

나. 중도절단의 이유

- loss to follow up
- drop out
- termination of the study
- death from unrelated cause

다. 중도절단의 형태

- Right censoring: $T \in [R, \infty)$
- Left censoring: $T \in (0, L]$
- Interval censoring: $T \in [L, R]$

1.3. 생존함수

가. 확률함수

- 생존시간 임의변수: T
- 확률밀도함수: $f(t)$
- 분포함수: $F(t)=\Pr(T \leq t)$

나. 생존함수

- $S(t)=\Pr(T \geq t)$
- t 시점까지 사망하지 않고 생존할 확률

다. 위험함수(hazard function)

- $h(t)=f(t)/S(t)$
- t 시점까지 생존한 사람이 t 시점 바로 직후에서 순간적으로 사망할 조건확률
- hazard rate, failure rate, force of mortality
- $S(t)=\exp(-H(t))$, $H(t)$ = 누적위험함수

라. 위험함수의 형태

모형	위험함수의 형태
Exponential	일정
Weibull	단조감소 혹은 단조증가
Lognormal	증가하다가 감소

1.4 일반적인 통계분석방법과 생존분석의 비교

	일반적 방법	생존분석
자료의 요약	기술통계량 - 히스토그램, 돛수분포표 - 평균, 중위수, 분산, 사분위수범위	기술통계량 - life table 작성 - survival curve의 작성
k개 집단의 평균 비교	모수적 방법 - t-검정, 분산분석 비모수적 방법 - 윌콕슨검정, 크루스칼-왈리스검정	모수적 방법 - 우도비검정(likelihood ratio test) 비모수적 방법 - 로그순위검정(log-rank test) - 일반화된 윌콕슨검정
회귀분석	다중회귀분석 로지스틱회귀분석	모수적 회귀모형 Cox'의 비례위험회귀모형

2. 생존함수의 추정

2.1 Life table method

- 시간을 (k+1)개의 구간 $I_j = [a_{j-1}, a_j), j=1, 2, \dots, k+1$ 로 나눈다.
- N_j = 시간 a_{j-1} 에서 아직 살아 있는("at risk") 사람의 수
- D_j = I_j 구간에서 죽은 사람의 수
- W_j = I_j 에서 중도 절단된("withdrawals") 사람의 수
- $q_j = \frac{D_j}{N_j - W_j/2}, p_j = 1 - q_j$

- Probability of survival: $S_j = p_1 \cdot p_2 \cdot \dots \cdot p_j, j=1, 2, \dots, k+1$
- variance of survival(Greenwood)

$$\text{var}(S_j) = S_j^2 \sum_{i=1}^j \frac{q_i}{p_i(N_i - 0.5 W_i)}$$

Ex: Life Tables

Interval in years (I_j)	No. at risk (N_j)	No. of withdrawals (W_j)	No. of deaths (D_j)	N_j	q_j	p_j	Estimated survival P_j
[0,1)	374	0	90	374	0.241	0.759	0.959
[1,2)	284	0	76	284	0.268	0.732	0.556
[2,3)	208	0	51	208	0.245	0.755	0.420
[3,4)	157	12	25	151	0.164	0.834	0.350
[4,5)	120	5	20	117.5	0.170	0.830	0.291
[5,6)	95	9	7	90.5	0.077	0.923	0.268
[6,7)	79	9	4	74.5	0.054	0.946	0.254
[7,8)	66	3	1	64.5	0.016	0.984	0.250
[8,9)	62	5	3	59.5	0.05	0.950	0.237
[9,10)	54	5	2	51.5	0.039	0.961	0.228
[10, ∞)	47	0	47	47.0	1.000	0.000	0.000

2.2 Nonparametric method

가. 중도절단된 자료가 없는 경우

- empirical survival function: $S(t) = \frac{\text{No. of obs. } \geq t}{n}, t \geq 0$

