Modeling Tumor Control in SBRT for Hepatocellular Carcinoma: Dose, Fractionation, and Survival Analysis

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Abstract

Background: Hepatocellular carcinoma (HCC) is the most common type of liver cancer. Stereotactic body radiation therapy (SBRT) is a non-surgical treatment, but optimizing dose and fractionation remains challenging.

Objective: This study aims to develop a model for tumor control probability based on radiation dose and fractionation, providing insights into optimal treatment strategies that maximize tumor control while minimizing liver toxicity.

Methods: We analyzed clinical data from 390 HCC patients treated with SBRT at two institutions from Nov. 2008 to Sept. 2021. Cox proportional hazards models were applied to 21 DVH variables across seven α/β ratios. Mean AIC values were used to identify the most reliable α/β ratio and DVH metric. Kaplan-Meier survival analysis and Cox proportional hazard models were implemented to evaluate the impact of key treatment factors. The Schoenfeld residuals test was used to check the proportional hazard assumption.

Result: $\alpha/\beta = 20$ is the best-performing ratio and the 5th percentile DVH was the most predictive DVH metric, with the lowest mean AICs. Both Kaplan-Meier analysis and Cox modeling showed that both BED and 5th DVH were significantly associated with survival (both $p < 0.001$). Fractionation, treatment time, and tumor volume remained insignificant after adjusting for DVH metrics.

Conclusion: Lower percentile DVH doses, especially the 5th percentile, were stronger predictors of tumor control. The optimal α/β ratio is 20. Fractionation initially showed a negative impact on survival, but this effect disappeared after adjusting for DVH metrics. Treatment duration had no significant impact. These findings emphasize the need to consider voxel-based dose distributions in refining radiation therapy strategies.

Introduction

Hepatocellular carcinoma (HCC) is the most common liver cancer, often caused by cirrhosis from hepatitis B/C, alcohol consumption, or metabolic dysfunction-associated steatotic liver disease (MASLD) [1]. Stereotactic body radiation therapy (SBRT) is a non-surgical treatment for localized HCC [2]. It delivers high radiation doses in fewer sessions, making it suitable for patients ineligible for surgery. However, balancing radiation dose and fractionation to maximize efficacy while minimizing toxicity remains a key challenge. Biologically effective dose (BED), derived from the linear-quadratic (LQ) model, is commonly used to quantify the biological impact of a treatment regimen. However, tumor control also depends on factors such as fractionation and treatment duration.

This project aims to develop a model to evaluate tumor control probability based on radiation dose and fractionation, helping to determine the best treatment strategies that maximize efficacy while minimizing liver damage.

Methods

Study Design

We analyzed clinical data from 390 hepatocellular carcinoma (HCC) patients who received SBRT at the University of Michigan and Princess Margaret Cancer Center from Nov. 2008 to Sept. 2021. This retrospective study was based on one primary HCC dataset and seven different α/β ratios datasets, containing total radiation dose, treatment fractions, recurrence time, dose-volume histograms (DVH), gross tumor volume (GTV), and treatment duration.

In radiobiology, α represents cell damage caused by a single radiation hit, while β represents damage from accumulated multiple interactions. Their ratio (α/β) reflects the sensitivity of tissue to different radiation fractionation. Dose-volume histogram (DVH) metrics summarize radiation dose distributions within the tumor. The X-th percentile DVH represents the minimum dose received by X% of the tumor volume, capturing low-dose and high-dose distributions more precisely than the total dose. We evaluated the relationship between dose-volume

histogram (DVH) metrics and tumor control across different α/β ratios. We performed Cox proportional hazards models for each DVH variable across seven α/β ratio datasets (1, 2, 3, 5, 10, 20, and 100). We extracted the p-values to assess statistical significance and Akaike Information Criterion (AIC) values to compare model fits. Concerning the influence of random variations or outliers in models, we want to reduce the risk of selecting a model due to chance fluctuations. We calculated the mean AIC for each α/β ratio to determine the one consistently provided better model performance. The corresponding dataset was merged with the primary HCC dataset. Similarly, we computed the mean AIC and mean p-values for each DVH metric across different ratios to identify the most stable and predictive parameter.

After merging datasets, we computed the biologically effective dose (BED) using the following formulas, where D is the total radiation dose and d is the fraction dose.

$$BED = D \times \left(1 + \frac{d}{\alpha/\beta}\right), \quad EQD2 = \frac{BED}{1 + \frac{2}{\alpha/\beta}}$$

Statistical Method

We generated histograms for key variables selected based on their clinical relevance and potential impact on tumor control to check the distribution and applied corresponding transformations for those not normally distributed. After that, to assess multicollinearity, we computed a correlation matrix for key numerical variables and visualized it with a heatmap. Principal component analysis further identified and excluded redundant variables, and helped us to check how variables contributed to overall variance.

Kaplan-Meier survival analysis was performed to evaluate treatment effectiveness. An overall Kaplan-Meier survival curve was generated to provide a general assessment of survival probability. Patients were then stratified by BED, 5th percentile DVH, treatment fractions, and elapsed treatment time. Cut-off points were based on quartiles, tertiles, or medians. Survival curves were plotted for each group, using the log-rank test to assess survival differences.

Cox proportional hazards models were fitted using total fractionations, log elapsed time, and log gross tumor volume (GTV), adjusting BED or 5th percentile DVH. We also adjusted for

hospital differences using a categorical variable. The Cox proportional hazards model can handle censored survival data and assess treatment effects. Models were compared based on concordance results.

$$\lambda_1(t) = \lambda_0(t) \exp\left(\begin{array}{l}\beta_1 BED + \beta_2 \log(GTV) + \beta_3 \log(TreatmentTime) \\ + \beta_4 I(Fraction > 5) + \beta_5 I(hospital = UofM)\end{array}\right)$$

$$\lambda_2(t) = \lambda_0(t) \exp\left(\begin{array}{l}\beta_1 I(BED_{group} = Medium) + \beta_2 I(BED_{group} = High) + \beta_3 \log(GTV) \\ + \beta_4 \log(TreatmentTime) + \beta_5 I(Fraction > 5) + \beta_6 I(hospital = UofM)\end{array}\right)$$

$$\lambda_3(t) = \lambda_0(t) \exp\left(\begin{array}{l}\beta_1 5_{th} DVH + \beta_2 \log(GTV) + \beta_3 \log(TreatmentTime) \\ + \beta_4 I(Fraction > 5) + \beta_5 I(hospital = UofM)\end{array}\right)$$

$$\lambda_4(t) = \lambda_0(t) \exp\left(\begin{array}{l}\beta_1 I(5_{th} DVH_{group} = Medium) + \beta_2 I(5_{th} DVH_{group} = High) + \beta_3 \log(GTV) \\ + \beta_4 \log(TreatmentTime) + \beta_5 I(Fraction > 5) + \beta_6 I(hospital = UofM)\end{array}\right)$$

After modeling, we checked the proportional hazards assumption using the Schoenfeld residuals test to see whether time-dependent adjustments should be considered.

