11.2 Log-rank Test

Definition. To compare two survival curves, we can use the **log-rank test**. The hypotheses are $H_0 : S_1(t) = S_2(t)$ for all values of t, and $H_1 : S_1(t) \neq S_2(t)$ for at least one value of t. Let $t_1 < t_2 < \ldots < t_k$ denote the distinct ordered event times in both samples pooled together. At each time t_i, the observations may be summarized in a 2×2 table with the two samples represented by the rows, and the columns representing the number of individuals who experienced the event at time t_i (Event) and the number of those who were at-risk but didn't experience the event (No Event). Thus, there are a total of k 2×2 tables of the form

Sample	Event	No Event	Total
1	e_{1i}	$n_{1i} - e_{1i}$	n_{1i}
2	e_{2i}	$n_{2i} - e_{2i}$	n_{2i}
Total	e_i	$n_i - e_i$	n_i

Testing the null hypothesis of equality of the survival functions is tantamount to simultaneously testing k null hypotheses of independence of the row variable (sample 1 or 2) and the column variable (event or no event) in each table. Under the H_0, e_{1i} has a hypergeometric distribution with parameters n_i (the population size), n_{1i} (the size of the group of interest in the population), and e_i (the sample size). The mean and the variance of e_{1i} are $\mathbb{E}(e_{1i}) = \dfrac{n_{1i}e_i}{n_i}$ and $\mathbb{V}ar(e_{1i}) = \dfrac{n_{1i}n_{2i}(n_i - e_i)e_i}{n_i^2(n_i - 1)}$.

The log-rank test statistic is the standardized sum of e_{1i}'s over all tables, that is,

$$z = \frac{\sum_{i=1}^{k} e_{1i} - \mathbb{E}\big(\sum_{i=1}^{k} e_{1i}\big)}{\sqrt{\mathbb{V}ar\big(\sum_{i=1}^{k} e_{1i}\big)}} = \frac{\sum_{i=1}^{k}\big(e_{1i} - \frac{n_{1i}e_i}{n_i}\big)}{\sqrt{\sum_{i=1}^{k} \frac{n_{1i}n_{2i}(n_i - e_i)e_i}{n_i^2(n_i - 1)}}}.$$

Under H_0 this test statistic has approximately a $\mathcal{N}(0, 1)$ distribution. Equivalently, z^2 may be chosen as the test statistic. It has approximately a chi-square distribution with one degree of freedom.

Example. Researchers were interested in testing a new antibiotic treatment for pneumonia. Fourteen patients were enrolled in the study, half of whom were randomly assigned to the treatment group while the others received a placebo (the control group). The number of days until pneumonia symptoms disappeared were recorded. The observations were censored for those who still had symptoms at the end of the ten days or were lost to follow-up. The

data are

Treatment group (Tx)	3	3	4	4	4+	5	5
Control group (Cx)	4	5	5	6	6	6	10+

The test hypotheses are $H_0 : S_{\text{Tx}}(t) = S_{\text{Cx}}(t)$ for all t and $H_1 : S_{\text{Tx}}(t) \neq S_{\text{Cx}}(t)$ for some t. For both groups combined, there are four distinct event times 3, 4, 5, and 6 days. Therefore, to compute the log-rank test statistic, we first populate four 2×2 tables and calculate the relevant quantities for them. The calculations follow.

For $t_1 = 3$,

Group	Event	No Event	Total
Tx	2	5	7
Cx	0	7	7
Total	2	12	14

$e_{11} = 2, \ \mathbb{E}(e_{11}) = \dfrac{(7)(2)}{14} = 1$, and $\mathbb{V}ar(e_{11}) = \dfrac{(7)(7)(12)(2)}{(14)^2(13)} = \dfrac{6}{13}$.

For $t_2 = 4$,

Group	Event	No Event	Total
Tx	2	3	5
Cx	1	6	7
Total	3	9	12

$e_{12} = 2, \ \mathbb{E}(e_{12}) = \dfrac{(5)(3)}{12} = \dfrac{15}{12}$, and $\mathbb{V}ar(e_{12}) = \dfrac{(5)(7)(9)(3)}{(12)^2(11)} = \dfrac{105}{176}$.

