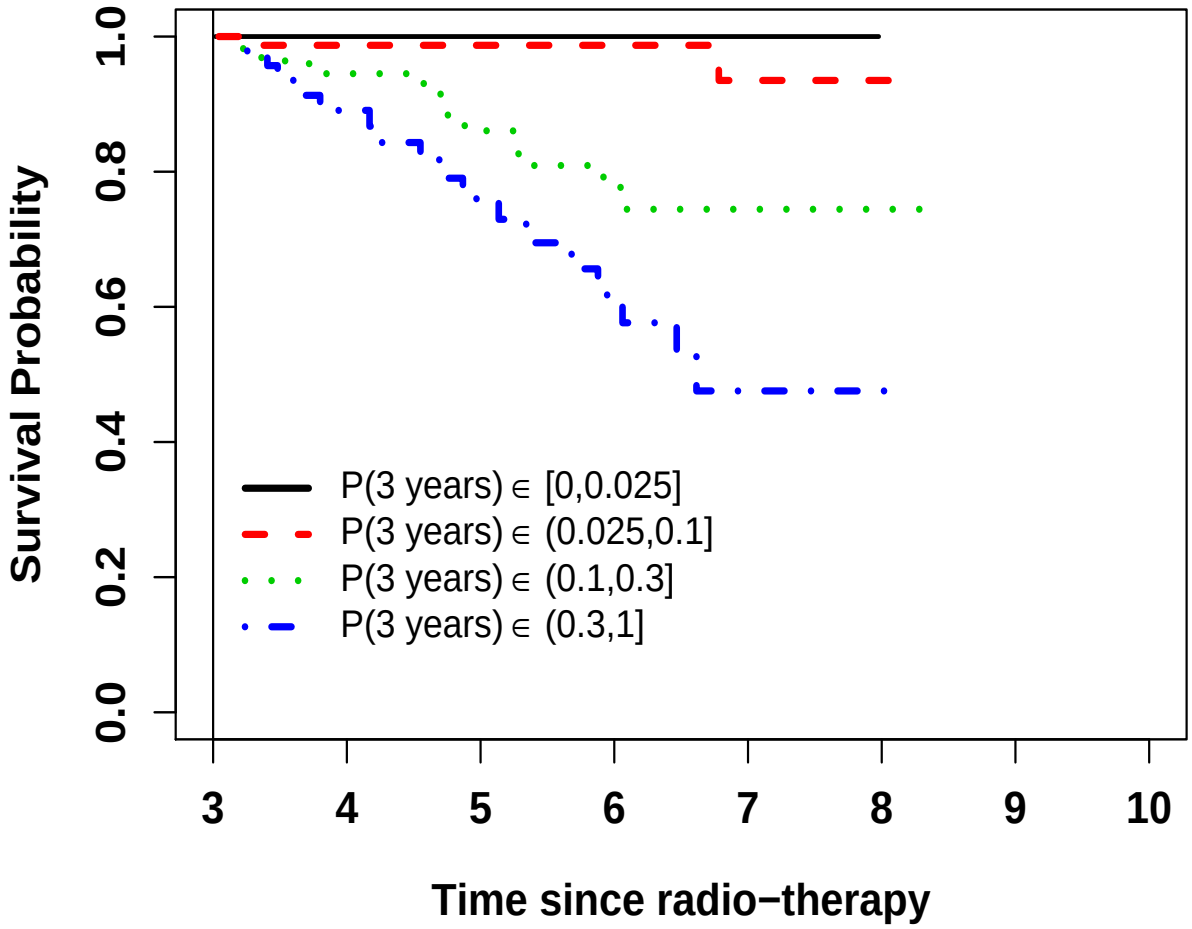
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Is this worth all the trouble? Simpler approaches:

