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Progress in the management of solid tumours

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Breast cancer

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Summary

The management of patients with breast cancer has been changing over the last few years and this article highlights some areas of particular interest. The changes have been brought about against a background of an increasing disease incidence coupled with increasing political aspirations from patients and their relatives. This paper focuses on organisational aspects of breast cancer care, screening, induction and high-dose chemotherapy, clinical trials, genetics, training of surgical and nonsurgical oncologists and future prospects.

Keywords: breast cancer, management, treatment

Organisation

Breast cancer has traditionally been dealt with by surgeons as part of their general workload. This has resulted in uneven administration of treatments with some patients receiving suboptimal treatment.[1] It has long been assumed that the use of chemotherapy and clinical workload have an impact on survival but hard evidence has been lacking until recently.[2] With this, and increasing patient demands, the drive for site specialisation has become irresistible. The publication in the UK of documents such as the British Breast Group guidelines on provision of breast services,[3] the British Association of Surgical Oncology guidelines on treatment[4] and the Cancer Relief Macmillan Fund list of services available in each Trust,[5] have all contributed to the debate on who should manage these patients and what facilities are needed. All reports agree that there should be multimodality care with surgeon, clinical and medical oncology as well as breast nurse specialists available to all patients. These disciplines must meet regularly and all patients should be treated according to agreed protocols. In addition, the British Breast Group document stresses the need for audit and data management and 'guestimates' that the minimum number of cases needed to be seen by any one team is 70 per year, fewer than this not allowing the necessary concentration of staff and equipment. The report of the Expert Advisory Group on Cancer Services to the Chief Medical Officer[6] proposes three tiers of patient care–primary, cancer units and cancer centres. The managment of common solid tumours will be carried out in cancer units which will be based in District General Hospitals where primary treatment (surgery and chemotherapy) will be given. Many patients will still have to travel for radiotherapy to the centres where rarer tumours or dose-intense regimes will be dealt with. Most District General Hospitals will see more than 70 cases of breast cancer a year and may achieve cancer unit status for breast cancer. One effect of adopting these working practices will be the necessity for some surgeons to relinquish breast work, especially if they are only dealing with small numbers. Others may welcome the opportunity to learn techniques such as cytology or even take on reconstructive skills if they are nominated to provide a breast service. The surgical body has, on the whole, welcomed these changes and the establishment of a breast surgeons interest group within the British Association of Surgical Oncology has led to much interest.

Patients with breast problems are not universely managed by surgeons. For example, in France and Germany, gynaecologists are primarily responsible while in many countries the patient may be referred from the primary care physician to a radiologist for imaging and only on to a surgeon if a lesion is found. The concept of the breast-care physician has emerged and it is not uncommon to see breast clinics supported by nonoperating doctors.

Screening

In the UK, the National Health Service's Breast Screening Programme has now completed the prevalence round for the country and many centres are well into the first incidence round. In 1993 (the last year for which figures are available) 1209 290 women were screened and 6695 cancers detected (July 1995). Of these, 589 671 were prevalence screens and 521 181 incidence screens. A high rate of breast cancer was detected in those patients referred for an early recall as well as in women over the age of 65. Following recommendations from the Royal College of Radiologists, two views of each breast will be obtained at the time of first mammograms (prevalence screen) rather than the one initially proposed in the Forrest report. There is evidence that this will result in a higher pick-up of cancers with a reduced recall rate for technical reasons.[7] Although the cost per person screened will increase by £4, the cost per cancer detected is estimated to remain around £5330 per case.

