Evaluating and Extending Three-Arm Study in the Treatment of Superficial Bladder Cancer

P8108 Final Project, Fall 2022

Yunyi Jiang, Xiao Ma, Waveley Qiu,
Xuehan Yang, Congyang Xie

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Background

Superficial Bladder Cancer

- Also known as Stage 1 bladder cancer
- Common diagnosis (75% of bladder cancer cases[1]) and rarely life-threatening on its own.
- Thought to arise due to urinary issues[1] or through "abnormalities of tryptophan metabolism"[2]
- Natural history study conducted in Sweden saw that "death was directly related to tumor grade, number of tumors, and volume of recurrences."[3]

Pyridoxine and Thiotepa

- *Pyridoxine* (vitamin B_6) thought to reduce "abnormalities of tryptophan metabolism"
- *Thiotepa* has been the standard of care for the treatment of superficial bladder cancers.
- Effects of these two therapies compared in randomized clinical trial conducted by Byar and Blackard in 1977

Byar and Blackard (1977)

- Primary clinical interest: prevent and reduce recurrence of Stage 1 bladder cancer.
- Event time agnostic analysis conducted included comparing overall rates and percentages of occurrence between groups
  - Pairwise difference detected in rate of recurrence between thiotepa and placebo, and thiotepa and pyridoxine
  - No other differences in event incidence between groups detected
- Survival analysis conducted involved the construction of life-table estimates.
  - Life-table analysis indicate that the time to first recurrence was significantly different between pyridoxine and placebo groups.
  - Secondary analysis restricted to subjects who experienced recurrence after at least 10 months of follow-up

Proposed Project

Motivation

- Clinical interest in seeing if any of the three treatments decrease incidence of event (recurrence, death) or time to those events.
- Research ought to be reproducible, especially if data are open-source

Analysis Plan

1. Use non-survival analysis methods to see if differences in recurrence and overall status exist between treatment groups, irrespective of time.
2. Construct survival models to analyze recurrence trends to see if differences exist between treatment groups in time to first recurrence, with initial tumor number and initial largest tumor size as covariates.

- Semi-parametric: Cox Proportional Hazards Model
- Parametric: Weibull and Exponential Models
- Non-parametric: KM

3. Compare results to original Byar and Blackard study.

bladder1 Dataset

- `id`: Patient ID
- `treatment`: Placebo, pyridoxine (vitamin B6), or thiotepa
- `number`: Number of tumors at beginning of study (BOS)
- `size`: Size of largest tumor at BOS
- `recur`: Number of recurrences
- `start`, `stop`: The start and end time of each time interval
- `status`: Patient status at end of interval
  - 0: Censored
  - 1: Recurrence
  - 2: Death from bladder disease
  - 3: Death from other/unknown cause
- `rtumor`: Number of tumors at time of recurrence.
- `rsize`: Size of largest recurrent tumor at time of recurrence.
- `enum`: Event number (by patient)

0. Exploratory Data Analysis

Counts by Treatment Group

	Placebo	Pyridoxine	Thiotepa	Total
Total Subjects	48	32	38	118
Number Censored	0	0	0	0
Number with Recurrence	29	15	18	62
Number without Recurrence	19	17	20	56
Number Died	11	7	11	29

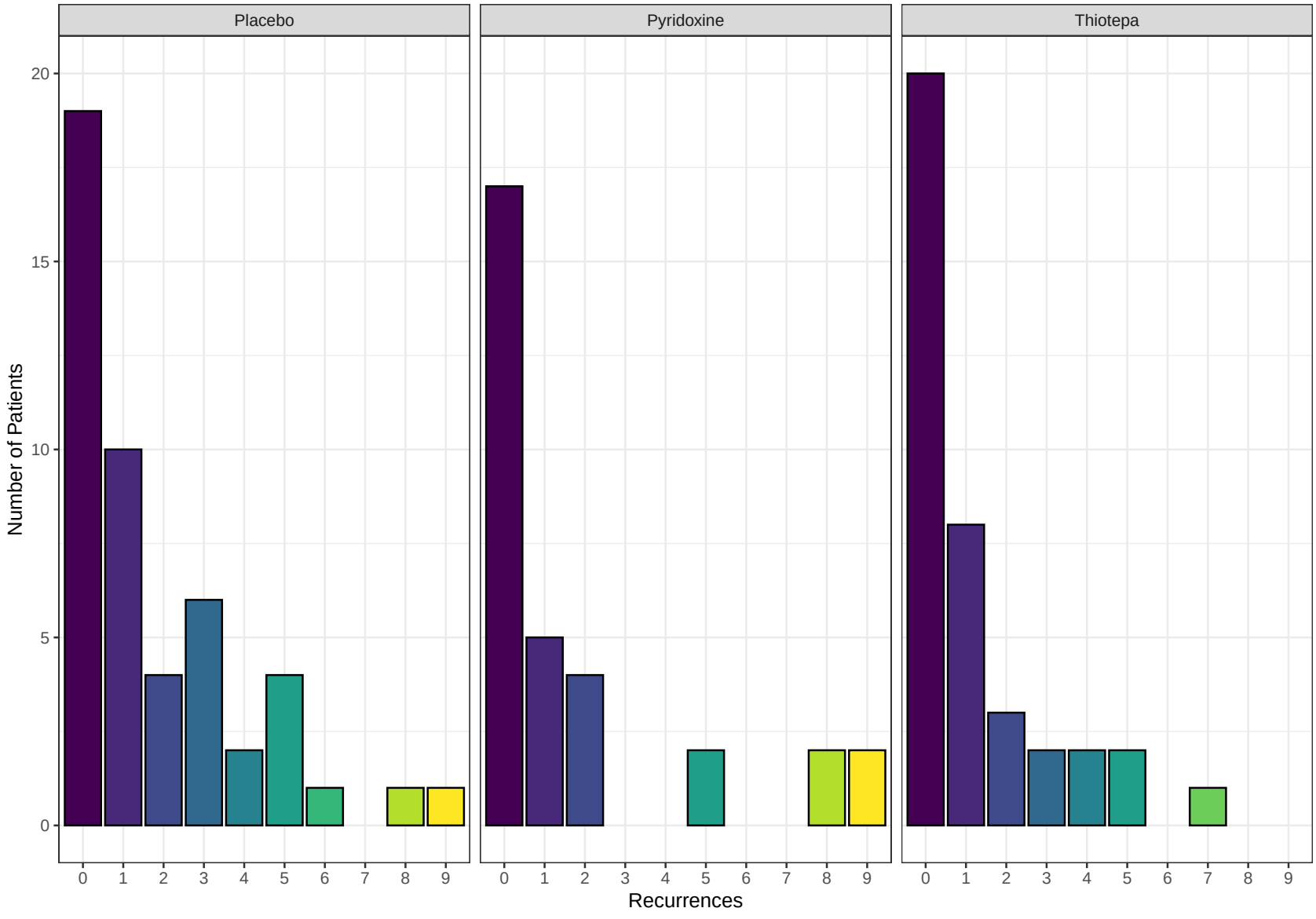
Descriptive Statistics by Treatment Group