. 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

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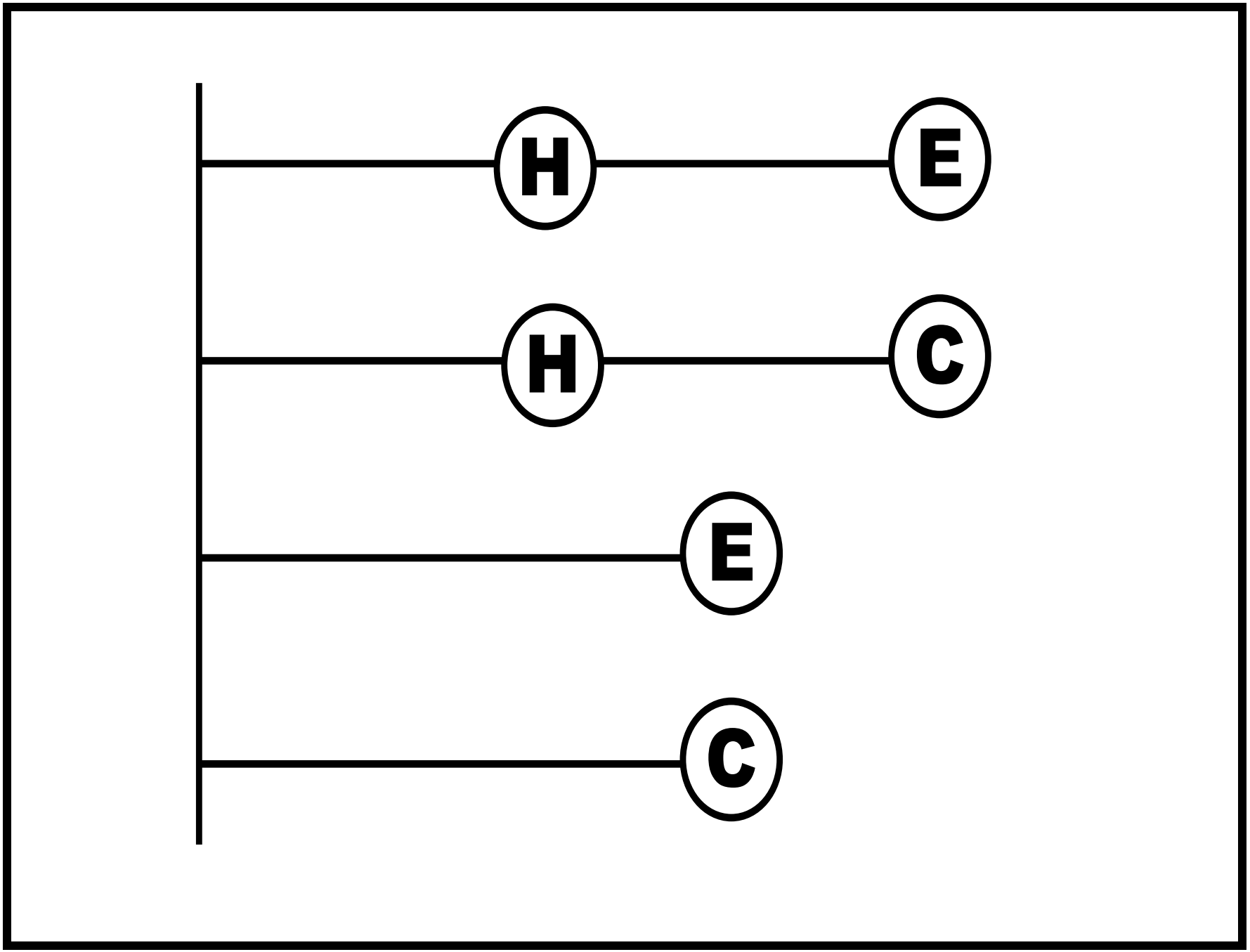
Hormonal therapy and dependent censoring

- Salvage hormonal therapy (HT) is sometimes given when a patient exhibits a rising trend in PSA, before a clinical event.
- HT delays occurence of the clinical event
- HT is a nuisance factor present in the data.
- A different problem would be estimating the effect of HT.


H
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$$\lambda_i(t \mid X_i, Z_i, sl_i, HT_i)$$
$$= \lambda_0(t)$$
$$\exp[\eta g(Z_i(t)) + \omega sl_i(t) + \gamma X_i + \phi HT_i(t)]$$

