

Chapter 12. Analysis of survival

D.M. Parkin¹ and T. Hakulinen²

¹*International Agency for Research on Cancer,
150 cours Albert Thomas, 69372 Lyon Cédex 08, France*

²*Finnish Cancer Registry, Liisankatu 21B, 00170 Helsinki, Finland*

Introduction

Population-based cancer registries collect information on all cancer cases in defined areas. The survival rates for different cancers calculated from such data will therefore represent the average prognosis in the population and provide, theoretically at least, an objective index of the effectiveness of cancer care in the region concerned. By contrast, hospital registries are generally concerned with the outcome for patients treated in a single institution, and may in fact be called upon to evaluate the effectiveness of different therapies.

This chapter is mainly concerned with describing the methods of calculating survival for population-based data. However, the analytical methods apply equally to hospital data, and can be used to describe the experience of any group of cancer patients. It should be noted that a descriptive analysis of survival is not, however, sufficient for evaluating the effectiveness of different forms of treatment, which can only be determined by a properly conducted clinical trial.

Case definition

The first stage in survival analysis is to define clearly the group(s) of patients registered for whom calculations are to be made. These will generally be defined in terms of:

- cancer type (site and/or histology)
- period of diagnosis
- sex
- stage of disease

Stage of disease will generally be presented in rather coarse categories—a maximum of four—and derived from the clinical evaluation (see Chapter 6, item 23) or surgical–pathological (Chapter 6, item 24) evaluation. Results may be expressed by age group, race, treatment modality etc.

A population-based registry should confine analysis of survival to those cases who are residents of the registry area, since patients migrating into the area for treatment

purposes will probably be an atypical subgroup with a rather different survival experience from the average.

The nature of the cases to be included should also be defined—for example, a decision must be taken on whether to include cases for which the most valid basis of diagnosis is on clinical grounds alone. A particular problem arises with the cases registered on the basis of a death certificate only (DCO), for whom no further information was available on the date of diagnosis of the cancer (for such cases, the recorded incidence date (Chapter 6, item 16) is necessarily the same as the date of death, and such cases would be deemed to have a survival of zero). An analogous problem is that of cases diagnosed for the first time at autopsy.

Hanai and Fujimoto (1985) have discussed this problem. When a proportion of cases are registered as DCO, it can be assumed that an equivalent number of cases have escaped registration at the time of diagnosis but, being cured (or at least, still alive), have not been included in the registry data. If this assumption is true, inclusion of such cases would result in computed survival rates being lower than true survival, owing to the inclusion of an excess of fatal cases in the registry data-base. Furthermore, since the incidence date (Chapter 6, item 16) and date of death (item 32) are the same, duration of survival is considered to be zero. In computation of cumulative survival by the life-table method (see below), such individuals are included with persons surviving less than one year, and the one-year survival rate is artificially reduced. However, if such cases comprise a substantial proportion of the total cases registered, their exclusion from population-based data means that survival no longer reflects average prognosis of incident cancer in the community.

When duration of disease is recorded on the death certificate, this might be used to fix the date of diagnosis (or incidence date); in such circumstances DCO cases should be included. Otherwise the choice is arbitrary. The most usual practice is to omit DCO cases, but this is probably because most published work on survival derives from registries with quite a small proportion of such cases. An alternative solution is to report two survival rates—one for incident cases including DCO cases, and the other for reported cases excluding DCO cases. In any case, the proportion of DCO cases should be stated in the survival report.

Definition of starting date

For the population-based registry, the starting date (from which the survival is calculated) is the incidence date (Chapter 6, item 16). For hospital registries, the date of admission to hospital would be used. Where survival is being used to measure the end results of treatment, date of onset of therapy might be appropriate. In clinical trials where the end results of treatment are compared, the date of randomization should be used (Peto *et al.*, 1976, 1977).

Follow-up

To calculate survival, registered cases must be followed up to assess whether the patients are alive or dead.

Passive follow-up

This relies upon the notification of the deaths of registered patients using the death certificate file for the region. Collation of the two files—the death certificate file from vital statistics and the registry file of registered cases—is performed either in the cancer registry or in the local or national department of vital statistics. In the matching process, national index numbers (if available) or a combination of several indices, such as name, date of birth and address, are used for patient identification.

In passive follow-up, any registered cancer patient whose death has not been notified to the registry by the department of vital statistics (in other words, all unmatched cases) is considered to be surviving. The result of passive follow-up may, therefore, be an overestimate of the true survival rate: the size of the error is due both to the accuracy of the matching process and to the emigration of registered cancer cases elsewhere. It is occasionally possible to have access to a file of registered emigrants (e.g., in Finland), so that such persons can be excluded from the list of those under follow-up.

Active follow-up

Some regional (population-based) cancer registries in North America collect follow-up information from each reporting hospital cancer registry; these in turn conduct annual follow-up surveys of registered cancer cases through the patient's own doctor. This kind of survey is termed a 'medical follow-up'. With this kind of follow-up, the quality as well as duration of survival may be assessed.

Most population-based cancer registries elsewhere do not have a follow-up system for individuals, but they may use surveys or registries set up for other purposes to indirectly determine the patient's survival or death. Many registries therefore use sources such as a population register (city directory), a comprehensive register for a national health service, a health insurance or social security register, electoral lists, driving licence register etc. These techniques may also be used to trace the fate of cases lost during medical follow-up.

