Throat Cancer Analysis

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Abstract

We utilize survival analysis methods on data from the Radiation Oncology Group in the United States. We were most interested in seeing if a mix treatment of radiation and chemotherapy had a differing effect then the standard radiation treatment. We considered variable such as sex, site of where the cancer was, and the tumore stage in the anaylsis. Ultimately we found that there were no significant differences in treatment plans even when stratified by variables of interest. A Cox Proportional Hazard Model also yeilded no significant results.

Introduction

The Radiation Oncology Group in the United States conducted a study in which a primary question was to test the effect that a mix treatment plan of radiation and chemotherapy had compared to that of just radiation on patient survival. For this paper we are interested in how the variables of treatment, sex, site, and tumor stage effect patients survival. We suspect that treatment has differing effects between the levels of sex, site, and T_stage.

About the Data

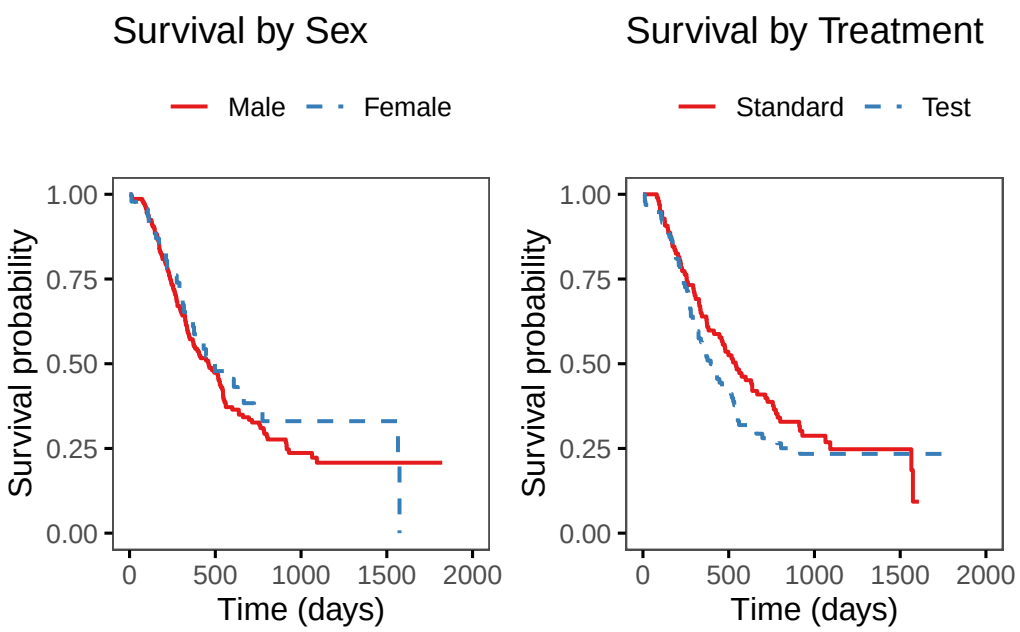
The original study included 15 sites of throat and mouth. The one we will conduct analysis on just included three sites in the throat: Faucial Arch, Tonsillar Fossa, and Pharyngeal Tongue, this comprises our variable `Site`. The variable `Tx` is the treatment. 1 is encoded for the standard radiation therapy, 2 is encoded for the test therapy, that is the combined treatments of radiation and chemotherapy. `Sex` variable is self explanatory, 1 is encoded male and 2 is encoded female. `T_stage` had four factor levels these were tumors less than 2cm, tumors between 2cm and 4cm, tumors greater than 4cm and tumors that were encoded as massive. There were two observations that had missing observations in variables that were not used in the paper. These were removed because the scope of the paper had not been decided at the time.