All analyses were conducted by R (version 3.4.3), with survival analysis performed using the 'survival' and 'survminer' packages. Correlation analysis was visualized with 'corrplot', and PCA was conducted using 'FactoMineR'."

Result

The mean AIC showed that α/β=20 (526.816) had the best model fit. So we merged the dataset for α/β=20 with the primary HCC dataset. The heatmap of p-values showed that lower dose percentiles are consistently the most predictive for tumor control, and the 5th percentile DVH has the lowest mean AIC (521.22) and the lowest mean p-value ($3.15e{-}6$).

Most variables were approximately normally distributed, but gross tumor volume (GTV) and elapsed treatment time were highly right-skewed, clustering near zero. We applied logarithmic transformation. Specifically, we used log(GTV + 0.1) to handle a large amount of small values and zeros, and log(elapsed time + 1) for stability and interoperability.

The correlation heatmap showed a strong correlation among the total dose, BED, and 5th DVH. Log treatment time had moderate correlations with total dose ($r = 0.66$), BED ($r = 0.53$), and 5th DVH ($r = 0.55$). The PCA biplot supported these findings. Total dose, 5th DVH, and BED were closely aligned, indicating they contributed similarly. The log treatment time was pointing similarly with BED or 5th DVH, but remained some different. Fractionation and log tumor volume were pointing distinctly, indicating they captured different variances. Based on these, we selected fractionation, log treatment time, and log tumor volume for further analysis. BED and 5th DVH were temporally both reserved to be compared.

The overall Kaplan-Meier survival curve showed a decline in survival probability over time, with a sharper drop after 2,000 days. Patients were stratified into low, medium, and high BED groups using tertiles (Figure 1). Survival was significantly different across groups ($p < 0.0001$). Higher BED was associated with better outcomes, suggesting radiation doses can improve tumor control. Similarly, patients were grouped by 5th DVH (Figure 2), resulting in similar significance ($p < 0.0001$). Patients were then divided into three tertile-based groups, and four quartile-based groups based on fractionation, but survival differences were not significant (Figure 3). We reclassified them into two groups using the median. Those receiving more than five fractions had significantly lower survival ($p \approx 0.007$). These findings also suggested that the survival effects of fractionation are more obvious with broader classification, which could be used in further analysis. Finally, patients were divided into three groups using the tertile. No significant differences were observed ($p = 0.23$), suggesting that the total treatment time did not have a crucial impact on tumor control.

Among the four Cox models, the one using 5th DVH as a categorical variable had the highest concordance (0.744). In this model (Table 1), the medium and high 5th DVH groups had significantly lower recurrence or death hazards than the low DVH group ($p = 0.009$, $p < 0.001$), with hazard reductions of 58.7% (HR = 0.413) and 81.1% (HR = 0.189), respectively. Log tumor size ($p = 0.103$), log treatment time ($p = 0.694$), fractionation ($p = 0.311$), and hospital ($p = 0.453$) were not significantly associated with survival. These results suggest that a higher maximum radiation dose received by 5% of the tumor voxels is related to improved survival,

while tumor size, treatment duration, fractionation, and hospital had minimal impact. The Schoenfeld residuals test found no violations of the proportional hazards assumption (all p-values > 0.05). Residual plots confirmed that the estimated effects were stable over time, with lines remaining smooth within confidence bands, indicating no time-dependent effects.

Discussion

Our study examined how radiation dose, fractionation, and treatment duration affect tumor control in HCC patients treated with SBRT. Lower percentile DVH doses, especially the 5th percentile, better predict tumor control. The α/β ratio of 20 better reflects HCC's radiation response. These results highlight the need to consider low-dose regions in treatment planning, as traditional BED calculations may not fully capture dose distribution within the tumor.

However, using retrospective data may introduce selection bias. Moreover, we analyzed DVH metrics separately, while clinical decisions often consider multiple dose-volume constraints. Future research should explore models combining multiple DVH features for better prediction. Fractionation and treatment duration showed little impact on survival, but further validation is needed across different patient groups and treatment protocols. Machine learning could help identify complex dose-response relationships and improve predictive accuracy.

Conclusion

This study showed that lower percentile DVH doses, especially the 5th percentile, better predict tumor control than BED metrics in HCC patients treated with SBRT. The optimal α/β ratio was estimated to be 20, supporting its potential use in dose calculations. Higher fractionation (>5 fractions) may result in worse survival, but DVH metrics were stronger predictors when considered together. Treatment duration showed no significant impact on tumor control. Delivering a higher dose may be more critical for improving outcomes than adjusting the treatment scheme. These findings highlight the importance of voxel-based dose distributions in radiation planning. Further studies and multi-variable models are needed to confirm these results and improve treatment strategies.

Generative AI Statement

I used ChatGPT 4.0 to assist in this report. Specifically, I provided ChatGPT with initial drafts of the Abstract, Results, Discussion, and Conclusion sections and asked it to check the clarity, logic, vocabulary, and grammar. Additionally, I used ChatGPT to give me advice on deciding which tables or figures should be more important based on the primary questions, and which of them could be included in the appendix. Moreover, I used ChatGPT to solve the errors when running the R code and asked it to suggest packages and functions. I did not directly use ChatGPT for data processing, or code generation. I did not use ChatGPT to decide on which methods should I use for this project.

References

[1] M. Sherman, "Hepatocellular carcinoma: epidemiology, risk factors, and screening," in *Seminars in liver disease*, vol. 25, no. 02. Copyright© 2005 by Thieme Medical Publishers, Inc., 333 Seventh Avenue, New ..., 2005, pp. 143–154.

[2] C. Mazzarelli, D. Sibio, L. Cesarini, M. Patel, C. De Mattia, R. Viganò, G. Perricone, F. Aprile, M. Cucco, C. Becchetti *et al.*, "Stereotactic body radiation therapy (sbrt) for hcc treatment: a single institution experience," *Digestive and Liver Disease*, vol. 56, pp. S93–S94, 2024.

