ON CLINICAL TRIALS AND SURVIVAL ANALYSIS

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SYNOPSIS

Clinical trials are needed to evaluate the efficacy of treatment regimens which have not been proven in clinical practice, especially with respect to new drugs and operative procedures. The ultimate measure of success is patient survival, although the same approach is applicable for morbid events like the relapse of a disease or the rejection of a transplanted organ. The main elements of a clinical trial are discussed. The life-table method of survival analysis and the logrank statistical test are presented, with guidelines on the interpretation of the conventional survival rates.

INTRODUCTION

The assessment of therapeutic efficacy among treatment regimens is a topic of major concern to all doctors. One is sometimes hard put to distinguish the genuine from the fake, the effective from the ineffective and the necessary from the unnecessary. The fact that there is so much controversy, as in cancer, over the various claims of specific **'cures'** is indication enough that the situation is far from satisfactory. Whether it be a new drug or an old operative procedure, the physician or surgeon needs a more objective and scientifically-based evaluation of its effectiveness than has previously been done.

At the heart of the problem is the practitioner's concern with patient survival. An operation may be successful or a drug well tolerated, but ultimately what really matters is whether patients can survive longer than would be expected in the absence of treatment. Unfortunately, what is not so easily measured and assessed is the quality of life, an equally important consideration which includes the less tangible pyscho-social aspects like the patient's perception of his own existence. The doctor should also be concerned with the patient's quality of life; to offer a mutilating and painful operation without any real potential gain in survival time would be inhumane.

It must be emphasised, however, that evaluation of treatment effects need not centre only on death and survival. Morbid events sometimes can be just as important as, for example, the relapse of a leukaemic process, rejection of a transplanted organ, or re-infarction in a group of myocardial infarction survivors. The results are similarly recorded according to the dichotomous situation of **'success and failure'.** The term **'survival'** is taken in the broader sense of bodily, organ, tissue and even equipment (e.g. pacemaker) survival.

Admittedly, basic research in the development of new drugs and new operative procedures, at this moment, are beyond the resources of Singapore's institutions. On the other hand, the application of any therapeutic regimen can be usefully assessed in the context of local patients and circumstances. Even the non-researcher will have to evaluate the results of other studies,

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a task that is becoming increasingly difficult as more and more new drugs get introduced.

Thus, the purpose of this article is three-fold:

(1) To stimulate a greater interest among practitioners in the conduct of clinical trials and survival studies;

(2) To provide some guidelines in the evaluation of clinical trials and their results;

(3) To introduce the main elements of survival analysis.

THE CLINICAL TRIAL

It is not the intention of this article to discuss the very important ethical issues of clinical trials. They are not advocated for every present and future drug or procedure. A treatment regimen that is well established with satisfying results does not need further study, unless some unusual observations are reported. But where there is doubt (old therapies) or ignorance (new ones), there is a case for clinical trials. Proceeding with an unproven regimen can be just as disastrous as doing away with it. Only a well conducted trial can help resolve some of these uncertainties.

A clinical trial usually involves the comparison of two groups of patients, one with the treatment under study and the other (control) with some other treatment or placebo. They are usually compared on the basis of their survival experiences in which any differences, if statistically significant, may be indicative of the effect of the treatment concerned.

In view of the likely influence of sex, age, ethnicity and other prognostic factors on survival, comparison groups must be comparable if results are to be informative. In general, there are two types of comparisons:

(a) Historical comparison - where the control is based on a previous group of patients in the experience of the practitioner or department. In a situation where the disease is highly fatal (almost incurable), any success would be significant. But in all other situations, differences between treatment groups would be difficult to interpret as the historical controls may be quite differently organised in terms of diagnostic criteria, clinical states and supportive care.

(b) Concurrent comparison - where the control is based on a parallel group of patients, preferably allocated randomly from a pool of patients. Although there is no guarantee of comparability, especially in small trials, any discrepancy would hopefully occur in a random fashion. To be certain, one must still review the distribution of descriptive characteristics in both groups before making any firm conclusions. The scheme of action is shown in Figure 1.

