An overview of time-to-event analysis for dental researchers

Tabitha K. Peter

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Introduction

Welcome to the tutorial "An overview of time-to-event analysis for dental researchers." The objective of this tutorial is to explain the foundational concepts of time-to-event analysis for an audience of dental researchers. After introducing some key terms, I will explain the essential concepts of time-to-event analysis using a data set from the dental research literature. See this link for the full text of the publication based on a time-to-event analysis of this data set.

Word bank

We begin our exploration of time-to-event analysis by defining some terms. Notice that several of these words are part of the common vernacular, but have a particular meaning within the context of time-to-event analysis.

- **Observation**: The unit of study. These units could be people, as in the case of a clinical investigation where each unit of study is a patient. An observation could also be a dental implant, a set of dentures, or a plate of bacteria. Regardless of the research context, the observation is studied by the researcher for a specified amount of time. For each observation, there is a time of entry into the study, and a time of last observation. In addition to these dates/times, information about the details of an observation are also recorded.
- **Time**: The units of time that have passed since an observation's entry into the study. In time-to-event analysis, the date/time of entry into the study is labeled as 0, and the subsequent units of time (e.g. days, weeks, years) count forward from that starting time. For example, suppose the observations in my study are patients treated in a specific dental clinic, and I am recording time in years. If Patient A enters the study in 2018 and I study that patient until 2022, then I would call 2018 "year 0" and 2022 "year 3." Note that the time of entry into the study often differs among observations. Returning to our example, suppose Patient B enters my study in 2019. In this case, "time 0" for Patient B is 2019. When I make generalizations about all the patients in the study, I would reference "time 0", understanding that this is different calendar years for patients A and B.
- **Event**: The occasion, occurrence, or sign related to the outcome of interest. Every scientific investigation should have an established research objective that informs the choice of an outcome. The choice of this outcome informs the choice of event for a time-to-event analysis. Suppose I want to compare different kinds of dentures to assess which ones are more durable (i.e. which dentures last the longest). In this case, I would need to define what it means for a denture to "last" - perhaps this means that the denture still fits well and does not require replacement. For this example, the outcome of interest could be the amount of time until replacement, and the "event" could be defined as replacement. The observations in the study would be dentures, and the goal would be to study the dentures over time and record the dates and details of those which require replacement. We would say that the dentures which need to be replaced are the 'observations which have an event.'
- **Censored**: The state of observations which do **not** have an event recorded during the time of the

study. We describe such observations as "being censored", as opposed to those observations which have events. Censoring can occur when an observation is lost to follow up or does not have an event before the end of a study. Suppose again that I am studying different kinds of dentures to compare their longevity. If a denture is still functioning at the time when I stop collecting data, then I would record this as a censored observation. If a denture is lost to follow up (meaning that the patient with the denture does not return to my clinic after enrolling in the study), I would also mark that denture as censored. In both cases, I would not know how long the denture lasted.

- **Survival time**: The time elapsed from the time of entry into the study until the time of either an event or censoring. Consider a denture that I begin studying in 2013 and which needs a replacement in 2021. I would say this denture had an event, and it had a survival time of 8 years.
- **Median survival time**: The time by which approximately half of all the observations in a study had experienced an event. For example, suppose I am studying 50 patients with full dentures, and the event of interest is replacing those dentures. If after 9 years, 25 of those dentures have been replaced, I would report 9 years as the median survival time.
- **Nth year survival (e.g. 3 year survival)**: The proportion of observations that have not had an event after 'n' units of time (where 'n' can be any number). Back to the denture example, suppose I am interested in studying 10 year survival in a data set of 50 dentures. If after 10 years, 15 dentures (30% of 50) have still not been replaced, then I would report 10-year survival as 30%.
- **Kaplan-Meier plot**: This name is a reference to the foundational publication by Kaplan and Meier (1958) and the work generated from its ideas. In brief, Kaplan and Meier presented a method for working with data that has censoring. Kaplan-Meier plots are curves that can be used to illustrate the time-to-event phenomena over time. These plots represent both events and censored observations. We will examine some examples of these curves later in the tutorial.
- **Cox (proportional hazards) model**: This is a reference to the foundational publication by Cox (1972). In brief, Cox proposed a method for a regression-like analysis which is specially crafted for time-to-event data. The Cox regression model lets us make generalizations about the impact of independent variables on the outcome of interest using hazard ratios. We will see an example of this kind of model later in the tutorial.

