Chinese Journal of Cancer Research 8(1):72-78, 1996.

A MICROCOMPUTER PROGRAM FOR CALCULATING THE CONFIDENCE INTERVALS OF SURVIVAL PROBABILITY IN MEDICAL FOLLOW-UP STUDIES

Xiang Yongbing 项永兵 Gao Yutang 高玉堂 Jin Fan 金凡

Department of Epidemiology, Shanghai Cancer Institute, Shanghai 200032

In cancer survival analysis, it is very frequently to estimate the confidence intervals for survival probabilities. But this calculation is not commonly involve in most popular computer packages, or only one methods of estimation in the packages. In the present paper, we will describe a microcomputer program for estimating the confidence intervals of survival probabilities, when the survival functions are estimated using Kaplan-Meier product-limit or life-table method. There are five methods of estimation in the program (SPCI), which are the classical (based on Greenwood's formula of variance of $S(t_i)$), Rothman-Wilson, arcsin transformation, log(-log) transformation, logit transformation methods. Two example analysis are given for testing the performances of the program running.

Key words: Survival analysis, Confidence intervals; Kaplan-Meier estimator, Life-table estimator, Microcomputer, BASIC.

In medical follow-up studies on cancer or other chronic diseases, it is very frequently to estimate the survival probabilities, or median survival times at a specified time t, and also often to estimate their confidence intervals.[1-8] The nonparametric methods to estimate the confidence intervals or limits of survival probabilities with censored observations have been developed by many authors.[1-8] Afifi, Elashoff and Lee[8] have recently provided a very excellent review of methods on the estimation of nonparametric confidence intervals for survival probabilities.

In this paper, we developed a microcomputer program for calculating the confidence intervals of survival probabilities, according to the methods of survival function estimation (Kaplan-Meier product-limit or life-table estimator). In the most popular computer packages which have the procedure on survival analysis, there are only one method or not the function or procedure to estimate the confidence intervals and frequently give the estimations of standard errors for survival probabilities. In our program (SPCI) there are five methods of estimating confidence intervals, except for the two simultaneous confidence intervals of Hall and Wellner[9] and Nair[10] which seldomly used in practice.

In the next section, we will give a short review on the methods of estimating the confidence intervals for survival probabilities. Program description in section 3. Two examples analysis are presented in section 4. In section 5 we discuss the performance of the five methods in estimation of confidence intervals, and the results of our two examples.

MATERIALS AND METHODS

Consider n individuals in the sample, let $S(t_i)$ be the cumulative probabilities of the Kaplan-Meier product-limit or life-table estimator of $S(t_i)$, and Var $[S(t_i)]$ be the variance estimator based on Greenwood formula.[11] Also let the follow-up time scales be $t_1,\ldots,$

Accepted April 7, 1995

t_m, $Z_{a/2}$ be the upper $(1-a/2)$th standard normal quantile. When $S(t_i)$ was estimated by using life-table method, the follow-up time (t_i) was often divided into several groups or intervals. We will describe it in detail later.

Non-transformation Methods

Method 1 —— Classical method, or Greenwood confidence intervals: The Greenwood confidence intervals for $S(t_i)$ at the time scale of i=1, ..., m are

$$\hat{S}(t_i) \pm Z_{a/2} \cdot \sqrt{\hat{Var}[\hat{S}(t_i)]}, \quad i=1, 2, \ldots, m.$$

Method 2 —— Rothman-Wilson confidence intervals: Rothman[12] proposed an alternative method for confidence intervals, also using Greenwood's formula,[11] and no transformation. He first derive the so-called 'effective sample size' as the same way described by Cutler and Ederer,[13] then use the survival probabilities $S(t_i)$ and the 'effective sample size' N' to construct the confidence intervals provided that $N'S(t_i)$ has a binomial distribution. The confidence bands become

$$\frac{N'}{N'+Z^2_{a/2}}\left[\hat{S}(t_i)+\frac{Z^2_{a/2}}{2N'}+Z_{a/2}\cdot\sqrt{\frac{\hat{S}(t_i)\cdot[1-\hat{S}(t_i)]}{N'}+\frac{Z^2_{a/2}}{4N'^2}}\right],$$

in which, the 'effective sample size' may calculate from

$$N'=\frac{\hat{S}(t_i)\cdot[1-\hat{S}(t_i)]}{\hat{Var}\,\hat{S}(t_i)}$$

Transformation Methods

The confidence intervals of $S(t_i)$ may be constructed by the use of some large-sample distributions, such as the arcsin, log(-log) and logit transformations of the $S(t_i)$. According to the papers of Anderson, Bernstein and Pike,[2] Afifi, Elashoff and Lee,[8] and under these transformations the confidence intervals based on the 'effective sample size' approach are as follows.