A further refinement (so as to remove as much bias as possible) would be to keep patients and their attending doctors from knowing which treatment the patients are on. This is known as the "double-blind" trial. If only the patient is unaware, then it is a "single-blind" trial. Usually a third party (the moderator) will

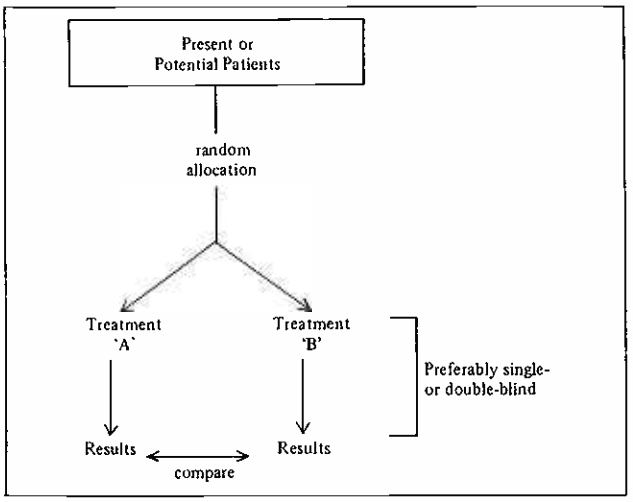

Figure 1 Scheme of Action in Randomised Controlled Trial

have the full facts and will monitor the situation to avoid any possible complications. The practitioner would be alerted if any untoward effects should occur so that a decision can be made whether to stop or continue with the trial for a particular individual or for the whole group.

With acute diseases, patients either recover or die within a short span of time. The end-results can be easily presented in a four-fold table:

	Treatment A	Treatment B
Cured		
Not cured		

Statistical analysis would be straightforward, with actual tests depending on the details of study design (e.g. whether matched or unmatched).

For chronic diseases like hypertension, atherosclerotic disease, cancer and metabolic disorders, analysis of follow-up events (e.g. death) is much more complicated. The approach for acute conditions would be inadequate because of the variable time-lapse between diagnosis and end-result. The method of choice is the actuarial life-table approach of survival analysis, which does not merely count the number of events but show the rate at which they occur in each time-interval. Treatment results can then be compared on the basis of their effects on survival patterns as derived by this statistical method.

SURVIVAL ANALYSIS

As stated earlier, survival analysis is applicable to both mortal and morbid events. To simplify this discussion, reference will primarily be restricted to mortality although the same principles can be applied to morbid events. The main techniques of survival analysis and statistical inference are given in Peto et al (1, 2).

In the ideal situation, a group of patients would be followed-up from the same starting point until all have died or at least after a number of years (say, five) have elapsed. Theoretically, then, one has to gather patients as of a particular point in time (e.g. date of

first diagnosis) and ensure that they are not lost for the duration of the study.

In practice, the situation is far from ideal. Patients are often gathered over a period of time. Some get 'lost' in the process of follow-up when they abscond treatment or are 'withdrawn alive' at the termination of the study. Figure 2 shows an example of a common case-series in an ordinary clinical practice. Patients enter the series at different times and leave with different survival durations.

The life-table approach was first described by Greenwood (3) and popularised by Berkson and Gage (4, 5), Merrell and Shulman (6), as well as Cutler and Ederer (7). Basically, it is a follow-up cohort study that attempts to summarise the overall survival experiences of a series of cases. The method begins by re-arranging the survival durations so that the cases have a common starting point (time zero). Instead of calendar years, one is dealing with time intervals as shown in Figure 3.

For each subject, there is a starting point. It has to be a definite event, one that is not vague like the date of initial symptoms. Usually the date of initial diagnosis is taken. Sometimes, even that is unclear. The date of hospital admission at which diagnosis was made is a good compromise.

The end-point or event to be studied must be just as clearly defined. It may be death, relapse or rejection. Death as an event is nearly always definite and well documented. But for morbid events, working definitions are required to indicate what 'success' and 'failure' mean.