For $t_3 = 5$,

Group	Event	No Event	Total
Tx	2	0	2
Cx	2	4	6
Total	4	4	8

$e_{13} = 2, \ \mathbb{E}(e_{13}) = \dfrac{(2)(4)}{8} = 1$, and $\mathbb{V}ar(e_{13}) = \dfrac{(2)(6)(4)(4)}{(8)^2(7)} = \dfrac{3}{7}$.

For $t_4 = 6$,

Group	Event	No Event	Total
Tx	0	0	0
Cx	3	1	4
Total	3	1	4

$e_{14} = 0$, $\mathbb{E}(e_{13}) = \dfrac{(0)(3)}{4} = 0$, and $\mathbb{V}ar(e_{13}) = \dfrac{(0)(4)(1)(3)}{(4)^2(3)} = 0$. This case may be omitted from further calculations.

The log-rank test statistic is

$$z = \frac{2 - 1 + 2 - \frac{15}{12} + 2 - 1}{\sqrt{\frac{6}{13} + \frac{105}{176} + \frac{3}{7}}} = 2.2554.$$

The two-sided P-value is $2\mathbb{P}(Z > 2.2554) = 0.0241 < 0.05$, hence we reject H_0 and conclude that the two survival curves differ at some points.

Next, we conduct the log-rank test and plot the curves using SAS and R.

In SAS:

```
data pneumonia;
input group$ days censored @@;
cards;
Tx 3 0 Tx 3 0 Tx 4 0 Tx 4 0 Tx 4 1 Tx 5 0 Tx 5 0
Cx 4 0 Cx 5 0 Cx 5 0 Cx 6 0 Cx 6 0 Cx 6 0 Cx 10 1
;

proc lifetest plots=(survival);
time days*censored(1);
strata group;
run;
```

Test of Equality over Strata

| Test	Chi-Square	DF	Pr > Chi-Square
Log-Rank	5.0868	1	0.0241
Wilcoxon	4.7154	1	0.0299
−2Log(LR)	0.4899	1	0.4840

Product-Limit Survival Estimates
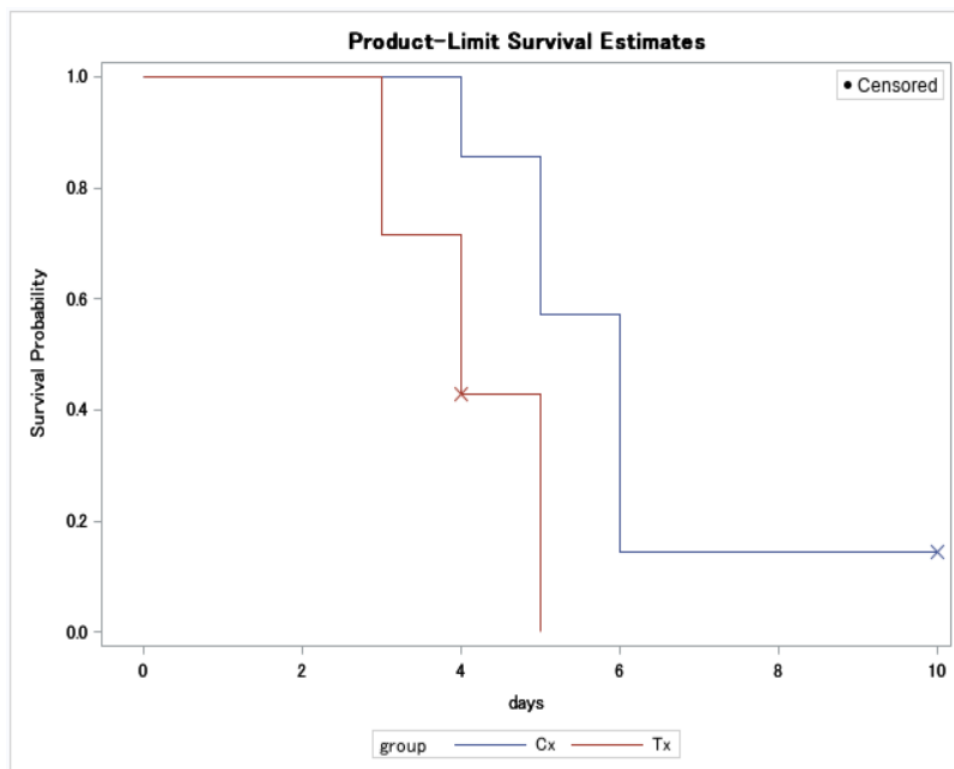
In R:

```
group<-c("Tx","Tx","Tx","Tx","Tx","Tx","Tx","Cx",
"Cx","Cx","Cx","Cx","Cx","Cx")
days<-c(3, 3, 4, 4, 4, 5, 5, 4, 5, 5, 6, 6, 6, 10)
censored<-c(0, 0, 0, 0, 1, 0, 0, 0, 0, 0, 0, 0, 0, 1)
```

library(survival)
#survdiff() performs log-rank test
survdiff(Surv(days, censored==0) $\sim$ group)


```
Chisq= 5.1  on 1 degrees of freedom, p= 0.02
```