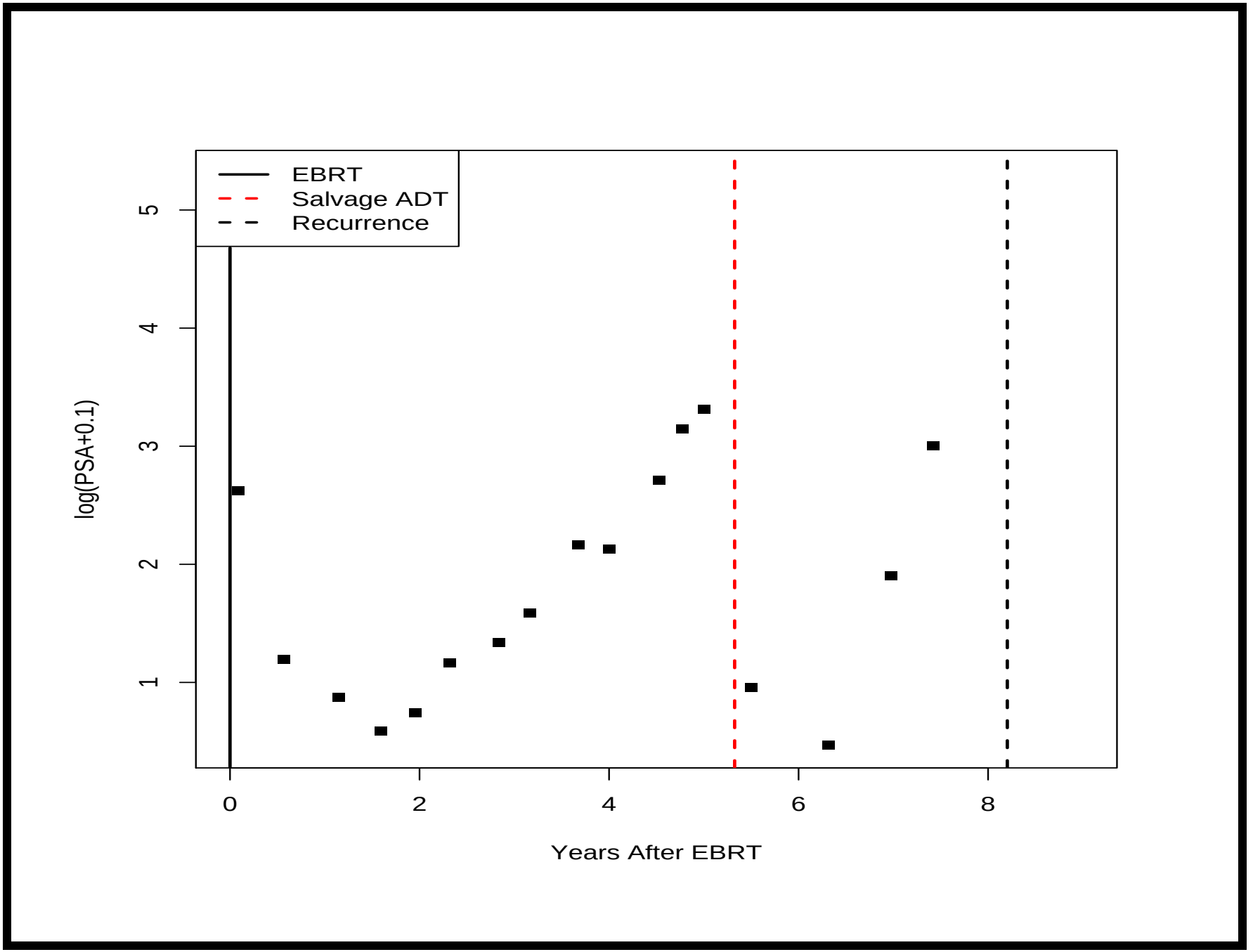
$sl_i(t) =$ slope of $Z_i(t)$

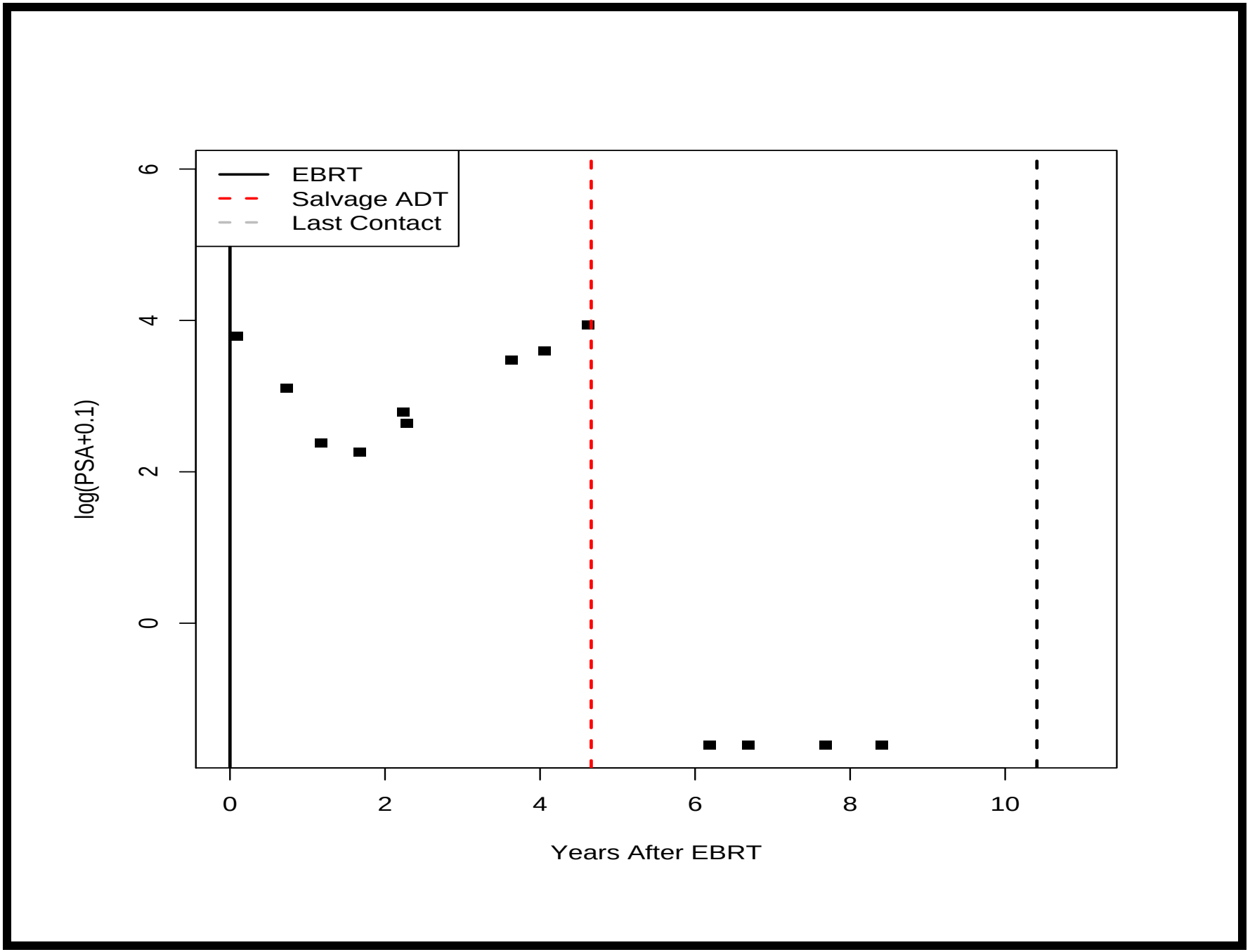
$$HT_i(t) = \begin{cases} 0 & \text{if} \quad t < S_i \\ 1 & \text{if} \quad t > S_i \end{cases}$$