Tables & Figures

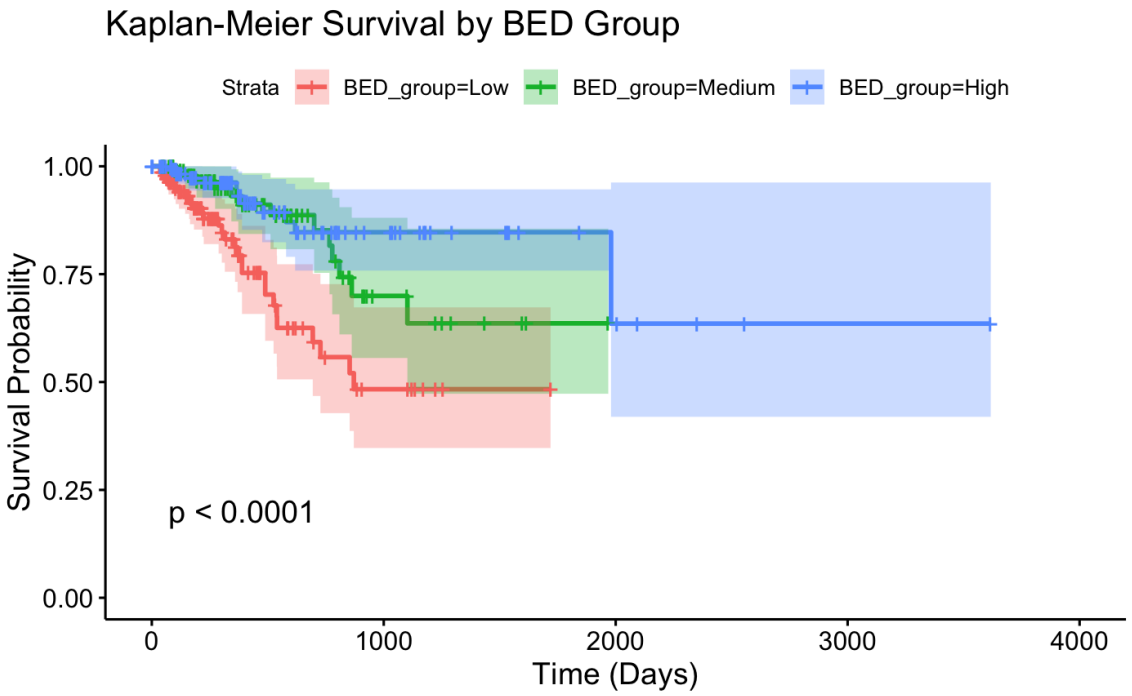

Figure 1: Kaplan-Meier survival curve for HCC patients grouped into three categories based on biologically effective dose (BED) levels, using the tertiles as cut-off points.

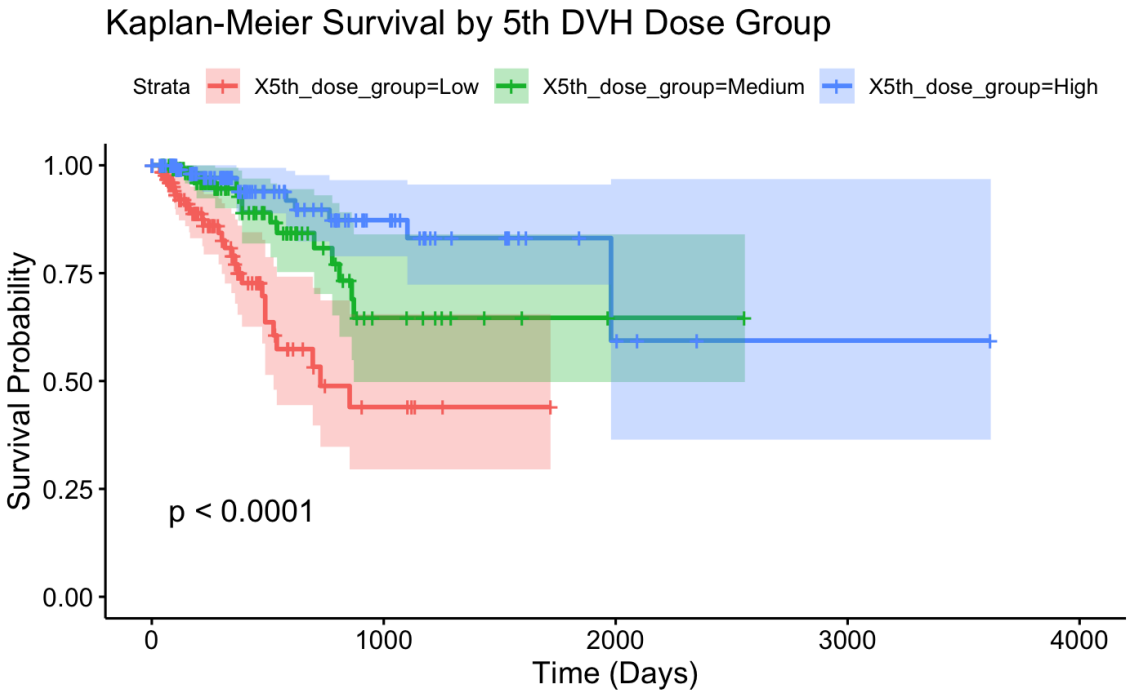

Figure 2: Kaplan-Meier survival curve for HCC patients grouped into three categories based on 5th Percentile DVH levels, using the tertiles as cut-off points.