Exploratory Data Analysis

Table 1: Distributions Status, Sex, Treatment (Tx), and T_Stage

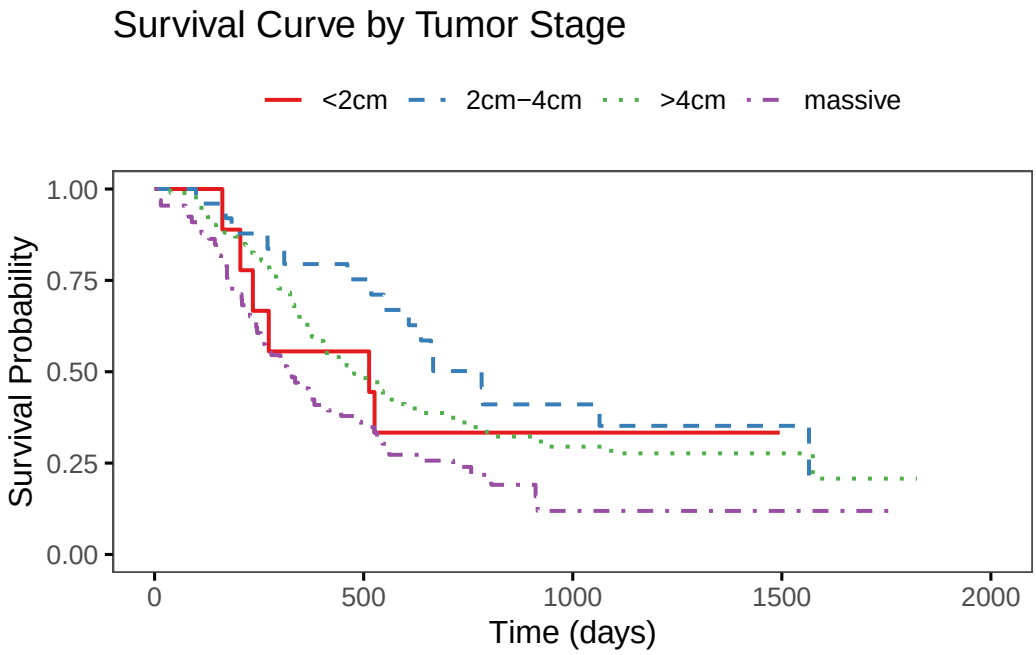
Censored	Dead	Male	Female	Standard	Test	< 2cm	2cm-4cm	> 4cm	massive
53	140	147	46	98	95	9	26	92	66

The table above shows distributions for variables of interest: Status, Sex, Tx, and T_Stage. We see that we have 53 censored variables. This would mean that 27.46% of our observations are censored. There is also a disproportionate number of Males to Females in this study. The treatment (Tx) groups are balanced. T_stage is unbalances with the majority of our cases being severe. That is tumor sizes being either greater than 4cm or classified as massive by the study. This a variable we suspect to affect treatment (Tx) effectiveness.