Extended example with dental data

Prepare the data set

First, load the data set into `R`.

Once the data is loaded, take a look to see the contents of the data set. I notice that there are a lot of options for 'clinic' – this tells me I will need to combine some categories before analyzing the data.

```
## Rows: 1,002
## Columns: 23
## $ RecordID        <dbl> 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16,~
## $ No_Cases        <dbl> 2, NA, 1, 1, 1, 1, 2, NA, 4, NA, NA, 2, NA, 2, NA, 1, ~
## $ Age             <dbl> 67, NA, 67, 73, 81, 64, 76, NA, 62, NA, NA, 65, NA, 87~
## $ Gender          <chr> "F", NA, "F", "M", "F", "F", "F", NA, "F", NA, NA, "F"~
## $ CRA             <chr> "Not High Risk", NA, "High Risk", "Not High Risk", "Hi~
## $ Tooth_Number    <dbl> 13, 31, 2, 3, 13, 30, 11, 3, 3, 4, 13, 6, 9, 11, 4, 12~
## $ Tooth_Type      <chr> "P", "P", "P", "P", "P", "P", "A", "P", "P", "P", "P",~
## $ Jaw             <chr> "Mx", "Md", "Mx", "Mx", "Mx", "Md", "Mx", "Mx", "Mx", ~
## $ Repair_Material <chr> "Amal", "Amal", "Amal", "Amal", "Amal", "Amal", "RMGI"~
## $ Date_Repair     <date> 2017-12-04, 2018-05-14, 2016-07-26, 2017-04-06, 2015-~
## $ Surfaces        <chr> "Other", "Other", "Other", "L", "L", "B", "L", "B", "O~
## $ No_Surfaces     <dbl> 1, 1, 1, 2, 2, 1, 2, 2, 1, 1, 1, 1, 1, 1, 1, 1, 2, 2, ~
```

```
## $ RCT            <dbl> 1, 1, 1, 0, 0, 0, 0, 0, 1, 0, 0, 1, 1, 0, 0, 0, 1, 0, ~
## $ Crown_Type     <chr> "PFM", "PFM", "PFM", "PFM", "PFM", "Other", "PFM", "PF~
## $ Clinic         <chr> "FGP", "FGP", "FAMD", "FAMD", "GMU", "FGP", "FAMD", "F~
## $ Provider_Type  <chr> "faculty", "faculty", "faculty", "faculty", "student",~
## $ Failure        <chr> "0", "0", "0", "0", "0", "0", NA, NA, NA, NA, "0", "0"~
## $ Last_exam      <date> 2019-06-24, 2019-06-24, 2019-05-15, 2019-02-22, 2018-~
## $ Failure_Date   <date> NA, NA, NA, NA, NA, NA, 2018-06-12, 2019-04-09, 2018-~
## $ Failure_Reason <chr> NA, NA, NA, NA, NA, NA, "TE_or_Redo", "Caries_or_Repai~
## $ Status         <dbl> 0, 0, 0, 0, 0, 0, 1, 1, 1, 1, 0, 0, 0, 0, 0, 0, 0, 1, ~
## $ End_Date       <date> 2019-06-24, 2019-06-24, 2019-05-15, 2019-02-22, 2018-~
## $ Time           <dbl> 1.55236140, 1.11156742, 2.80082136, 1.88090349, 2.7022~
##
##   ADMS   CCST CODHDG   FAMD  FDDAU FEECLS    FGP    GMU  HDGEN HDPROS LTDCAR
##      5      6      3    440     80      1    181     27      1      2      1
##   OPER   PROS   SPEC   <NA>
##    112     65     78      0
```

I make some changes to the formatting of the data, so that I am ready to analyze the data. The goal of this analysis is to describe what factors influence the length of time that a crown margin repair lasts.

Descriptive analysis

Once I have verified that the data set is ready for analysis, I create a "Table 1" that summarizes each variable in the data set.