나. 중도절단된 자료가 있는 경우

- t_1, t_2, \dots, t_k : 사망이 일어나는 시간
- 생존함수의 추정

$$S(t) = \prod_{t_j < t} \frac{n_j - d_j}{n_j}$$

- 생존함수의 추정치의 variance

$$\text{var}(S(t)) = S(t)^2 \sum_{t_j < t} \frac{d_j}{n_j(n_j - d_j)}$$

Median Survival Time

● No censored case

$$t_{(1)}, t_{(2)}, \dots, t_{(n)}$$

$$M = t_{(\lfloor \frac{n+1}{2} \rfloor)} \quad \text{if } n \text{ is odd}$$

$$= \frac{1}{2} (t_{(\frac{n}{2})} + t_{(\frac{n}{2} + 1)}) \quad , \text{ if } n \text{ is even}$$

● Censored case

- Use Kaplan-Meier Survival curve

- Find M , such That $S(M) = 0.5$

● confidence intervals for a median

$$SE(M) = SE_G(S(M)) \left\{ \frac{t_{small} - t_{large}}{S(t_{small}) - S(t_{large})} \right\}$$

$$SE_G(S(t)) = S(t) \left\{ \sum_{j=0}^{t-1} \frac{d_j}{n_j(n_j - d_j)} \right\}^{\frac{1}{2}}$$

: Greenwood formula

3. Kaplan-Meier방법에 의한 생존함수의 비교

가. 두집단의 생존함수가 차이가 있는 가를 검정하기 위한 가설

$$H_0: S_1(t) = S_2(t) \quad H_1: S_1(t) \neq S_2(t)$$

나. 검정통계량

- 로그-순위 검정(log-rank test)
- 윌콕슨검정(Wilcoxon test)

Data: Lung Cancer Survival Data

t	x_1	x_2	x_3	t	x_1	x_2	x_3
Standard, Squamous				Test, Squamous			
411	70	64	5	999	90	54	12
126	60	63	9	231*	50	52	8
118	70	65	11	991	70	50	7
92	40	69	10	1	20	65	21
8	40	63	58	201	80	52	28
25*	70	48	9	44	60	70	13
11	70	48	11	15	50	40	13
Standard, Small				Test, Small			
54	80	63	4	103*	70	36	22
153	60	63	14	2	40	44	36
16	30	53	4	20	30	54	9
56	80	43	12	51	30	59	87
21	40	55	2				
287	60	66	25				
10	40	67	23				
Standard, Adeno				Test, Adeno			
8	20	61	19	18	40	69	5
12	50	63	4	90	60	50	22
				84	80	62	4
Standard, Large				Test, Large			
177	50	66	16	164	70	68	15
12	40	68	12	19	30	39	4
200	80	41	12	43	60	49	11
250	70	53	8	340	80	64	10
100	60	37	13	231	70	67	18

x_1 =performance status

x_2 =age

x_3 =months from diagnosis to entry into study

x_4 =1 if tumor type is squamous, 0 otherwise

x_5 =1 if tumor type is small, 0 otherwise

x_6 =1 if tumor type is adeno, 0 otherwise

x_7 =1 if treatment is test, 0 if it is standard

<SAS program>

```
data lung;
  infile 'a:lung1.txt';
  input days status perform age mondiag squam small adeno treat @@
run;

proc lifetest data=lung plots=(s);
  time days*status(0);
  strata treat;
run;
```


<SAS output>

Product-Limit Survival Estimates

TREAT = 0

DAYS	Survival			Number Failed	Number Left
	Survival	Failure	Standard Error		
0.000	1.0000	0	0	0	21
8.000	.	.	.	1	20
8.000	0.9048	0.0952	0.0641	2	19
10.000	0.8571	0.1429	0.0764	3	18
11.000	0.8095	0.1905	0.0857	4	17
12.000	.	.	.	5	16
12.000	0.7143	0.2857	0.0986	6	15
16.000	0.6667	0.3333	0.1029	7	14
21.000	0.6190	0.3810	0.1060	8	13
25.000*	.	.	.	8	12
54.000	0.5675	0.4325	0.1090	9	11
56.000	0.5159	0.4841	0.1106	10	10
92.000	0.4643	0.5357	0.1109	11	9
100.000	0.4127	0.5873	0.1099	12	8
118.000	0.3611	0.6389	0.1076	13	7
126.000	0.3095	0.6905	0.1039	14	6
153.000	0.2579	0.7421	0.0985	15	5
177.000	0.2063	0.7937	0.0913	16	4
200.000	0.1548	0.8452	0.0818	17	3
250.000	0.1032	0.8968	0.0689	18	2
287.000	0.0516	0.9484	0.0502	19	1
411.000	0	1.0000	0	20	0