#computing the KM estimates
days.surv<-survfit(Surv(days, censored==0)$\sim$ group, se.fit=FALSE)
#plotting the KM survival curves
plot(days.surv, mark.time=TRUE, pch=4, col=c("blue","red"), main="Kaplan-Meier Survival Curves", xlab="Days", ylab="Survival Distribution Function")
legend("topright", lty=1, col=c("blue","red"), legend=c("Cx","Tx"), text.col=c("blue","red"))
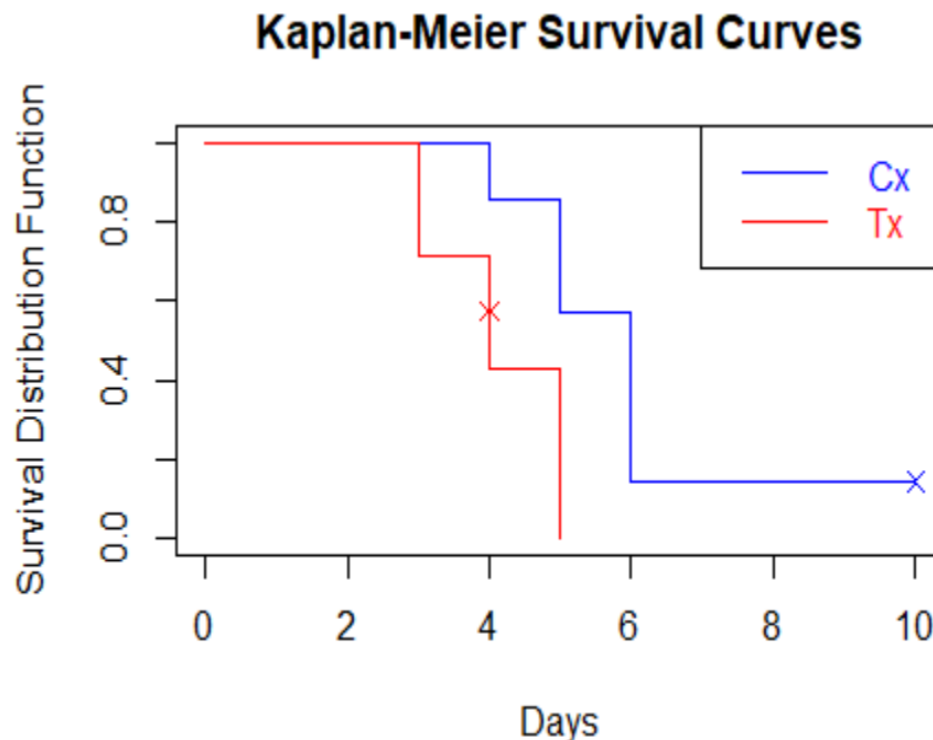
Example. A retrospective cohort study was performed in 77 patients with nasopharyngeal cancer diagnosed and treated in a specialized clinic. The prognostic impact of gender, smoking, and type of treatment on subject survival were evaluated using the Kaplan-Meier survival curves and log-rank

tests. The data are given in the file "nasopharyngeal_cancer_data.csv".