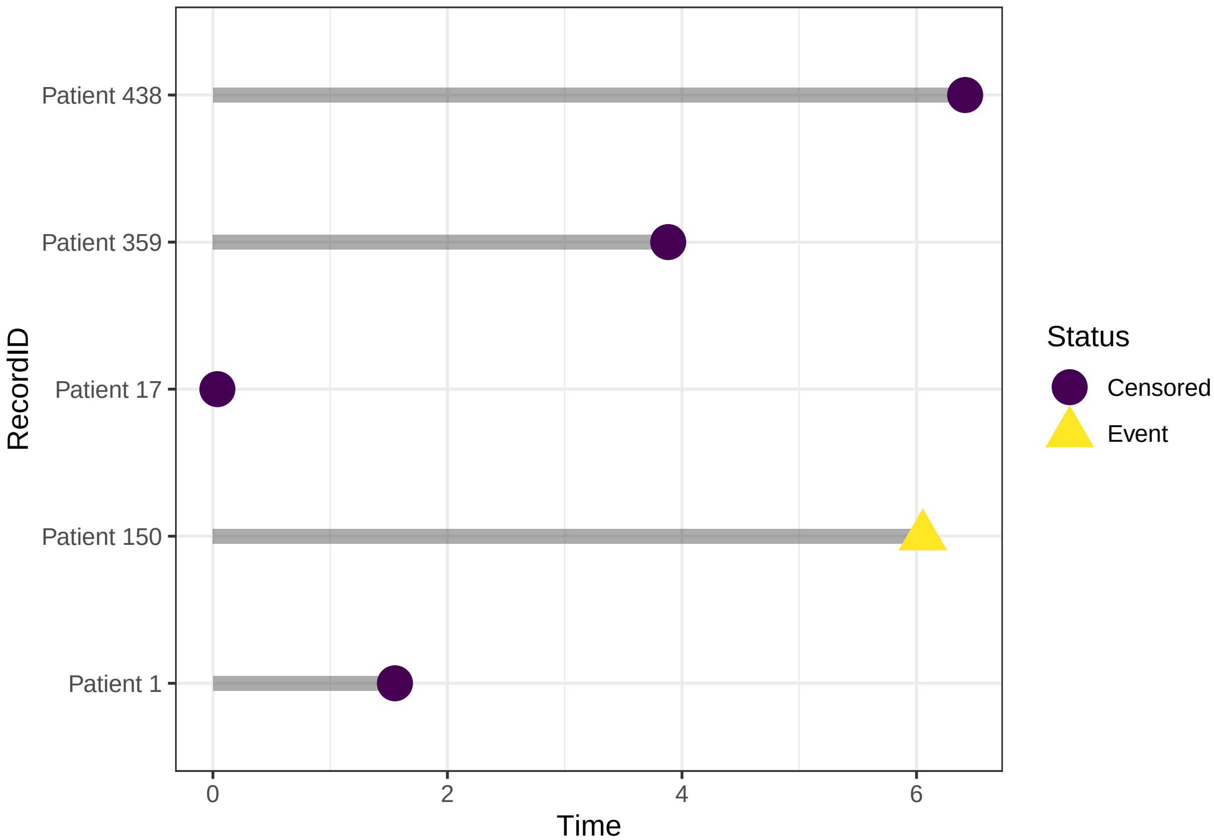
Table 1: Table 1: Description of Data

	Overall (N=1002)
Age	
N-Miss	445
Mean (SD)	74.530 (12.106)
Range	32.000 - 104.000
Gender	
N-Miss	446
F	294 (52.9%)
M	262 (47.1%)
CRA	
N-Miss	613
High Risk	159 (40.9%)
Not High Risk	230 (59.1%)
Tooth_Type	
N-Miss	4
A	190 (19.0%)
P	808 (81.0%)
Jaw	
Md	474 (47.3%)
Mx	528 (52.7%)
Repair_Material	
N-Miss	1
Amal	379 (37.9%)
GI	114 (11.4%)
RBC	92 (9.2%)
RMGI	416 (41.6%)
Surfaces	
B	403 (40.2%)