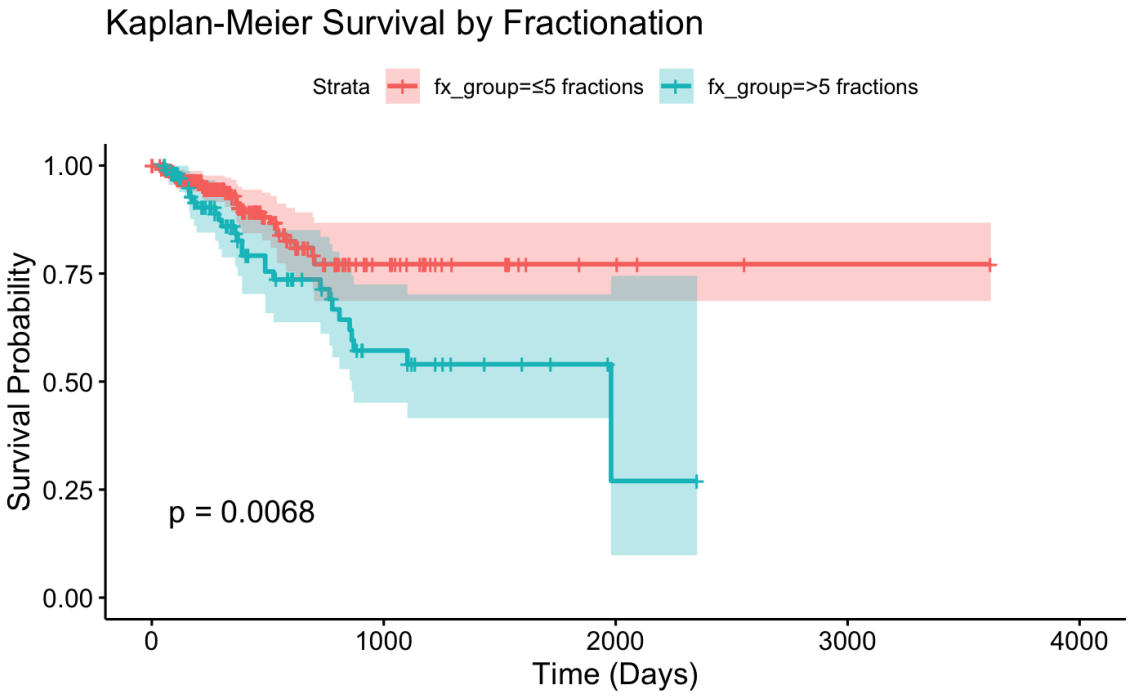

Figure 3: Kaplan-Meier survival curve for HCC patients grouped into two categories based on the number of treatment fractions they received, using the median fraction of 5 as cut-off points

Variable	Coef	Exp(Coef)	SE(Coef)	Pr($>|z|$)
5th DVH = Medium	-0.885	0.413	0.338	0.009
5th DVH = High	-1.664	0.189	0.485	<0.001
log GTV	0.138	1.148	0.084	0.103
log treatment time	0.092	1.096	0.233	0.694
fraction >5	0.507	1.661	0.501	0.311
hospital is U of T	-0.395	0.674	0.527	0.453

Table 1: Cox proportional hazards model results, showing the estimated coefficients, exponentiated coefficients (hazard ratios), standard errors, and p-values. Significant results are marked with ** ($p < 0.01$) and *** ($p < 0.001$).

Appendix

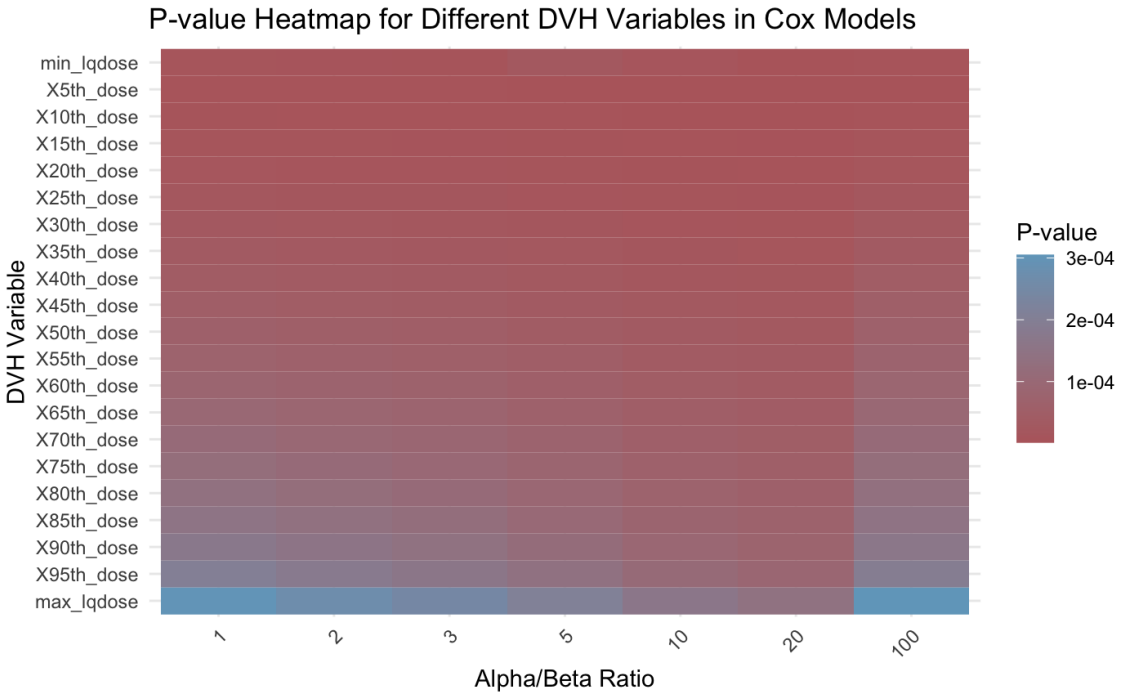

Figure 4: P-value heatmap for different DVH variables across various alpha/beta ratios in Cox models. The color gradient represents the significance level, with lower p-values indicated in red and higher p-values in blue.

Ratio	Mean AIC
1	528.382
2	528.056
3	527.786
5	527.503
10	526.970
20	526.816
100	529.664

Table 2: Mean AIC values for different α/β ratios. Lower AIC values indicate better model performance, with $\alpha/\beta = 20$ yielding the lowest AIC, suggesting it may be the most appropriate estimate for HCC response to radiation.

DVH Variable	Mean AIC	DVH Variable	Mean AIC
min_lqdose	523.658	X50th_dose	528.794
X5th_dose	521.220	X55th_dose	529.219
X10th_dose	521.827	X60th_dose	529.595
X15th_dose	523.351	X65th_dose	529.946
X20th_dose	524.530	X70th_dose	530.254
X25th_dose	525.469	X75th_dose	530.530
X30th_dose	526.298	X80th_dose	530.791
X35th_dose	527.035	X85th_dose	531.075
X40th_dose	527.707	X90th_dose	531.387
X45th_dose	528.289	X95th_dose	531.769
		max_lqdose	532.787

Table 3: Mean AIC values for different DVH variables, presented in two columns for better readability. Lower AIC values indicate better model performance, with the 5th and 10th percentile doses showing the lowest AIC, suggesting they are the most predictive DVH metrics for tumor control.