Active follow-up will reveal a number of patients who cannot be traced, and whose vital status is unknown. When calculating survival by the actuarial method (see below), one assumes that such patients were alive and present in the region (and therefore part of the population at risk) for exactly half the period since they were last traced. However, it is likely that most of them are still alive (if they had died, the registry would hear of them via a death certificate); the result will generally be to bias survival rates downwards, so that they underestimate the true rates. Patients lost to follow-up should be kept to a minimum.

Survival intervals

Survival can be expressed in terms of the percentage of those cases alive at the starting date who were still alive after a specified interval. The choice of interval is arbitrary, and the most appropriate will depend upon the prognosis of the cancer concerned. In interpreting survival rates, the number of individuals entering a survival interval should also be taken into account. Survival rates probably should not be published for

intervals in which fewer than 10 patients enter the interval alive, because of instability of the resulting estimates.

The methods described in this chapter permit description of the entire survival experience of a group of cancer patients. Potential users of the methodology should be encouraged to examine survival at more than one point in time. It should be noted that the five-year rate has conventionally been used as an index for comparing survival across groups of patients by site, sex etc. and is often taken as a measure of cure rate. There is, however, evidence that with many cancer sites the period of five years is too short for this purpose (Hakulinen *et al.*, 1981).

Calculation of survival rates

The following section has been modified from the booklet *Reporting of Cancer Survival and End Results 1982*, published by the American Joint Committee on Cancer.

Cancer registries will usually wish to calculate survival of cases registered in a period of several years before a given date. In the examples below, the principles are illustrated for a very small group of patients (50) diagnosed with melanoma in a 15-year period up to 1 June 1985. Survival of these patients will be assessed on the basis of follow-up information available until the end of 1987, that is, the closing date of the study is 31 December 1987. Table 1 gives the basic data required.

Table 1. Data on 50 patients with melanoma

Patient number	Sex	Age	Date of diagnosis (month/year)	Last contact			Complete years lived since diagnosis
				Date (month/year)	Vital status ^a	Cause of death ^b	
1	M	63	10/70	10/70	D	M	0
2	M	42	7/72	1/78	D	O	5
3	M	41	3/73	4/73	D	M	0
4	F	57	6/73	7/74	D	M	1
5	M	35	9/73	10/87	A	—	14
6	F	48	10/73	8/74	D	M	0
7	M	43	4/74	2/77	D	M	2
8	F	27	1/75	1/75	D	M	0
9	F	56	12/76	10/87	A	—	10
10	F	33	1/77	11/87	A	—	10
11	F	37	4/77	4/87	A	—	10
12	F	58	9/77	8/87	A	—	9
13	M	21	2/78	5/78	D	O	0
14	M	71	2/78	11/86	A	—	8
15	F	66	6/79	8/79	D	M	0
16	F	35	7/79	12/87	A	—	8
17	F	31	10/79	11/87	A	—	8
18	M	35	3/80	6/87	A	—	7
19	F	44	4/80	7/87	A	—	7
20	M	26	4/80	10/87	A	—	7
21	M	57	10/80	6/81	D	M	0
22	M	54	12/80	2/81	D	M	0
23	M	63	1/81	1/82	D	M	1
24	F	32	1/81	10/83	D	M	2

Table 1 — continued

Patient number	Sex	Age	Date of diagnosis (month/year)	Last contact			Complete years lived since diagnosis
				Date (month/year)	Vital status ^a	Cause of death ^b	
25	F	43	4/81	2/87	A	—	5
26	F	76	7/81	2/86	D	M	4
27	M	31	9/81	11/87	A	—	6
28	M	77	11/81	2/87	A	—	5
29	F	59	11/81	4/87	A	—	5
30	F	76	12/81	9/87	A	—	5
31	M	39	3/82	8/85	D	M	3
32	F	50	7/82	4/87	A	—	4
33	F	38	10/82	6/87	D	M	4
34	F	82	3/83	12/87	A	—	4
35	M	65	4/83	7/83	D	M	0
36	M	40	4/83	10/87	A	—	4
37	M	22	6/83	2/87	A	—	3
38	F	25	1/84	11/87	A	—	3
39	M	33	4/84	11/87	A	—	3
40	F	51	5/84	7/87	A	—	3
41	F	40	7/84	11/87	A	—	3
42	M	70	9/84	9/85	D	O	1
43	M	47	9/84	12/85	D	M	1
44	M	67	10/84	4/86	D	O	1
45	F	58	1/85	8/87	A	—	2
46	M	75	1/85	10/87	A	—	2
47	M	40	4/85	7/87	A	—	2
48	F	35	4/85	7/87	A	—	2
49	F	49	5/85	12/86	D	M	1
50	F	21	6/85	3/87	A	—	1

^a A, alive; D, dead ^b M, melanoma; O, other

Calculation by the direct method

The simplest way of summarizing patient survival is to calculate the percentage of patients alive at the end of a specified interval such as five years, using for this purpose only patients exposed to the risk of dying for at least five years. This approach is known as the direct method.