	Overall (N=1002)
L	214 (21.4%)
Other	385 (38.4%)
No_Surfaces	
1	724 (72.3%)
2	278 (27.7%)
RCT	
N-Miss	6
No RCT	648 (65.1%)
RCT	348 (34.9%)
Crown_Type	
N-Miss	3
C	55 (5.5%)
Other	384 (38.4%)
PFM	560 (56.1%)
Clinic	
FAMD	440 (43.9%)
FDDAU	80 (8.0%)
FGP	181 (18.1%)
OPER	112 (11.2%)
Other	46 (4.6%)
PROS	65 (6.5%)
SPEC	78 (7.8%)
Provider_Type	
faculty	356 (35.5%)
student	646 (64.5%)
Failure	
N-Miss	326
0	566 (83.7%)
1	1 (0.1%)
no follow up	109 (16.1%)
Last_exam	
N-Miss	435
Median	2019-01-18
Range	2013-02-19 - 2019-09-23
Failure_Reason	
N-Miss	675
Caries_or_Repair	145 (44.3%)
TE_or_Redo	182 (55.7%)
Status	
Censored	673 (67.2%)
Event	329 (32.8%)
Time	
Mean (SD)	2.448 (2.179)
Range	0.000 - 12.118

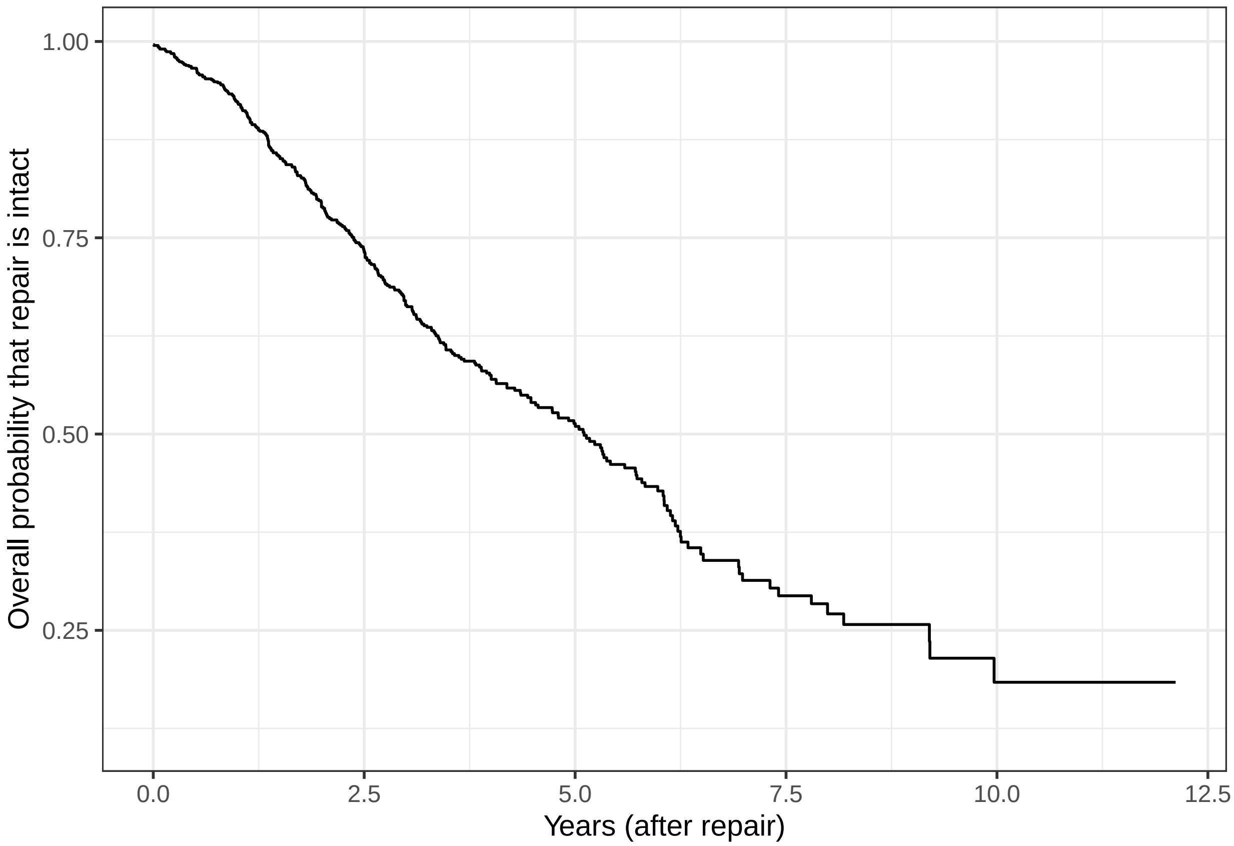
Timeline chart

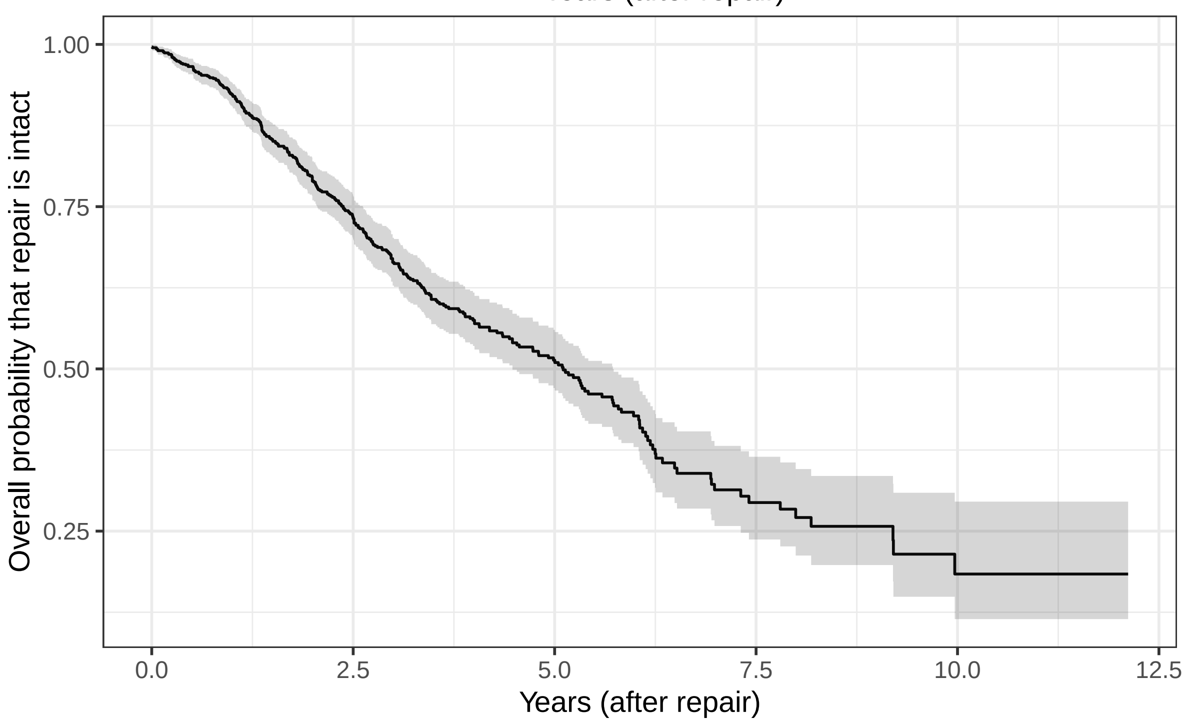
To illustrate the stories of specific patients, I draw a timeline chart (some people call this type of graph a "swimlane diagram").



Kaplan-Meier plot

To get an idea of the overall trajectory of the time that the crown margin repairs are lasting, a create a Kaplan-Meier (KM) plot. As time goes on, there are fewer repairs upon which to draw estimates, so our estimates become more uncertain at later years. To visualize this uncertainty, we can add confidence intervals to the plots. A risk table provides details to supplement the general pattern illustrated in the KM plot.





At Risk	1002	421	140	30	6	0
Events	4	188	285	323	329	329

Analysis

Median survival

Remember: The median survival time is **not** just the median of all the survival time values. When we are talking about median survival, we have to account for the fact that some repairs are censored – we do not know everything about each repair in our study! The Kaplan-Meier method for calculating median survival takes censoring into account. We can do this calculation in `R` with the `survfit` function from the `survival` package.

Median survival time	95% CI (lower)	95% CI (upper)
5.106	4.476	5.722

Nth year survival

We are also often interested to estiamte the survival probability of a repair making it ___ number of years. Below, I use the same `survfit` function to estimate 1, 3, and 5 year survival with the KM method.

NB: to make the following tables have a readable format, I wrote my own `R` function `nth_yr_surv()` - the code for this function is the `data\R.R` file.