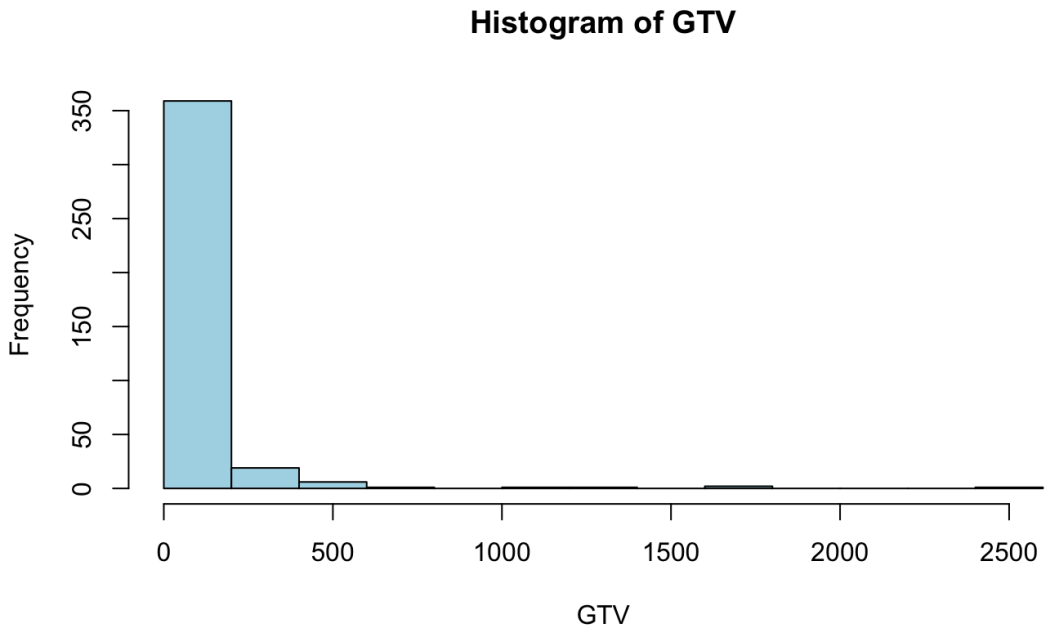

Figure 5: Distribution of gross tumor volume, visualized in histogram

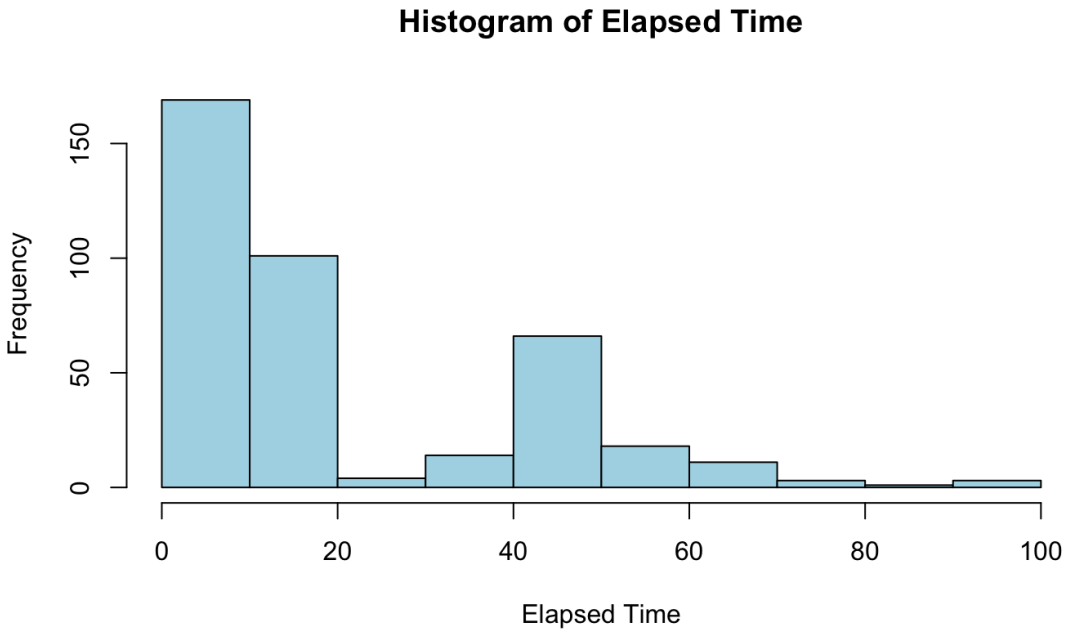

Figure 6: Distribution of Number of days from first day of treatment to last day of treatment, visualized in histogram

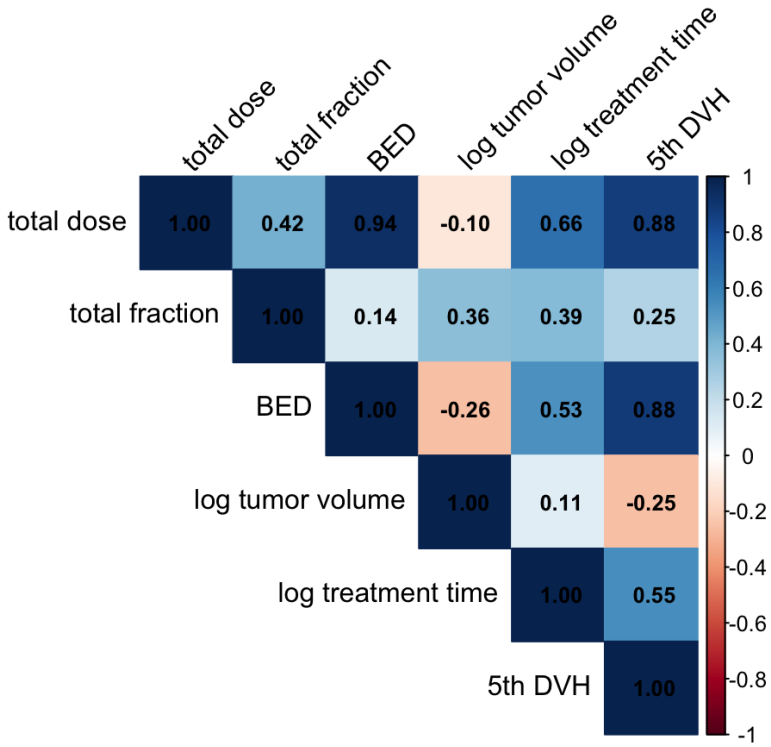

Figure 7: Carme's Heatmap for variables: total prescribed dose cumulatively throughout treatment, total number of fractionations cumulatively throughout treatment, biologically effective dose(BED), Gross tumor volume after log transformation, and the treatment duration time after log transformation.