The set of data in Table 1 indicates that there were contacts with patients during 1987, but these contacts occurred during different months of the year. It is known that all patients last contacted in 1987 were alive on 31 December 1986, but it is not known whether they were all alive at the end of 1987. Thus, 31 December 1986 will be designated the effective closing date of the study. This means that all those patients first treated on 1 January 1982 or later had not been at risk of dying for at least five years at the time of the closing date. Thus 20 of the 50 patients (numbers 31 to 50) must be excluded from the calculation by the direct method.

Examination of the entries in the 'Vital Status' column in Table 1 for the 30 patients at risk for at least five years, indicates that 16 patients were alive at last

contact and 14 had died before December 1982. However, one of these patients (No. 2) had lived five complete years before his death. Therefore, 17 of the 30 patients were alive five years after their respective dates of first treatment and, thus, the five-year survival rate is 57%.

Calculation by the actuarial method

The direct method for calculating a survival rate does not use all the information available. For example, the data indicate that patient No. 31 died in the fourth year after treatment was started and that patient No. 32 lived for more than four years. Such information should be useful, but it could not be used under the rules of the direct method because the patients were diagnosed after December 1981.

The actuarial, or life-table, method provides a means for using all the follow-up information accumulated up to the closing date of the study. The actuarial method has the further advantage of providing information on the survival pattern, that is, the manner in which the patient group was depleted during the total period of observation (Cutler & Ederer, 1958; Ederer *et al.*, 1961).

The methods described here are designed for the individual investigator who wants to analyse carefully the survival experience of a small series of patients—in this example, 50 patients. However, the same basic methodology is used in analysing large series with a computer (e.g., Hakulinen & Abeywickrama, 1985).

Observed survival rate

The life-table method for calculating a survival rate, using all the follow-up information available on the 50 patients under study, is illustrated in Table 2. There are six steps in preparing such a table.

(1) The vital status of the patients (alive or dead) and withdrawals in each year since diagnosis (from Table 1) are used for the entries in columns 3 and 4. The sum of the entries in columns 3 and 4 must equal the total number of patients. It should be noted that the 17 patients alive at the beginning of the last period since diagnosis in column 2 (five years and over) were also entered in column 4 (number last seen alive during year).

(2) The number of patients alive at the beginning of each year is entered in column 2 and is obtained by successive subtraction. Thus, of 50 patients diagnosed, nine died during the first year and 41 were alive one year after diagnosis. In the second interval, six died and one was withdrawn alive, leaving 34 patients under observation at the start of the third interval (two years after diagnosis).

(3) The effective number exposed to risk of dying (column 5) is based on the assumption that patients last seen alive during any year of follow-up were, on the average, observed for one-half of that year. Thus, for the third year the effective number is $34 - (1/2 \times 4) = 32.0$, and for the fourth year it is $28 - (1/2 \times 5) = 25.5$.

(4) The proportion dying during any year (column 6) is found by dividing the entry in column 3 by the entry in column 5. Thus, for the first year, the proportion dying is $9/50.0 = 0.180$ and for the second year it is $6/40.5 = 0.148$.

Table 2. Calculation of observed survival rate, and its standard error, by the actuarial (life-table) method

(1) Year after diagnosis	(2) No. alive at beginning of year	(3) No. dying during year	(4) No. last seen alive during year	(5) Effective no. exposed to risk of dying	(6) Proportion dying during year	(7) Proportion surviving year	(8) Proportion surviving from first treatment to end of year	(9) Entry (5) minus entry (3)	(10) Entry (6) divided by entry (9)
(i)	(l_i)	(d_i)	(w_i)	(r_i) ^a	(q_i) ^a	(p_i) ^a	(Πp_i)	($r_i - d_i$)	($\frac{q_i}{r_i - d_i}$)
0	50	9	0	50.0	0.180	0.820	0.820	41.0	0.0044
1	41	6	1	40.5	0.148	0.852	0.699	34.5	0.0043
2	34	2	4	32.0	0.063	0.937	0.655	30.0	0.0021
3	28	1	5	25.5	0.039	0.961	0.629	24.5	0.0016
4	22	2	3	20.5	0.098	0.902	0.567	18.5	0.0053
>5	17	—	17	—	—	—	—	—	—
Total		20	30						0.0177