In SAS:

```
proc import out=cancer_data datafile="./nasopharyngeal_cancer_data.csv"
dbms=csv replace;
run;

proc lifetest data=cancer_data plots=(survival);
time years*censored(1);
run;
```
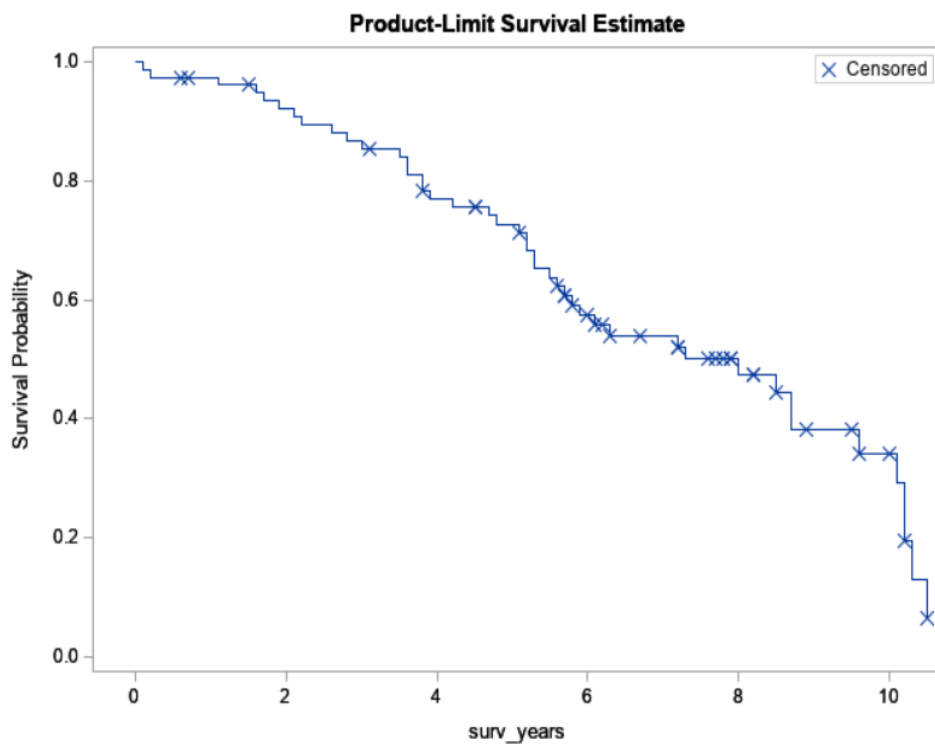


```
proc lifetest data=cancer_data plots=(survival);
time years*censored(1);
strata gender;
run;
```
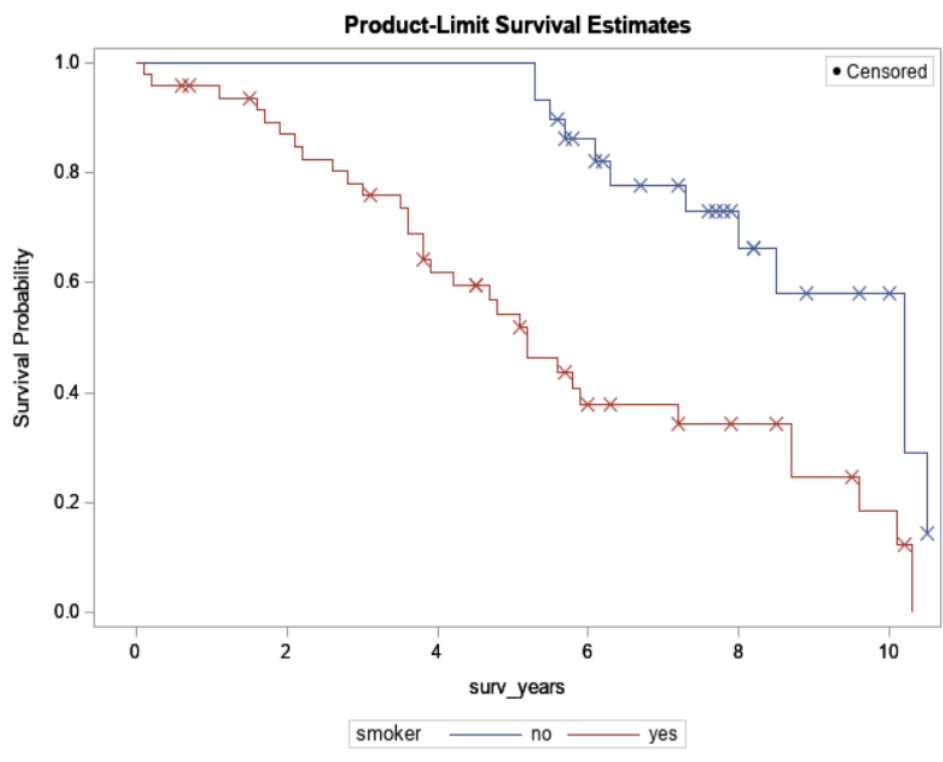
Test of Equality over Strata			
Test	Chi-Square	DF	Pr > Chi-Square
Log-Rank	7.1188	1	0.0076
Wilcoxon	11.9693	1	0.0005
-2Log(LR)	5.2550	1	0.0219