* Censored Observation

Summary Statistics for Time Variable DAYS

Quantile	Point	95% Confidence Interval	
	Estimate	[Lower,	Upper)
75%	177.000	92.000	250.000
50%	92.000	16.000	153.000
25%	12.000	10.000	56.000

Mean 109.079 Standard Error 25.096

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The LIFETEST Procedure

Product-Limit Survival Estimates

TREAT = 1

DAYS	Survival	Failure	Survival		
			Standard Error	Number Failed	Number Left
0.000	1.0000	0	0	0	19
1.000	0.9474	0.0526	0.0512	1	18
2.000	0.8947	0.1053	0.0704	2	17
15.000	0.8421	0.1579	0.0837	3	16
18.000	0.7895	0.2105	0.0935	4	15
19.000	0.7368	0.2632	0.1010	5	14
20.000	0.6842	0.3158	0.1066	6	13
43.000	0.6316	0.3684	0.1107	7	12
44.000	0.5789	0.4211	0.1133	8	11
51.000	0.5263	0.4737	0.1145	9	10
84.000	0.4737	0.5263	0.1145	10	9
90.000	0.4211	0.5789	0.1133	11	8
103.000*	.	.	.	11	7
164.000	0.3609	0.6391	0.1119	12	6
201.000	0.3008	0.6992	0.1082	13	5
231.000	0.2406	0.7594	0.1019	14	4
231.000*	.	.	.	14	3
340.000	0.1604	0.8396	0.0944	15	2
991.000	0.0802	0.9198	0.0738	16	1
999.000	0	1.0000	0	17	0

* Censored Observation

Summary Statistics for Time Variable DAYS

Quantile	Point	95% Confidence Interval	
	Estimate	[Lower,	Upper)
75x	231.000	84.000	991.000
50x	84.000	20.000	231.000
25x	19.000	15.000	84.000
Mean	243.085	Standard Error	86.694

Summary of the Number of Censored and Uncensored Values

TREAT	Total	Failed	Censored	%Censored
0	21	20	1	4.7619
1	19	17	2	10.5263
Total	40	37	3	7.5000