	Placebo	Pyridoxine	Thiotepa	Total
Total Subjects	48.00	32.00	38.00	118.00
Number of Subjects with Recurrence	29.00	15.00	18.00	62.00
% Recurrence	60.42	46.88	47.37	52.54
Average Time on Study	31.83	31.03	31.13	31.39
Median Time on Study	30.00	35.50	32.50	31.50
Total Time on Study	1528.00	993.00	1183.00	3704.00
Number of Recurrences	87.00	57.00	45.00	189.00
Rate Recurrence (per 100 person-months)	5.69	5.74	3.80	5.10

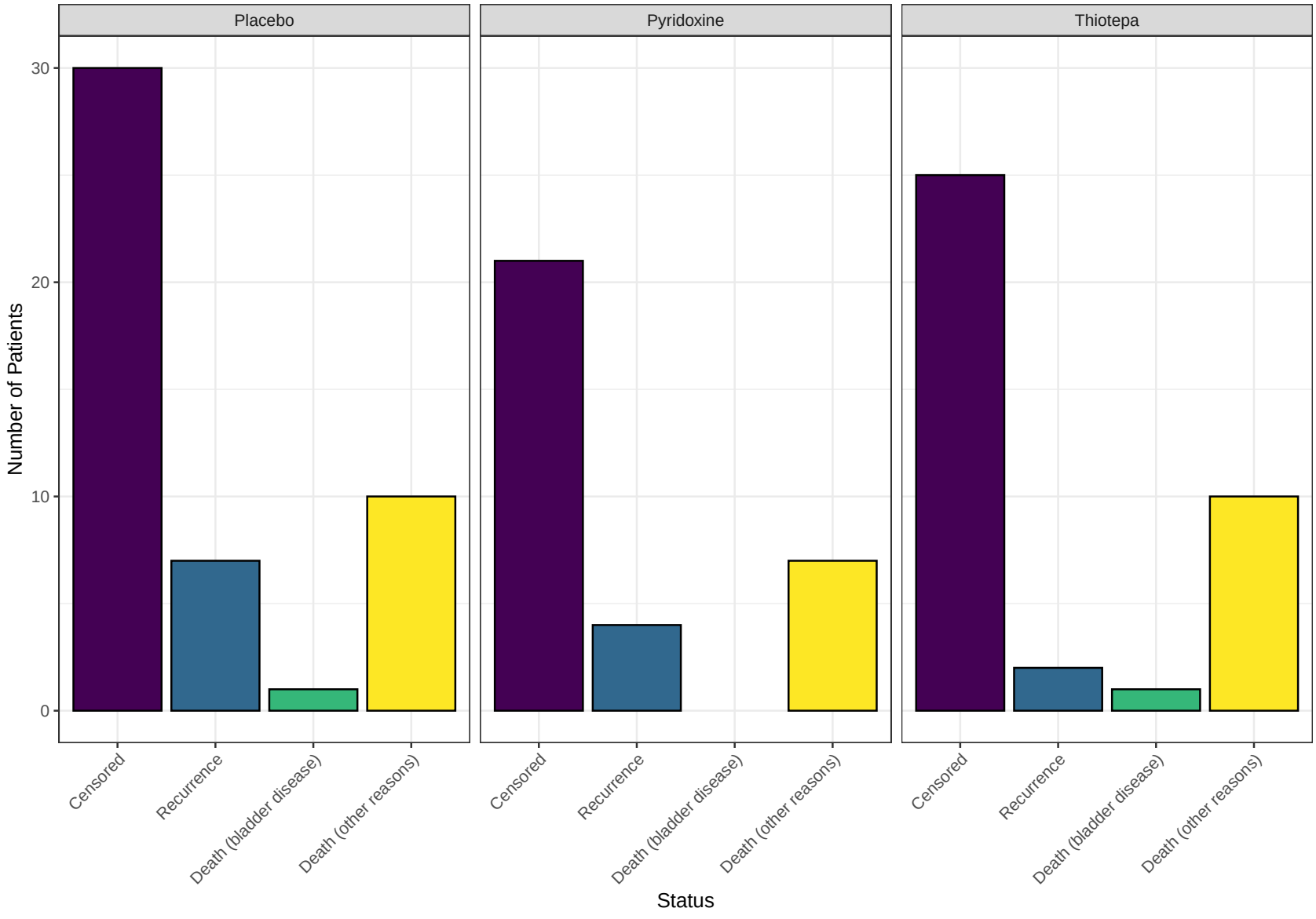
Tumor Descriptive Statistics

	Placebo	Pyridoxine	Thiotepa	Total
Average # of Tumors (BOS)	1.92	2.00	2.32	2.07
Median # of Tumors (BOS)	1.00	1.00	1.00	1.00
Average Largest Tumor Size (BOS)	2.06	2.06	1.92	2.02
Median Largest Tumor Size (BOS)	1.00	1.00	1.00	1.00
Average # of Recurrences	1.81	1.78	1.18	1.60
Median # of Recurrences	1.00	0.00	0.00	1.00
Average # Tumors at Recurrence	4.43	5.25	5.00	4.77
Median # of Tumors at Recurrence	3.00	5.50	5.00	3.00