Product-Limit Survival Estimates
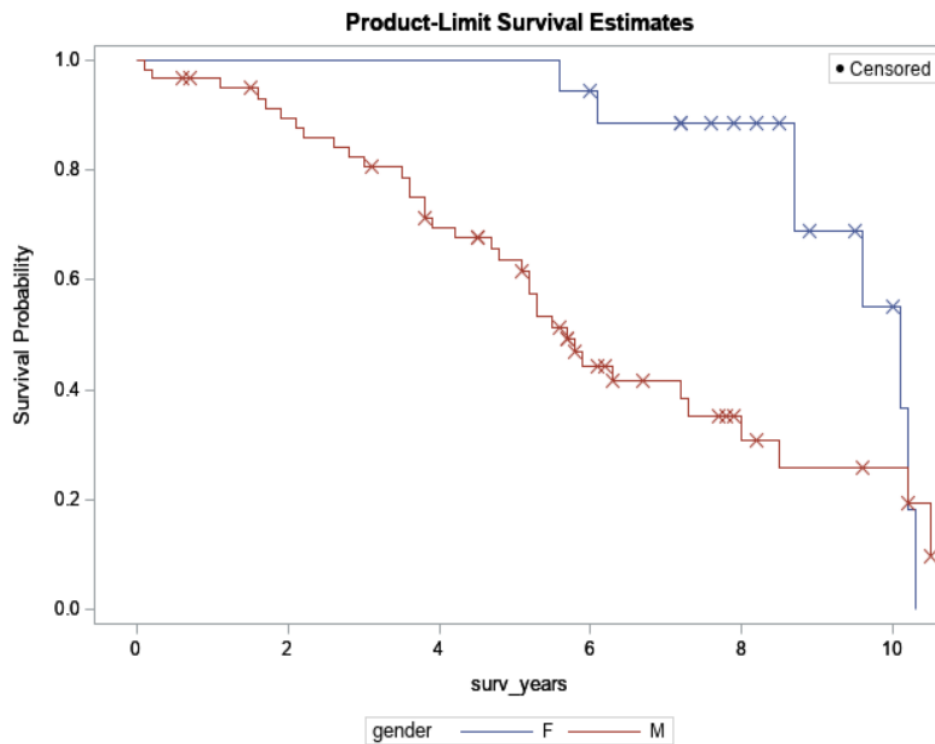
The p-value < 0.05 indicates that the survival curves differ. Women tend to survive longer.

```
proc lifetest data=cancer_data plots=(survival);
time years*censored(1);
strata smoker;
run;
```

Test of Equality over Strata

| Test	Chi-Square	DF	Pr > Chi-Square
Log-Rank	14.1641	1	0.0002
Wilcoxon	16.7924	1	<.0001
-2Log(LR)	8.6357	1	0.0033

Product-Limit Survival Estimates

The p-value < 0.05 indicates that the survival curves differ. Non-smokers tend to survive longer.

```
proc lifetest data=cancer_data plots=(survival);
time years*censored(1);
strata therapy;
run;
```