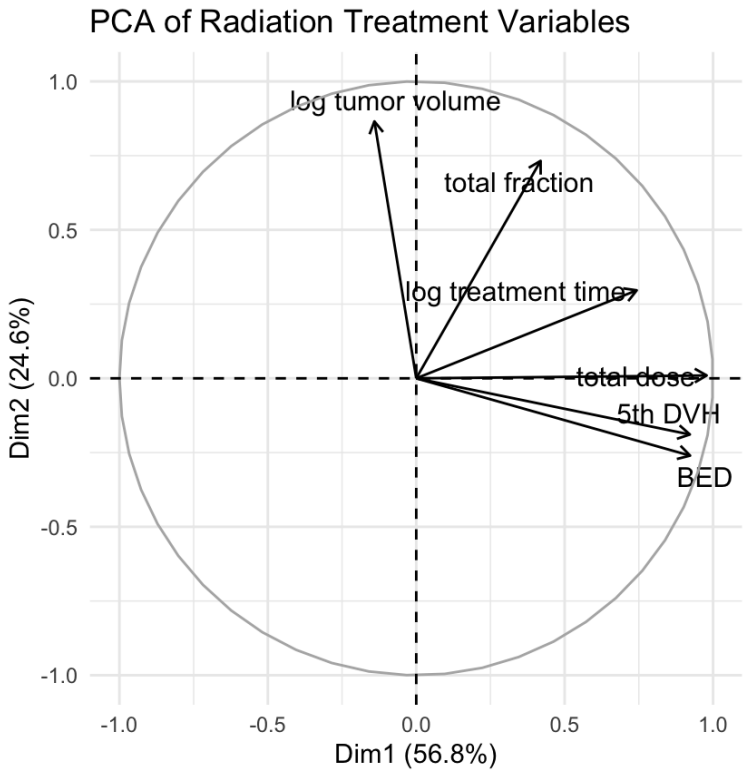

Figure 8: Principal Component Analysis (PCA) biplot showing the relationships among total prescribed dose cumulatively throughout treatment, total number of fractionations cumulatively throughout treatment, biologically effective dose(BED), Gross tumor volume after log transformation, the treatment duration time after log transformation, and Maximum radiation received by 5% of the voxels in a tumor. The arrows represent the contributions of each variable to the first two principal components.

