Analysis of Overall Survival and Prostate Specific Survival: An Example data analysis report generated in R, LaTeX, and put together via `knitr`

Prepared for Data Analysts

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1 Introduction

An example data analysis report. The data set is fictitious. Consider this work only as an example of reproducible report writing.

Collaboration Considerations This report was authored in using R, `knitr`, and LaTeX. While there are many advantages to authoring reports in LaTeX, namely reproducible research via literate programming, there are some disadvantages as well. If the reader would like the plain .tex files for reference and editing please let DeWitt know and the files will be made available. It is expected that the collaborators for this project will be using Microsoft Office, or similar programs, to author manuscripts, abstracts, and posters. The text of this .pdf report should be easy to copy and paste into Office type products. However, the tables in this document may not.

To make the process of reproducing the tables presented in this document in a Office type software package easier html versions of the tables have been provided to the collaborators as well. It is important to note that there are two files, a .css file and a .html file, which need to be in the same directory for the rendering of the .html tables to work. Opening the .html file in any web browser or may be imported directly into an Office program. These tables will require some formatting modifications.

Graphics presented in this report are also sent to the collaborators as individual .pdf files. The graphics can be provided in any major graphics format, size, and resolution as needed. For example, if a file is needed as a 7 inch by 7 inch .tiff file with 1200 dpi resolution, please send such requests to DeWitt and the graphics files will be produced as needed. Many journals have specific requirements for graphics and provide, via the journals' websites, guidelines for authors.

2 Methods

Data was created and modified to be used only for example purposes.

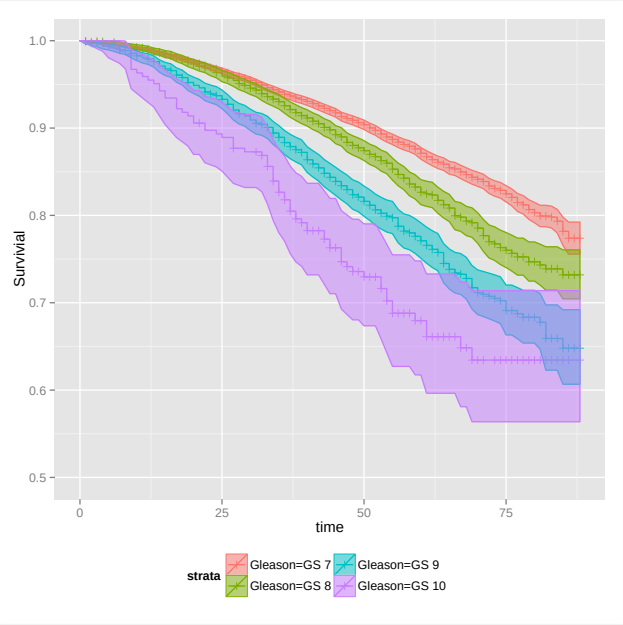
Data analysis was done in R version 3.0.2 (2013-09-25) [1]. Survival analysis was done using the `survival` pacakge [2] with the default Efron method for tie handling in the Cox proportional hazard models. Graphics were produced via the `ggplot2` package [3].

3 Analysis and Results

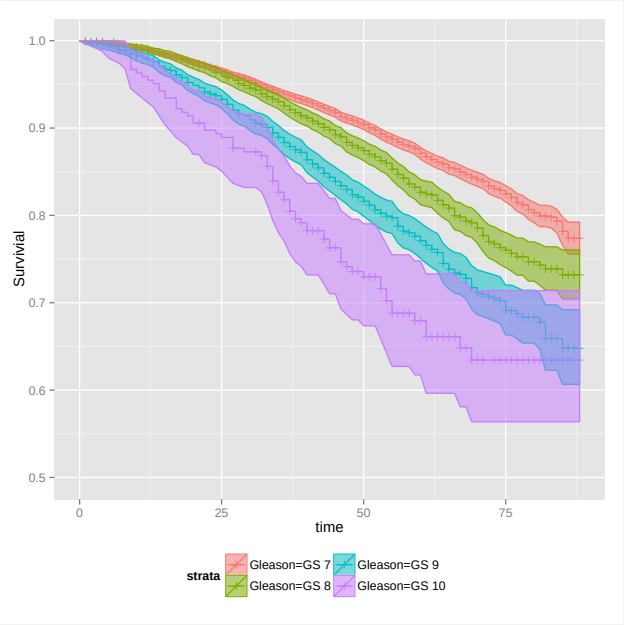
3.1 Data Set Description

The data contained information on the following variables and the levels for each. There is additional information in the data set on the Gleason scores. For patients with a Gleason score of 7, the primary-secondary values of '3+4' and '4+3' are available. The following analysis uses a Gleason Score variable with the total score used in

Figure 1: KM plots for OS and PCSS by Gleason Score.