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Test of Equality over Strata			
Test	Chi-Square	DF	Pr > Chi-Square
Log-Rank	1.8994	1	0.1681
Wilcoxon	0.7236	1	0.3950
-2Log(LR)	1.7597	1	0.1847
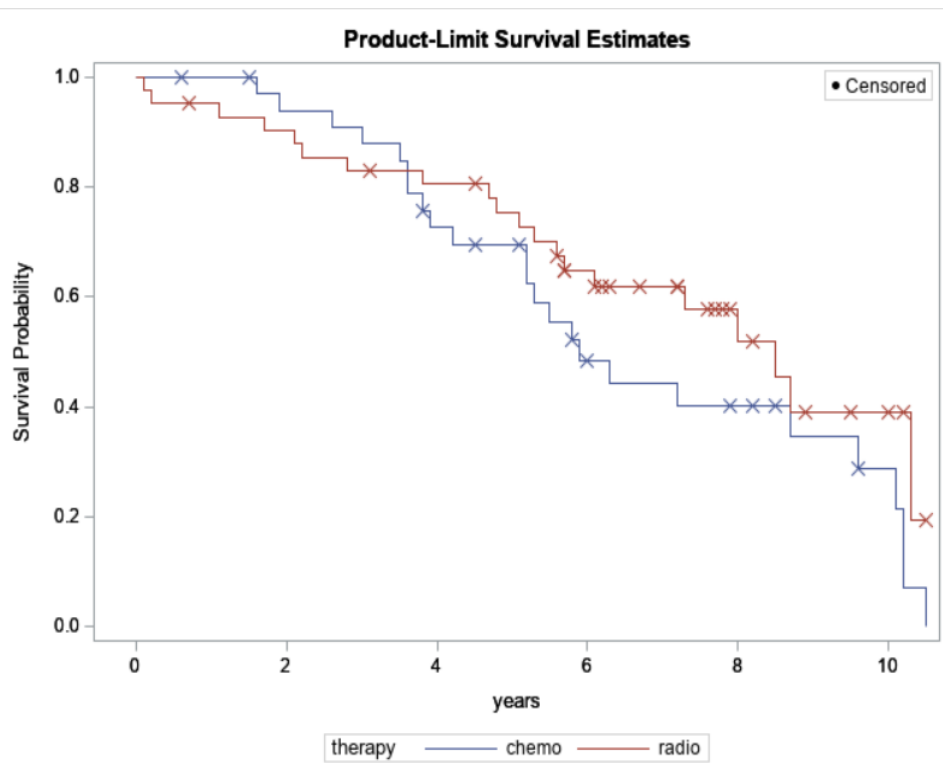
The p-value > 0.05 indicates that the survival curves do not differ. The type of treatment has no effect on survival distribution.

In R:
cancer.data<- read.csv("./nasopharyngeal_cancer_data.csv", header=TRUE, sep=",")

library(survival)
#fitting overall KM survival curve
overall.surv<-survfit(Surv(years, censored==0) ~ 1, data=cancer.data, se.fit=FALSE)