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The LIFETEST Procedure

Testing Homogeneity of Survival Curves over Strata
Time Variable DAYS

Rank Statistics

TREAT	Log-Rank	Wilcoxon
0	3.2286	41.000
1	-3.2286	-41.000

Covariance Matrix for the Log-Rank Statistics

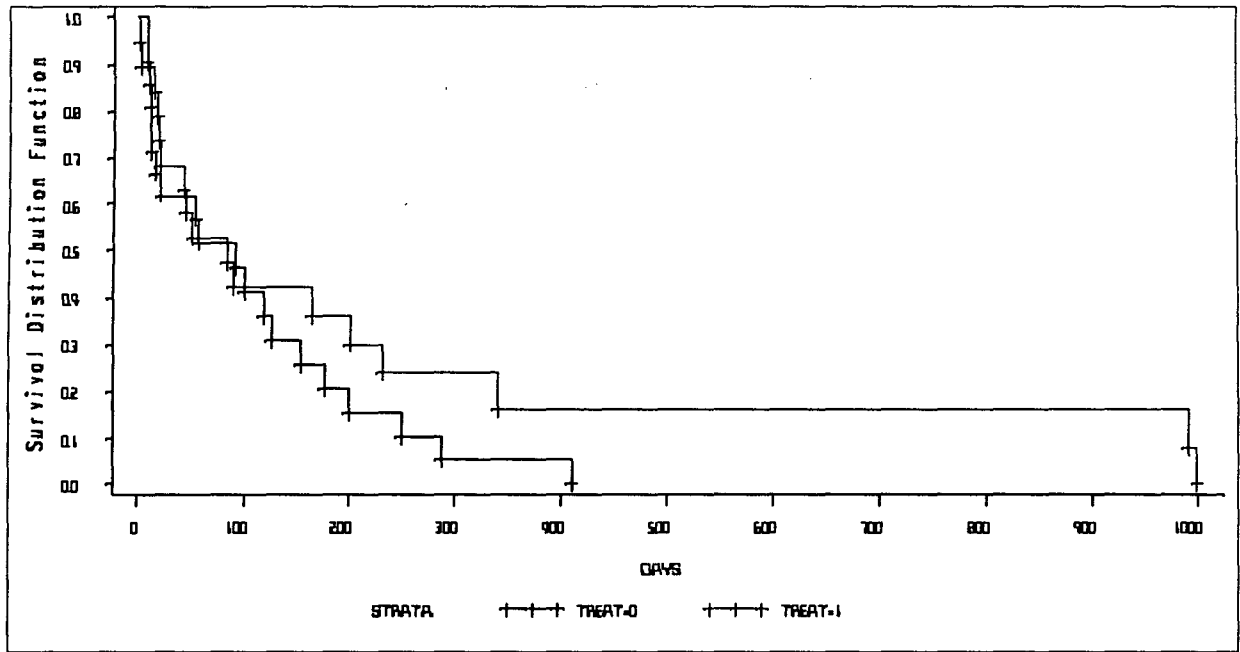
TREAT	0	1
0	8.53645	-8.53645
1	-8.53645	8.53645

Covariance Matrix for the Wilcoxon Statistics

TREAT	0	1
0	5261.19	-5261.19
1	-5261.19	5261.19

Test of Equality over Strata

Test	Chi-Square	DF	Pr >
			Chi-Square
Log-Rank	1.2211	1	0.2691
Wilcoxon	0.3195	1	0.5719
-2Log(LR)	4.3999	1	0.0359



4. 중도절단된 자료에서의 회귀분석적 방법

4.1 회귀분석의 적용

두 집단 혹은 그 이상의 집단에 따라서 생존확률이 차이가 있는지는 log-rank test 등으로 비교할 수 있다. 경우에 따라서 연구대상이 이질적인 모집단으로 추출되어 제반 이질적인 특성을 고려하여 집단 간의 생존확률을 비교할 필요가 있다. 이 때 제반 특성변수를 통제하는 방법이 회귀분석이다.

4.2 모수적 회귀분석

가. 특징

생존함수, 위험함수에 특정한 분포를 가정한다.

나. 모수적 모형의 종류

- Exponential model
- Weibull model
- Extreme value model
- Normal model
- Log-normal model
- Gamma model
- Log-gamma model
- Log-logistic model

다. SAS에서의 절차

```
proc lifereg;
```

라. an example

<SAS program>

```
proc lifereg data=lung;  
    model days*status(0)=perform age mondiag squam small adeno treat  
    /d=exponential;  
run;
```

<SAS output>

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Lifereg Procedure

Data Set =WORK.LUNG
Dependent Variable=Log(DAYS)
Censoring Variable=STATUS
Censoring Value(s)= 0
Noncensored Values= 37 Right Censored Values= 3
Left Censored Values= 0 Interval Censored Values= 0

