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Quality Assurance of Surgery in Clinical Trials

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IT IS widely accepted that quality assurance of radiotherapy and chemotherapy should form an intrinsic part of prospective randomised multi-centre trials for cancer. For these semi-quantiative disciplines, the mechanism of quality assurance is not too difficult to apply. The craft of surgery poses more problems. Although audit of outcome is now widely practised, the assessment of surgical techniques is much more difficult.

The sceptics might argue that surgical technique is not important, outcome being determined by stage of disease at presentation and use of adjuvant therapy. In this they would be wrong, since in early breast cancer, assessment of stage is based not just on clinical evaluation but also on nodal status, which is provided by both the surgeon and the pathologist. The importance of exact evaluation of the axilla has been furnished by the Danish Breast Cancer Cooperative Group who proved that the extent of axillary clearance affects prognosis [1].

A total of 13851 node-negative patients was entered into two programmes, DBCG 77 and 82. These cases were sub-categorised on the basis of lymph nodes examined by pathologists (a reflection of both the extent of surgery and the assiduousness of pathological investigation). It was found that a true state of node negativity could not be confirmed unless a minimum of 10 nodes was examined. Furthermore, those patients who had 10 or more negative nodes examined had a significantly better axillary relapse-free survival ($P < 0.001$), relapse-free survival ($P < 0.0001$) and overall survival ($P < 0.005$).

As was originally shown by the Guys Hospital wide excision trial, the extent of local treatment does influence survival [2]. Since local treatment and axillary nodal status are the major determinants of survival and are significant factors for entry in trials, it is important that there should be quality assurance of surgical techniques, such as local excision and axillary clearance. If this is not done, promising new adjuvant therapies will not be properly tested because of the heterogeneous nature of the patients in the trials.

To this end, the EORTC Breast Cancer Co-operative Group have set up a working party to study quality assurance of surgery. The aim of the project is to examine the surgical technique used in participating centres, to draw up guidelines and to monitor the adherence to these. Eventually it should be possible to extend these quality assurance criteria from specialised centres to non-academic hospitals, so that the general surgical treatment of patients entering both trials and also undergoing empirical treatment may be improved.

In this issue, a group from St Vincent's Hospital, Dublin, addressed the question of auditing axillary clearance (pp. 148–149). A series of 100 sequential axillary clearances was performed by a variety of grades of surgeon, and the procedure was then assessed by a second surgeon who resected any further tissue present in the operative field, and this was arbitrarily designated level IV nodes. During the first 6 months of audit, level IV nodes were retrieved by the inspecting surgeon in 28/60 (47%) and metastatic tumour was present in 2%. In the second 6 months of audit, level IV nodes were found in only 8/40 (20%). The presence of metastatic tumour in level IV nodes did not lead to any change in pathological stating. Interestingly, level IV nodes were present after axillary clearance by surgeons of all grades of experience.

The EORTC Breast Cancer Cooperative Group is adopting a different approach, since auditing, as performed in Dublin, is only applicable in a single centre. It is less practical when analysing surgery in many centres at the same time. Documentation on decision-making and the surgical act itself is essential, but is too often underestimated and lacking in patient files and clinical trial forms. Even after editing a manual, which contains definitions of surgical procedures, much uncertainty persists and, in practice, actual surgery may not always meet the definition.

We looked at a method of analysing the manner in which surgery (local tumour excision and axillary clearance) is actually delivered by improving documentation on the procedure, since this is probably the only practical way of gathering information in large multicentre clinical trials. Too often analyses may rely on pathology reports which are subject to lack of quality as well.

In this project, we started with detailed computer-based checklists on tumour excision and axillary clearance which are to be completed by the participating surgeons. Site visits (some kind of audit) confirm whether the procedures performed are delivered as they are described in the checklists.

The preliminary results have already revealed a lot of major and minor differences, but future analysis and discussion must decide on the importance of those detected variations in terms of outcome, i.e. local control, cosmesis and complications. Furthermore, we will be able to draw up more strict surgical recommendations in future trial protocols. Acceptable variations in techniques will be defined, and we will add more specific questions in the forms dealing with surgery to be as sure as possible that the procedure has been performed as prescribed (for eventual stratification). In addition, the surgeons' personal preferences, such as the siting of the breast incision, closure of the breast tissue or not, and in continuous or separate incisions for axillary surgery, must be recorded since these differences will be important when analysing cosmetic results of breast conserving treatments.

As a group concerned with breast cancer, we should be able to present a standard of reference not only for the good

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functioning of our own trials, but for every surgeon dealing with breast cancer. This standard should be adapted when new elements in cancer treatment are available. We should take the responsibility of promoting the implementation of these standards in non-specialised centres dealing with breast cancer. Furthermore, this quality assurance experience in breast conservative treatment could enhance similar projects in other aspects of oncological surgery.

Until quality assurance becomes an integral part of surgical treatment for cancer, there will be an unnecessary additional chaotic component within clinical trials. For improvements in systemic therapy to become manifest, it is important that local therapy is optimal, and the best method for improving surgery will be by means of quality assurance.

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Papers

Immunological Response to Intrathecal and Systemic Treatment with Ganglioside Antibody R-24 in Patients with Malignant Melanoma

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Murine monoclonal antibody (MAb) R-24 reacts with the ganglioside GD3 that is highly expressed on malignant melanoma. 2 patients with melanosis of the meninges received MAb R-24 intrathecally. Regressive changes in tumour cells were observed in both patients after intrathecal application of MAb R-24 (1–10 mg, 8–10 h, over 5–6 weeks). The first patient suffered from brain metastases and died a few weeks later, whereas the second achieved a complete remission with no evidence of disease 6 years after intrathecal R-24 treatment. No R-24-related neurotoxicity has occurred to date. The administration of MAb R-24 caused an increase of inflammatory cells in the cerebrospinal fluid (CSF) of both patients. Cytotoxic lymphocytes, cultured from the CSF, showed high cytolytic activity against allogeneic melanoma cells *in vitro*. In addition, 15 patients with advanced melanoma, in which the brain was not affected, were treated with R-24 intravenously using high dose R-24 (5 or 10 mg/m^2) or low dose R-24 (1 mg/m^2). No remissions were registered in the high dose group, with only 1/6 patients experiencing a mixed response. In contrast, 2/9 patients treated with low dose R-24 achieved a partial remission, one achieving a minor response and the other a mixed response. Toxicity was related to the dose of R-24 administered. Urticaria, burning and pruritus were the prominent side-effects, mostly occurring at the high dose level. Immunological monitoring during and after intravenous treatment showed no significant changes in peripheral blood lymphocytes, natural killer cell activity or antibody-dependent cellular cytotoxicity, although transient changes were observed. There was no correlation between immunological parameters and clinical response.
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INTRODUCTION

A LARGE NUMBER of antigens have been identified on human melanoma cells using monoclonal antibody (MAb) technology. Gangliosides in particular are strongly expressed on the cell surface of malignant melanoma. Several MAbs directed against the gangliosides (GD2, GD3, GM2 and GM3) have been developed [1–8]. The mouse MAb R-24 generated by Dippold and colleagues reacts with the trisaccharide structure NeuAcα2-8NeuAcα2-3Gal, which must be in a terminal position of the molecule [1,9,10]. This epitope is found in the disialoganglioside GD3 which is highly expressed on malignant melanoma and other tumours, and tissues of neuroectodermal origin [8,11–14].