plot(overall.surv, mark.time=TRUE, pch=4, col="blue", main="Overall KM
Survival Curve", xlab="Years", ylab="Survival Distribution Function")
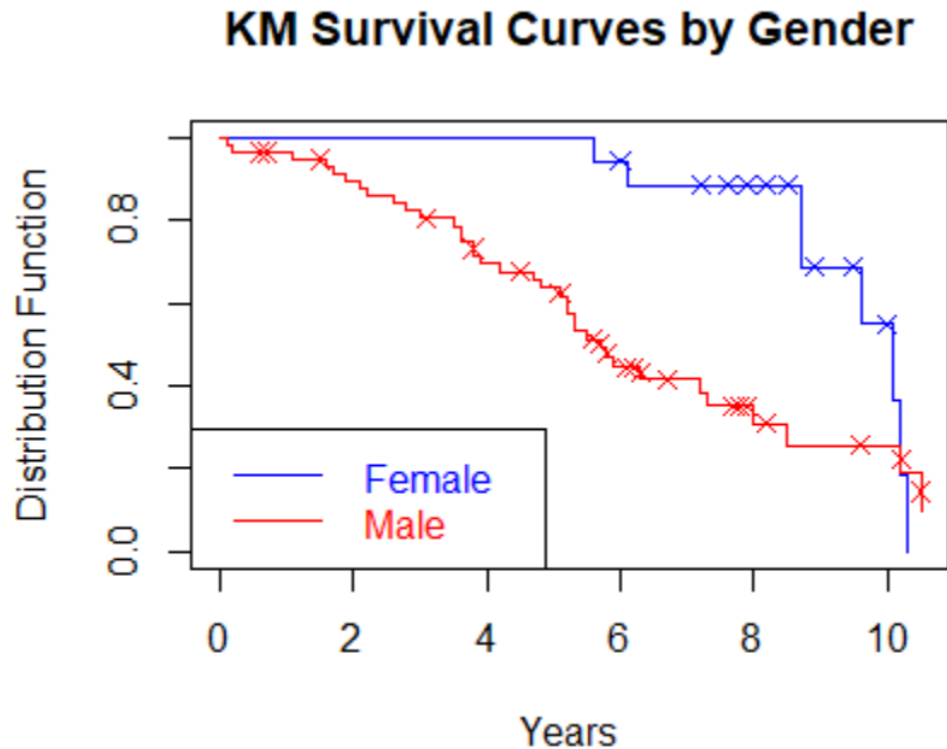
Overall KM Survival Curve
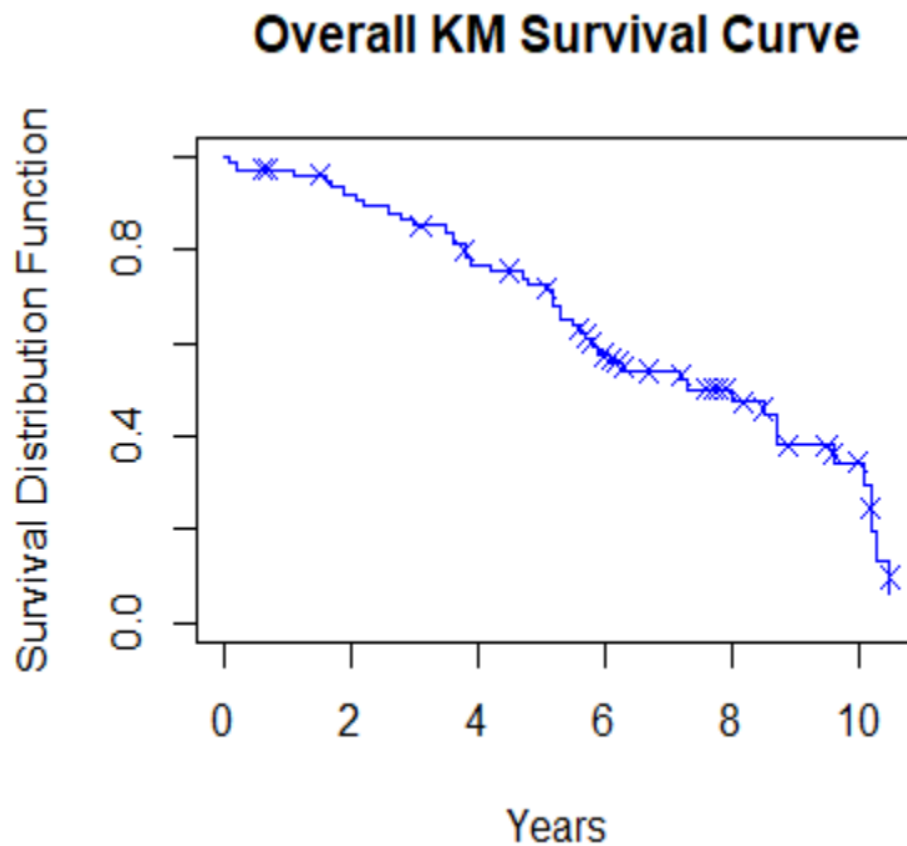
#KM curves and log-rank test by gender
gender.surv<-survfit(Surv(years, censored==0) ~ gender, data=cancer.data,
se.fit=FALSE)
survdiff(Surv(years, censored==0) ~ gender, data=cancer.data)

```
 Chisq= 7.1  on 1 degrees of freedom, p= 0.008
```

plot(gender.surv, mark.time=TRUE, pch=4, col=c("blue","red"), main="KM
Survival Curves by Gender", xlab="Years", ylab="Survival Distribution

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Function")
legend("bottomleft", lty=1, col=c("blue","red"), legend=c("Female","Male"),
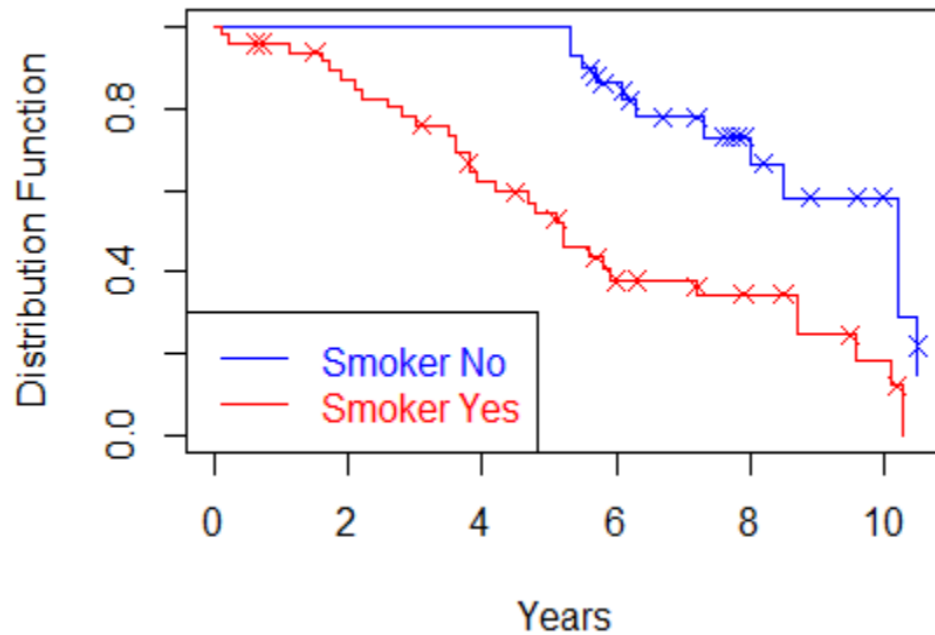text.col=c("blue","red"))