^a Where $r_i = l_i - \frac{w_i}{2}$

$$q_i = d_i / r_i$$

$$p_i = 1 - q_i$$

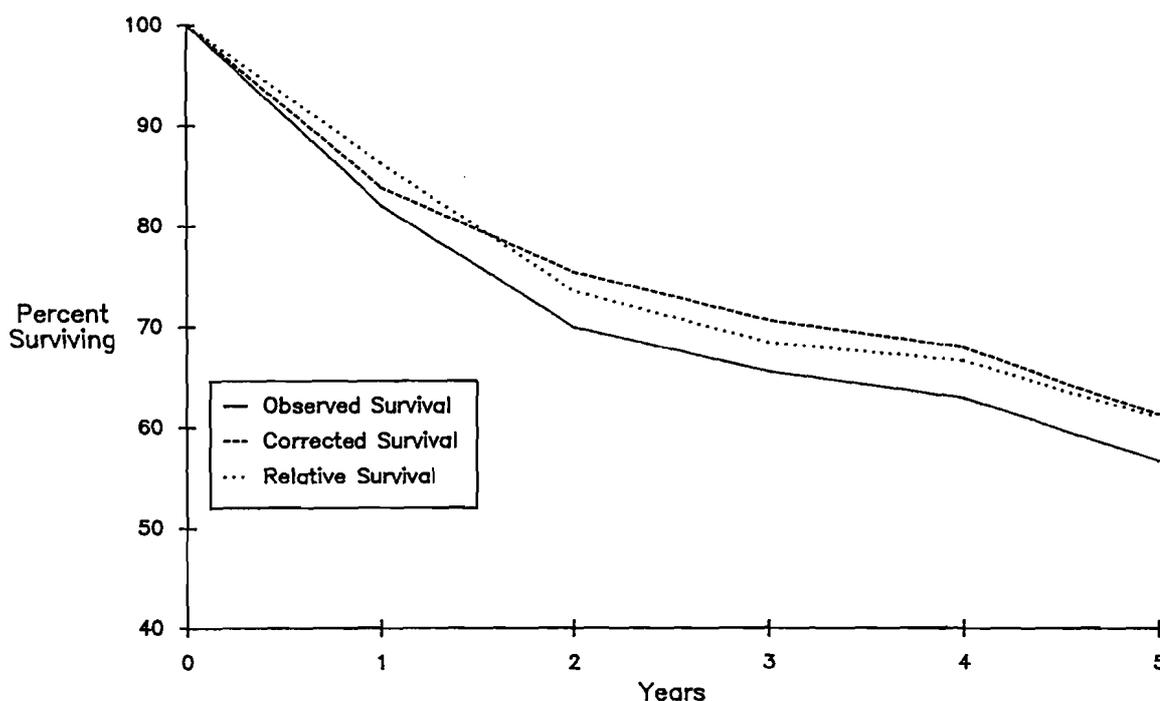


Figure 1. Observed, corrected and relative cumulative survival rates among melanoma patients

Based on data in Tables 1 and 2.

(5) The proportion surviving the year (column 7), that is, the observed annual survival rate, is obtained by subtracting the proportion dying (column 6) from 1.000.

(6) The proportion surviving from diagnosis to the end of each year (column 8), that is, the observed cumulative survival rate, is the product of the annual survival rates for the given year and all preceding years. For example, for the fifth year the proportion 0.567 is the product of all entries in column 7 from the first to the fifth years.

The five-year survival rate calculated by the life-table method is 0.567 or 57%. In this example the result, obtained by using the information available on all 50 patients, agrees with that based on the 30 patients used in the calculation by the direct method. Such close agreement by the two methods will usually not occur when some patients have to be excluded from the calculation of a survival rate by the direct method. In such instances, the life-table method is more reliable because it is based on more information.

One advantage of the life-table method is that it provides information about changes in the risk of dying in successive intervals of observation. Thus, column 6 (q_i) shows that the proportion of patients dying in each of the first four years after diagnosis decreased from 18% in the first year to 4% in the fourth. (The increase to 10% in the fifth year may be due to chance, since the numbers involved are small—only 22 patients were alive at the beginning of the fifth year).

The cumulative rates in column 8 may be used to plot a survival curve, providing a pictorial description of the survival pattern (Figure 1).

Table 3. Calculation of the corrected survival rate

(1) Year after diagnosis	(2) No. alive at beginning of year	(3) No. dying during year		(4) No. last seen alive during year	(5) Effective no. exposed to risk of dying ^a	(6) Proportion dying ^a during year	(7) Proportion surviving ^a to end of year	(8) Cumulative proportion surviving ^a
		(a) From disease	(b) From other causes					
(i)	(l _i)	(d(m) _i)	(d(o) _i)	(w _i)	(r _i) ^b	(q _i) ^b	(p _i) ^b	(Πp _i)
0	50	8	1	0	49.5	0.162	0.838	0.838
1	41	4	2	1	39.5	0.101	0.899	0.754
2	34	2	0	4	32.0	0.063	0.937	0.706
3	28	1	0	5	25.5	0.039	0.961	0.679
4	22	2	0	3	20.5	0.098	0.902	0.613
>5	17	—	—	17				
Total		17	3	30				

^a Note 'dying' and 'surviving' in columns 5–8 refer to deaths (and survivals) from the disease of interest

^b Where $r_i = l_i - \frac{(w_i + d(o)_i)}{2}$

$$q_i = d(m)_i / r_i$$

$$p_i = 1 - q_i$$

Corrected survival rate¹

The observed survival rate described above accounts for all deaths, regardless of cause. While this is a true reflection of total mortality in the patient group, the main interest is usually in describing mortality attributable to the disease under study. Examination of Table 1 reveals that in four instances melanoma was not the cause of death (patients No. 2, 13, 42 and 44). Three of these deaths occurred within the first five years of follow-up and thus influenced the five-year survival rate calculated in Table 2.

Whenever reliable information on cause of death is available, a correction can be made for deaths due to causes other than the disease under study. The procedure is shown in Table 3. Observed deaths are recorded as being from the disease (column 3a) or from other causes (column 3b). Patients who died from other causes are treated in the same manner as patients last seen alive during year (column 4), that is, both groups are withdrawn from the risk of dying from melanoma. Thus, the effective number exposed to risk of dying (from melanoma) (column 5) in the second year of observation is equal to $41 - (2 + 1)/2 = 39.5$.