(a) (OS_GS.pdf) KM plot for OS by Gleason Score.



(b) (PCSS_GS.pdf) KM plot for PCSS by Gleason Score.

all cases save GS 7 which is reported with primary-secondary delineations. Table 1 on page 6 report the observed data set overall and by Gleason score. There is a total of 19,039 data records avaiable for analysis.

3.2 Seven Year Survival

Table 2 reports the Kaplan-Meier estimates for survival at 88 months, the maximum follow up time observed, for each Gleason score. The estimated survival by primary-secondary patterns for Gleason scores 7 is also reported.

3.3 Primary-Secondary Levels or Sums?

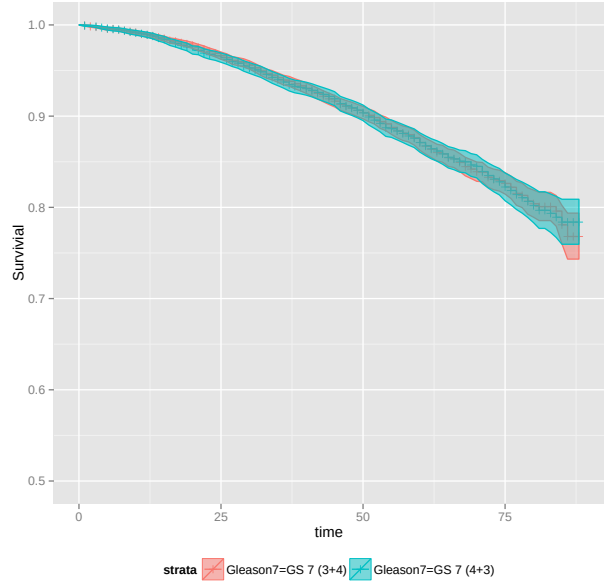
In this section of the analysis we investigate if there is any difference in the OS or PCSS between the primary-secondary levels by Gleason score. Results of six separate Cox PH regression models, one to compare the relative difference in the hazard for OS and PCSS between the two levels of delineation in each Gleason 7, 8, or 9 score, are reported in Table 3. These results indicate there is no statistically significant differences in the hazards between the different delineations for Gleason 8 and 9 for either OS or PCSS. There is a statistically significant difference in the hazard between GS 7 (4+3) and GS 7 (3+4).

Figure 1 are the Kaplan-Meier survival curves for overall and prostate cancer survival for each Gleason score. Figure 2 show the Kaplan-Meier plots for the primary/secondary patterns within Gleason 7, 8, and 9. Table 4 report the number of patients at risk overall and the number of deaths observed for each Gleason score.

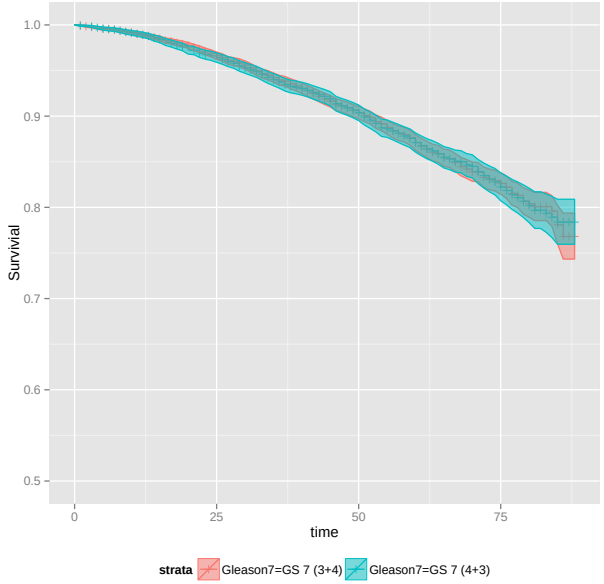
3.3.1 Should the primary/secondary patterns be used in a multivariable model?

The results of the Cox proportional hazard regression models for overall survival and prostate cancer specific survival are presented in Table 6 on page 9. Both univariable and multivariable regression models are presented. The univariable models are built with only the noted predictor variable whereas the multivariable models use the era, age, PSA, T Stage, and Gleason score jointly as predictors for survival.

Figure 2: KM plots for OS and PCSS by primary-secondary patterns for Gleason 7, See Table 3 for the log-rank test p-values.



(a) (OS_Gleason7.pdf) KM plot for OS by primary-secondary patterns within the 12,986 patients with a Gleason score of 7.



(b) (PCSS_Gleason7.pdf) KM plot for PCSS by primary-secondary patterns within the 12,986 patients with a Gleason score of 7.