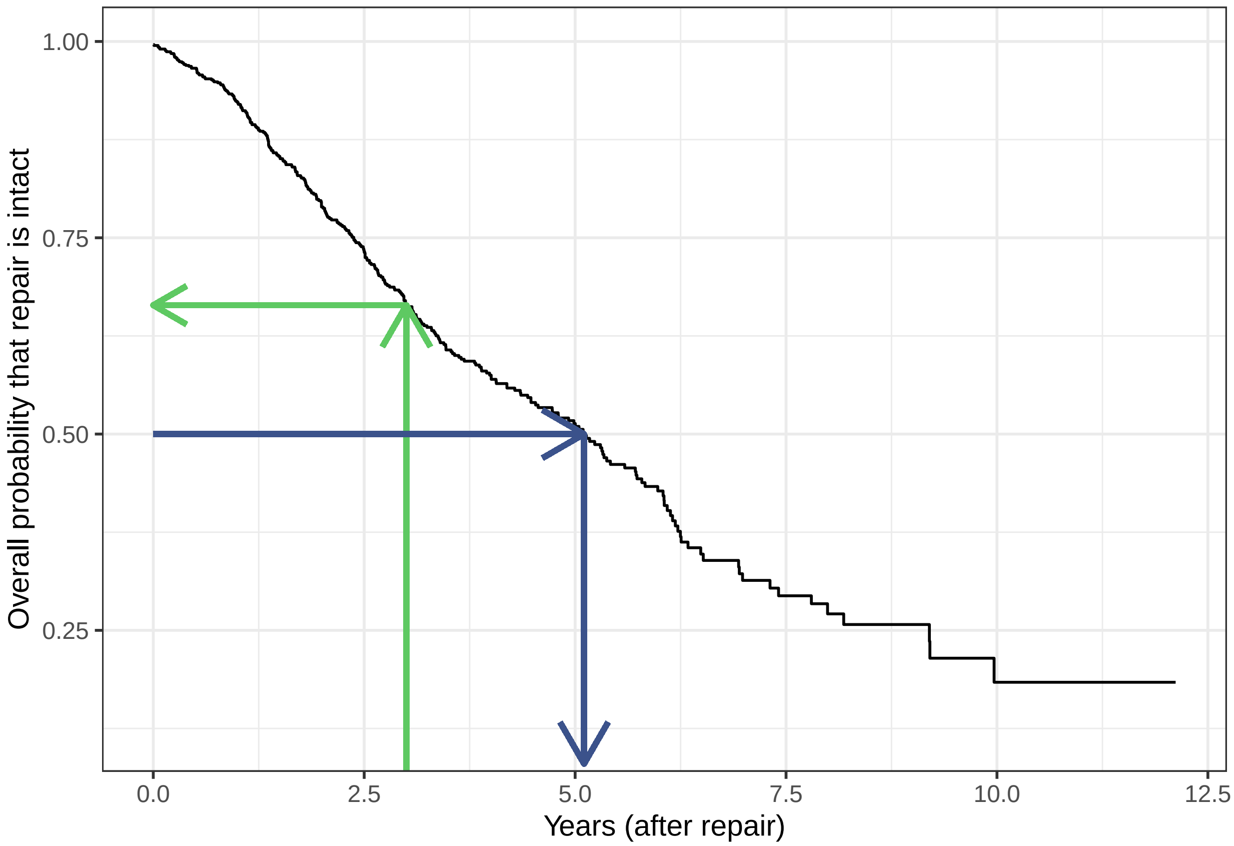
Time	Number at risk	Number of events	Probability of survival	Standard Error	95% CI (lower)	95% CI (upper)
1	690	64	0.923	0.009	0.904	0.941

Time	Number at risk	Number of events	Probability of survival	Standard Error	95% CI (lower)	95% CI (upper)
1	690	64	0.923	0.009	0.904	0.941
3	342	161	0.664	0.019	0.628	0.702

Time	Number at risk	Number of events	Probability of survival	Standard Error	95% CI (lower)	95% CI (upper)
1	690	64	0.923	0.009	0.904	0.941
3	342	161	0.664	0.019	0.628	0.702
5	140	60	0.513	0.023	0.471	0.560

