PERGAMON

European Journal of Cancer 38 (2002) 937–942

European Journal of Cancer

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Surgical trials in oncology: the importance of quality control in the TME trial

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Received in revised form 18 December 2001; accepted 4 February 2002

Abstract

Results from randomised trials provide the best scientific evidence of efficacy or inefficacy of the therapy. The evaluation of surgical procedures involves problems in addition to those associated with medical experimentation. Surgery, unlike a pill, is not a standardised, reproducible entity, but a unique product whose details are defined by, for example, the skill of the surgeon. Quality assurance is important for treatment and also for data handling. The different treatments (surgery, pathology, radiotherapy, etc.) should be familiar to all participating physicians prior to the start of the trial. Instructions can be given by means of a well-written protocol, videotapes, workshops and instructors at the dissection table. The data collection and data check should be done by data managers and co-ordinators for the separate disciplines. Errors and missing data should be completed and feedback to the physician is essential. Close contact between an active co-ordinating data centre, including co-ordinators for the separate disciplines, and all participating physicians is essential to conduct a quality controlled multicentre, multidisciplinary trial. Continuous enthusiasm can be maintained by the organisation of regular workshops, distribution of newsletters and trial up-dates at scientific meetings. The efforts from all of the involved co-ordinators, data managers, instructors and physicians have resulted in a very successful trial with rapid accrual, good quality treatments and procedures, good quality data, and a high participation rate among hospitals and patients. Quality control is expensive and labour-intensive, but it is worthwhile. © 2002 Published by Elsevier Science Ltd.

Keywords: Surgical; Trial; Quality control; Instruction

1. Introduction

The first randomised clinical trial was carried out more than 50 years ago, when the efficacy of streptomycin in the treatment of tuberculosis was demonstrated [1]. Since then, many, mainly medical, randomised trials have been conducted. The contribution of surgical randomised trials has been relatively low, although results from randomised trials are the only results used for evidence-based medicine. Occasionally, medical breakthroughs are not substantiated by a randomised trial. The famous French army surgeon Ambroise Paré (1509–1590) made his important discovery about the treatment of soldiers' wounds by chance. Paré had run out of burning oil to scorch the wound, so he had to try an alternative method. He made a dressing of egg whites, oil of roses and turpentine. The dressing successfully sealed the wound and provided relief from pain.

In 1996, Richard Horton, Editor of the *Lancet*, wrote a commentary entitled 'Surgical research or comic opera: questions, but few answers [2]. He reported that only 7% of papers published in nine general surgery journals were randomised trials and almost half of the publications were case studies and he therefore concluded that surgeons did not seem to see research as a key issue in their practice. Obviously, he received a lot of criticism from the surgical community [3]. In this paper, we will describe difficulties in the randomisation procedure in surgical trials and, in conjunction, the importance of quality control, and we will illustrate it with an example.

2. Randomisation

Randomisation of patients to evaluate surgical procedures involves problems in addition to those associated

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0959-8049/02/$ - see front matter © 2002 Published by Elsevier Science Ltd.
PII: S0959-8049(02)00045-X

with medical experimentation. Surgery, unlike a pill, is not a standardised, reproducible entity, but rather a unique product whose details are defined by variables, which include, for examples the skill of the surgeon. The skill level will not only vary among surgeons, but will increase for the same surgeon while he/she gains experience [4]. Furthermore, surgeons with specific interest will perform better [5,6]. These surgeons are also well disposed to develop new techniques in their own centre and subsequently analyse their series. This is one of the reasons why so many informative non-randomised hospital or personal series are published.

Pharmaceutical companies on the other hand extensively sponsor new drug trials. These new drugs are from the start tested in the proper way, through phase I, II and III trials. Surgical trials, however, cope with many variables and have enormous difficulties in obtaining money. In The Netherlands, we are relatively fortunate to have two major, independent, grant-giving bodies for cancer clinical trials: the Dutch Cancer Foundation, which supports local and central data management and the Dutch Health Council, where also financial support for salaries of co-ordinators and, for examples for reimbursement of expenses for pathologists and instructor surgeons can be applied for. Both organisations will only support randomised trials. Prospective registration studies are therefore hard to run.