Sensitivity analyses suggests estimates of η, ω, γ 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


EBRT
Salvage ADT
Recurrence
log(PSA+0.1)
1
2
3
4
5
0
2
4
6
8
Years After EBRT

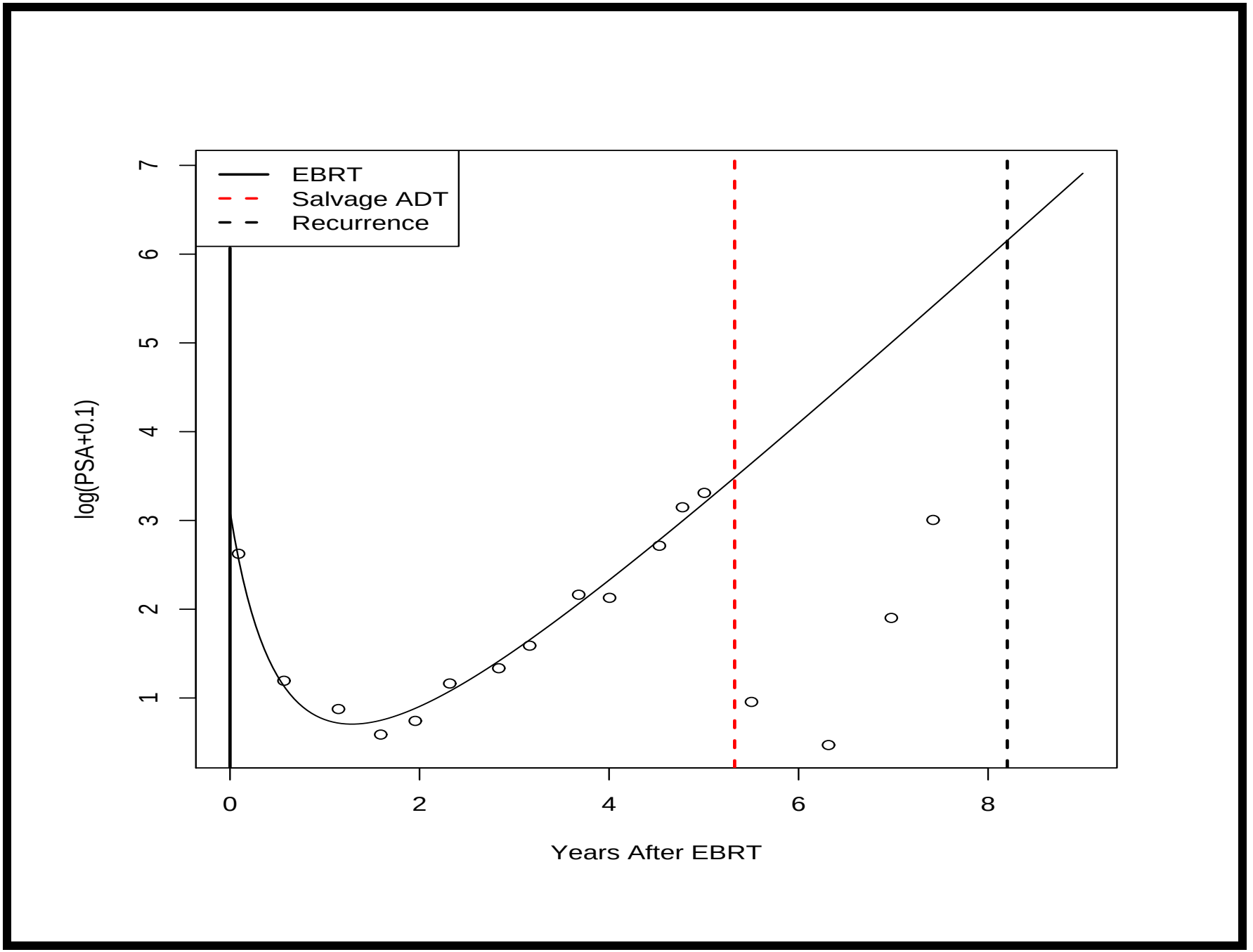

EBRT
Salvage ADT
Last Contact
log(PSA+0.1)
0
2
4
6
0
2
4
6
8
10
Years After EBRT

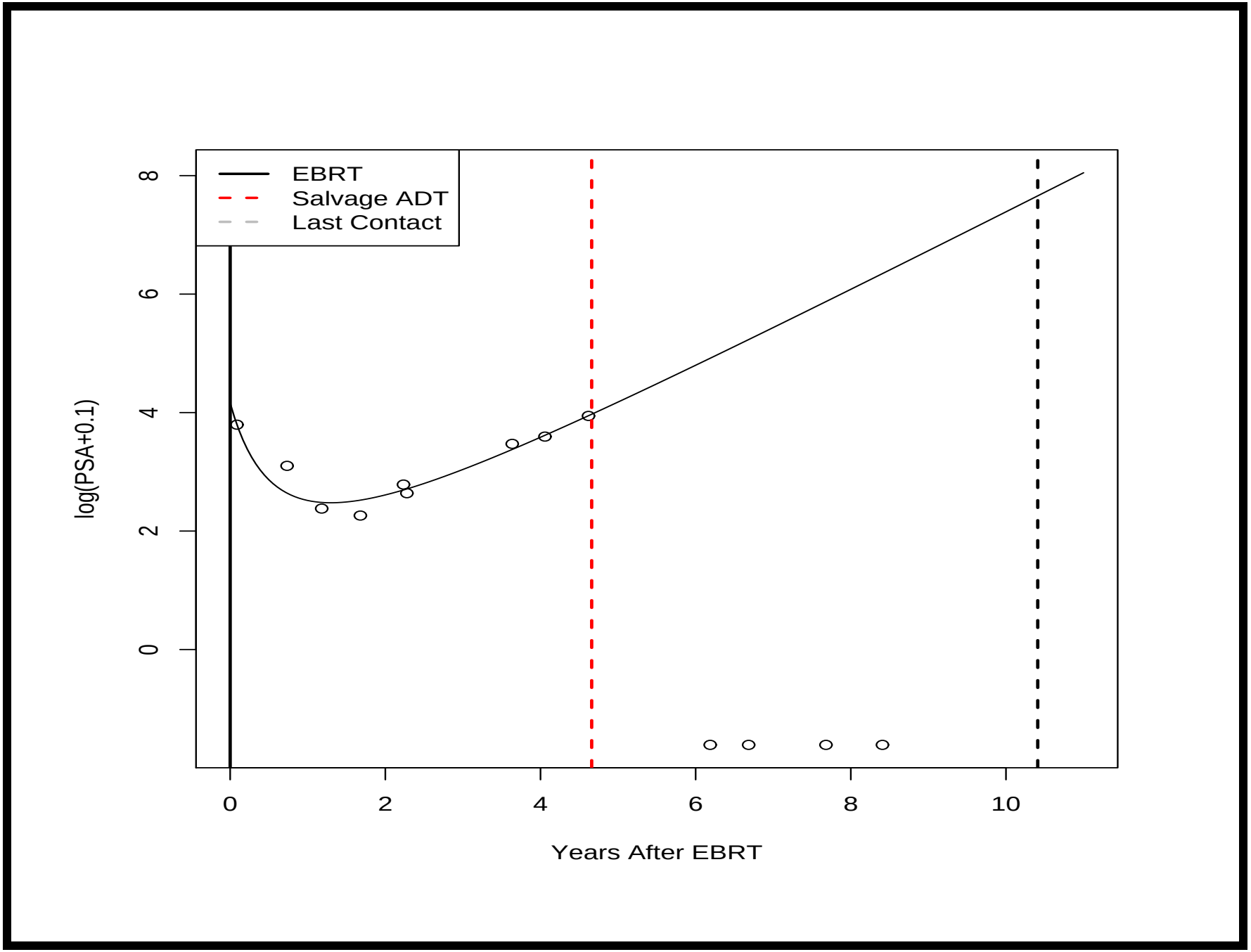
"Casual" model

- $\lambda_i^{(0)}(t)$ 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
  - ϕ could depend on covariates
- Approach, estimate jointly ϕ and $\lambda_i^{(0)}(t)$

Model for $\lambda_i^{(0)}(t)$

- Think of $\lambda_i^{(0)}(t)$ as a "latent curve" for patient i
- $\lambda_i^{(0)}(t) = \lambda_0(t) \exp[\eta g(Z_i(t)) + \omega sl_i(t) + \gamma X_i]$
- $Z_i(t)$ and $sl_i(t)$ are deterministic, defined by random effects and parameters
- Note $Z_i(t)$ and $sl_i(t)$ in this model are values as if salvage therapy is not given
- Involves values of $Z_i(t)$ and $sl_i(t)$ after S_i


EBRT
Salvage ADT
Recurrence
log(PSA+0.1)
1
2
3
4
5
6
7
0
2
4
6
8
Years After EBRT


EBRT
Salvage ADT
Last Contact
log(PSA+0.1)
0
2
4
6
8
0
2
4
6
8
10
Years After EBRT

- Fit joint model
  - Longitudinal model for PSA in absence of hormone therapy (delete PSA data after S_i)
  - $\lambda_0(t)\exp[\eta g(Z_i(t)) + \omega sl_i(t) + \gamma X_i + \phi I(t > S_i)]$
- Note, Z_i and sl_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
- $exp(\hat{\phi}) = 0.24, \quad 95\%\ CI = (0.17, 0.33)$
- Other approaches,
  - sequential propensity score matching (sequential stratification),
    $exp(\hat{\phi}) = 0.29, \quad 95\%\ CI = (0.21, 0.40)$
  - 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,...,305
- For each index case find "similar" people who are still at risk, $C_{jk} = 0, k = 1, ..., n_j$

- 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 $sl_i(t)$
  - We used matched sets of size 10

Marginal Structural Models

- The standard MSM is estimating a different quantity than ϕ
- 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
  - $exp(\hat{\phi}) = 0.24, \qquad 95\%\ CI = (0.17, 0.33)$
- Sequential stratification,
  - $exp(\hat{\phi}) = 0.29, \qquad 95\%\ CI = (0.21, 0.40)$
- MSM,
  - $exp(\hat{\phi}) = 0.16, \qquad 95\%\ CI = (0.04, 0.67)$

