Statistical aspects of a co-operative trial on the treatment of ovarian carcinoma

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Introduction

For at least four reasons it is very important, even essential, to involve a statistician at a very early stage in the planning of a clinical trial.

Firstly, the trial must be designed so that an unequivocal result can be obtained at the end of the trial. In statistical terms, ‘confounding’ of variables has to be avoided. If, for example, one had two treatment regimens which differed both in the type of operation and in the dose of radiotherapy, a difference between them could be due to the operation difference, or the radiotherapy difference, or partly due to both, or due to the interaction of surgery and radiotherapy.

The second reason for consulting the statistician is to ensure that the data resulting from the trial can be analysed. Perhaps additional data on each patient are desirable, or a simple modification of the experimental design or the measurements made might enable a more powerful statistical analysis to be carried out. Also, the statistician may be able to suggest additional analyses not thought of in the initial planning of the trial. Without consultation before the trial, the data may be unsuitable for further analysis, or indeed for any analysis at all.

Thirdly, it is very important to consider how many cases are necessary for the trial. On grounds of simple economy, it is wasteful to collect data on more patients than are required in order to reach an acceptably precise result. Also, in medical experimentation ethical considerations become very important. If one of the treatments being compared is superior, it is very desirable to find this out as quickly as possible so that no more patients will then receive the inferior treatments. But, if too few patients are studied in the trial, the superiority of this treatment might not be discovered, and may well never be. As shall be seen later, it is as important to be certain that no difference exists between the treatments as it is to claim that there is a difference.

Fourthly, and finally, the statistician can give valuable guidance on the practical aspects of recording, storing and analysing the data. Major savings in effort, and increases in accuracy, can be obtained if the data collection is arranged with storage on punched cards and analysis by computer in mind. These advantages do, however, require advance planning.

These four aspects of planning of the Ovarian Cancer Clinical Survey (OCCS) will now be considered, and although they will be discussed under separate headings, it will be clear that all these considerations are interdependent.

Design

The aim of the OCCS is to study the effect of a hormone (SH 582 or Depostat) on ovarian carcinoma. The design of this trial is intended to ensure that the resulting treatment groups can be validly compared.

The first consideration of importance was defining the patients to be included in the trial. After much discussion by the trial steering committee it was decided that two categories of patients would need to be catered for, namely, those for whom no further treatment after operation and/or radiotherapy would be ethical until active disease was again noted, and those who required systemic treatment immediately after operation and/or radiotherapy. Within these two categories the allocation of patients was to be on a random basis. For the first category, two treatment groups were decided on viz. (1) SH 582, (2) no further treatment at present. The second category of patient was to be allocated to one of three treatment groups: (1) SH 582, (2) a cytotoxic drug, (3) SH 582 plus a cytotoxic drug. The allocation of the patients into treatment groups being made randomly provides a valid statistical basis for treatment comparisons.

Analyses

The primary criterion of success in the treatment of malignant disease is survival time from first treatment. This requires the precise date of operation to be known for all patients, and a follow-up procedure has to be used in order to ascertain if and when the patient dies. The optimum method of analysis for such data is the life table method (Berkson & Gage, 1950; Cutler & Ederer, 1958; Irwin, 1971). This method enables survival curves for the various treatments to be compared, and makes efficient use of the data even when all the
patients have not been followed up for the same length of time. In addition, the patient survivals will be monitored during the course of the follow-up period using the sign method of sequential analysis (Armitage, 1960) so that any major treatment differences can be noted as early as possible.

Although survival is the major criterion of treatment success, recurrence or progression of active disease and the patient's general condition and quality of life are also important. For this reason the trial questionnaires include several questions on the presence or absence of metastases in various body sites, and also questions regarding the appetite, activity, pain and weight of the patient. The various laboratory measures requested also assist in assessing the patient's general condition.

Finally, discriminant function analysis (Cooley & Lohnes, 1962; Rao, 1952) will be used in order to find possible predictors of treatment response. This is an attempt to use the data obtained at the initial examination of the patient, at operation, and from the laboratory tests in order to predict which patients will respond well to what treatment. This aim is the most important justification of the large amount of detail requested on each patient.

**Numbers required**

Having decided on the trial design, the information to be collected, and its intended analyses, it is very important to ensure that a suitable number of patients is aimed for.

It is first necessary to decide on the precision desired in the treatment comparisons, that is, how small a treatment difference it is important to detect. On discussion, the steering committee of the OCCS decided that it was highly desirable to detect a 5% increase in survivals in 2 years of follow-up, and that a 10% difference between treatments was the minimum acceptable sensitivity of the trial. Thus, if the existing treatment gave 20% surviving in 2 years, it would be hoped that an improvement to 25% surviving could be detected.

Secondly, the statistical errors which might be made in comparing the treatments have to be considered. If no real difference between the treatments exists, and the trial data show a difference, a Type I error has been made. The level of significance of the statistical test is the probability of making this Type I error. Conversely, if a real difference exists between the treatments and no such difference is found, a Type II error has been made. The probability of not making a Type II error, that is, of finding a difference if there is one, is known as the power of the statistical test. Clearly, both errors are highly undesirable and should be made unlikely to occur. It was decided, therefore, to set the likelihoods of both errors at \( P = 0.05 \).

For a non-sequential comparison of proportions or percentages, it can be calculated (Cochran & Cox, 1957) that, for a 5% treatment difference and Type I and II error rates of \( P = 0.05 \), the minimum number of patients required per group is 701. For a 10% treatment difference a maximum of 648 patients per group is needed. As there are five main treatment groups in the OCCS, the minimum total number of patients required is 3505 for a 5% treatment difference. At worst, a 10% treatment difference will be detectable with 3240 patients. The maximum sensitivity is obtained when the percentage of survivals is near to 0% or 100% and the minimum sensitivity when the percentage of survivals is near to 50%.

**Data handling**

Clearly, a vast amount of data will result from the OCCS. Over 3000 patients, with a registration form, a radiotherapy form and a follow-up every month or 2 months for at least 2 years, will need to be recorded, stored and analysed. It was therefore considered to be extremely important to minimize the work of the clinician in recording the data, and forms which can be completed by ticking one of several alternatives were designed.

A major requirement in designing these forms was that they were computer and punch-card compatible. Thus, all the answers were numerically coded for ease of data processing. At the survey centre the data can then be stored compactly, and sorted and analysed by electromechanical and electronic means.

**Conclusion**

As can be seen, a great deal of thought and planning has already gone into the preparation of the OCCS. The medical participants are all agreed on the worthwhileness of the study, and every attempt has been made to ensure that the clinician's task in recording the data will be simple and convenient. The decision to ask for large amounts of data, both in terms of detail on each patient and in terms of patient numbers, was not taken lightly but it is hoped that this brief discussion of the statistical aspect of the OCCS will make this decision seem to be soundly based.

**References**


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