It is also difficult to conduct a randomised trial in an evolutionary phase of a new operation [7,8]. A prerequisite for a trial is that the participating surgeons are equally conversant with both techniques. An alternative to this problem could be the use of a randomised-surgeon design where groups of surgeons will perform conventional surgery and other groups of surgeons will perform the new type of surgery [8,9]. However, a main objective of performing surgical trials is the improvement of outcome, which would occur at a slower pace if the surgeons kept using conventional techniques.

3. Quality control

Surgeons, training and infrastructure to perform surgical trial treatments need to be defined in detail in a protocol. Not only the type of surgery, but also the type of reconstruction, the treatment of complications, pathological examination, etc. A new technique should be introduced at several levels, e.g. by booklets, videotapes, workshops and at the dissection table by instructor surgeons.

In surgical trials, the level of training and expertise of those performing the procedures must be comparable and should always be documented [9]. Documentation should be done in the local surgical report, as well as in detailed case report forms. After the introduction of the new technique, operations of patients in trials should be attended by an instructor surgeon, not only to teach the local surgeon, but also to guarantee the standardisation and quality of the operation [10].

Quality control involving surgical treatment in multi-institutional cancer trials is also important since the results of local or systemic adjuvant therapy might be obscured or overestimated by inadequate surgery or pathological examination of the specimen. In rectal cancer, for example, 27% local recurrence was observed in a surgery alone group versus 11% in combination with preoperative radiotherapy [11]. In stage II and III breast cancer, for example, mastectomy plus cyclophosphamide, methotrexate and 5-fluorouracil (CMF) gave a local recurrence rate of 32% versus 9% in the mastectomy plus CMF plus postoperative irradiation group [12]. Both studies showed that the radiotherapy group also had a better survival. In those two studies published in the *New England Journal of Medicine*, the surgery without radiotherapy groups experienced recurrence rates which for most well trained surgeons would be unacceptable. Most trials, especially those evaluating systemic treatment do not use clear definitions or descriptions of the procedures. McArdle and Hole stated 10 years ago that "some surgeons perform less then optimal surgery; some are less competent technically than their colleagues; and some fail to supervise surgeons in training adequately... If by more meticulous attention to detail the results of surgery could be improved, and our results suggest that this would not be difficult, the impact on survival might be greater than that of any of the adjuvant therapies currently under study" [5].

4. Example of the development of a surgical trial

Japanese gastric cancer patients have a much better survival than Western patients. One of the reasons could be the more extensive surgery [13]. A similar problem occurred in the field of rectal cancer: extended surgery [14] and Total Mesorectal Excision (TME) [15,16] have led to strikingly lower local recurrence rates. This knowledge has led to the design of two randomised surgical trials: a pure surgical trial of D1 dissection versus D2 dissection in gastric cancer [17] and a trial in rectal cancer, the genesis of which will be explained below [18].

In The Netherlands, several population-based studies observed local recurrence rates of approximately 20% [19–21]. The goal of any new trial was to achieve standardisation of rectal surgery leading to lower local recurrence rates. Since 1994, some enthusiastic surgeons throughout The Netherlands developed the idea further. Meetings were organised and two newsletters were distributed. The idea for a phase III rectal cancer trial at that moment was to randomise patients for standard D1/D2 dissection plus preoperative radiotherapy versus

extended D3 dissection alone. The hypothesis was that extended surgery was as good as limited surgery plus preoperative radiotherapy. A pilot study had been carried out from November 1994 to March 1995, by Professor Moriya from the National Cancer Center in Tokyo. He visited 24 hospitals throughout The Netherlands as an instructor surgeon [22]. Many Dutch surgeons, however, feared a considerable morbidity following the use of the Japanese D3 technique in Dutch patients, as was experienced with the D2 dissection in the Dutch Gastric Cancer Trial, as well as the MRC trial, in which postoperative mortality after D2 dissection was twice as high as after D1 dissection [23,24]. Moriya therefore performed a more or less 'modified D3 dissection' [22]. This changed the views to a TME approach, as advocated by Heald and Enker many years earlier [15,16].