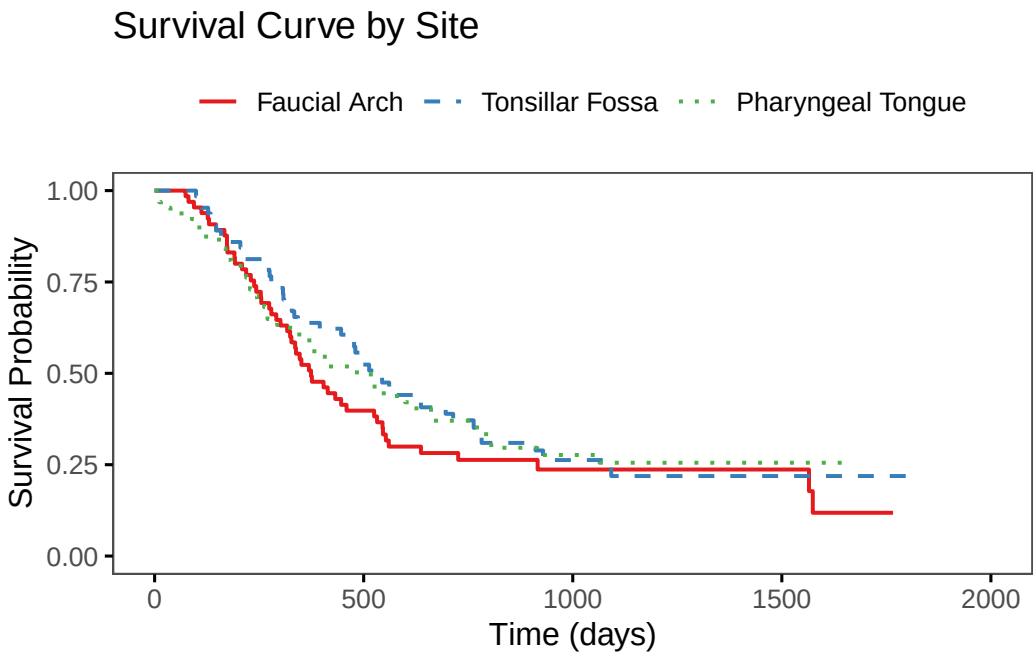


Above we have the Kaplan-Meier survival curves stratified by `Sex` and Treatment (`Tx`). Looking at the plot for sex we see that the curves are pretty much on top of each other until later in the study. The plateau in the female group could be a consequence of the smaller sample size. We are not too worried about the divergence between the curves towards the end of the study but will check if Sex violates Proportional Hazard Assumption when we do Cox Regression.

Looking now at the Survival plot for Treatment we see that in the beginning the curves stay on top of each other but by day 300 they diverge with the standard treatment having a higher survival time. They end up aligning again by day 1000 and the survival time for those in the test group end up higher than in the standard.



Now looking at the KM-curve stratified by Tumor Stages we see a clear difference in survival times among `T_Stage`. We see the most serious case, a tumor classified as "massive" have the steepest drop off in survival time and remains the lowest through out the study. The next lowest is a tumor classified as being greater than 4 centimeters. This variable will be checked for violation of the proportional hazard assumption when we do cox regression.



Above we have the Survival curves for `Site`. They are mostly similar other than around day 400 by the suffers of Facial Arch. All the curves plateau together at .25 around day 1000. It does not look like these variables are significantly different.

Methods

Two treatments were provided in this study and its important to assess if one is better than the other. We will use a Stratified Log Rank Test to asses if the new `test` treatment is better than `standard` by controlling for the variable `T_Stage`. Many variables in the study assess a the severity of a patients diagnosis, we believe the `T_Stage` does the best in consolidating that information. Other variables of that we will stratify will be `Sex` and `Site`.

We are then interested in estimating the hazard rate of a patients cancer journey by taking into account all variables included in the study and will do so using Cox Proportional Hazard Model.

Stratified Log Rank Test

Our null hypotheses is that there is no difference between the hazard functions of treatment groups within each level of `T_Stage`. Our null is that at least one hazard function of treatment differs within a group.

Formally:

$$\mathrm{H}_0 : \quad \lambda_1(t|\mathrm{Tx}) = \lambda_2(t|\mathrm{Tx}) \quad \forall t, \mathrm{Tx} \tag{1}$$

$$\mathrm{H}_1 : \quad \lambda_1(t|\mathrm{Tx}) = \theta\lambda_2(t|\mathrm{Tx}) \quad \forall t, \mathrm{Tx} \tag{2}$$

The assumption of the Log Rank Test are as follows:

- Censoring is unrelated to a prognosis.
- The survival probabilities are the same for subjects recruited earlier and later in the study
- The events happened at the time specified

Cox Proportional Hazard Model

Cox Proportion Hazard Model takes the form:

$$\lambda(t, \vec{x}_i) = \lambda_0(t)\exp(\vec{x}_i\vec{\beta})$$

Where $\vec{x}_i$ is the vector of covariates for the i^{th} observation and $\vec{\beta}$ are the parameters we will estimate with a partial likelihood function. Understand that $\lambda_0(t)$ is the baseline hazard function. It is the risk of failure at time t when all covariates are zero. $\exp(\vec{x}_i\vec{\beta})$ is the scaling factor. It is a function of covariates.