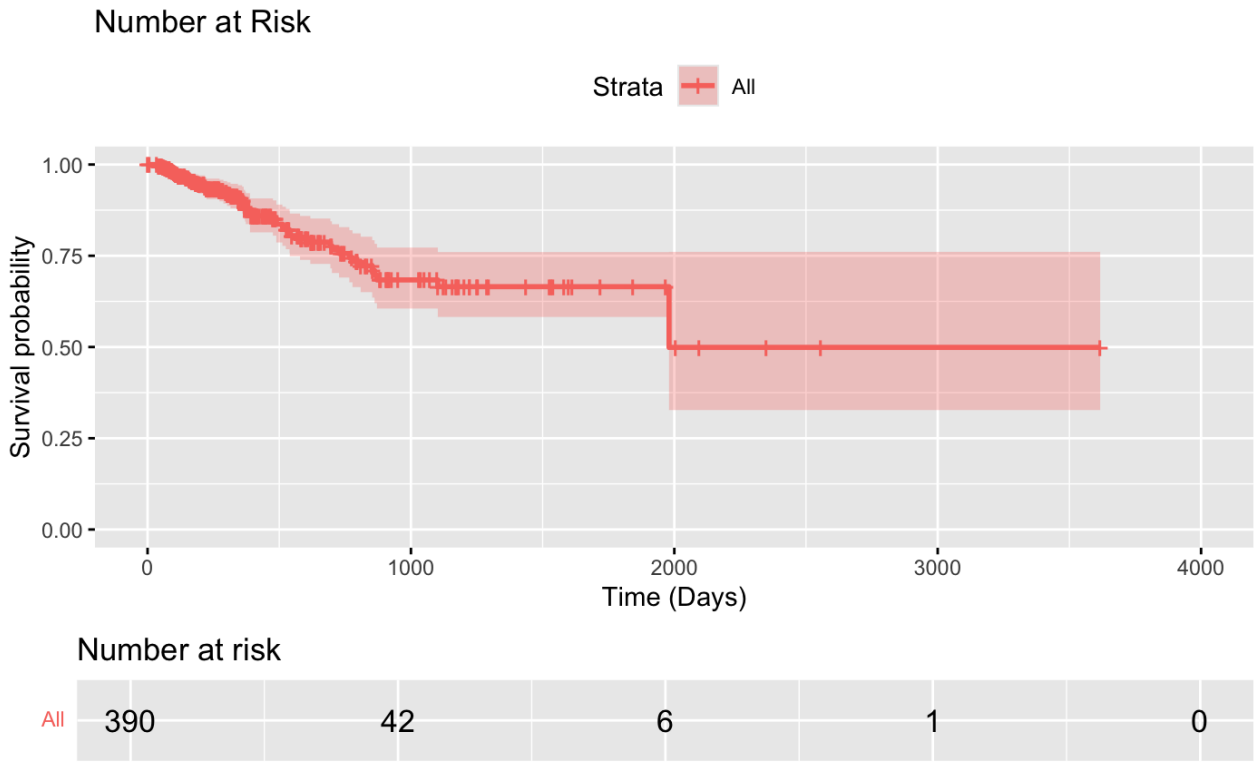

Figure 9: Kaplan-Meier survival curve for all HCC patients

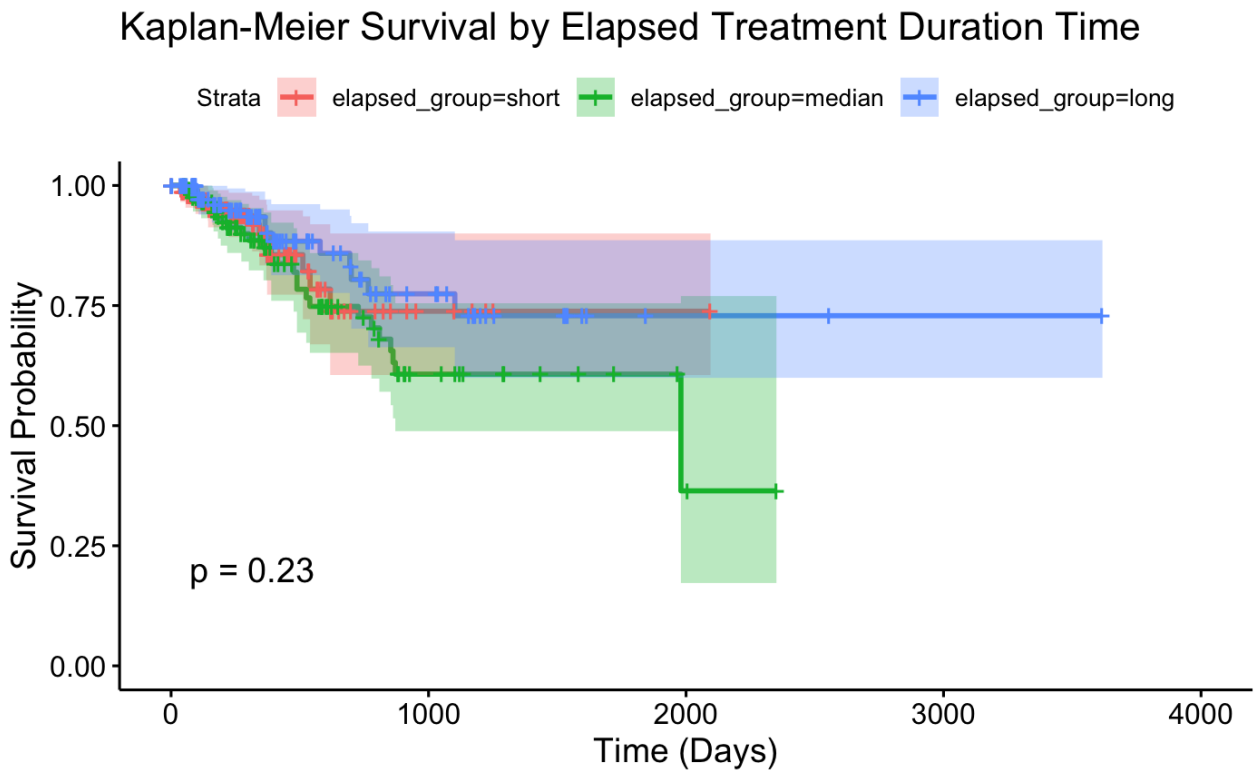

Figure 10: Kaplan-Meier survival curve for HCC patients grouped into three categories based on the treatment duration time, using the tertiles as cut-off points.

Model	Concordance (C-index)
Model 1	0.687
Model 2	0.709
Model 3	0.728
Model 4	0.744

Table 4: Concordance results of four Cox Proportional Hazard models using total fractionations, log elapsed time, log gross tumor volume (GTV), and hospital (U of M or U of T), adjusting BED or 5th percentile DVH as continuous or categorical variables. Higher concordance approaching 1 indicates better model discrimination, meaning the model more accurately distinguishes between patients with different survival outcomes.

Variable	Chi-Square (chisq)	df	p-value
X5th_dose_group	2.927	2	0.23
log GTV	2.303	1	0.13
log treatment time	0.474	1	0.49
fraction group	1.100	1	0.29
hospital	0.667	1	0.41
GLOBAL	7.647	6	0.27

Table 5: Results of the Schoenfeld residual test for the proportional hazards assumption. The chi-square statistic (chisq) and corresponding p-values assess whether the proportional hazards assumption holds for each covariate in the Cox model. A non-significant p-value ($p > 0.05$) suggests no violation of the assumption. These results were obtained using the `cox.zph()` function in R.

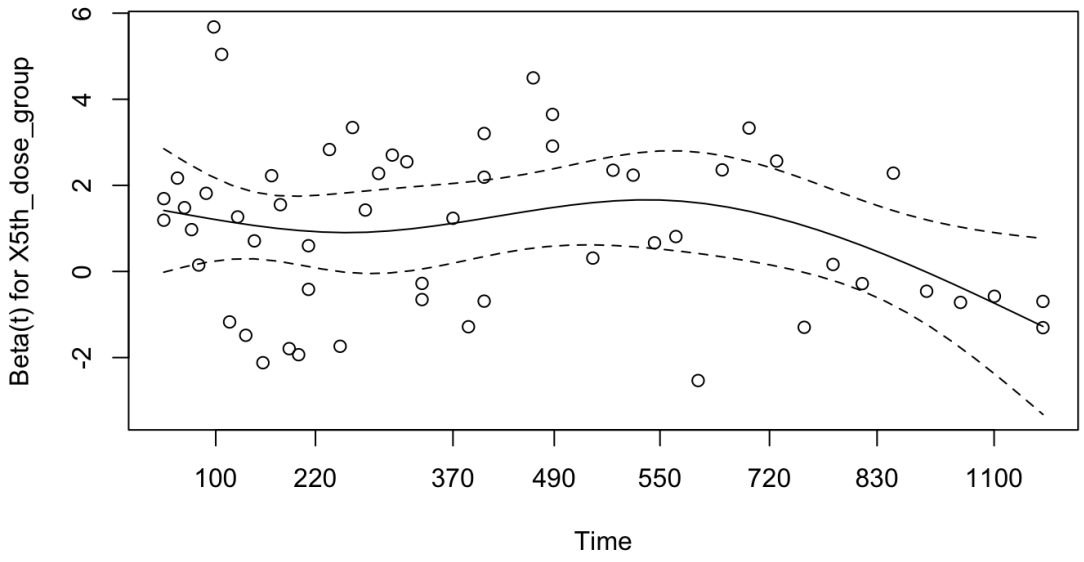

Figure 11: Schoenfeld residual plot for the 5th percentile DVH group, showing the estimated time-dependent beta coefficient with 95% confidence intervals.

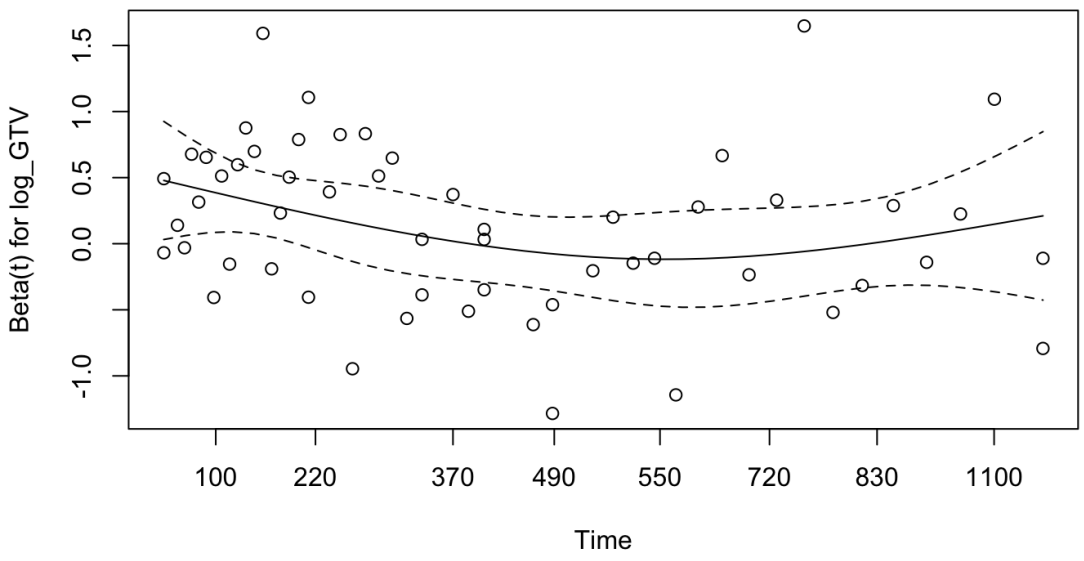

Figure 12: Schoenfeld residual plot for log-transformed gross tumor volume (GTV), testing the proportional hazards assumption.