The five-year corrected survival rate is 0.613 or 61%, compared to an observed

¹ There is no standard nomenclature for the actuarial survival rate corrected by the exclusion of deaths due to causes other than the disease in question. The authors prefer the term 'corrected survival'; alternatives are 'net survival' or 'disease-specific (here melanoma-specific) survival'. The term 'adjusted survival' has been avoided because of the confusion that might arise when age-adjustment procedures (see p. 170) are employed.

rate of 57%. The corrected rate indicates that 61% of patients with melanoma escaped the risk of death from the disease within 5 years of diagnosis.

Use of the corrected rate is particularly important in comparing patient groups that may differ with respect to factors such as sex, age, race and socioeconomic status, which may strongly influence the probability of dying from causes other than the cancer under study. Figure 1 compares the observed and corrected survival for the 50 patients, the gap between the observed and corrected curves representing normal (non-melanoma) mortality.

Relative survival rate

Information on cause of death is sometimes unavailable or unreliable. In this case, it is not possible to compute a corrected survival rate. However, it is possible to account for differences among patient groups in normal mortality expectation, that is, differences in the risk of dying from causes other than the disease under study. This can be done by means of the relative survival rate, which is the ratio of the observed survival rate to the expected rate for a group of people in the general population similar to the patient group with respect to race, sex, age and calendar period of observation.

Expected survival probabilities can be obtained from general population life-tables by multiplication of the published annual probabilities of survival. The appropriate probability, depending on the sex and age of the patient, and the year of registration, is obtained from the life-table. Table 4 provides the necessary data (from Finland) for calculating the expected five-year survival of patient No. 1, a male aged 63 in 1970. In Finland the general population annual mortality rates are published for one-year age groups every five years, and indicate averages over five-year calendar periods. Patient No. 1 was 63 years old in period 1966–70 (in 1970, in fact), and lived for the following five years (covered by period 1971–75). The general population mortality rates corresponding to the ageing of the patient are taken from the published general population life-tables as annual normal probabilities of death for the patient (Official Statistics of Finland, 1974, 1980). These are subtracted from 1.0 in order to get the corresponding normal probabilities of survival. In order to make allowance for the fact that the patient was not exactly 63 years old, but more likely on average close to 63.5 years at the beginning of follow-up, moving averages are calculated from the annual normal survival probabilities. The five probabilities corresponding to ages 63.5 to 67.5 are multiplied to give the expected probability of surviving five years. In this example the result is 0.812.

For the entire group of patients in Table 1, the average expected survival is the sum of the individual five-year probabilities, divided by the total number of subjects (50). Suppose this is 0.94, or 94%.

$$\begin{aligned} \text{Relative survival rate} &= \frac{\text{Observed survival rate}}{\text{Expected survival rate}} \times 100 \\ &= \frac{0.57}{0.94} = 61\% \end{aligned}$$

which in this case is identical to the corrected survival rate.

Table 4. Calculation of the five-year expected survival probability using the general population mortality (in Finland)

Age	Calendar period	Annual probability of death ^a	Annual probability of survival	Two-year moving average
63	1966–70	36.08	0.96392	
64	1971–75	35.28	0.96472	0.964320
65	1971–75	38.75	0.96125	0.962985
66	1971–75	41.40	0.95860	0.959925
67	1971–75	46.24	0.95376	0.956180
68	1971–75	48.52	0.95148	0.952620

^a Annual probability of death per 1000 (Official Statistics of Finland, 1974, 1980)

In practice, it is usual to calculate relative survival rates for each interval, and cumulatively for successive follow-up intervals (see Ederer *et al.*, 1961).

Use of the relative survival rate does not require information on the actual cause of death (and whether the cancer caused a death, or was merely incidental to something else). This can be quite a major advantage (Hakulinen, 1977). However, it does presuppose that the population followed is subject to the same force of mortality as that used in the life-table. When an appropriate life-table is not available (e.g., for a particular ethnic or socioeconomic group), the corrected rate may be preferable. In any case, the method used should be specified, and when comparing survival of different patient groups, the same method should be used for each.

If the relative survival rate is to be used for follow-up periods of longer than 10 years, the paper by Hakulinen (1982) should be consulted, which shows how to deal with biases resulting from ageing of the base population and from differences in the age-specific cancer incidence trends.

Calculation by the Kaplan–Meier Method

A widely used procedure for calculating survival, for which many computer programs are available, is the Kaplan–Meier method (Kaplan & Meier, 1958). It is similar to the actuarial method, but instead of a cumulative survival rate at the end of each year of follow-up, the proportion of patients still surviving can be calculated at intervals as short as the accuracy of recording date of death permits.

The method is illustrated in Table 5, using the data from Table 1, where the time of observation for each death or withdrawal can be estimated to the nearest month. The calculations are almost identical to those for the actuarial method, except that time intervals of one month are used, and that patients withdrawn from observation are considered to have survived throughout the time interval (one month) in which they occur.

The survival curve calculated by the Kaplan–Meier method is illustrated in Figure 2. It consists of horizontal lines with vertical steps corresponding to each death, in contrast to the line graph of the actuarial method.