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 ϕ using 3 methods

Table 2: True ϕ=-1.5

Method	estimate	Emp.SD	Ave.SE	Coverage
Two-stage	-1.464	0.149	0.146	94.0%
Sequential Strat	-1.386	0.182	0.145	81.5%
MSM	-0.690	0.377	0.144	12.5%

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

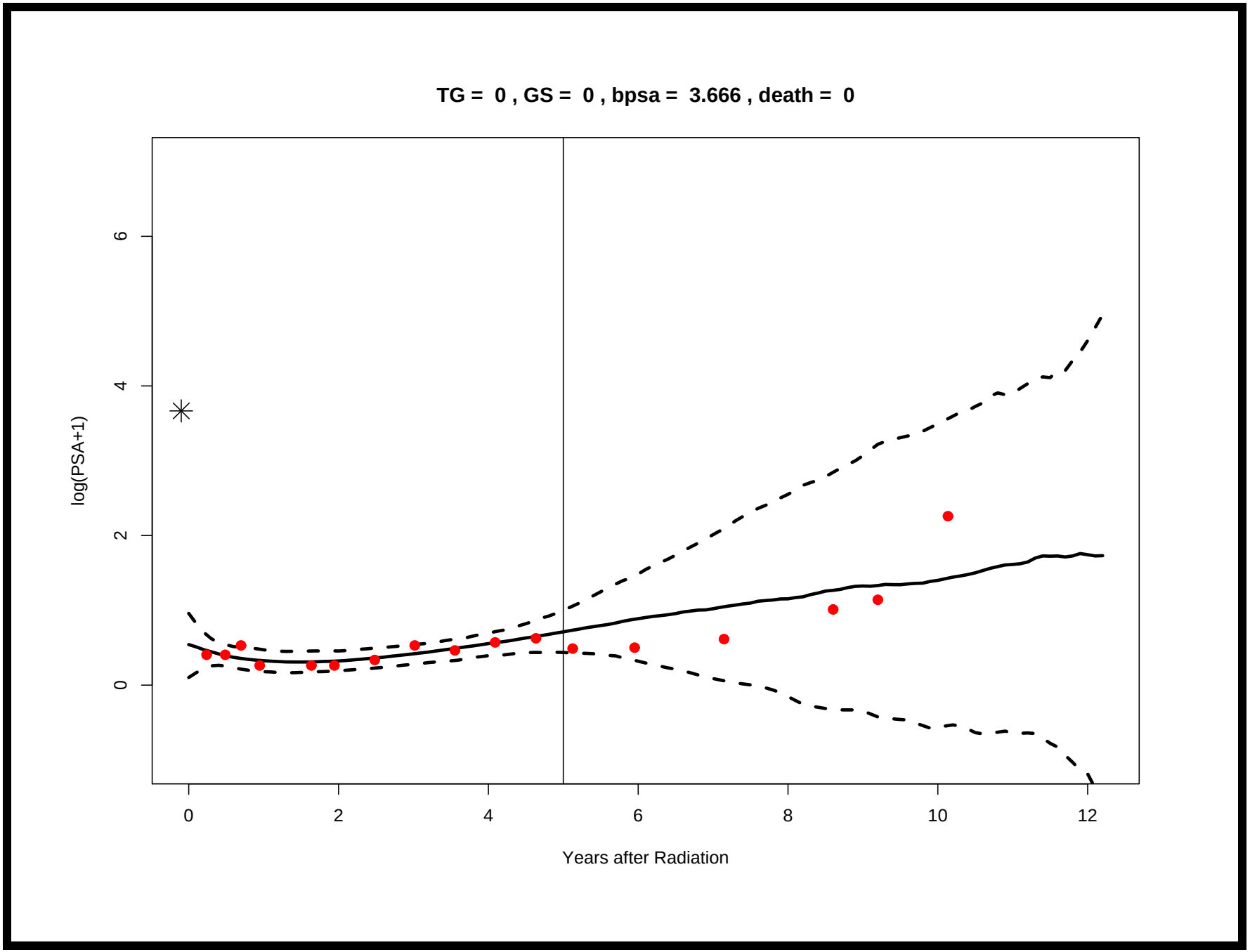
- $Z_i(t) = \sum_{k=1}^{K} \eta_k B_k(t) + \sum_{k=1}^{K} b_{ik} B_k(t)$
  - $B_k(t)$ are B-splines
  - η_k has dimension K
  - $\mathbf{b_i} \sim MVN_K(0, \Sigma)$
  - $\Sigma = Cov(\mathbf{b_i})$ will have lots of parameters $(K(K+1)/2)$
  - Number of parameters $= K + K(K+1)/2$