Second and third proposals were to compare conventional surgery with TME surgery or compare in a two-by-two factorial design yes/no preoperative radiotherapy and conventional versus TME surgery. Both designs, however, would allocate 25–50% of the patients to the inferior arm of conventional surgery without preoperative irradiation. Another problem with all of the designs was the already routinely used preoperative radiotherapy in many hospitals. The trial would therefore accrue only a few patients. Other problems were that the data from the literature were so convincing with regard to the superiority of the TME technique over conventional surgery, that a majority of the Dutch surgeons had the opinion that it would be unethical to randomise patients in such a design, and they were also eager to learn a new technique. It was also not clear what the definition of conventional surgery was. A final proposition was made: compare TME surgery with or without preoperative radiotherapy; in other words: is radiotherapy still beneficial in combination with good surgery?

Financial support is crucial, especially in multicentre trials [25,26]. Approval by the Dutch Cancer Foundation for the last design was obtained in August 1995, merely for local and central data management support. The omission of a pure surgical trial of conventional surgery versus TME surgery was a major concern for the Dutch Health Council for 3 years. Final approval and financial support for a surgical co-ordinator, pathology co-ordinator, quality of life co-ordinator, a second central data manager, and also compensation of the costs for instructor surgeons and pathologists was only obtained in April 1998.

The rectal cancer trial was launched in January 1996. In The Netherlands, each hospital has its own Medical Ethical Committee and each committee had to approve the protocol. In our country, we have at our disposal an excellent data management network, financed by the Dutch Cancer Society. In practice, this means that every data centre linked to one of the comprehensive cancer centres receives a fee per randomised patient in their region. All Dutch hospitals are covered by this system. Data managers working in the field of cancer clinical trials are all members of the Dutch Working group for Data managers (DWD), similar to a network in the UK [27]. The DWD group organises biannual meetings and a yearly course. At those meetings, new protocols and several aspects of cancer treatments are discussed and uniformity on case report form completion is accomplished.

5. Instruction and quality control within the TME trial

From the early days of the trial, it was stated that the study should be a quality-controlled study. This meant quality control in radiotherapy, pathology and surgery.

5.1. Radiotherapy instruction

Results from a questionnaire which was mailed to all 21 Dutch radiotherapy departments showed that the use of the 5×5 Gy scheme, as used in Sweden [28] was accepted by most institutes. Treatment details, like volume and fields were described meticulously in the protocol. A simulation procedure was mandatory and all institutes had to use the three or four fields portal box technique in order to avoid serious non-surgical morbidity which was observed in the Stockholm trial using less fields [29].

5.2. Pathology instruction

The TME procedure provides an excellent specimen and therefore the pathologist was able to check if the procedure had been performed according to the protocol using the transverse slicing method of Quirke, which is highly predictive for the development of a local recurrence [30].

Thus, surgeons as well as pathologists had to learn new skills which were very different from their daily practice. How did we facilitate this learning process? In addition to the TME study protocol, a special pathology protocol was written which was distributed to 43 pathology laboratories. A pathology workshop was organised in December 1995 with the attendance of Dr Quirke. We also produced a sheet with a step-to-step protocol to be used at the dissecting table. The pathology co-ordinator had set up a Pathology Review Committee to discuss problems and review the slides, reports and photographs of the specimen.

5.3. Surgery instruction

How to learn a new surgical technique? Firstly, we produced a videotape on radicality and autonomic nerve preservation, with operations performed by Professor Moriya. Mr Heald from Basingstoke was installed as a

visiting professor in Leiden, funded by the Dutch Cancer Foundation. He performed almost 30 operations throughout The Netherlands and produced two videotapes, which were distributed to all participating hospitals. He has attended all seven of our workshops, which were organised all over the country from May 1996 until April 2000.

The Netherlands is divided into nine comprehensive cancer centre regions. From each region, a few experienced TME surgeons were chosen. In total, 21 instructor surgeons were selected. Their task was to introduce, teach and control the TME operations in their region. In each hospital, the first five TME procedures had to be supervised by an instructor surgeon. This requirement meant that 66% of the TME operations during the first year were attended by instructor surgeons. This instructor system had also successfully been used in the Dutch D1-D2 gastric cancer trial [10].

6. Logistics of the TME trial

6.1. Randomisation and case report forms

To facilitate the selection of eligible patients, we made pocket-size cards listing all criteria, the randomisation scheme and the phone number for randomisations at the central data centre in Leiden.