Log Likelihood for EXPONENT -56.92056385

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Lifereg Procedure

Variable	DF	Estimate	Std Err	ChiSquare	Pr>Chi	Label/Value
INTERCPT	1	0.83295227	1.370156	0.369573	0.5432	Intercept
PERFORM	1	0.05400238	0.010812	24.94587	0.0001	
AGE	1	0.00903528	0.019666	0.211073	0.6459	
MONDIAG	1	0.00339933	0.011675	0.084781	0.7709	
SQUAM	1	0.36261291	0.444564	0.665301	0.4147	
SMALL	1	-0.1270625	0.486347	0.068256	0.7939	
ADENO	1	-0.8689621	0.586136	2.197886	0.1382	
TREAT	1	0.26974154	0.388209	0.482797	0.4872	
SCALE	0	1	0			Extreme value scale parameter

Lagrange Multiplier ChiSquare for Scale 1.255606 Pr>Chi is 0.2625.

```

<SAS program>
proc lifereg data=lung;
  model days*status(0)=perform age mondiag squam small adeno treat
  /d=weibull;
run;

```

<SAS output>

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Lifereg Procedure

```

Data Set          =WORK.LUNG
Dependent Variable=Log(DAYS)
Censoring Variable=STATUS
Censoring Value(s)= 0
Noncensored Values= 37 Right Censored Values= 3
Left Censored Values= 0 Interval Censored Values= 0

```

Log Likelihood for WEIBULL -56.41988629

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Lifereg Procedure

Variable	DF	Estimate	Std Err	ChiSquare	Pr>Chi	Label/Value
INTERCPT	1	0.82902474	1.215583	0.465121	0.4952	Intercept
PERFORM	1	0.05379252	0.009586	31.48849	0.0001	
AGE	1	0.00972409	0.017518	0.308124	0.5788	
MONDIAG	1	0.00411114	0.010421	0.155646	0.6932	
SQUAM	1	0.39951807	0.394528	1.025458	0.3112	
SMALL	1	-0.1316886	0.425171	0.095934	0.7568	
ADENO	1	-0.8809291	0.513423	2.943954	0.0862	
TREAT	1	0.25698121	0.346468	0.550144	0.4583	
SCALE	1	0.87276657	0.115169			Extreme value scale parameter

Exponential Model

- Estimating the hazard rate

$$- \lambda = \frac{d}{(f+F)}$$

- d : Number of deaths
- f : total survival times who have died
- F : total follow-up times who have censored

- Assessing the exponential model

$$- \log(-\log S(t)) = \log \lambda + \log t \\ = a + b\chi$$

- $a = \log \lambda$
 $b = 1$
 $\chi = \log t$

- Confidence interval for λ

$$- \exp(L), \exp(U) \\ - L = \log(\lambda) - 1.96 SE(\log \lambda) \\ U = \log(\lambda) + 1.96 SE(\log \lambda) \\ SE(\log \lambda) = \frac{1}{d}$$

Weibull Model

- Estimation

- Use Maximum likelihood estimation

- Graphical methods

$$- \log(-\log S(t)) = k \log \lambda + k \log t \\ = a + b\chi$$

- $a = k \log \lambda$
 $b = k$
 $\chi = \log t$

4.3 준모수적 회귀분석모형

가. 비례위험모형(proportional hazard model)

- multiplicative effect

- $h(t|x) = h_0(t) \exp(x\beta)$

$h_0(t)$: baseline hazard function

x: covariate

β : regression parameter

나. 준모수적 비례위험모형(semi-parametric proportional hazard model)

$h_0(t)$: nonparametric hazard function

다. 비례위험 회귀모형에서 회귀계수의 해석

$$\begin{aligned} \frac{h(t, X_k = x+1)}{h(t, X_k = x)} &= \frac{h_0(t) \exp(b_1 X_1 + \dots + b_k(x+1) + \dots + b_p X_p)}{h_0(t) \exp(b_1 X_1 + \dots + b_k(x) + \dots + b_p X_p)} \\ &= \exp(b_k) \end{aligned}$$

다른 독립변수가 일정할때 X_k 가 1 단위 증가하면 사망할 상대위험도는 $\exp(b_k)$ 증가한다.