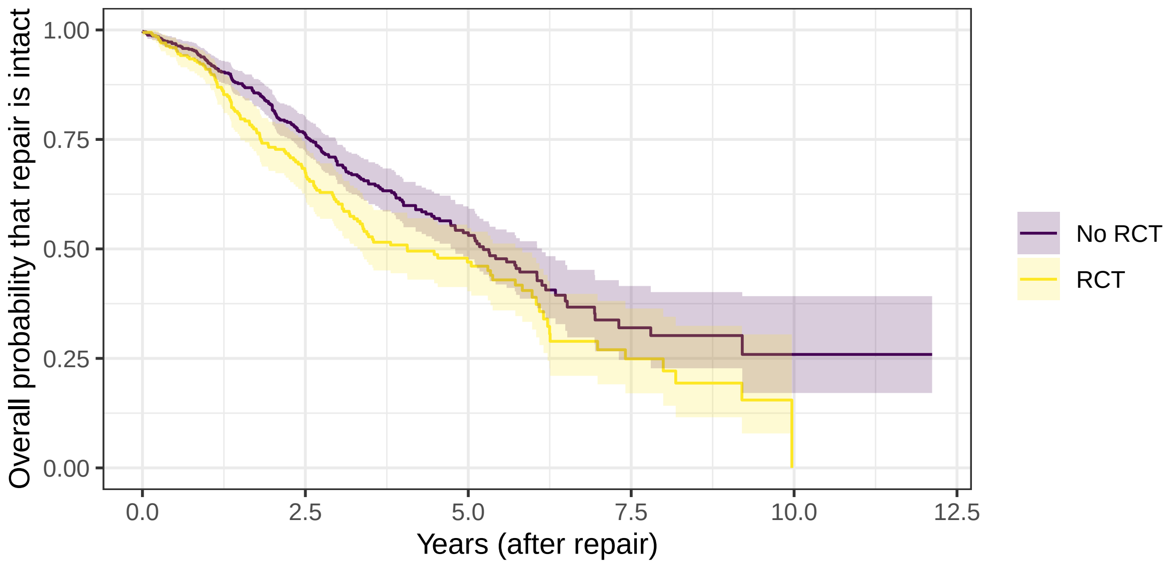
Plot 3 year survival probability and median survival time

To show the difference between estimating ___ year survival and estimating the median survival time, I can plot these both on the same plot.



Up to this point, we have been studying a Kaplan-Meier plot that describes the entire data set (all crown margin repairs). In practice, the objective is often to compare two subgroups from within the data set – for instance, suppose we are interested in comparing how well crown margin repairs lasted between the root canal treated (RCT) and non-RCT groups. The plot below draws two Kaplan-Meier survival curves – one for each of these subgroups. We notice that across time, the curve representing the RCT teeth is consistently below the curve representing the non-RCT teeth. This indicates that the curve for the RCT teeth is *dropping (decreasing) faster*, illustrating that the crown margin repairs done on RCT treated teeth do not last as long as the repairs done on non-RCT teeth.

In addition to the curves in this graph, we also see the confidence intervals at each time point illustrated by the tinted area around each curve. The yellow and purple tinted areas overlap with each other quite a bit, which symbolizes that the difference between crown margin repairs done on RCT teeth and non-RCT teeth is subtle – the repairs last only slightly longer on the non-RCT teeth.