The Proportional Hazard Assumption of Cox Proportional Hazard Model: Consider two individuals i and j, each with their own vector of covariates.

$$\frac{\lambda(t,\vec{x}_i)}{\lambda(t,\vec{x}_j)} = \frac{\lambda_0(t)\exp(\vec{x}_i\vec{\beta})}{\lambda_0(t)\exp(\vec{x}_j\vec{\beta})} = \exp(\vec{\beta}(\vec{x}_i - \vec{x}_j)) = \theta$$

The hazard ratio of two individuals remains proportional over time.

Results

Stratified Log Rank Test

Our first Log Rank test only considered treatment (`Tx`). It yielded a p-value of .291. We will fail to reject the null that the treatments have differing hazard rates.

Table 2: Stratified Log-Rank Test for Tx

Chi.square	df	p.value
1.11	1	0.291

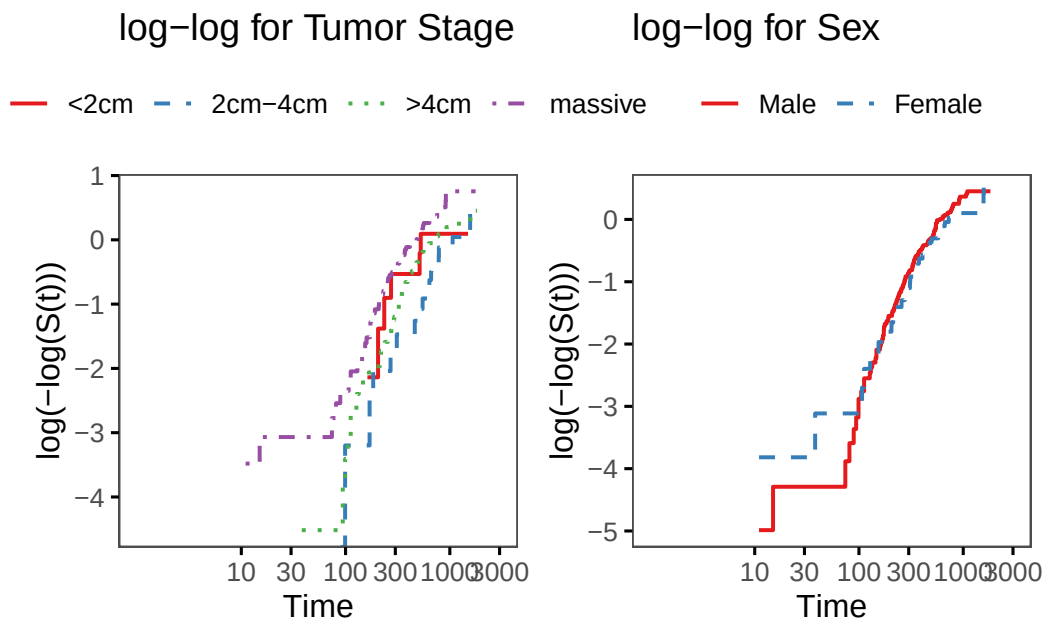
We also ran Log Rank Tests stratified for `T_Stage`, `Sex`, and `Site`. As you can see none of them were found to be significant. Thus we fail to reject the null that the hazard rates between `Tx` within their respective groups differ.

Table 3: Log Rank Results for T_Stage, Sex, and Site

Chi.square	df	p.value	Chi.square	df	p.value	Chi.square	df	p.value
1.39	1	0.239	1.3	1	0.254	1.3	1	0.254

Cox Proportional Hazard Model

Below we check the proportion hazard assumption using log-log survival curves one our three variables of interest. We see in the first graph `T_Stage` is proportional for all factors except tumors < 2cm. The < 2cm red line is very step like. This makes us think that the small size of the group is contributing to it not being proportional to the rest. `Sex`, although it crosses several time is basically on top of each other and considering it's long rank was insignificant I would assume its θ to be 1.



`Faucial Arch` violates the PH assumption. It crosses both levels. Lastly `Tx` crosses at day 100 and seems to diverge around day 300. The divergences is not severe considering the log-log emerges at the end. None of the graphs show a perfect proportional hazard but none of them, except `Site`, are exceptional in their violation. We will run a Cox Proportional Hazard Model with stratified by `Site` with `Tx` ,`Sex`, and `T_Stage` as standard covariates.