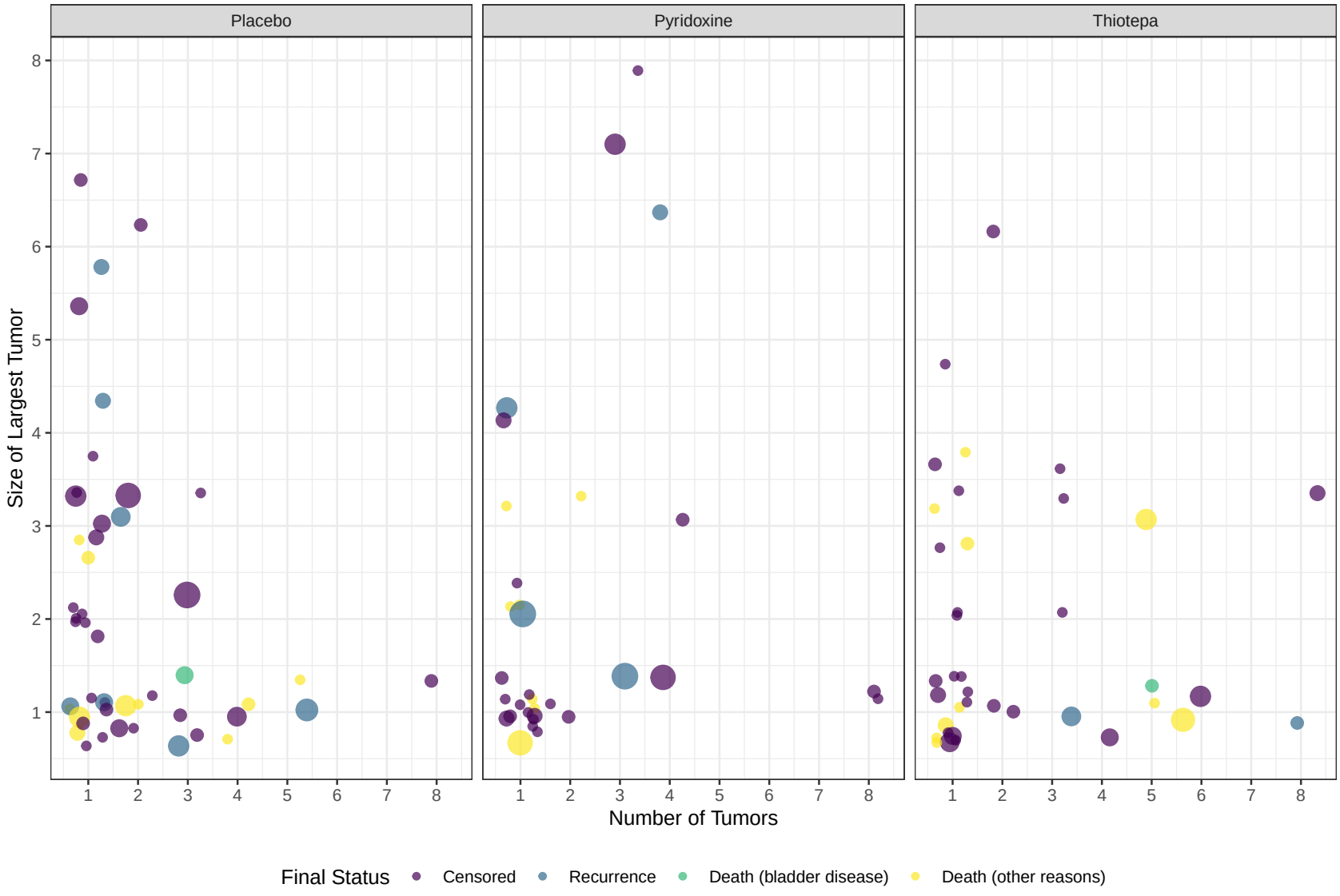
Distribution of Number of Recurrences by Treament



Distribution of Final Status by Treatment



Distribution of Number of Tumors and The Largest Initial Tumor Size (BOS)



Note: Size of point on plot determined by number of recurrences.

1. Non-Survival Analysis

Absolute Comparison: Counts of Events by Treatment (Poisson Regression)

```
glm(n ~ status + recur + treatment, family =
"quasipoisson")
```

term	estimate	std.error	statistic	p.value
treatmentPyridoxine	-0.41	0.28	-1.44	0.15
treatmentThiotepa	-0.23	0.27	-0.87	0.38

Relative Comparison: Frequencies of Events by Treatment (Chi-square Test)

treatment	any_recurrence	no_recurrence
placebo	29	19
pyridoxine	15	17
thiotepa	18	20

```
##
##  Pearson's Chi-squared test
##
## data:  to_chi_sq[2:3] %>% as.matrix()
## X-squared = 2.0137, df = 2, p-value = 0.3654
```

Relative Comparison: Rates of Events by Treatment (F-test)

- Assume that time to first recurrence follows an exponential distribution.
- Cox (1953)[4] proposes a pairwise comparison of rates by using the test statistic $F = \frac{T_1/(d_1+0.5)}{T_2/(d_2+0.5)}$
  - T_1 and T_2: total patient time for each treatment group
  - d_1 and d_2: total number of events for each treatment group
  - Degrees of freedom: $v_1 = (v_1' + v_1^*/2) = 2d_1 + 1$ and $v_2 = (v_2' + v_2^*/2) = 2d_2 + 1$

Relative Comparison: Rates of Events by Treatment (F-test)

```
## $comparison
## [1] "placebo vs. pyro"
##
## $p_value
## [1] 0.5214143
```

```
## $comparison
## [1] "placebo vs. thio"
##
## $p_value
## [1] 0.01280195
```

```
## $comparison
## [1] "pyro vs. thio"
##
## $p_value
## [1] 0.01903914
```

