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Clinical Problems

Organization of Clinical Trial on National Scale: Management of Early Cancer of the Breast

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Summary

From a study of the organization of a national clinical trial on the management of early cancer of the breast in women there appear to be overwhelming advantages in studying large numbers of patients. To this end centres abroad have been encouraged to join. All the evidence at present suggests that it is feasible to organize a study on this scale, that the documentation and follow-up are accurate, and that the enthusiasm of the participants can be successfully fostered and maintained.

Introduction

There can be no doubt about the magnitude of the problem of the management of early cancer of the breast. It is the commonest malignant disease in women in the United Kingdom; one in 17 develops the disease and over 10,000 die from it each year.¹ Despite all our efforts over the past few decades there is little information about which of the different forms of present-day therapy alters the course of the disease for the good of the patient, which has little or no effect, and which may even be harmful. Experience points to the fact that only prospective, randomized clinical trials involving many patients are likely to provide firm facts on which rational decisions can be based. Few such clinical trials have been carried out.²⁻⁶ All treatment methods compared were based on the traditional view of tumour spread,⁷ where it is assumed that malignant cells in

the breast or regional nodes must be either surgically removed or "sterilized" by radiotherapy.⁸ Thus all methods compared showed a final common pathway of "radical" intent.

In 1969 over 100 clinicians, representing most of the regions in the United Kingdom, met at Cambridge to discuss the management of early cancer of the breast. The outstanding feature was the doubt and uncertainty about the best form of treatment. A survey was then carried out on the management of early cancer of the breast in almost all the regions throughout the United Kingdom. As a direct result of these promptings and inquiries an investigation was launched to study two competing forms of therapy based on conflicting concepts of the biological behaviour of breast tumours.⁸ Our survey indicated that the commonest form of radical therapy practised today is simple mastectomy with post operative radiotherapy. The Association of Surgeons confirmed that more clinicians adopted this form of treatment than any other.⁹ In addition it appears to be as successful as other forms of radical therapy.³ For these reasons simple mastectomy and radiotherapy was chosen as best representing the traditional approach. There were strong arguments that simple mastectomy alone would best represent the "conservative" attitude.

There is increasing evidence that defence mechanisms, possibly involving the regional lymph nodes and the lympho reticular system as a whole, may play a part in the tumour-host relationship.¹⁰ The radiotherapy regimens usually employed in the treatment of breast cancer depress not only local immune reactions¹¹ but lymphoreticular activity throughout the body.^{12 13} Indeed in some people radiotherapy may result in the early appearance of distant metastases.¹⁴ Our survey of the regions indicated that simple mastectomy alone would be acceptable to most clinicians. In this group a "watch policy" was adopted. If lymph nodes required treatment at a later date this would be carried out.

On further exploration of the problem there appeared to be overwhelming advantages in admitting large numbers of patients to the trial. The reasons are discussed below. This inevitably led to the idea of a trial on a national scale. After two years

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we have now passed the half-way stage of the largest clinical trial ever undertaken in the United Kingdom as regards numbers of participants. We hope that our experience will be of value not only to those interested in the management of early cancer of the breast but also to those who may become concerned in the many other problems in medicine which demand clinical trials on a similar scale.

Scale of Trial

Experience with controlled trials²⁻⁴ and uncontrolled series¹⁵⁻¹⁷ indicates that one form of therapy may confer at most only a slight advantage over another. Possibly the outcome of the present study will be similar, despite the fact that the two treatment groups are based on widely different approaches. Indeed, to show that there is no significant difference between the two would be an important advance. If we could avoid subjecting patients to the unnecessary discomfort and occasional morbidity of radiotherapy then all the effort would be worth while.

On the other hand, if a real difference of an important size does exist between the two methods sufficient numbers should be admitted to the trial to give a good chance of detecting that difference. Seven per cent. is probably the smallest difference in results that would influence a clinician's choice of treatment in the future. To stand a greater than 90% chance of detecting such a difference the number of patients required is about 2,000, (Fig. 1).¹⁸

FIG. 1—Relation between number of patients in trial of two treatment regimens and chance of detecting 7% difference in results.

There is another compelling argument for admitting large numbers of patients to the trial. While possibly there will be little or no difference in the results of the two treatment regimens when taken as a whole there may well be pronounced differences in subgroups, defined by clinical or pathological criteria. Indeed the results in subgroups divided according to, say, menopausal status, clinical staging, or histological factors may give us a further insight into the biological nature of the disease and may allow us to individualize treatment in the future.

With this end in view we have been indeed fortunate that large centres in Scandinavia, Switzerland, the Irish Republic, Canada, and New Zealand have joined the study. In addition, and of great importance, there is an agreement to exchange information with the National Surgical Adjuvant Breast Project in the United States.

Organization

PROTOCOL

Women under 70 years of age with stage 1 or stage 2 (T_{1+2} ; N_{0+1} ; M_0) carcinoma of the breast are eligible for inclusion

in the trial. A simple mastectomy is performed in all patients without surgical attention to the axillary lymph nodes. The operation specimen is cut in a standard manner so that tumour grade, lymphocyte infiltration of the tumour, and other histological features are recorded. Samples of the tissue are sent to the two project pathologists who review all the cases in the trial, so that uniformity of reporting is assured.