Method 3 —— Arcsin transformation intervals: The approximate 100(1−a)% confidence intervals are

$$\sin^2\left\{\arcsin\left[\sqrt{\hat{S}(t_i)}\right] \pm \frac{Z_{a/2}}{\sqrt{4N'}}\right\}.$$

where the N' is as the same of method 2.

Method 4 —— Log(-log) transformation intervals: The approximate 100(1−a)% confidence intervals are

$$\exp[-\exp(A \pm Z_{a/2}\cdot B)]$$

where

$$A=\log[-\log\hat{S}(t_i)],$$

$$B=\frac{\sqrt{\hat{Var}[\hat{S}(t_i)]}}{\hat{S}(t_i)}\cdot[\log\hat{S}(t_i)].$$

Method 5 — Logit transformation intervals: Under the logit transformation, it yield the lower and upper intervals for $S(t_i)$ of

$$\frac{\hat{S}(t_i)}{(1-F)\cdot\hat{S}(t_i)+F} - \frac{F\cdot\hat{S}(t_i)}{(F-1)\cdot\hat{S}(t_i)+1},$$

where

$$F=\exp\left[\frac{Z_{a/2}}{\sqrt{N'\cdot\hat{S}(t_i)\cdot(1-\hat{S}(t_i))}}\right].$$

in which N' is also the same as method 2.

Progrom Description

Program and Requirement

The program (SPCI.BAS) was written in IBM personal computer BASIC (version 3.20) language, and the executable file (SPCI.EXE) was then generated using any IBM personal computer BASIC compiler program.

The source program consists of 150 lines and the executable file requires about 25 kb of disk storage. The program can run on any IBM microcomputers or its compatible with the version of Disk Operation System (DOS) 3.20. No special requirement for the hardware of computer. There are three fixed levels of intervals in the program, they are 90%, 95% and 99%. If to calculate other levels of confidence intervals, one can easily modify the source program for adding any other confidence levels.

Input

Table 1 is the screen style of the program input, the user can select the methods of estimating of survival probabilities (Kaplan-Meier or Life-table), and the confidence levels to estimate. The row data has a fixed file name (KM.DAT or LT.OUT) used by program. Table 2 is an example of data file including the risk number at the each time t_i and the number of failure in time interval (t_i, t_{i+1}). The format of input data file must be a standard ASCII text file, only has two columns of risk and failure number of patients for Kaplan-Meier estimator of $S(t_i)$, or three columns of risk, failure and censored number of patients for life-table estimator of $S(t_i)$.

Table 1. Screen input style of the program SPCI

```
A>SPCI [enter]
  Please select:
    Kaplan-Meier or Life-table estimator (K or L)? K
    Levels of confidence (1–90%, 2–95%, 3–99%)? 2
  Running ......
```

Output

Computational results are written to the fixed file name of KMCI.OUT or LTCI.OUT (ASCII file), and automatically type the results to the printer by the program. The output contains the columns of row data and the approximate (1−a)% confidence intervals estimated from five methods described above.

Table 2. Data format or structure of input for Kaplan-Meier estimator (example)

21	3
17	1
15	1
12	1
11	1
7	1
6	1

Note: If for life-table method, another column of censored number required

RESULTS

In this section we present the analysis of two examples to illustrate the performances of the program SPCI with the data taken from medical follow-up studies.

Data from Clinical Trials (Small Sample Size)

In the clinical trial for investigating the effective of 6-mercaptopurine (6-MP) in the treatment of leukemia patients conducted by Freireich, et al.,[14] some patients serving as treatment group and others as a control. There are 21 patients in each group. Treatment allocation of this clinical trial was randomized. Table 3 display the row data sets on times of remission of the patients.

Table 3. Times of remission (weeks) for leukemia patients (from Freireich, et al.)