Randomisation was performed centrally using predefined lists with stratification per hospital and expected resection type. All in- and exclusion criteria were checked by phone and the allocated treatment and patient trial number were given immediately thereafter. Usually, randomisation of the patient was done by the surgeon.

Case report forms were mailed after randomisation for every single patient, to every individual doctor involved in the treatment of the patient. This labour-intensive system of data collection differed from most other systems. The forms usually point out one responsible investigator or data manager for all case report forms and the forms are delivered in a file. We had arranged that the surgeon was responsible for the completion of the surgery forms, the pathologist for the pathology form and the radiotherapist for the radiotherapy form. The local data manager received a copy of the randomisation form and was responsible for the on-study, follow-up, recurrence and death forms and could support the local investigator. The main advantages of this extensive system were that the investigator knew exactly which forms had to be filled in and, moreover, that all involved specialists were prospectively aware that their patient was participating in a multidisciplinary trial (see Fig. 1).

Before randomisation, the surgeon should have handed over a pretreatment quality of life questionnaire to the patient since quality of life was a secondary endpoint in the trial. In reality, it turned out to be more practical and easier for the surgeon that the questionnaire was mailed, via the data centre with a self-addressed return envelope, to the patient's home. Follow-up questionnaires were also sent directly to the patient (to reduce the burden on the surgeon as much as possible) at 3, 6, 12, 18 and 24 months after surgery. The compliance rate was 85%. Furthermore, a sub-set of patients was visited by the quality of life co-ordinator for face-to-face interviews on treatment preferences and costs.

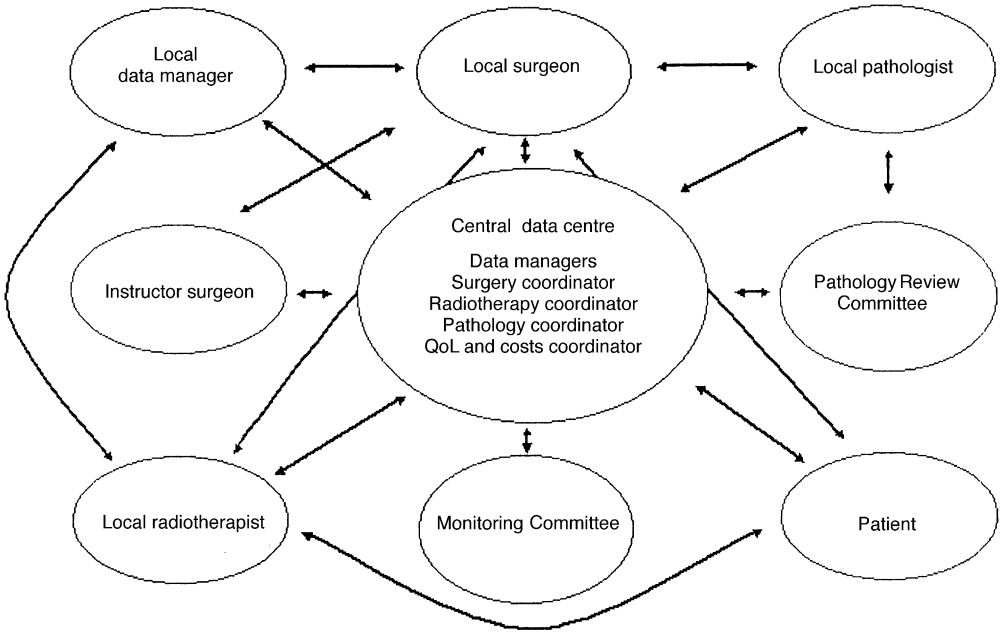

Fig. 1. Organisation of the TME trial. QoL, quality of life.

6.2. Data check

Returned forms were checked manually for correctness and completeness. In addition to the case report forms, surgeons were requested to send a copy of the surgery report and discharge letter for verification of the data on the case report forms. Pathologists were asked to send a copy of the pathology report, a slide of the tumour for later revision by the Pathology Review Committee, photographs of the specimen and two paraffin blocks: one with tumour and one which contained normal tissue. The pathology co-ordinator also collected fresh frozen tumour and normal tissue by visiting the different pathology laboratories. These materials are stored in a tumour bank at the central Leiden University Medical Center (LUMC) data centre. Paraffin blocks and fresh frozen material is being used for additional research.