In the postoperative period the patients are allocated at random into one of two treatment groups. The irradiated group is given a course of radiotherapy to the skin flaps, regional lymph node areas, and the chest wall (see Table). The "watch

Radiotherapy Protocol. Range of Values in Rads for Minimum Deep Tissue Dosage on Chest Wall and Doses at Mid point of the Axilla and at Estimated Depth of Supraclavicular and Internal Mammary Glands

	(18 Days) 3 Weeks	(25 Days) 4 Weeks	(32 Days) 5 Weeks	(39 Days) 6 Weeks
3 Fractions a week	2,850-3,150	3,200-3,500	3,450-3,850	3,700-4,050
5 Fractions a week	3,250-3,600	3,650-4,000	3,950-4,350	4,200-4,600

Multiply by 1.1 for supervoltage.

policy" group does not receive any further primary treatment. Treatment to the regional nodes is permitted, however, if there is evidence of progression of the disease, as manifested by continuous enlargement or fixation of nodes or the appearance of symptoms referable to the axilla. The type of treatment of local or distant recurrence is not defined and is left to the clinician's judgement, but all details are recorded in the patient's progress notes.

DOCUMENTATION

A separate form is used for each patient and is kept by the clinician responsible for the patient for 10 years or until the patient's death. Information is recorded by ticking answers to questions on the form, which are specially arranged for ease of transfer to a computer. A total of 186 items of information are recorded for each patient entering the trial, and this gives a more detailed account of the patient's condition than is usually recorded in surgical practice throughout the country. The information is automatically duplicated and a copy is sent to the secretariat, where it is checked, transferred to punch tape, and loaded into an ICL 1900 computer for storage and analysis at appropriate intervals.

Several checks have been incorporated into the administrative system so that the accuracy and completeness of documentation are of the highest order. All the cards which are used to allocate treatment are coded so that the secretariat can check the randomness of allocation of treatment at each hospital. Finally, a random sample of data from the forms are compared with the information recorded in 10% of the patients' own hospital case sheets every six months to ensure that they correspond one to the other.

SECRETARIAT

The secretariat is situated at King's College Hospital, London. It consists of a graduate administrator, who is responsible for checking the accuracy of the information flowing into the centre from the regions and submitting the data to the computer; she is helped by a part-time secretary. There are two surgeons, who are engaged for a large part of their time in the trial: one is a lecturer in Surgery and the other is a research Fellow paid by the Cancer Research Campaign. The housing of the administrator, secretary, and two surgeons is such that they are in close communication each day, and this ensures a smooth running of the machinery of the secretariat. They are at all times responsible to a working party.

WORKING PARTY

The working party, composed of 12 people, meets every three months to decide policy on major issues as they arise during the progress of the trial. The members are selected for the most part to represent geographical areas heavily committed in the trial. They comprise surgeons, radiotherapists, and pathologists. The representation is flexible. With the development of the trial additional members are co-opted at appropriate times. The secretariat reports to the working party about the details of the trial. The working party represents the main source of decision making in the short term in the policy of the trial.

COMMUNICATIONS

Perhaps the outstanding feature from experience of running this trial is the emphasis on close personal contact between the participants, the secretariat, and the working party. In the first place the two surgeons of the secretariat have systematically visited all centres. They have explained in detail the protocol, the form used by the clinician, and the trial as a whole to the participants. Often a second visit with a discussion restricted to specific problems has been invaluable to all concerned.

There is a great risk that a central organization may become impersonal and remote. For this reason all the participants, working party, and secretariat have attended annual general meetings at the Royal College of Surgeons in London. Here progress is presented and difficulties can be voiced. Ideas and views for future trials are discussed. Personnel from all regions of the country can meet and discuss in small groups their particular difficulties in the management of cancer of the breast. The other form of communication, six months after the annual general meeting, is a bulletin which gives an interim report of the progress of the trial.

Results

It is far too early and certainly inadvisable to give results of treatment at this time. Nevertheless, an indication of the progress of the trial, which started in May 1970, can be given. The scale of the trial in the United Kingdom amounts to a national effort. This fact has been recognized by the Cancer Research Campaign, which is providing financial support and lending its name to the trial. There are now 1,050 patients included in the study. The number is increasing continuously (Fig. 2), and the average rate of admission has

FIG. 2—Rate of admission of patients into present trial.

risen within the past six months from about 50 to 70 a month. The initial data from the first 662 patients have been analysed to assess the tumour size and lymph node status of the patients in the two treatment groups (Figs. 3 and 4). There are no statistical differences between these factors, and this confirms the success of random allocation of treatment. The follow-up rate two years after the trial began was 97%.

FIG. 3—Distribution of tumour sizes among the first 662 patients.

FIG. 4—Axillary lymph node status among the first 662 consecutive patients.

This paper is written on behalf of the surgeons, radiotherapists, and pathologists from 80 institutions on whose efforts the success of this venture depends. We suffered a great loss on the death of Mr. Brian Truscott, of Cambridge. He was one of the instigators of the trial and gave unstinting support. We gratefully acknowledge the encouragement and guidance of the working party, comprising Professor J. S. Mitchell, Professor J. G. Murray, Dr. D. Brinkley, Dr. J. Haybittle, Dr. G. A. Gresham, Dr. C. Elston, Mr. W. Ross, Dr. G. A. Edelstyn, and Dr. T. Wheeler. We thank the Cancer Research Campaign for their financial support for this project. A preliminary report of this trial was given to the Surgical Research Society in July 1971, and a dissertation for the Moynihan prize was read in April 1972 to the Association of Surgeons.

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