Treatment (6-MP)	6^+, 6, 6, 6, 7, 9^+, 10^+, 10, 11^+, 13, 16, 17^+, 19^+, 20^+, 22, 23, 25^+, 32^+, 32^+, 34^+, 35^+
Control group	1, 1, 2, 2, 3, 4, 4, 5, 5, 8, 8, 8, 8, 11, 11, 12, 12, 15, 17, 22, 23

$^+$ censored observations

The Kaplan-Meier produce-limit method was used to estimate the cumulative survival probabilities $S(t_i)$ at each special time t_i. The Kaplan-Meier estimator of $S(t_i)$ is of the form

$$\hat{S}_{KM}(t_i) = \Pi \left[\frac{n(t_i) - d(t_i)}{n(t_i)} \right],$$

and its variance of

$$\hat{SE}_{KM}(t_i) = \hat{S}_{KM}(t_i) \cdot \sqrt{\Sigma \frac{1-\hat{S}(t_i)}{n(t_i) - d(t_i)}}$$

where $S(t_i)$ is the time point estimators of survival probabilities. Table 4, 5 show the results of the Kaplan-Meier estimators of two groups.

Using our program, one can very easily to calculate the confidence intervals for survival probabilities. Table 6, 7 are the five results of 95% confidence intervals for the cumulative survival curve of two patient groups at each time (death time) point.

Data from Cancer Registry (Large Scale Follow-up Studies)

In large medical follow-up studies, especially for cancer registry the life table analysis[13] is an efficient method for estimating the survival probabilities and its confidence intervals. The times of follow-up are often divided into several groups or intervals, frequently using year as one time interval. If the prognosis or survival experience of patients is poor, the month, half of year, etc. can be used as one time interval. It is well known that censored survival data can be handled in the life table analysis using the adjusted number of risk to replace the risk number of patients in estimating survival probabilities. In medical follow-up studies, the censored data include two parts of patients who lost to follow-up and are still alive at the end of follow-up.

The estimator of life-table method has the form of

$$\hat{S}_{LT}(ti) = \Pi \left[1- \frac{d(t_i)}{n(t_i) - \frac{w(t_i)}{2}} \right],$$

and its variance formula is

$$\hat{SE}_{LT}(t_i) = \hat{S}(t_i) \cdot \sqrt{\Sigma \frac{1-\hat{S}(t_i)}{[1-\hat{S}(t_i)] \cdot [n(t_i) - \frac{w(t_i)}{2}]}},$$

in which the definition of $S(t_i)$ as before.

The sample data is the follow-up data on male stomach cancer diagnosed during 1972 to 1976 in Shanghai Urban collected from Shanghai Cancer Registry. The closing date is the end of 1987. The results of life-table analysis are displayed in Table 8. Table 9 is the output of analysis using our program SPCI for this sample data.

Table 4. Kaplan-Meier product-limit estimators for treatment group

Time i-	Risk number n (t_i)	Failure number d (t_i)	Point probabilities s(t_i)	Cumulative probabilities S(t_i)	Standard errors SE(t_i)
6-	21	3	0.8571	0.8571	0.0764
7-	17	1	0.9421	0.8075	0.0869
10-	15	1	0.9333	0.7536	0.0963
13-	12	1	0.9167	0.6908	0.1068
16-	11	1	0.9091	0.6280	0.1141
22-	7	1	0.8571	0.5383	0.1282
23-	6	1	0.8333	0.4486	0.1346

Note: The estimators are only for failure times.

Table 5. Kaplan-Meier product-limit estimators for control group

Time i-	Risk number $n(t_i)$	Failure number $d(t_i)$	Point probabilities $s(t_i)$	Cumulative probabilities $S(t_i)$	Standard errors $SE(t_i)$
1-	21	2	0.9048	0.9048	0.0641
2-	19	2	0.8947	0.8095	0.0857
3-	17	1	0.9412	0.7619	0.0929
4-	16	2	0.8750	0.6667	0.1029
5-	14	2	0.8571	0.5714	0.1080
8-	12	4	0.6667	0.3810	0.1060
11-	8	2	0.7500	0.2857	0.0986
12-	6	2	0.6667	0.1905	0.0857
15-	4	1	0.7500	0.1429	0.0764
17-	3	1	0.6667	0.0952	0.0641
22-	2	1	0.5000	0.0476	0.0465
23-	1	1	0.0000	0.0000	0.0000

Note: The same as Table 4

Table 6. Estimators of 95% confidence intervals for cumulative survival probabilities for treatment group of Table 4