2. Survival Analysis: Time to First Recurrence

Semi-parametric Approach: Cox-PH Model

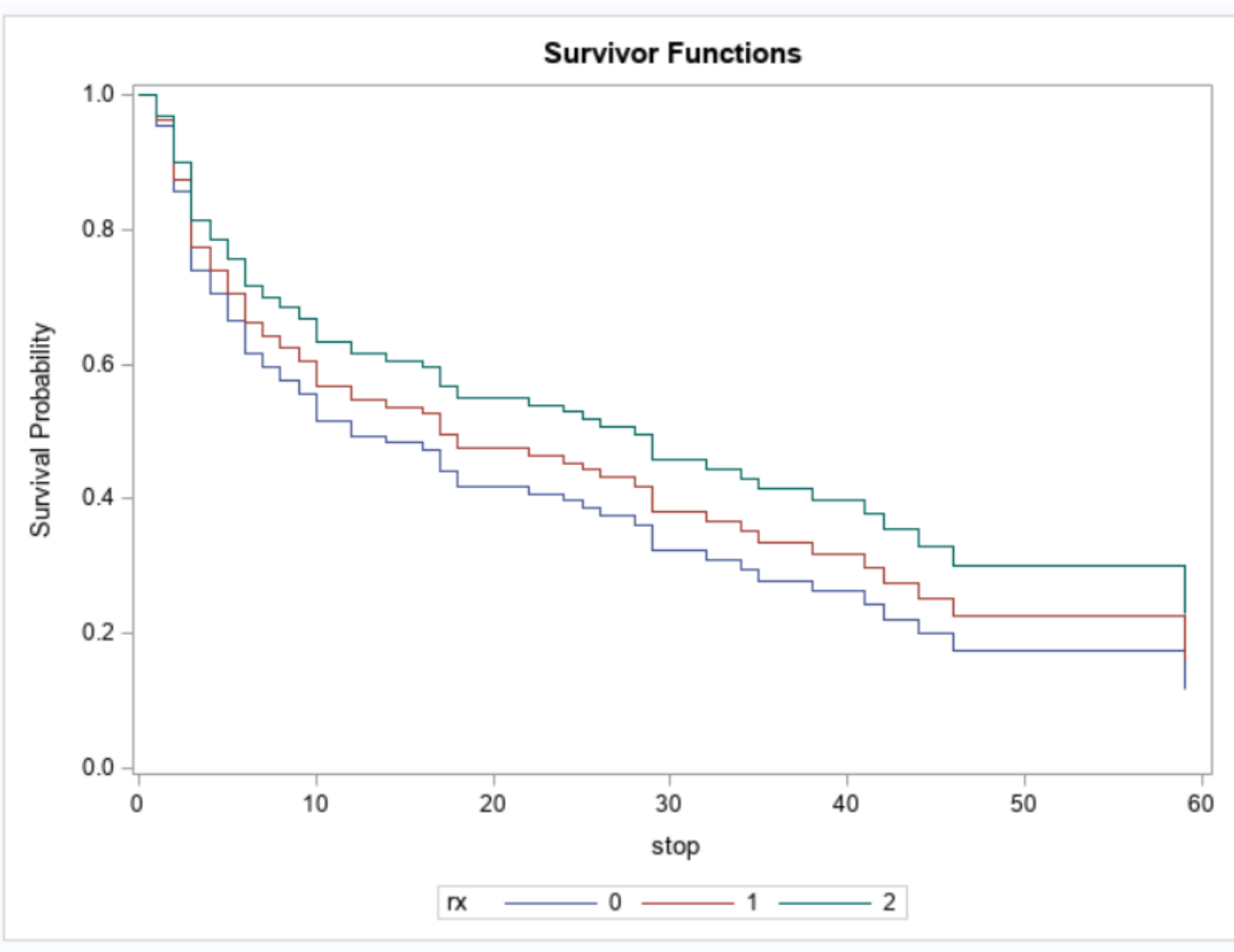
Model Fit Statistics		
Criterion	Without Covariates	With Covariates
-2 LOG L	648.479	636.519
AIC	648.479	644.519
SBC	648.479	653.946

Testing Global Null Hypothesis: BETA=0			
Test	Chi-Square	DF	Pr > ChiSq
Likelihood Ratio	11.9607	4	0.0176
Score	14.3756	4	0.0062
Wald	13.7107	4	0.0083

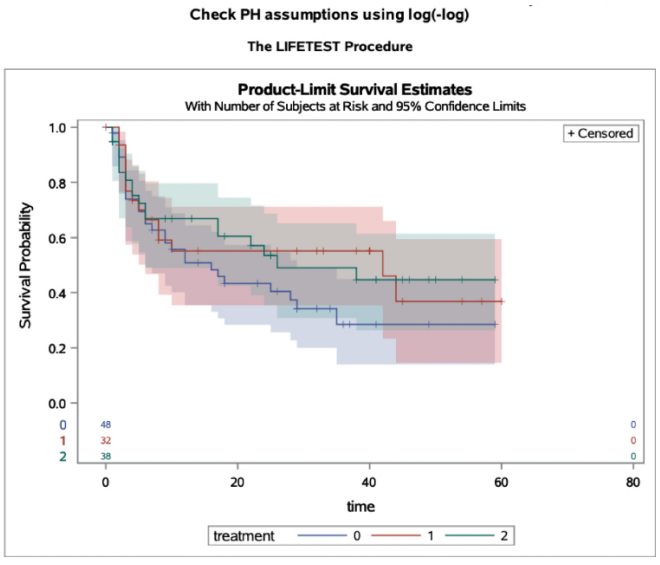
Type 3 Tests			
Effect	DF	Wald Chi-Square	Pr > ChiSq
rx	2	1.8115	0.4042
number	1	13.2340	0.0003
size	1	0.0224	0.8809