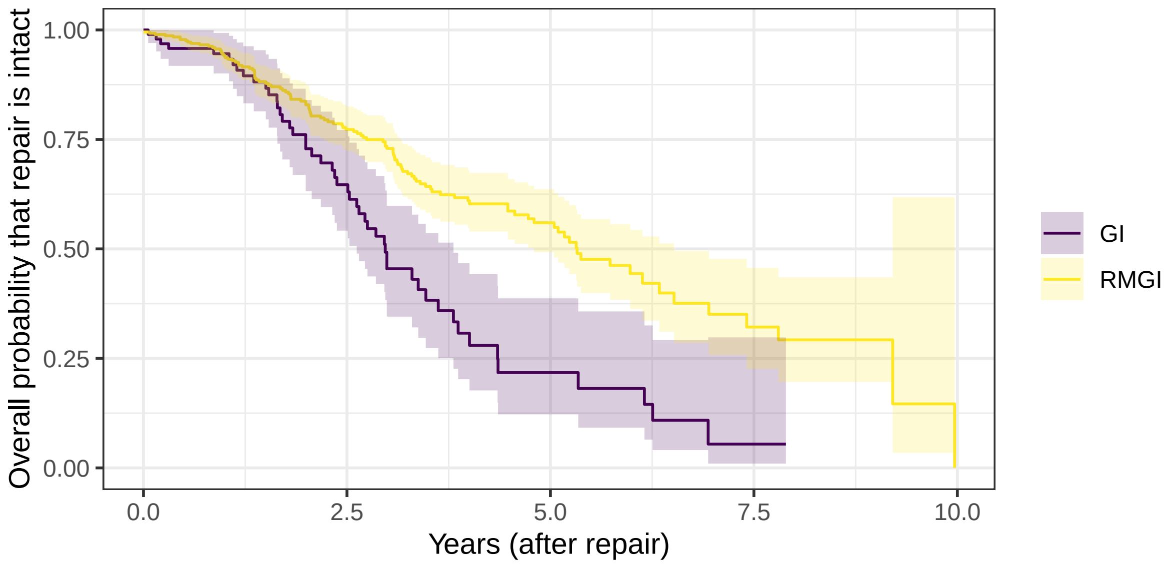
No RCT

At Risk	648	283	89	18	6	0
Events	2	110	171	194	196	196

RCT

At Risk	348	137	51	12	0	0
Events	2	78	113	128	132	132

As a second example of comparing Kaplan-Meier plots between groups, let us suppose that we are working in a materials science context, where we are interested in comparing crown margin repairs that were done with glass ionomer (GI) to repairs done resin-modified glass ionomer (RMGI). We see in the next figure that the survival curve representing the GI group is much lower than the curve for the RMGI group for all times after two years. We also see that the space between the two curves increases over time - the two curves are diverging. The confidence intervals do not overlap much at all after 2.5 years. These survival curves indicate that the crown margin repairs done with RMGI lasted notably longer than the repairs done with GI. There is evidence in this data set that the modification to GI makes a positive impact on the expected lifespan of crown margin repairs.



GI

At Risk	114	39	6	1	0
Events	0	25	45	49	49

RMGI

At Risk	416	174	56	11	0
Events	2	62	98	112	115

Our final survival analysis tool for this tutorial is a Cox proportional hazards model. This model examines each of the variables (i.e. the independent variables) in relationship the time-to-event outcome. A table summarizes the results of this Cox model using hazard ratios (HR), 95% confidence intervals (CI), and p-values.

Characteristic	**HR**	**95% CI**	**p-value**
No_Cases	1.15	1.03, 1.28	0.012
Age	1.01	0.99, 1.02	0.5
Gender			
F			
M	1.20	0.80, 1.80	0.4
CRA			
High Risk			
Not High Risk	0.80	0.52, 1.22	0.3
Tooth_Type			
A			
P	1.84	0.97, 3.52	0.064
Jaw			
Md			
Mx	0.59	0.36, 0.95	0.030
Repair_Material			
Amal			
GI	2.51	1.24, 5.09	0.011
RBC	1.42	0.56, 3.61	0.5
RMGI	1.29	0.80, 2.07	0.3
Surfaces			
B			

Characteristic	HR	95% CI	p-value
L	1.27	0.72, 2.25	0.4
Other	1.65	0.96, 2.86	0.071
No_Surfaces			
1			
2	1.41	0.89, 2.22	0.14
RCT			
No RCT			
RCT	1.56	1.02, 2.38	0.038
Crown_Type			
C			
Other	1.11	0.39, 3.15	0.8
PFM	1.03	0.37, 2.84	>0.9
Clinic			
FAMD			
FDDAU	1.87	1.00, 3.50	0.050
FGP	2.33	0.84, 6.45	0.11
OPER	0.99	0.54, 1.82	>0.9
Other	1.36	0.54, 3.46	0.5
PROS	1.90	0.58, 6.16	0.3
SPEC	1.39	0.53, 3.66	0.5
Provider_Type			
faculty			
student	1.99	0.93, 4.28	0.076

References

Cox, David R. 1972. "Regression Models and Life-Tables." *Journal of the Royal Statistical Society: Series B (Methodological)* 34 (2): 187–202.

Kaplan, Edward L, and Paul Meier. 1958. "Nonparametric Estimation from Incomplete Observations." *Journal of the American Statistical Association* 53 (282): 457–81.