Time	Method 1		Method 2		Method 3		Method 4		Method 5	
i-	lower	upper	lower	upper	lower	upper	lower	upper	lower	upper
6-	0.7075	1.0068	0.6639	0.9400	0.8383	0.8750	0.6197	0.9516	0.6386	0.9532
7-	0.6363	0.9771	0.6044	0.9128	0.7795	0.8326	0.5631	0.9228	0.5832	0.9256
10-	0.5641	0.9418	0.5437	0.8808	0.7170	0.7872	0.5032	0.8894	0.5248	0.8937
13-	0.4808	0.8996	0.4738	0.8419	0.6446	0.7340	0.4316	0.8491	0.4556	0.8557
16-	0.4039	0.8510	0.4104	0.7996	0.5746	0.6789	0.3675	0.8049	0.3929	0.8142
22-	0.2865	0.7892	0.3171	0.7432	0.4752	0.5998	0.2678	0.7468	0.2974	0.7618
23-	0.1844	0.7120	0.2393	0.6799	0.3836	0.5137	0.1880	0.6801	0.2185	0.7024

Table 7. Estimators of 95% confidence intervals for cumulative survival probabilities for control group of Table 5

Time	Method 1		Method 2		Method 4		Method 3		Method 5	
i-	lower	upper	lower	upper	lower	upper	lower	upper	lower	upper
1-	0.7792	1.0303	0.7225	0.9518	0.8937	0.9153	0.6700	0.9753	0.6887	0.9761
2-	0.6414	0.9775	0.6093	0.9140	0.7830	0.8347	0.5689	0.9239	0.5885	0.9266
3-	0.5797	0.9441	0.5578	0.8850	0.7281	0.7941	0.5194	0.8933	0.5397	0.8973
4-	0.4650	0.8683	0.4617	0.8201	0.6212	0.7107	0.4253	0.8250	0.4467	0.8321
5-	0.3598	0.7831	0.3731	0.7476	0.5193	0.6228	0.3380	0.7492	0.3597	0.7599
8-	0.1732	0.5887	0.2153	0.5834	0.3327	0.4305	0.1831	0.5778	0.2032	0.5975
11-	0.0925	0.4789	0.1464	0.4913	0.2471	0.3259	0.1166	0.4818	0.1343	0.5076
12-	0.0225	0.3584	0.0860	0.3907	0.1653	0.2170	0.0595	0.3774	0.0734	0.4115
15-	-0.0068	0.2925	0.0600	0.3361	0.1250	0.1617	0.0357	0.3212	0.0468	0.3614
17-	-0.0303	0.2208	0.0382	0.2775	0.0847	0.1063	0.0163	0.2613	0.0239	0.3113
22-	-0.0435	0.1387	0.0228	0.2123	0.0436	0.0518	0.0033	0.1970	0.0067	0.2714
23-	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000

Table 8. Results of life-table analysis of follow-up data on male stomach cancer diagnosed during 1972 to 1976 in Shanghia Urban

Time (year) i-	Risk no. $n(t_i)$	Failure no. $d(t_i)$	censored no. $w(t_i)$	Adjusted no. $n'(t_i)$	Interval probabilities $S(t_i)$	Cumulative probabilities $S(t_i)$
0-	8287	3125	1	8286.5	0.62288	0.62288
1-	5161	2857	0	5161.0	0.44643	0.27807
2-	2304	843	1	2303.5	0.63404	0.17631
3-	1460	379	0	1460.0	0.74041	0.13054
4-	1081	186	0	1081.0	0.82794	0.10808
5-	895	122	0	895.0	0.86369	0.09335
6-	773	89	0	773.0	0.88486	0.08260
7-	684	57	1	683.5	0.91661	0.07571
8-	626	38	0	626.0	0.93930	0.07111
9-	588	28	1	587.5	0.95234	0.06772

Note: The standard errors are not listed.

Table 9. Results of 95% confidence intervals for survival of male stomach cancer diagnosed during 1972 to 1976 in Shanghai Urban

Time	Method 1		Method 2		Method 3		Method 4		Method 5	
i-	lower	upper	lower	upper	lower	upper	lower	upper	lower	upper
0-	0.6124	0.6333	0.6184	0.6333	0.6204	0.6253	0.6123	0.6332	0.6124	0.6333
1-	0.2684	0.2877	0.2685	0.2878	0.2761	0.2800	0.2685	0.2878	0.2685	0.2878
2-	0.1681	0.1845	0.1683	0.1847	0.1751	0.1775	0.1682	0.1846	0.1682	0.1847
3-	0.1233	0.1378	0.1235	0.1380	0.1297	0.1314	0.1234	0.1379	0.1235	0.1380
4-	0.1014	0.1148	0.1016	0.1149	0.1074	0.1087	0.1015	0.1149	0.1016	0.1149
5-	0.0871	0.0996	0.0873	0.0998	0.0928	0.0939	0.0872	0.0997	0.0873	0.0998
6-	0.0767	0.0885	0.0769	0.0887	0.0821	0.0830	0.0768	0.0887	0.0769	0.0887
7-	0.0700	0.0814	0.0702	0.0816	0.0753	0.0761	0.0701	0.0815	0.0702	0.0816
8-	0.0656	0.0766	0.0658	0.0768	0.0707	0.0715	0.0657	0.0768	0.0658	0.0769
9-	0.0623	0.0731	0.0625	0.0733	0.0674	0.0681	0.0624	0.0733	0.0625	0.0733