It can be seen that one of the main advantages of the life-table method is that it can accommodate data that are incomplete (called censored data). By including censored data, it makes the reasonable assumption that the survival experiences of those lost or withdrawn are, on the average, similar to those still remaining. For each interval, the average observation-time contributed by these censored subjects would be included in the denominator. Nevertheless, survival probabilities (rates) based on a series with 10% or more lost cases should be taken with some caution.

The key component of the life-table is the risk of mortality (q) derived for each time-interval. Its complement is the probability of survival ($p = 1 - q$). The structure of the life-table is given in Table 1.

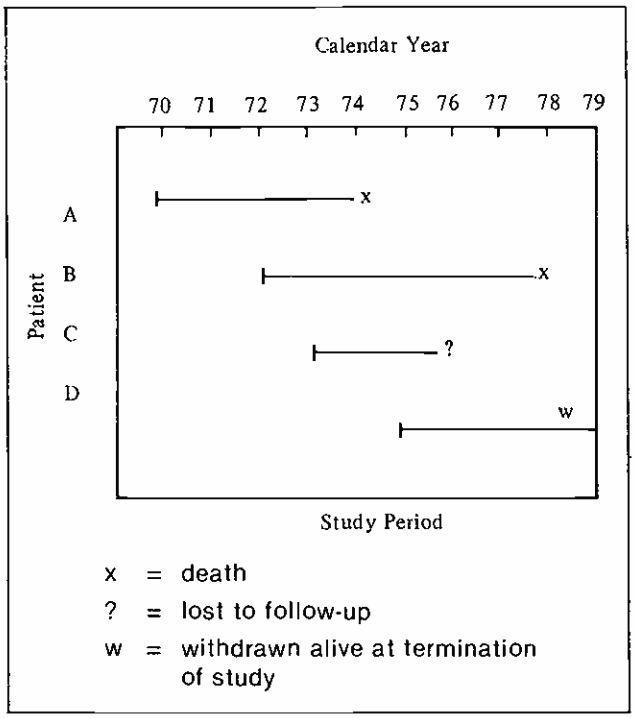

Figure 2 Example of Entry and Exit in a Typical Case Series (lines indicate duration of illness)

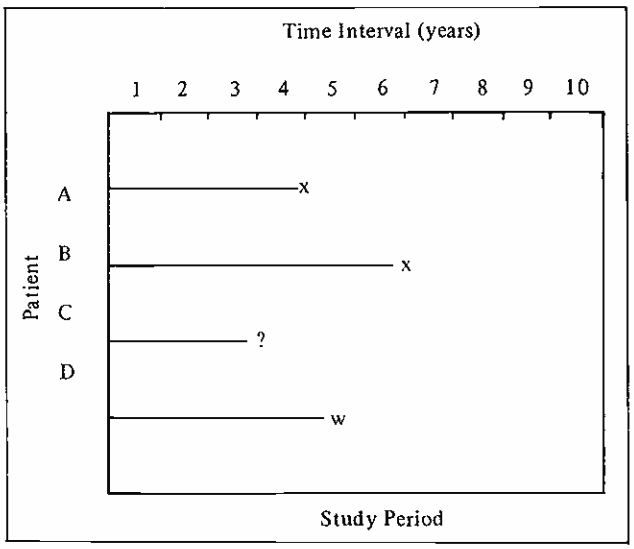

Figure 3 Re-arrangement of Survival Durations from Time Zero

Table 1
Structure of Life-Table
(with fictitious figures to illustrate computations)

1 Time interval from date of diagnosis	2 No. of patients at start of interval	3 No. lost to follow-up	4 No. with-drawn alive at study termination	5 No. dying in interval	6 Popn. at risk of dying	7 Probability of dying in interval	8 Probability of surviving in interval	9 Cumulative probability (rate) of survival
(x)	(n_x)	(ℓ_x)	(w_x)	(d_x)	$[n_x - \frac{(\ell_x + w_x)}{2}]$	$[q_x = \frac{(5)}{(6)}]$	$[p_x = 1-q_x]$	$[p_x = p_{x-1}\,p_x]$
0	90	—	—	—	—	—	—	100%
1	90	3	1	2	88	0.023	0.977	97.7
2	84	1	1	2	83	0.024	0.976	95.4
3	80	1	1	3	79	0.038	0.962	91.8