라. an example

<SAS program>

```
proc phreg data=lung;  
    model days*status(0)=perform age mondiag squam small adeno treat;  
run;
```

<SAS output>

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The PHREG Procedure

Data Set: WORK.LUNG
Dependent Variable: DAYS
Censoring Variable: STATUS
Censoring Value(s): 0
Ties Handling: BRESLOW

Summary of the Number of
Event and Censored Values

Total	Event	Censored	Percent Censored
40	37	3	7.50

Testing Global Null Hypothesis: BETA=0

Criterion	Without Covariates	With Covariates	Model Chi-Square
-2 LOG L Score	204.801	175.776	29.026 with 7 DF (p=0.0001) 30.138 with 7 DF (p=0.0001)
Wald	.	.	25.664 with 7 DF (p=0.0006)

Analysis of Maximum Likelihood Estimates

Variable	DF	Parameter Estimate	Standard Error	Wald Chi-Square	Pr > Chi-Square	Risk Ratio
PERFORM	1	-0.058459	0.01368	18.25079	0.0001	0.943
AGE	1	-0.013052	0.02058	0.40221	0.5260	0.987
MONDIAG	1	0.000762	0.01182	0.00415	0.9486	1.001
SQUAM	1	-0.367046	0.48477	0.57328	0.4490	0.693
SMALL	1	-0.007721	0.50675	0.0002321	0.9878	0.992
ADENO	1	1.112940	0.63306	3.09069	0.0787	3.043
TREAT	1	-0.379709	0.40580	0.87554	0.3494	0.684

Binary variables

$$\lambda(t) = \lambda_0(t) \exp(\beta x)$$

•

$$x = \begin{cases} 0 \\ 1 \end{cases}$$

• Relative hazard

$$HR = \frac{\lambda(t|x=1)}{\lambda(t|x=0)} = \exp(\beta)$$

Continuous variables

• x = continuous variable

$$HR = \frac{h(t|x_1)}{h(t|x_0)} = \exp(\beta(x_1 - x_0))$$

• Hazard ratio from the mean

$$HR = \frac{h(t|x)}{h(t|\bar{x})} = \exp(\beta(x - \bar{x}))$$

Selecting variables within a Cox Model

1. Step-up selection

- (1) start with the null model : $L_{(0)}$
- (2) Select $\chi_{(1)}$ with likelihood ratio test comparing $L_{(1)} - L_{(0)}$ for *each* $\chi_{(i)}$
- (2) Select $\chi_{(2)}$ with likelihood ratio test comparing $L_{(2)} - L_{(1)}$ for *each* $\chi_{(i)}$

2. Step-down selection

- 1) Start with the full model : $L_{(F)}$
- 2) Remove $\chi_{(1)}$ with likelihood ratio test comparing $L_{(F)} - L_{(-1)}$
- 2) Remove $\chi_{(2)}$ with likelihood ratio test comparing $L_{(-1)} - L_{(-2)}$

3. All possible combinations

- (1) Compute the null model : $L_{(0)}$
- (2) Compute all possible model and compare the null model with likelihood ratio test

Time -dependent covariates

- Fixed and updated covariates
 - fixed : single point in time
 - updated : updated with time
- Cox model
 - $h(t) = h_0(t) \exp(\beta\chi + \gamma z(t))$
 - χ : fixed covariates
 - $z(t)$: time dependent covariates

Binary variables

- Fixed covariate only
 - $x : h = \exp(\beta\chi)$
 - $x=0$ or $1 \Rightarrow h = \exp(\beta)$
 - x : baseline value
- Time - dependent covariate only
 - $z(t) : h(t) = \exp(\gamma z(t))$
 - $z(t) = 0$ or $1 \Rightarrow h = \exp(\gamma)$
 - $z(t)$: value during follow-up period
- Fixed and time-dependent covariate
 - $x + z(t) : h(t) = \exp(\beta\chi + \gamma z(t))$
 - $x = 0$ or $1, z(t) = 0$ or $1 \Rightarrow h = \exp(\beta + \gamma)$

Categorical variables

- Ordered categorical variables
- Not ordered variables

Continuous variables

- Mean value of time-dependent covariates
- Transformation method : log