DISCUSSION

To estimate the confidence intervals (limits or bands) for survival probabilities is commonly used in data analysis from medical follow-up studies. But there are only one method or not the function of the interval estimation of survival rates in most computer software or package which have the procedure on survival analysis. Our program SPCI is a simple microcomputer program in BASIC for calculating the intervals for survival probabilities, including five methods of estimation.

Several authors have investigated the behaviour of the methods for estimating the intervals of survival probabilities. Their simulation results indicate that when the number of sample size or observed events (deaths) increase, all the methods of computing confidence intervals behave well at the value of $S(t_i)$ given in the simulation studies. As indicated by these authors, methods 2, 4 and 5 give consistently better performances than do the methods 1 and 3, particularly for method 1. Methods 2, 4 and 5 are similar in terms of their coverage probabilities in small samples, but the coverage probabilities for method 1 is too wide and for method 3 is narrow.

In the first example of our analysis, the sample size is 42, and each group has 21 patients. As a small scale sample clinical trial it is used in our example. The results of 95% confidence intervals using methods 2, 4 and 5 are very similar. The bands using method 1 are widely large, and some of the intervals exceed 1.0 or is negative value. These results are not we expected. The bands using method 3 are too narrow than that of other methods. For a large sample follow-up study of our second example, the results of method 1 are too closer to the that of method 2, 4 and 5, but the results from method 3 also has narrow coverage probabilities.

From our experience in estimating the confidence intervals for survival probabilities, we recommend that one can use one of methods 2,4, and 5 to calculating the intervals in medical follow-up studies from small to large sample size.

Program Availability: The program SPCI is available on a standard 5-inch (360 kb or 1.2M) or 3.5-inch (1.44 M)double-sided, formatted diskette. Copies of executable program or source list will be provided on request.

REFERENCES

1. Brookmeyer R, Crowley J. A confidence interval for the median survival time. Biometrics 1982; 38:29.
2. Anderson JR, Bernstein L, Pike MC. Approximate confidence interval for probabilities of survival and quantiles in life-table analysis. Biometrics 1982; 38: 407.
3. Emerson JD. Nonparametric confidence intervals for the median in the presence of right censoring. Biometrics 1982; 38:17.
4. Slud EV, Byar DP, Green SB. A comparison of reflected versus test-based confidence intervals for the median survival time, based on censored data. Biometrics 1984; 40:587.
5. Elashoff RM, Lee JJ, Afifi AA. A note on confidence limits for quantiles with right censored data. Stat Med 1989; 8:1269.
6. Simon R, Lee YJ. Nonparametric confidence limits for survival probabilities and median survival time. Cancer Treatment Reports 1982; 66:37.
7. Breslow N, Crowley J. A large sample study of the life table and product limit estimates under random censorship. The Annals of Statistics 1974; 2:437.
8. Afifi AA, Elashoff RM, Lee JJ. Simultaneous nonparametric confidence intervals for survival probabilities from censored data. Stat Med 1986; 5:653.
9. Hall WJ, Wellner JA.. Confidence bands for a survival curve from censored data. Biometrika 1980; 67:133.
10. Nair VN. Confidence bands for survival functions with censored data: a comparative study. Technometrics 1984; 26:265.
11. Greenwood M. 'The error of sampling of the survivorship tables', Reports on Public and Medical Subjects, No. 33, Appendix I. London: H.M. Stationery Office. 1926.
12. Rothman KJ. Estimation of confidence limits for the cumulative probability of survival in life table analysis. J Chron Dis 1978; 31:557.
13. Cutler SJ, Ederer F. Maximum utilization of the life table method in analyzing survival. J Chron Dis 1958; 8:699.
14. Freireich EL, et al. The effect of 6-mercaptopurine on the duration of steroid-induced in acute leukemia. Blood 1963; 21:699.