Copies of important reports and letters were collected with the purpose of checking the correctness of key data on the case report forms. For the pathology data, for example, we published the data check results of the first 300 patients and concluded that there were major discrepancies between the case report forms and the pathology report, mainly in the data pertaining to the circumferential margin [31].

For all recurrences, diagnostic reports were collected to verify the correctness of the event. In some cases, the radiotherapy co-ordinator collected the actual photos if there were any doubts about a recurrence and the result was notified to the local physician.

Data were entered in a database (Medical Research Data Management) and automatic range- and cross-checks were carried out. In a second round, it had also been checked if the data were correctly entered onto the computer. Statistical analyses were performed with the Statistical Product and Service Solutions, SPSS 10 for Windows, 1999 (SPSS Inc., Chicago, IL, USA).

During the data check, special attention was paid to the eligibility criteria. These were also checked during the randomisation procedure, but some patients turned out to be ineligible afterwards. These patients had to be excluded from specific analyses. However, all patients were included in the analyses addressing the main question of the trial. We found that the percentage of ineligible patients varied dramatically between the participating hospitals, thus even more attention will be paid to the check of eligibility criteria in future trials, especially for certain centres. Every 6 months, two overviews were sent to all of the involved disciplines. In the first report, we gave an administrative overview with patient identifications, number of randomised patients and received forms. In the other overview, some key variables per patient were listed. For the surgeon, we showed, for example, TNM stage, residual tumour status, last date of follow-up, date of loco-regional recurrence, date of detection of distant metastases, date of death and overall survival in months. For the radiotherapist and the pathologist, similar overviews containing their specific data were given. Approximately 1 month thereafter, we sent a reminder to those who did not respond to the missing forms requests. As stated before, instructor surgeons were involved in the quality control and education of surgeons in their region. We also sent overviews to the instructors to facilitate and stimulate accrual in their region.

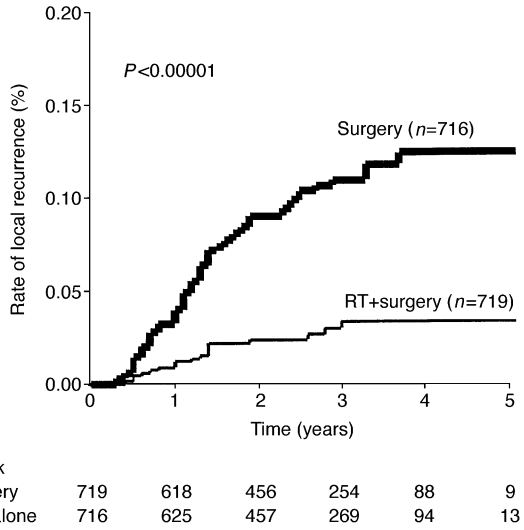

Fig. 2. Rates of local recurrence in 1435 eligible patients who underwent macroscopically complete local resection according to treatment group. At 3 years, the rate of local recurrence was 3.4% in the group assigned radiotherapy and surgery and 10.9% in the group assigned surgery alone. RT, radiotherapy.

Follow-up results of the trial have been published in the *New England Journal of Medicine* in August 2001 [18]. Median follow-up at the time of analysis was 2 years for the whole study population. In Fig. 2, an update of the Dutch patients is given, with a median follow-up of 2.9 years. The rate of local recurrence at 3 years in eligible patients with a macroscopically complete local resection ($n = 1435$) was 3.4% in the group assigned preoperative radiotherapy and 10.9% in the group assigned surgery alone ($P < 0.00001$). The hazard ratio for local recurrence in the surgery alone group compared with the radiotherapy group was 3.78 (95% Confidence Interval (CI) 2.25–6.35).

7. Conclusions

The efforts from all of the involved co-ordinators, data managers, instructors and physicians have resulted in a very successful trial with rapid accrual, good quality treatments and procedures, good quality data, and a high participation rate among hospitals and patients. Quality control is expensive and labour-intensive, but it is worthwhile. So, quality control is a fact, not a fantasy.

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