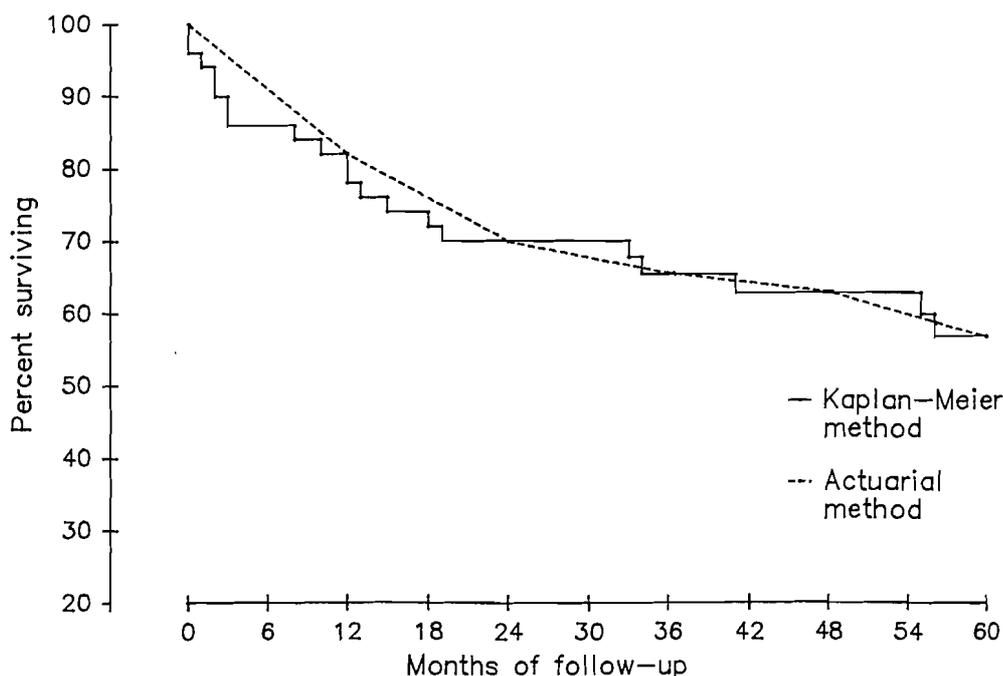


Figure 2. Kaplan-Meier survival curve for melanoma patients (compared with observed survival calculated by the actuarial method)

A corrected rate can be calculated with this method, by treating the three non-melanoma deaths occurring within the first five years of follow-up (marked by an asterisk in Table 5) as withdrawals. The relative survival rate is calculated by dividing the observed rate by the expected survival rate, as in the actuarial method.

Age-adjustment of survival rates

The use of corrected or relative survival rates accomplishes age-adjustment in part, since they make allowance for the association between age and dying from causes other than cancer. However, if there is an association between age and the risk of dying from the cancer in question, and it is desirable to make comparisons between case series of differing age structure, then, as with incidence rates, either the comparisons should be limited to age-specific survival rates, or age-standardization procedures should be used (Haenszel, 1964).

Standard error of a survival rate

The standard error and confidence intervals are used as a measure of precision of the survival rates, as already described for incidence.

Standard error of the survival rate computed by the direct method

$$\text{s.e.}(P) = \sqrt{\frac{P(1 - P)}{N}}$$

where P = survival rate

N = number of subjects

In the calculation of survival rate by the direct method (p. 163), the total number of patients observed for five years was 30, thus:

Table 5. Calculation of observed survival rate by the Kaplan–Meier method

Month after diagnosis (i)	Number alive at beginning of month (l_i)	Deaths (d_i)	With-drawals (w_i)	Proportion dying (q_i)	Proportion surviving (p_i)	Cumulative surviving (Πp_i)
0	50	2	0	0.040	0.960	0.960
1	48	1	0	0.021	0.979	0.940
2	47	2	0	0.043	0.957	0.900
3	45	2*	0	0.044	0.956	0.860
8	43	1	0	0.023	0.977	0.840
10	42	1	0	0.024	0.976	0.820
12	41	2*	0	0.049	0.951	0.780
13	39	1	0	0.026	0.974	0.760
15	38	1	0	0.026	0.974	0.740
18	37	1*	0	0.027	0.973	0.720
19	36	1	0	0.028	0.972	0.700
21	35	0	1			
27	34	0	2			
30	32	0	1			
33	31	1	1	0.032	0.968	0.677
34	29	1	0	0.034	0.966	0.654
38	28	0	1			
40	27	0	1			
41	26	1	0	0.038	0.962	0.628
43	25	0	1			
44	24	0	1			
46	23	0	1			
54	22	0	1			
55	21	1	0	0.048	0.952	0.598
56	20	1	0	0.050	0.950	0.568
57	19	0	2			
≥60	17	1*	16			

* 1 non-melanoma death

$$\text{s.e.}(P) = \sqrt{\frac{0.57 \times (1 - 0.57)}{30}} = 0.090$$

and the 95% confidence interval is given by:

$$\begin{aligned} & P \pm 1.96 \times \text{s.e.}(P) \\ &= 0.57 \pm 1.96 \times 0.09 \\ &= 0.39 \text{ to } 0.75 \end{aligned}$$

Standard error of the actuarial survival rates

Calculation of the standard error of the five-year survival rate obtained by the actuarial method uses the last two columns of figures in Table 2. Column 9 is obtained

by subtracting the values in column 3 from the values in column 5, while column 10 is obtained by dividing the entries in column 6 by the corresponding figures in column 9. The sum of the figures in column 10 is obtained and equals 0.0177. The standard error of the five-year survival rate by the actuarial method is the calculated five-year survival rate multiplied by the square root of the total of the entries in column 10, that is, $0.567 \times \sqrt{0.0177} = 0.075$. Expressed symbolically, and using the notation in Table 2:

$$\text{s.e.}(P) = P \sqrt{\sum \frac{q_i}{r_i - d_i}}$$

or

$$= P \sqrt{\sum \frac{d_i}{r_i(r_i - d_i)}}$$

This is known as Greenwood's formula.