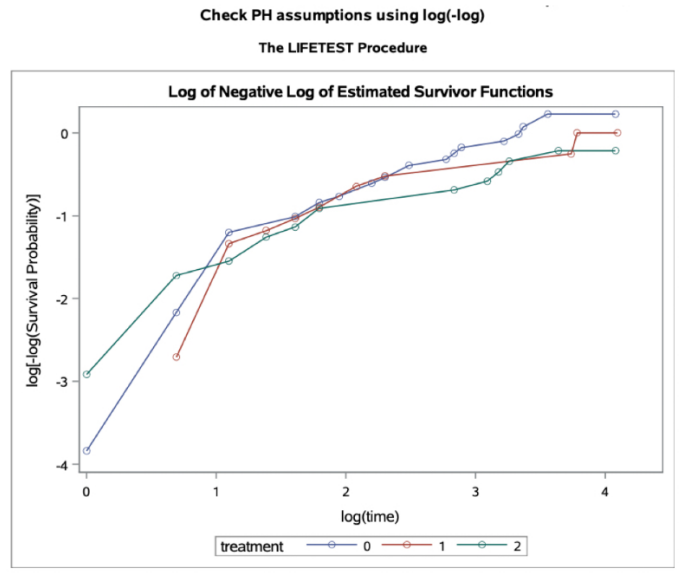
Analysis of Maximum Likelihood Estimates								
Parameter		DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio	Label
rx	1	1	-0.15671	0.28303	0.3066	0.5798	0.855	rx 1
rx	2	1	-0.37249	0.27676	1.8114	0.1783	0.689	rx 2
number		1	0.22060	0.06064	13.2340	0.0003	1.247	
size		1	0.01026	0.06846	0.0224	0.8809	1.010	

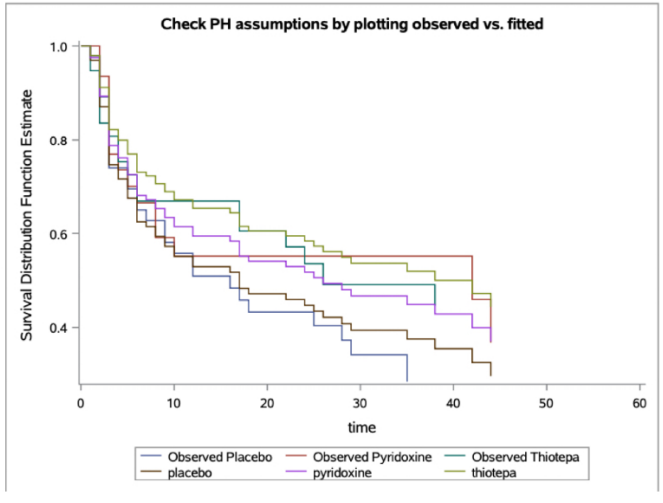
Semi-parametric Approach: Cox-PH Model Estimation