THE SURVIVAL PROPORTION (PROBABILITY OR RATE)

The statistic that is usually presented is the cumulative survival proportion (popularly referred to as the survival rate). The life-table would give the cumulative proportion for each time-interval as the group 'moves' from time zero. When the functions are plotted, they would look like the one in Figure 4.

By convention, the 5-year survival rate is the single most commonly quoted index of survival experience among cancer patients. For a disease as fatal as cancer, 5-year survival is as good as a cure. That is why the 5-year rate has been referred to as the cure rate. Conceptually however, it is misleading since survival merely indicates the state of being alive, with or without remnants of the disease. 5-year cancer survivors have been known to die subsequently of metastases, hardly an example of a cure.

Since the cumulative survival proportions represent the average experience of a group of patients, it would be dangerous to apply average experiences to individuals in particular situations. The nearer one is to death, the greater is the relative variability, and when death finally occurs, it is due to "some singular and essentially unpredictable event" (8). In the difficult task of prognostication, therefore, single figure predictions are useless and misleading. The only realistic and conceptually sound thing to do is to give average predictions with upper and lower limits (based on confidence intervals). For this purpose also, the observed survival proportions can be adjusted so as to remove the effect of causes other than the disease under study. This derived ratio of observed to expected survival is called the relative or corrected survival rate (9).

In a clinical trial, the total survival experiences of treatment and control groups are compared, using the non-parametric logrank test. The term "logrank" persists in statistical literature despite its obscure and poorly-reasoned origin. The conceptual basis and computation of the necessary components are, nevertheless, quite straightforward. The eventual product is a X^2 value [= Sum $\frac{(\text{Observed} - \text{Expected})^2}{\text{Expected}}$] with k-1 degrees of freedom (k = number of groups being compared).

CONCLUSIONS

The conduct of clinical trials and survival analysis is an excellent example of the direct application of epidemiological and biostatistical techniques in medical practice. One gets a good 'feel' for the data, as they relate to patients in one's own clinic or department. With co-operation on all sides, the practitioner can be encouraged and helped to mount more of such studies.

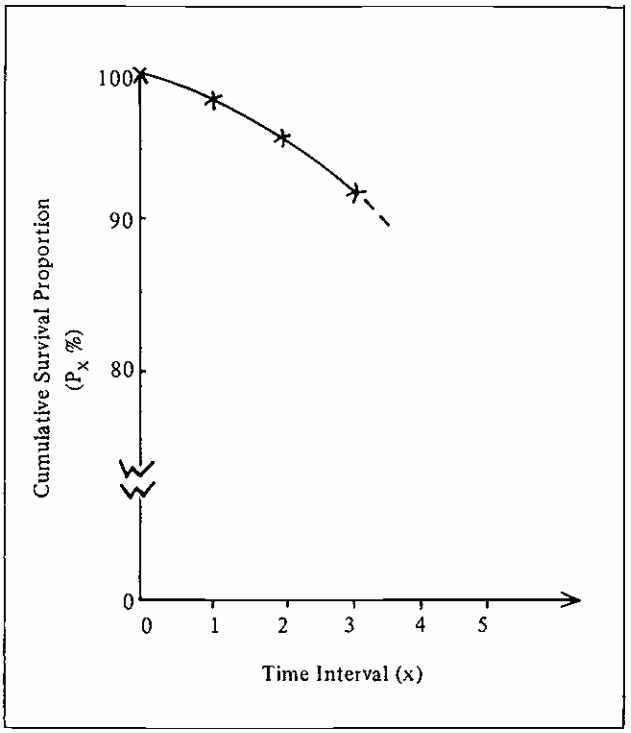

Figure 4 Survival Curve (based on Table 1)

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