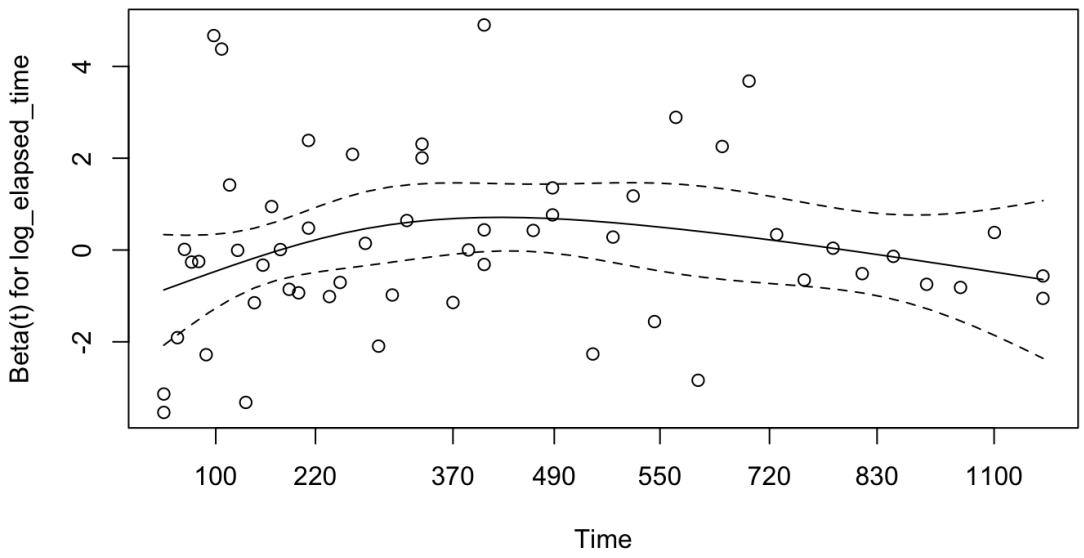

Figure 13: Schoenfeld residual plot for log-transformed elapsed treatment time, evaluating the proportional hazards assumption.

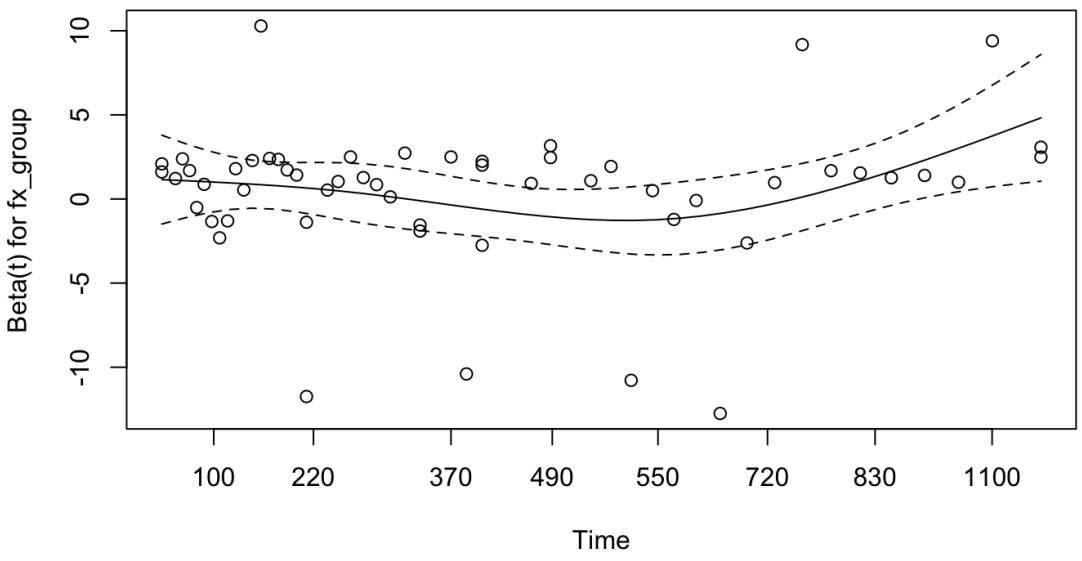

Figure 14: Schoenfeld residual plot for fractionation groups, checking time-dependent variations.

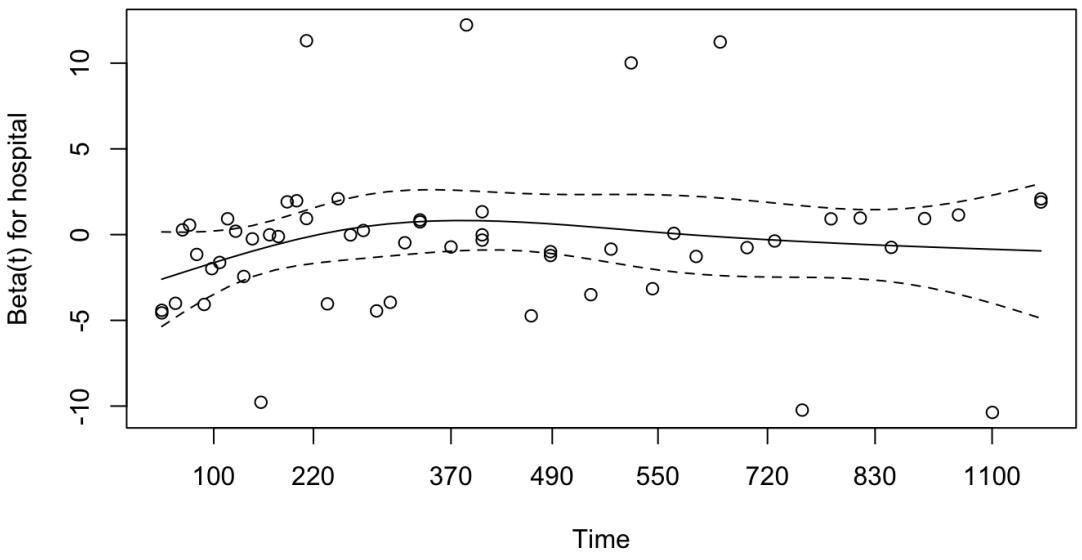

Figure 15: Schoenfeld residual plot for hospital variable, assessing its influence over time.