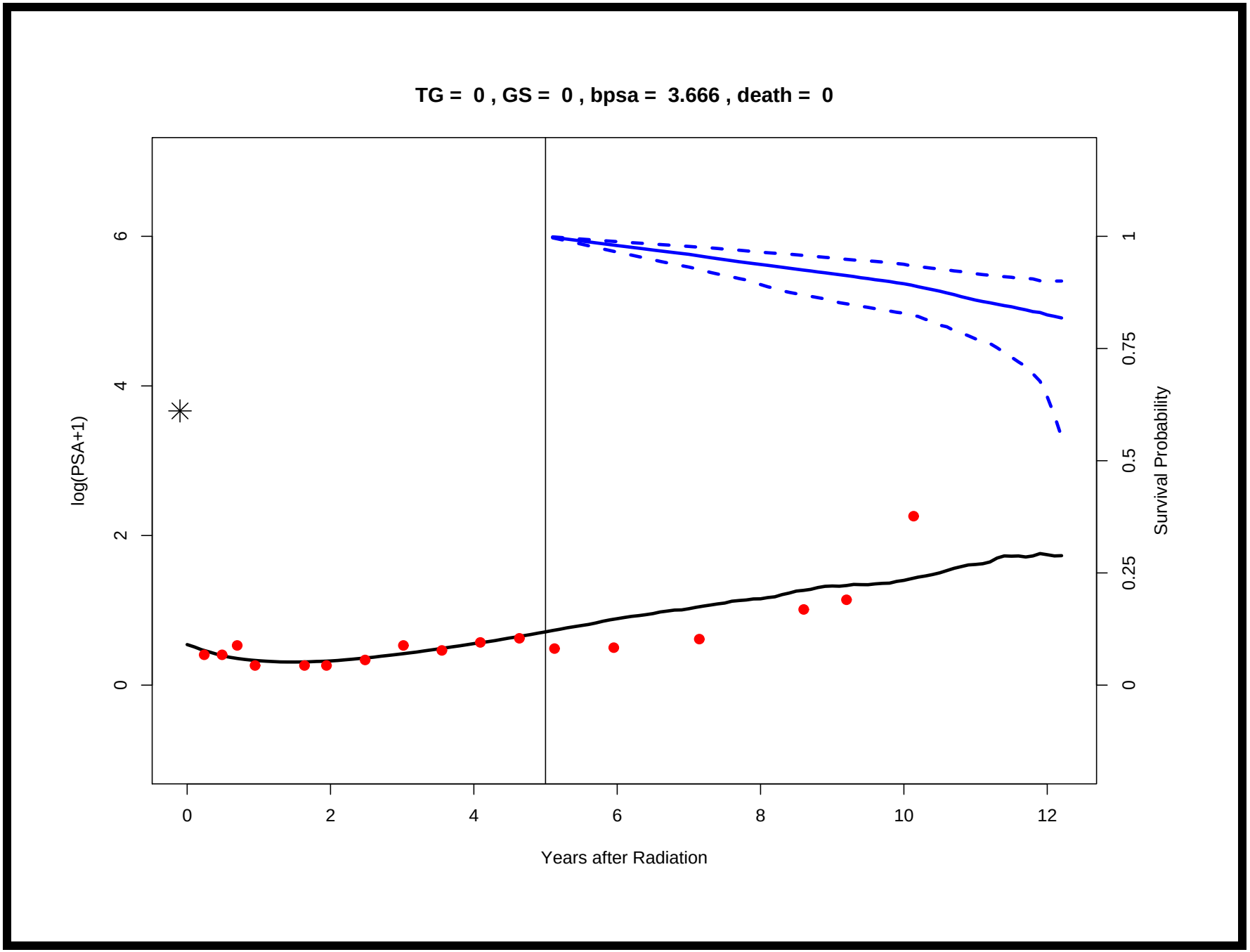
- Reparametrize η and $\mathbf{b_i}$ into linear (l) and non-linear (nl) parts to reduce dimension
- $\eta = \Phi^l \eta^l + \Phi^{nl} \eta^{nl}$
- $\mathbf{b_i} = \Phi^l \mathbf{b_i}^l + \Phi^{nl} \mathbf{b_i}^{nl}$
  - η^l and $\mathbf{b_i}^l$ have dimension 2
  - η^{nl} and $\mathbf{b_i}^{nl}$ have dimension K-2
  - $\eta_k^{nl} \sim N(0, \sigma_\eta^2), \quad b_{ik}^{nl} \sim_{i.i.d.} N(0, \sigma_b^2), \quad b_i^l \sim N_2(0, \Omega)$
  - Number of parameters = 7 (2 fixed, 5 random effects)

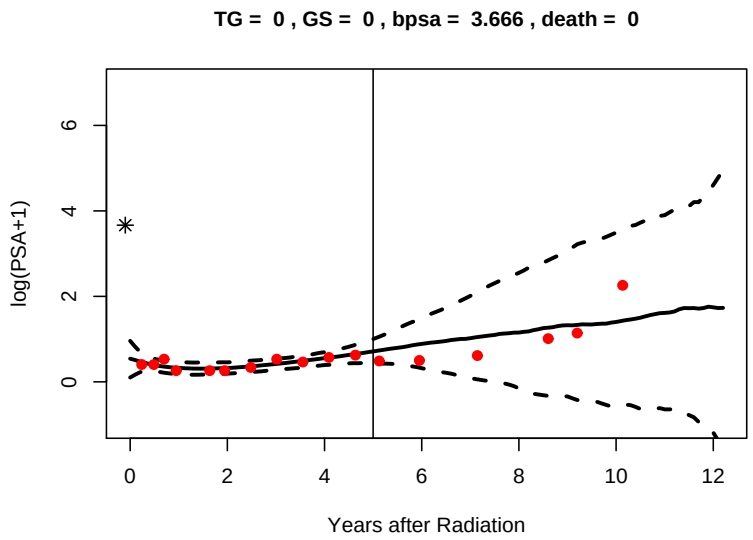
- $M = D'D$ where D is second order difference matrix
- Φ^l is $K \times 2$ matrix, contains basis of the null space of M,
  - columns are 1 and t.
- Φ^{nl} is $K \times (K-2)$ matrix
- $\Phi^{nl} = D'(DD')^{-1}$