For overall survival we find that the patients diagnosed in Era 2 have better outcomes, i.e., longer survival, than those diagnosed in the earlier Era 1. For example, the hazard ratio between Era 2 and Era 1 for overall survival based on the multivariable cox regression model is 0.84 (95% CI: 0.77, 0.92; p <0.001).

No statistically signficant difference in overall surverival was observed between Gleason 7 (4+3) and Gleason 7 (3+4), HR = 0.99 (95% CI: 0.90, 1.10; p = 0.915).

Testing for a difference in the hazard ratio between sequential Gleason scores is reported in Table 5. Considering that the data is fictitious and the methods for deliniating 3+4 and 4+3 was a coin flip, it's not surprsing that the hazard ratio between these two levels is not statistically different from 1. In general, and as expected for prostate cancer patients, as the Gleason score increases the hazard increases as well.

4 Conclusions

Reproducible research is a growing area of concern. Many tools exist for literate programming and the example here is only one approach.

Things to consider:

- portability,
- collaborations,
- robustness.

References

[1] R Core Team. *R: A Language and Environment for Statistical Computing*. R Foundation for Statistical Computing, Vienna, Austria, 2013.

[2] Terry Therneau. *survival: Survival Analysis*, 2013. R package version 2.37-4.

[3] Hadley Wickham and Winston Chang. *ggplot2: An implementation of the Grammar of Graphics*, 2013. R package version 0.9.3.1.

Table 1: Observed data overall and by Gleason Score. Reported values are counts and row percentages, i.e., the sum of the reported percentages over each row should sum to 100%.

	Overall		**GS 7 (3+4)**		**GS 7 (4+3)**		**GS 8**		**GS 9**		**GS 10**		**p-value**
	n	%	n	%	n	%	n	%	n	%	n	%	
	19,039	100	7,905	41.5	5,081	26.7	3,670	19.3	2,139	11.2	244	1.3	
Era													
Era 1	8,615	45.2	3,572	41.5	2,297	26.7	1,659	19.3	970	11.3	117	1.4	0.945
Era 2	10,424	54.8	4,333	41.6	2,784	26.7	2,011	19.3	1,169	11.2	127	1.2	
Age													
[40,50)	3,051	16.0	1,284	42.1	861	28.2	544	17.8	323	10.6	39	1.3	<0.001
[50,70)	5,945	31.2	2,601	43.8	1,658	27.9	1,005	16.9	608	10.2	73	1.2	
[70,85]	10,043	52.7	4,020	40.0	2,562	25.5	2,121	21.1	1,208	12.0	132	1.3	
T Stage													
T Stage 1	9,668	50.8	4,334	44.8	2,776	28.7	1,699	17.6	770	8.0	89	0.9	<0.001
T Stage 2	8,189	43.0	3,257	39.8	2,103	25.7	1,657	20.2	1,065	13.0	107	1.3	
T Stage 3/4	1,182	6.2	314	26.6	202	17.1	314	26.6	304	25.7	48	4.1	
PSA													
[0, 10) ng/ml	11,567	60.8	5,148	44.5	3,262	28.2	1,997	17.3	1,038	9.0	122	1.1	<0.001
[10, 20) ng/ml	4,372	23.0	1,709	39.1	1,136	26.0	927	21.2	531	12.1	69	1.6	
[20, Inf) ng/ml	3,100	16.3	1,048	33.8	683	22.0	746	24.1	570	18.4	53	1.7	

Table 2: Kaplan-Meier estimated survival at seven years by Gleason Score. Reported values are the estimated survival and the 95% confidence intervals for the estimated survival.

	OS			**PCSS**		
	survival	lower	upper	survival	lower	upper
Whole Sample	76.9%	75.8%	78.0%	76.9%	75.8%	78.0%
Gleason 7	79.8%	78.6%	81.1%	79.8%	78.6%	81.1%
Gleason 7 (3+4)	80.1%	78.5%	81.6%	80.1%	78.5%	81.6%
Gleason 7 (4+3)	79.3%	77.3%	81.5%	79.3%	77.3%	81.5%
Gleason 8	73.9%	71.4%	76.4%	73.9%	71.4%	76.4%
Gleason 9	65.9%	62.3%	69.8%	65.9%	62.3%	69.8%
Gleason 10	63.4%	56.4%	71.4%	63.4%	56.4%	71.4%

Table 3: Hazard ratios for the different primary-secondary delineations of the Gleason Score 7. Results in this table are from Cox Proportional Hazard models. Reported results are the hazard ratios (HR), lower and upper confidence bounds for 95 % confidence intervals and p-values are the result from log-rank tests for the models.