Thus the 95% confidence interval for the patients' five-year survival rate is $0.567 \pm 1.96 \times 0.075$, that is 0.42 to 0.72.

In practice, an approximation to the standard error of the actuarial survival rate may be quickly obtained from published tables prepared by Ederer (1960).

It should be noted that the standard error of the survival rate obtained by the actuarial method is smaller than that of the survival rate calculated by the direct method (0.075 versus 0.090). This difference reflects the advantage in terms of statistical precision resulting from the use of all available information, that is, information on patients under observation for less than five years.

For further information see Merrell and Shulman (1955) and Cutler and Ederer (1958).

Standard error of the relative survival rate

The standard error of the relative survival rate is easily obtained by dividing the standard error of the observed survival rate (obtained by either the direct or actuarial method) by the expected survival rate. Thus from the actuarial method the five-year survival rate is 57% and the expected survival rate is 94% with a resulting relative survival rate of 61%. The standard error of the observed survival rate is 0.075.

In this example the standard error of the five-year relative survival rate is

$$\frac{\text{Standard error of observed rate}}{\text{Expected survival rate}} = \frac{0.075}{0.940} = 0.080$$

The 95% confidence interval for the five-year relative survival rate is therefore:

$$0.61 \pm 1.96 \times 0.080 = 0.45 \text{ to } 0.77$$

Comparison of survival rates

In the simplest circumstances, it may be wished to compare two survival rates. If the 95% confidence intervals of two survival rates do not overlap, the observed difference would customarily be considered as statistically significant, that is, unlikely to be due

Table 6. Calculation of the observed survival rate, and expected numbers of deaths per year, for males and females

Year	l_i	d_i	w_i	r_i	q_i	p_i	Πp_i	Expected deaths ($r_i \times Q_i$) ^a
<i>Males</i>								
0	24	6	0	24.0	0.250	0.750	0.750	4.32
1	18	4	0	18.0	0.222	0.778	0.584	2.66
2	14	1	2	13.0	0.077	0.923	0.539	0.82
3	11	1	2	10.0	0.100	0.900	0.485	0.39
4	8	0	1	7.5	0.000	1.000	0.485	0.74
5	7	1	1	6.5	0.154			0.43
		—						—
		13						9.36
<i>Females</i>								
0	26	3	0	26.0	0.115	0.885	0.885	4.68
1	23	2	1	22.5	0.089	0.911	0.806	3.33
2	20	1	2	19.0	0.053	0.947	0.764	1.20
3	17	0	3	15.5	0.000	1.000	0.764	0.60
4	14	2	2	13.0	0.154	0.846	0.646	1.27
5	10	0	3	8.5	0.000			0.57
		—						—
		8						11.65

^a Q_i is the proportion of the whole series (males plus females) dying during the year (column 6 of Table 2)

to chance. This is not recommended, and more appropriate procedures are described below.

Standard statistical texts describe the z -test, which provides a numerical estimate of the probability that a difference as large as or larger than that observed would have occurred if only chance were operating. The statistic z is calculated by the formula:

$$z = \frac{|P_1 - P_2|}{\sqrt{(\text{s.e.}(P_1))^2 + (\text{s.e.}(P_2))^2}}$$

where

P_1 = the survival rate for group 1,

P_2 = the survival rate for group 2,

$|P_1 - P_2|$ = the absolute value of the difference, i.e., the magnitude of the difference, whether positive or negative

$\text{s.e.}(P_1)$ = the standard error of P_1

$\text{s.e.}(P_2)$ = the standard error of P_2 .

The statistic z is the standard normal deviate, so that if $z > 1.96$, the probability that a difference as large as that observed occurred by chance is $< 5\%$ and if $z > 2.56$, the probability is $< 1\%$.

For example, Table 6 shows the calculation of the observed five-year survival rate by the actuarial method for the 24 males ($P_1 = 0.485$) and the 26 females

($P_2 = 0.646$). Using Greenwood's formula, the standard error of P_1 is 0.105 and the standard error of P_2 is 0.105.

Thus:

$$z = \frac{|0.485 - 0.646|}{\sqrt{0.105^2 + 0.105^2}} = \frac{0.161}{0.148} = 1.09$$

The calculated z value is smaller than 1.96 and therefore not statistically significant at the 5% level. In order for a difference in survival rates as large as this to be statistically significant, the study would have to have involved more patients, so that the corresponding standard errors are smaller.