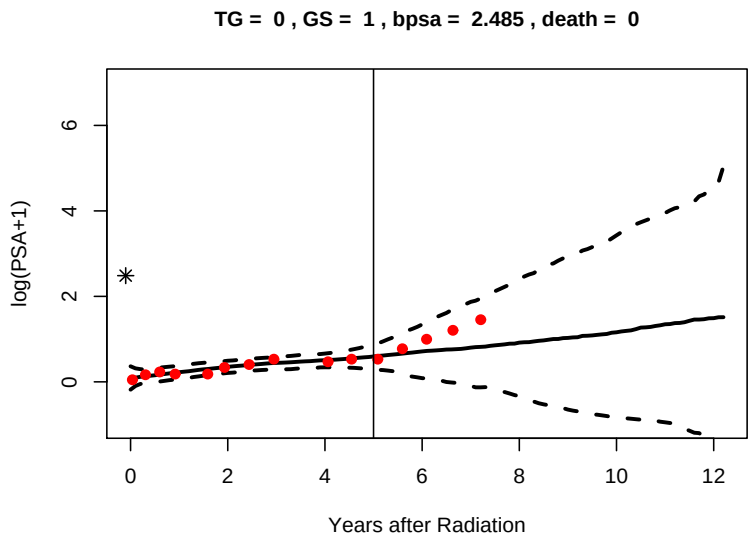
Dataset.

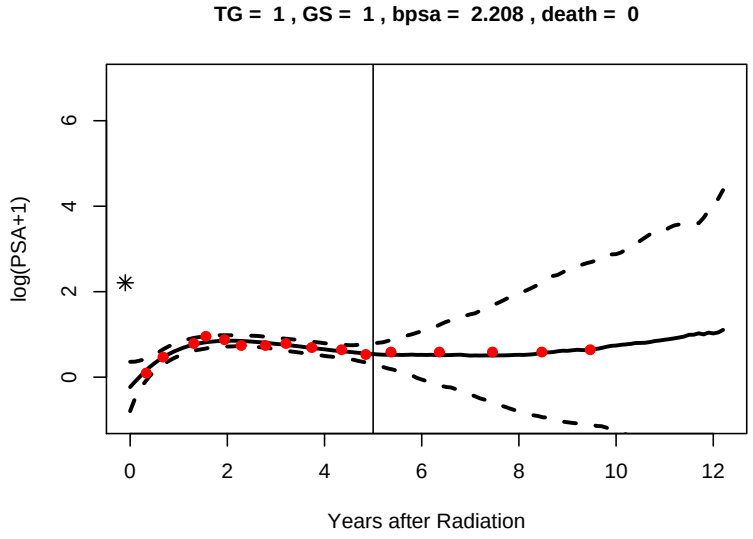
- Patients Initially Treated with Radiation Therapy plus Hormonal Therapy
  - n=2434
  - Heterogeneous pattern of PSA

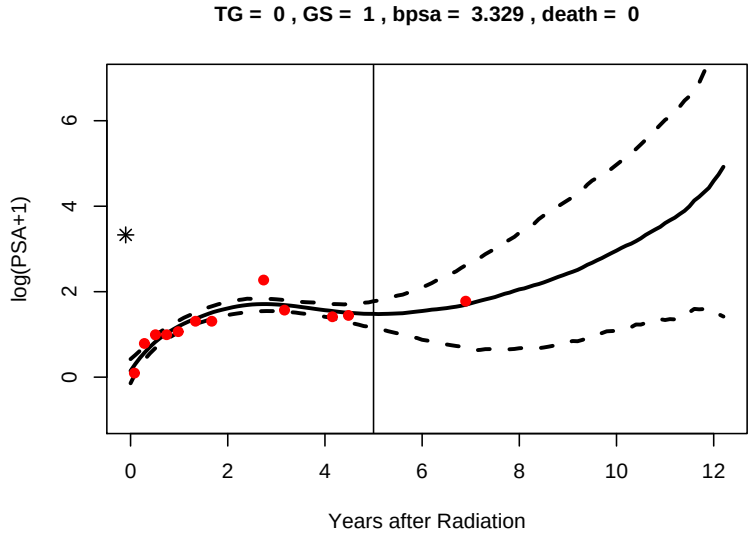

TG = 0 , GS = 0 , bpsa = 3.666 , death = 0
log(PSA+1)
0
2
4
6
0
2
4
6
8
10
12
Years after Radiation


TG = 0 , GS = 0 , bpsa = 3.666 , death = 0
log(PSA+1)
0
2
4
6
Survival Probability
0
0.25
0.5
0.75
1
0
2
4
6
8
10
12
Years after Radiation


TG = 0 , GS = 0 , bpsa = 3.666 , death = 0
log(PSA+1)
Years after Radiation


TG = 0 , GS = 1 , bpsa = 2.485 , death = 0
log(PSA+1)
Years after Radiation


TG = 1 , GS = 1 , bpsa = 2.208 , death = 0
log(PSA+1)
Years after Radiation


TG = 0 , GS = 1 , bpsa = 3.329 , death = 0
log(PSA+1)
Years after Radiation