Semi-parametric Approach: Cox-PH Assumptions

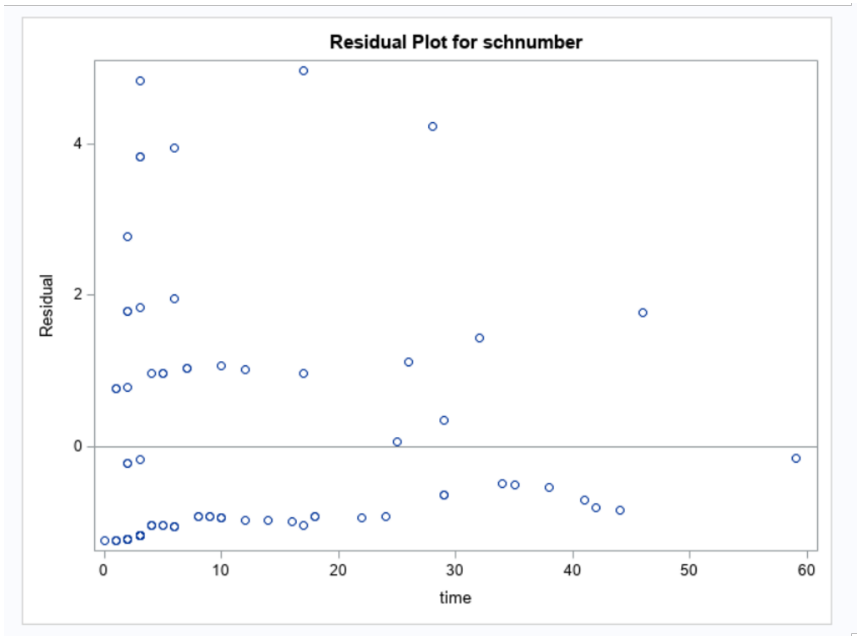


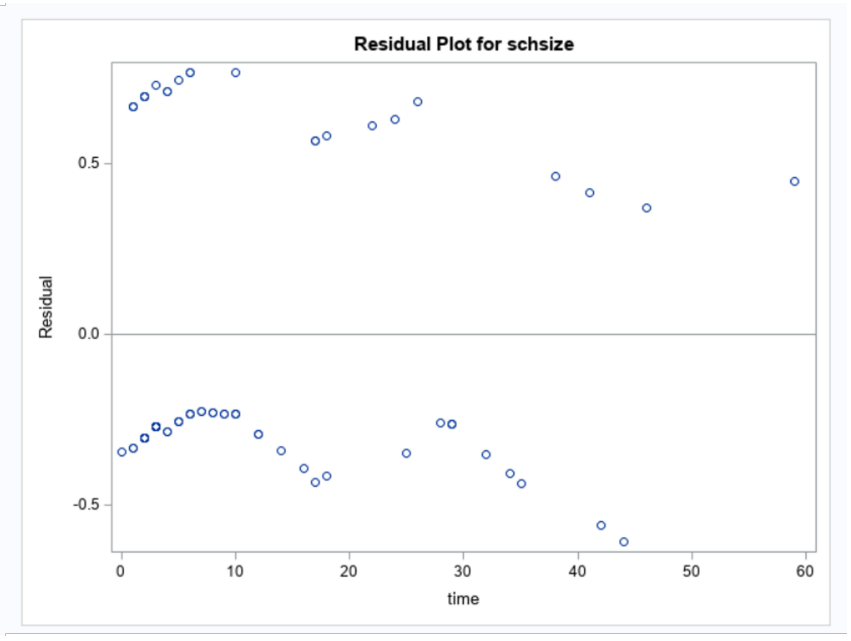




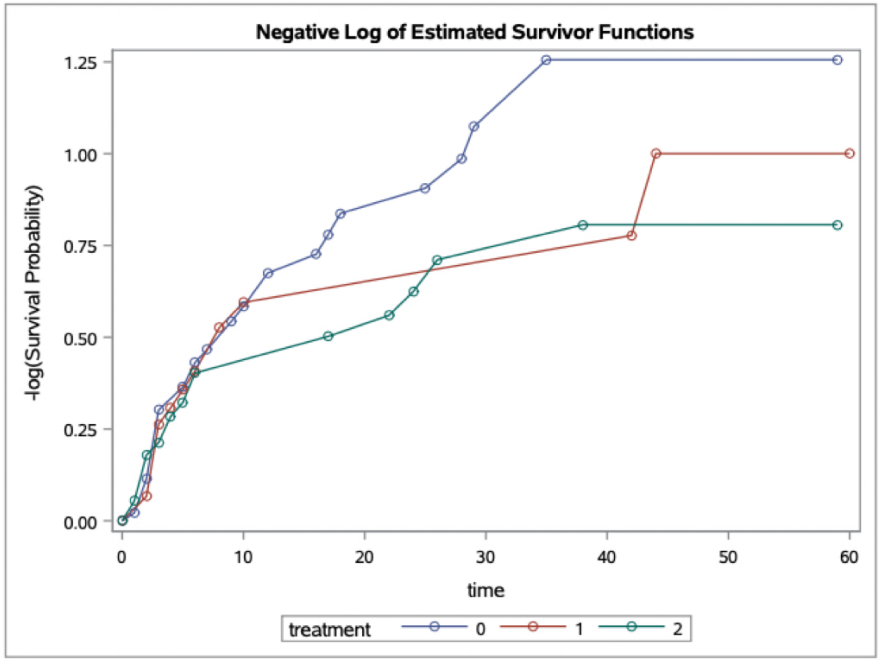
- -log(log) survival curves are crossed (not parallel)
- Separations between Observed and Fitted Plot are not significant
- PH assumption violated

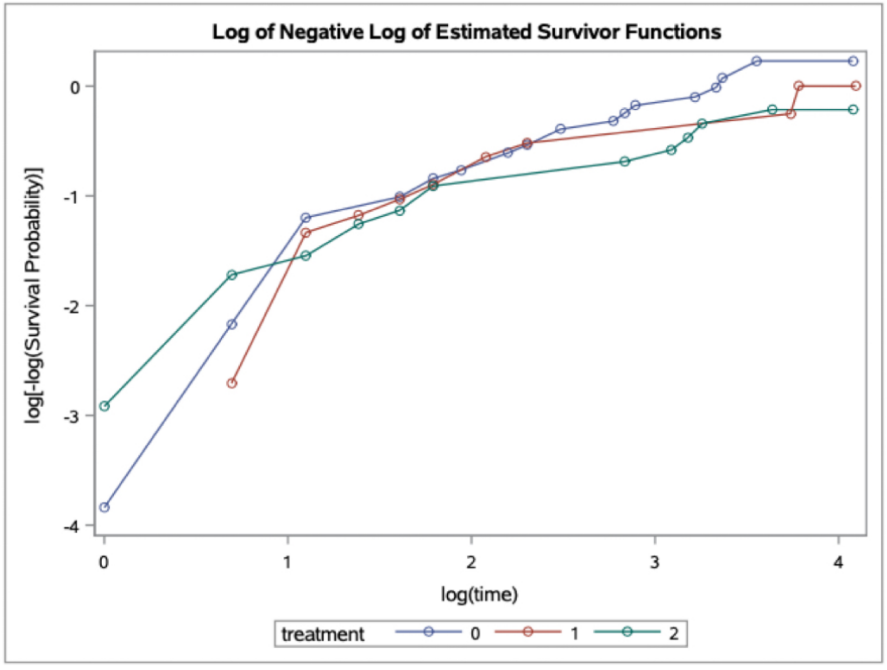
Semi-parametric Approach: Cox-PH Assumptions



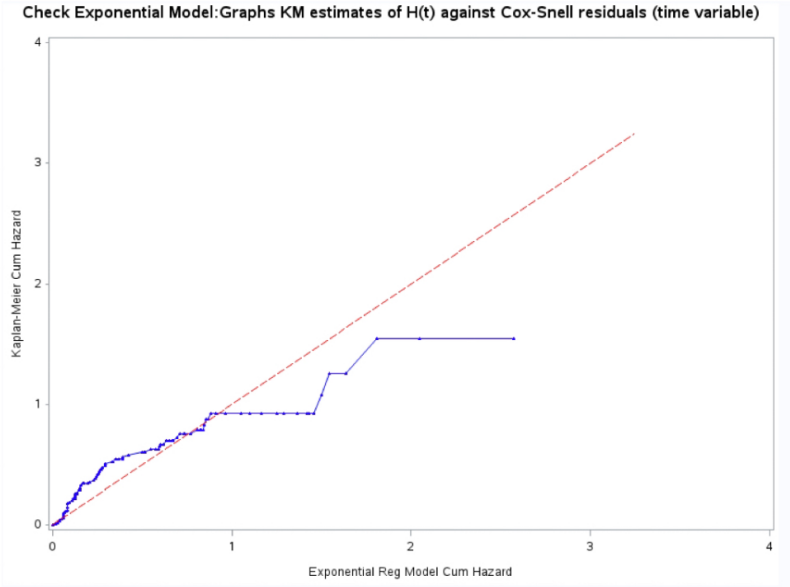


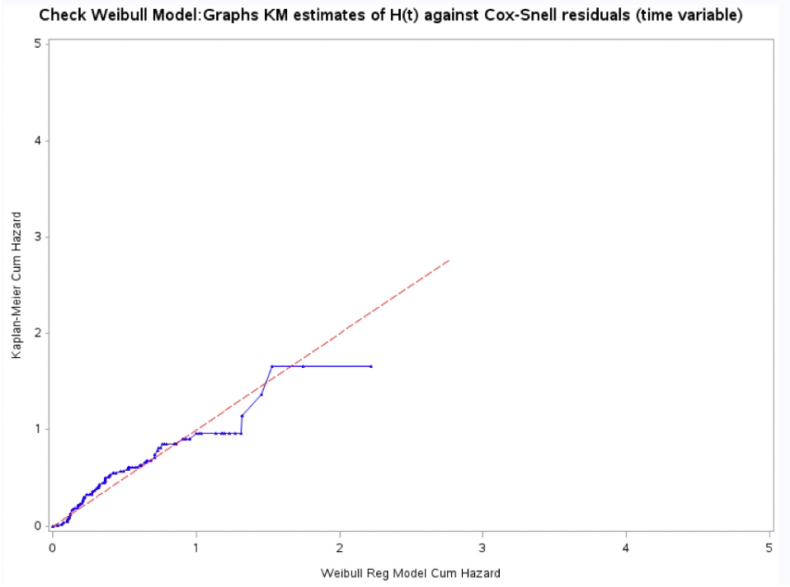
Parametric Approach: Exponential and Weibull Models