KM Survival Curves by Gender

#KM curves and log-rank test by smoker
smoker.surv<-survfit(Surv(years, censored==0) ~ smoker, data=cancer.data,
se.fit=FALSE)
survdiff(Surv(years, censored==0) ~ smoker, data=cancer.data)

```
Chisq= 14.2  on 1 degrees of freedom, p= 2e-04
```

plot(smoker.surv, mark.time=TRUE, pch=4, col=c("blue","red"), main="KM
Survival Curves by Smoker", xlab="Years", ylab="Survival Distribution
Function")
legend("bottomleft", lty=1, col=c("blue","red"), legend=c("Smoker No","Smoker
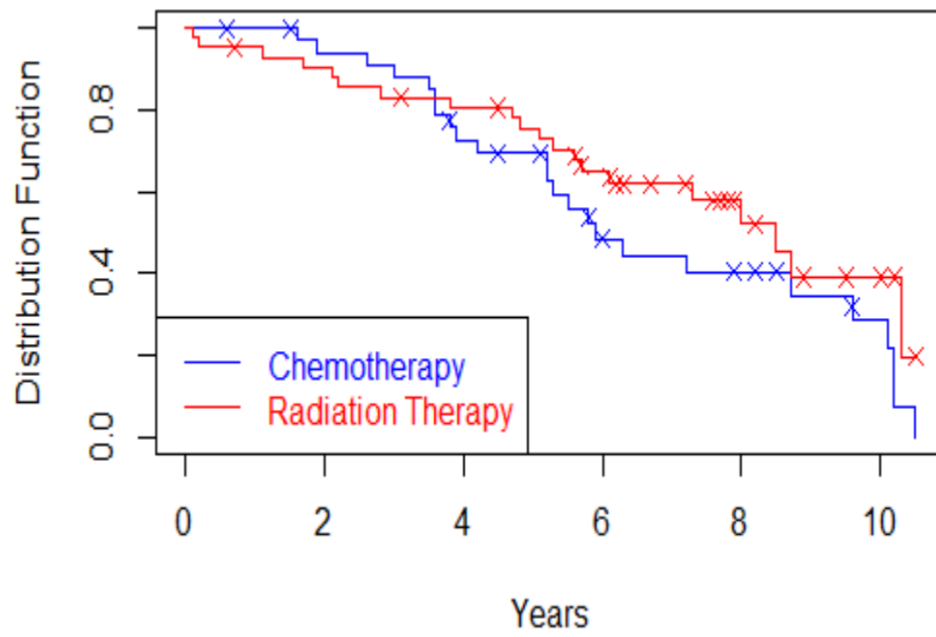Yes"), text.col=c("blue","red"))

KM Survival Curves by Smoker

#KM curves and log-rank test by therapy
therapy.surv<-survfit(Surv(years, censored==0) ~ therapy, data=cancer.data, se.fit=FALSE)
survdiff(Surv(years, censored==0) ~ therapy, data=cancer.data)

```
Chisq= 1.9  on 1 degrees of freedom, p= 0.2
```

plot(therapy.surv, mark.time=TRUE, pch=4, col=c("blue","red"), main="KM Survival Curves by Therapy", xlab="Years", ylab="Survival Distribution Function")
legend("bottomleft", lty=1, col=c("blue","red"), legend=c("Chemotherapy", "Radiation Therapy"), text.col=c("blue","red"))

KM Survival Curves by Therapy