A rather better test for comparing survival in several groups is the logrank test (see Peto *et al.*, 1977; Breslow, 1979). This test is not restricted to comparison of the survival at a single point of follow-up (as in the example above), but uses material from the entire period of follow-up. It is commonly used for comparing the survival experience of different treatment groups in clinical trials. Normally, the duration of survival from diagnosis to death for each patient is known rather accurately, so that a survival curve of the Kaplan-Meier type (Figure 2) can be drawn. For the purposes of illustration, however, an approximation to the logrank test can be applied to the data in Table 1, showing survival in two groups (males and females) at annual intervals. Note that this approximation is conservative and thus does not always lead to appropriately small p values (Crowley & Breslow, 1975). The use of the proper logrank test that can be found in most statistical software packages is recommended.

For each interval, the expected numbers of deaths are calculated for each group. This uses the number at risk of dying in each group (r_i), and the proportion dying during the year (Q_i) derived from all groups combined—in Table 6 for males and females combined (column 6 of Table 2). The total number of expected deaths for the subgroups is obtained by summation of expected numbers for each interval:

$$\text{Expected deaths} = \sum r_i Q_i$$

The equality of the survival curves can be tested by a chi-square test, with, for j subgroups under study, $(j - 1)$ degrees of freedom:

$$\chi^2 = \sum_{i=1}^j \frac{|O_i - E_i|^2}{E_i}$$

For example: In the comparison of males and females in Table 6, information on all deaths is used (these are all included with intervals less than 6 years):

For males, observed deaths to end of year five = 13
 expected deaths to end of year five = 9.36
 For females, observed deaths to end of year five = 8
 expected deaths to end of year five = 11.65

$$\begin{aligned} \chi^2 &= \frac{|13 - 9.36|^2}{9.36} + \frac{|8 - 11.65|^2}{11.65} \\ &= 2.56 \end{aligned}$$

With one degree of freedom, $p > 0.1$, a non-significant result.

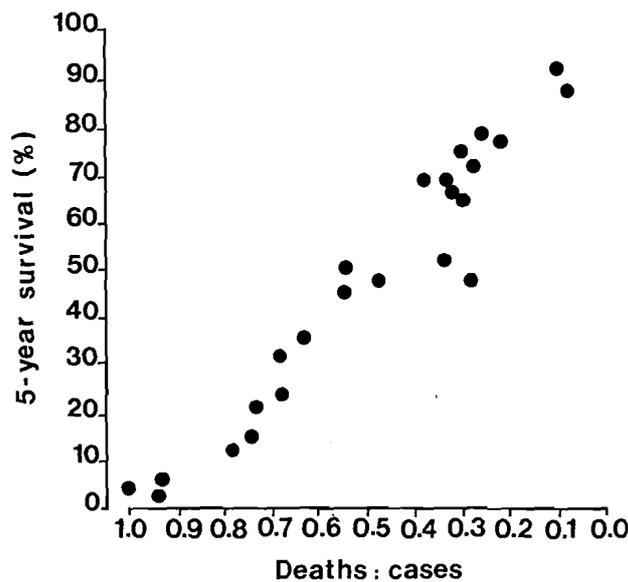


Figure 3. Relationship between five-year relative survival rates (cases registered 1973–76) and the ratio of deaths:cases in 1973–77, for 24 major cancer sites
Data from SEER programme.

The logrank test is included in the most common statistical software packages. For relative survival curves, tests have been designed by Brown (1983) and Hakulinen *et al.* (1987). They are available in the computer software by Hakulinen and Abeywickrama (1985).

In many circumstances, comparisons of survival between different patient groups should control for confounding factors, as in any epidemiological study. For example, one may wish to examine survival rates in patients treated in one group of hospitals versus those treated elsewhere, while taking into account possible differences between the two groups which might influence prognosis (e.g., age, ethnic group, social status, stage of disease). One method of handling this is stratification by the confounding factors (Mantel, 1966), but in recent years, there has been increasing use of modelling techniques based upon the proportional hazards model (Cox, 1972). Computer programs for this model exist in all major statistical software packages. Generalizations for the relative survival rates have been made by Pocock *et al.* (1982) and Hakulinen and Tenkanen (1987). The latter is based on GLIM (Baker & Nelder, 1978) and also accommodates non-proportional hazards.

Fatality ratio

For many registries, it may be impossible to carry out any kind of comprehensive follow-up of registered cases in order to compute survival. However, registries may present the fatality ratio as an indication of survival, i.e., the ratio of new cases to reported deaths from the same diagnosis occurring within a specified period. The same ratio, referred to as 'deaths in period' (Muir & Waterhouse, 1976) and more recently as the 'mortality/incidence ratio' (Muir *et al.*, 1987) has been used as a measure of the completeness of registration in the series *Cancer Incidence in Five Continents*. Of course, the incidence cases and mortality do not refer to identical cases, just to identical diagnoses, and the ratio is only an indirect description of the general

survival experience. Nevertheless, as shown in Figure 3, the relationship between five-year survival and the fatality ratio for different cancers within the same registry is likely, in practice, to be reasonably close. However, it is not clear whether any meaningful comparison of survival between registries is possible using fatality ratios.

Acknowledgement

The authors would like to thank Dr M. Myers, National Cancer Institute, Division of Cancer Prevention and Control, Biometry Branch, for his helpful comments and suggestions during the preparation of this chapter.