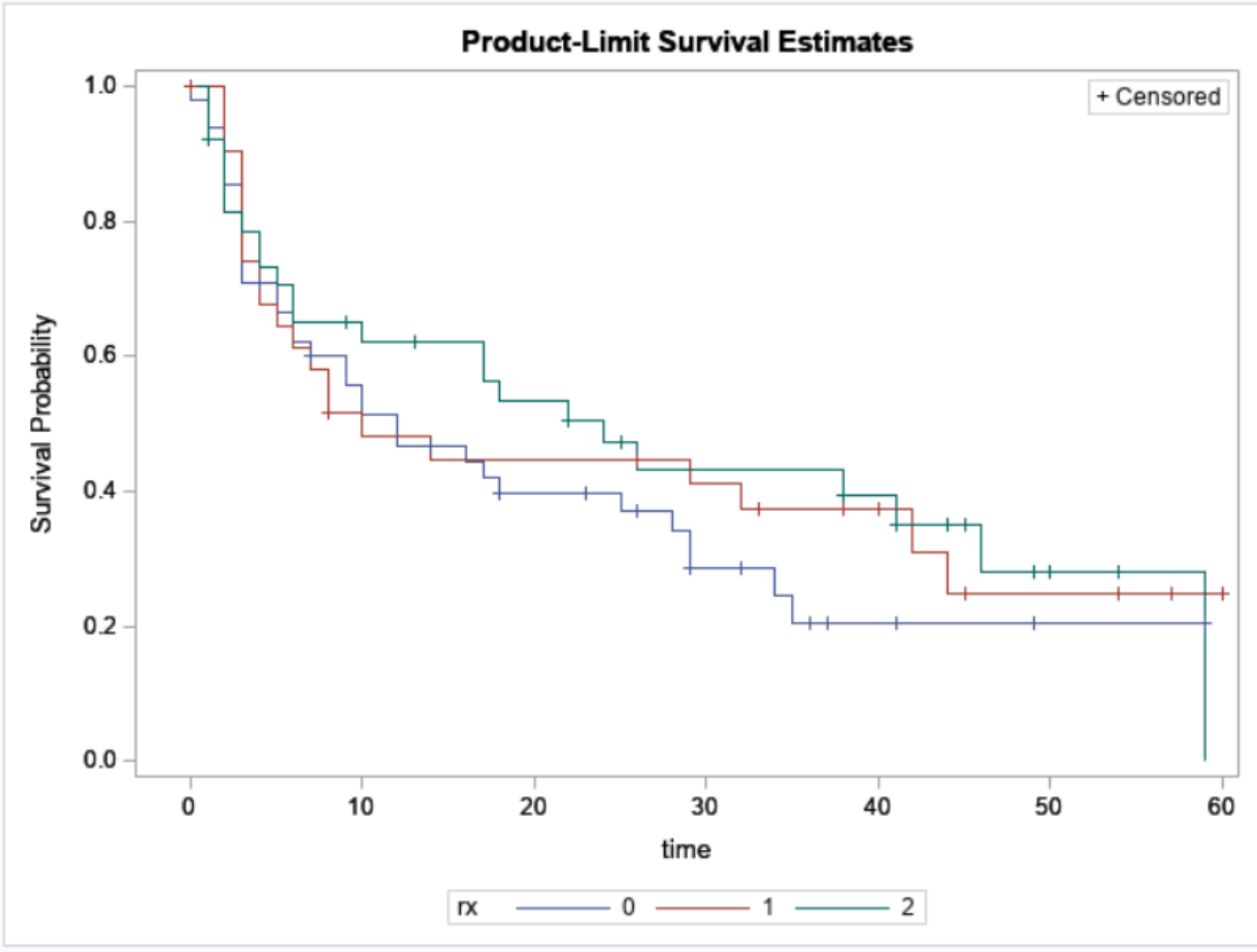
Parametric Approach: Graphical Assessment of Parametric Model Assumptions (using KM)





- KM estimates of H(t) VS. Cox-Snell residuals
- Hazard must be constant with time
- Both of the residual plots do not have a straight line

Non-parametric Approach: KM Estimate

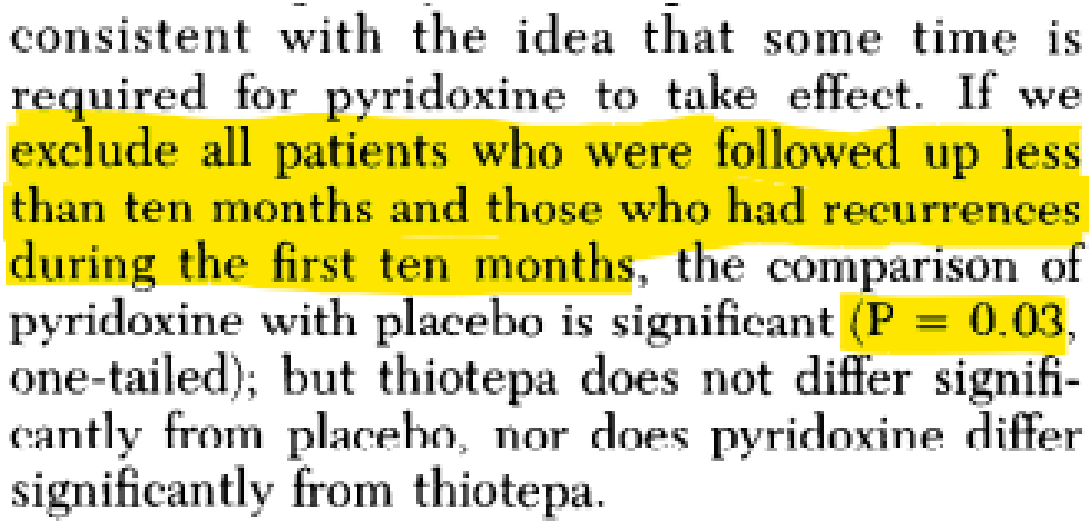


3. Review of Original Study

Review of Original Study

- Original study primarily focused on non-survival approaches, most results of which we were able to reproduce.
  - Only discrepancy existed wih original investigators reporting significant difference in rate of recurrence between both placebo/thiotepa and pyridoxine/thiotepa comparisons
  - Our analysis only indicated a significant difference in recurrence rate between placebo/thiotepa, consistent with KM findings
- Survival analysis results were similar
  - No difference between groups were found in the non-parametric approaches (KM in our project and life table in original study).