	OS				**PCSS**			
	HR	LCL	UCL	p-value	HR	LCL	UCL	p-value
GS 7 (3+4)	Reference							
GS 7 (4+3)	1.00	0.91	1.11	0.996	1.00	0.91	1.11	0.996

Table 4: Number of records and number of events for OS and PCSS by Gleason score and primary/secondary patterns.

	OS		**PCSS**	
	records	events	records	events
Gleason=GS 7	12,986	1,611	12,986	1,611
Gleason7=GS 7 (3+4)	7,905	980	7,905	980
Gleason7=GS 7 (4+3)	5,081	631	5,081	631
Gleason=GS 8	3,670	598	3,670	598
Gleason=GS 9	2,139	473	2,139	473
Gleason=GS 10	244	73	244	73

Table 5: Hazard ratios for sequential pairs of Gleason scores. The confidence intervals and p-values have been adjusted for multiple comparisons via a Bonferroni correction. These results use the coefficient estimates from the multivariable Cox PH regression models.

	OS				**PCSS**			
	HR	LCL	UCL	pvalue	HR	LCL	UCL	pvalue
Gleason 7 (3+4)	Reference				Reference			
Gleason 7 (4+3)	0.99	0.86	1.16	1.000	0.99	0.86	1.16	1.000
Gleason 7 (4+3)	Reference				Reference			
Gleason 8	1.23	1.04	1.46	0.001	1.23	1.04	1.46	0.001
Gleason 8	Reference				Reference			
Gleason 9	1.40	1.17	1.68	<0.001	1.40	1.17	1.68	<0.001
Gleason 9	Reference				Reference			
Gleason 10	1.44	0.99	2.08	0.016	1.44	0.99	2.08	0.016

Table 6: Hazard ratios (HR) along with 95% confidence intervals (LCL, UCL) and p-values for testing if the hazard ratio is statistically different from 1 are presented in this table for both univariable and multivariable regression models of both overall survival and prostate cancer specific survival.

	OS (univar)				OS (multivar)				PCSS (univar)				PCSS (multivar)			
	HR	LCL	UCL	p-value	HR	LCL	UCL	p-value	HR	LCL	UCL	p-value	HR	LCL	UCL	p-value
Era																
Era 1	Reference				Reference				Reference				Reference			
Era 2	0.83	0.76	0.90	<0.001	0.84	0.77	0.92	<0.001	0.83	0.76	0.90	<0.001	0.84	0.77	0.92	<0.001
Age																
[40,50)	Reference				Reference				Reference				Reference			
[50,70)	0.95	0.84	1.09	0.481	0.96	0.84	1.10	0.554	0.95	0.84	1.09	0.481	0.96	0.84	1.10	0.554
[70,85]	1.62	1.44	1.81	<0.001	1.61	1.43	1.80	<0.001	1.62	1.44	1.81	<0.001	1.61	1.43	1.80	<0.001
T.Stage																
T Stage 1	Reference				Reference				Reference				Reference			
T Stage 2	1.19	1.10	1.29	<0.001	1.12	1.03	1.21	0.006	1.19	1.10	1.29	<0.001	1.12	1.03	1.21	0.006
T Stage 3/4	1.54	1.34	1.77	<0.001	1.24	1.07	1.43	0.003	1.54	1.34	1.77	<0.001	1.24	1.07	1.43	0.003
PSA																
[0, 10) ng/ml	Reference				Reference				Reference				Reference			
[10, 20) ng/ml	1.45	1.32	1.58	<0.001	1.36	1.24	1.49	<0.001	1.45	1.32	1.58	<0.001	1.36	1.24	1.49	<0.001
[20, Inf) ng/ml	1.62	1.47	1.78	<0.001	1.50	1.36	1.66	<0.001	1.62	1.47	1.78	<0.001	1.50	1.36	1.66	<0.001
Gleason7																
GS 7 (3+4)	Reference				Reference				Reference				Reference			
GS 7 (4+3)	1.00	0.90	1.11	0.998	0.99	0.90	1.10	0.915	1.00	0.90	1.11	0.998	0.99	0.90	1.10	0.915
GS 8	1.34	1.21	1.48	<0.001	1.23	1.11	1.36	<0.001	1.34	1.21	1.48	<0.001	1.23	1.11	1.36	<0.001
GS 9	1.92	1.72	2.14	<0.001	1.72	1.54	1.92	<0.001	1.92	1.72	2.14	<0.001	1.72	1.54	1.92	<0.001
GS 10	2.74	2.16	3.47	<0.001	2.47	1.95	3.14	<0.001	2.74	2.16	3.47	<0.001	2.47	1.95	3.14	<0.001