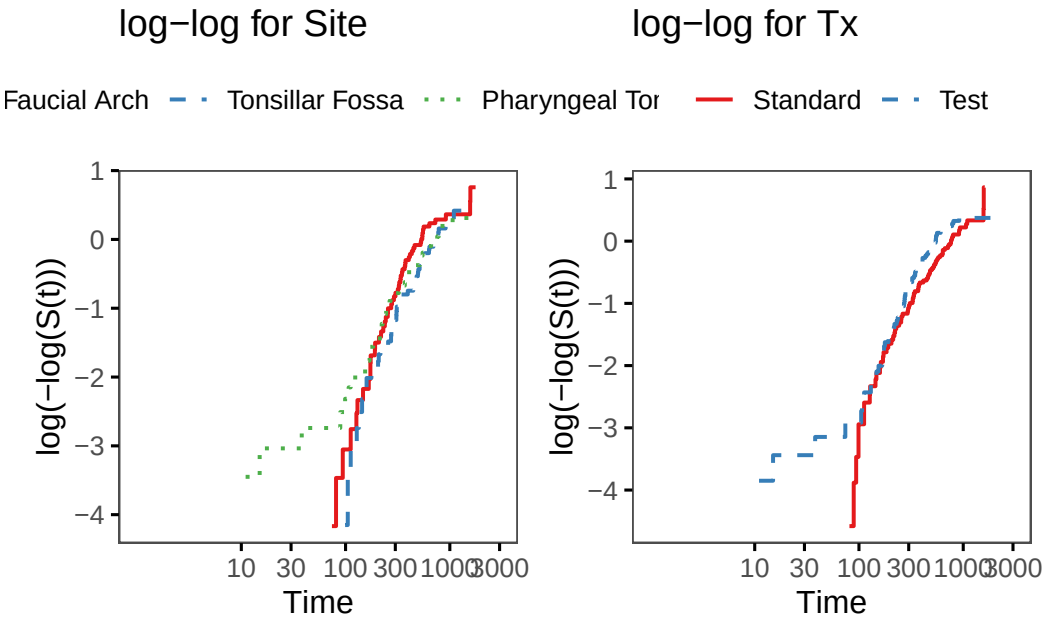


Table 4: Cox Proportional Hazards Model Summary Stratified by Site

Variable	Coefficient	Hazard.Ratio	p.value
TxTest	0.172	1.188	0.325
SexFemale	-0.067	0.935	0.745
T_Stage2cm-4cm	-0.294	0.745	0.546
T_Stage>4cm	0.019	1.019	0.965
T_Stagemassive	0.468	1.597	0.286

First we see that none of our coefficients are significant at even the most liberal level of 10%. The model estimates a 19% increase in hazard rate for the `test` treatment. A 6.5% decrease in hazard rate for `Female`. A 25.5% decrease in hazard rate for tumor size between 2cm and 4cm from tumor size less than 2cm. A 0.02% increase in hazard rate for size greater than 4cm from the baseline of 2cm. A 60% increase in hazard rate from a tumor classified as massive from the baseline. Although, there was some pretty decent percent increases, none of these are statistically significant and all had what would be considered high p-values.

Conclusion and Discussion

We conclude this paper by stating that none of the test we ran were statistically significant. We ran four log rank tests. One just to test whether the hazard rates were different between treatments. That yielded a high p-value. We then suspected that either `Site`, `Sex` or `T_stage` were effecting the out coming of the log rank tests. We stratified for each of the variables and our results were the same. We can conclude that there was no significant difference between radiation treatment and a mixed treatment plan. Even across variables that would suspect effect treatment.

We then ran a Cox Proportional Hazard Model using covariates `Tx`, `T_stage`, and `Sex`. This model was stratified by `Site` because `Site` did not satisfy the proportional hazard model. In the end we found none of our coefficients to be significant.

If we were to revisit this study we would attempt to include more variables that the original data set included. Some variables that would be interesting to explore would be institution that treatment happed at and the condition of the patient during the study.