Difference in Survival Curves after 10 months?



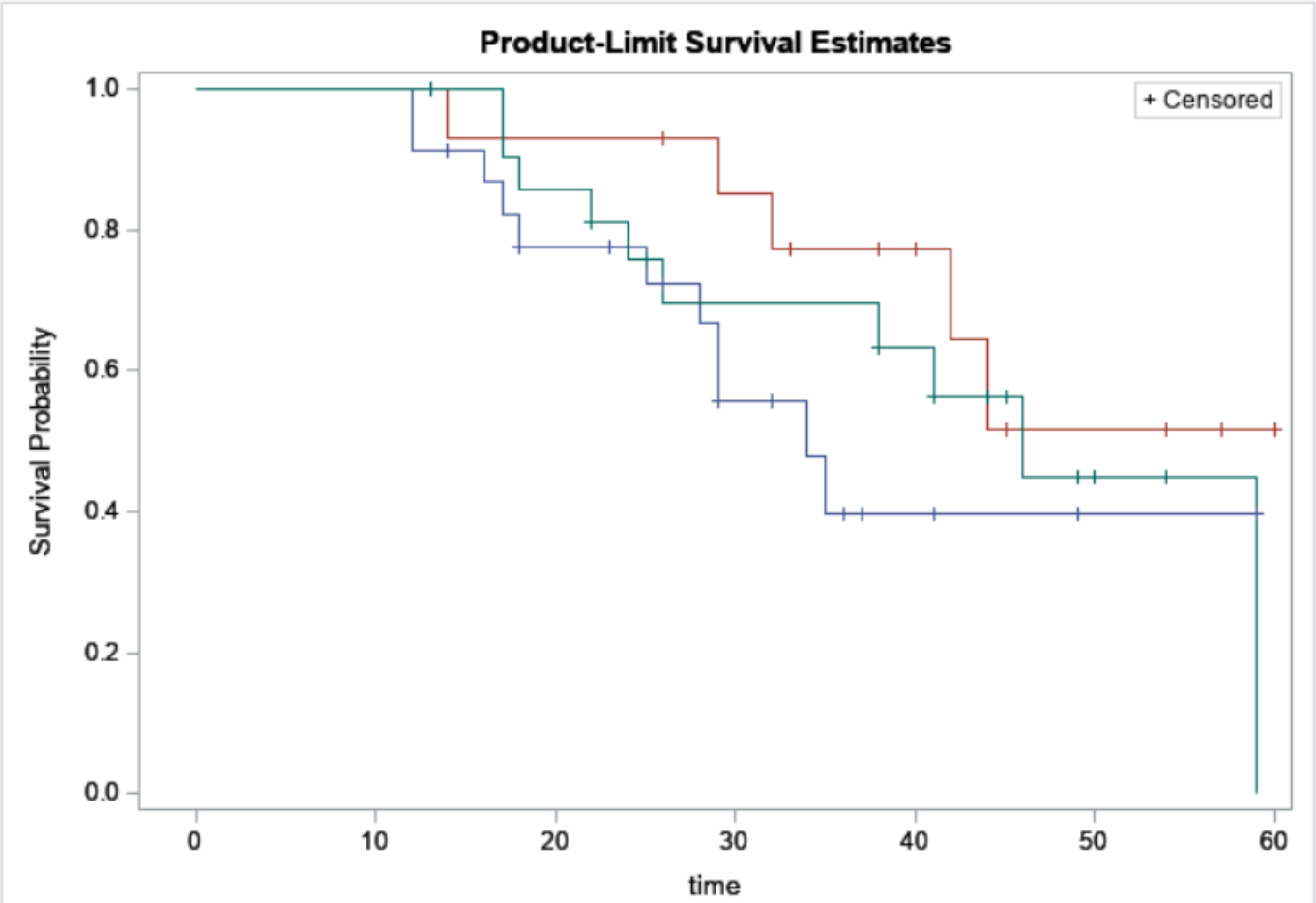
consistent with the idea that some time is required for pyridoxine to take effect. If we exclude all patients who were followed up less than ten months and those who had recurrences during the first ten months, the comparison of pyridoxine with placebo is significant ($P = 0.03$, one-tailed); but thiotepa does not differ significantly from placebo, nor does pyridoxine differ significantly from thiotepa.

Figure 1: Byar and Blackard (1977)

- Notwithstanding the accuracy of this statement, this p-value actually should not be taken as significant.
- 6 comparisons will have been conducted in total, need to adjust for multiple comparison (significance level will be < 0.03 if using Bonferroni's adjustment)

Difference in Survival Curves after 10 Months?

Adjustment for Multiple Comparisons for the Wilcoxon Test				
Strata Comparison			p-Values	
rx	rx	Chi-Square	Raw	Bonferroni
0	1	3.1202	0.0773	0.2320
0	2	1.0659	0.3019	0.9056
1	2	0.4059	0.5241	1.0000



Conclusion

Conclusion

- Treatments proposed in this study seemed to be much less effective than hypothesized in the prevention of superficial bladder cancer recurrence in both recurrence incidence and time-to-recurrence outcomes.
  - Thiotepa appears to have some effect in reducing rate of recurrence.
- Most results in study are reproducible, with some multiple comparison discrepancies.
- Natural history of superficial bladder cancer may have impacted non-significance of most results
  - Surgical treatments are usually most effective[1,5]
- Future studies can consider collecting time-varying covariates to improve ability to model time-to-recurrence outcome.

Thank you!

References

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