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Current controversy is directed towards the screening interval which is currently set at three years. Most practitioners feel this is too long and that 18-monthly or two-yearly screens are appropriate. Woodman *et al*[8] recently reported an excess of interval cancers, which was especially worrying in the third year. A similar level of interval cancers has been found in Yorkshire.[9] The difference between the true interval cancer (ie, not apparent on films even when re-read by a panel) and a missed 'cancer' is not apparent from these reports. It may be that two readings of the films will reduce the interval cancer rate; the cost implications of reducing the screening interval to, say, two years, will be high. The Breast Screening Programme is currently sponsoring an ongoing study of the frequency of screening as well as one on the role of screening for the under-50 age group. Although there is (understandably) pressure from this latter group for screening, a cost–benefit analysis does not currently justify this. There is increasing evidence that screening the over 65s will be beneficial; after all, breast cancer incidence carries on rising after 65. A trial for this age group has been announced by the Department of Health. Wright and Mueller consider that the cost–benefit ratio is too low and that there is too high a price to pay even for older women.[10] Their estimate of £558 000 per life saved is high. They conclude that 'the benefit achieved is marginal, the harm caused is substantial, and the costs incurred are enormous' and suggest that public funding for breast cancer screening is not justifiable. It may be that those identified as being at higher risk of developing breast cancer (ie, those with a strong family history) should be targeted for screening at an earlier age.

Quality assurance standards were introduced with the screening programme for the various disciplines. Interesting results on the variation in practice are becoming apparent; the pathology quality assurance group have data on how a set of 'control' slides were interpreted, showing good agreement for some conditions but marked discordance for others. Marked preferences for 'rounding' the size of lesions in multiples of 5 mm was evident.

The surgical quality assurance guidelines suggest that the screen-detected workload be referred to one or two surgeons with special expertise and this is happening in some areas. In others, however, the work is still going to a considerable number of different surgeons. These individuals are thus only seeing a few cases each year and many do not have access to the necessary equipment such as the ability to take peroperative specimen radiographs. This is reflected in a higher mastectomy rate than for those who see more cases per year. The gradual merging of the screening service with a symptomatic disease practice is likely to happen in the near future.

Induction chemotherapy

Primary medical, neo-adjuvant, or induction chemotherapy are terms used synonymously and indicate that chemotherapy is being administered as the first line of treatment. It was originally used to shrink (downstage) large tumours[11] but has now been extended in some centres to all tumours. No survival benefit for this form of treatment has yet been demonstrated but it is clear that a significant number of tumours can be shrunk and less radical surgery may be performed. Its use allows an estimate of the chemosensitivity of a tumour to be made, with lesions that shrink quickly being more likely to have a better overall response and less, if any, residual tumour at resection. Most would agree that this treatment is insufficient on its own and that some form of further intervention (surgery or radiotherapy) is essential if local recurrence rates are to be held down. It can be difficult to localise the tumour site if a good response has been achieved and marking the original site with clips or other metallic objects has been proposed. Radiological assessment of the response to treatment may not be helpful, as microcalcifications often remain and a scar where the tumour was may give an overestimate of residual disease. Serial monitoring with ultrasonography may be the best way of assessing response.

Chemotherapy regimens used have included MMM (mitoxantrone, mitomycin-C and methotrexate) and CMF (cyclophosphamide, methotrexate and 5-fluorouracil) given intravenously (box 1). An alternative route is to give the drugs into the arterial supply of the breast (the internal mammary and lateral thoracic vessels). This allows a high local concentration to be delivered and good response rates have been reported.[12,13] There are no comparative trials to indicate whether the intra-arterial route is quicker or offers other advantages. It is more time consuming and requires an interventional radiologist which makes it unlikely to be generally adopted.

Common chemotherapy regimens

CMF: cyclophosphamide, methotrexate, and 5-fluorouracil

MMM: mitomycin-C, methotrexate, and mitozantrone

FEC: 5-fluorouracil, epirubicin, and cyclophosphamide

ECF: epirubicin, platinum, and infusional 5-fluorouracil

Taxoids: paclitaxel and docetaxel

Box 1

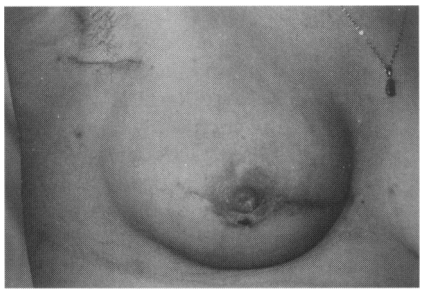

Figure 1 Immediate reconstruction after subcutaneous mastectomy for extensive duct carcinoma *in situ* with microinvasion. The scar has been carried round from the original medially placed biopsy site (performed elsewhere) and a second incision used to dissect the axilla. This photograph was taken two weeks after the operation

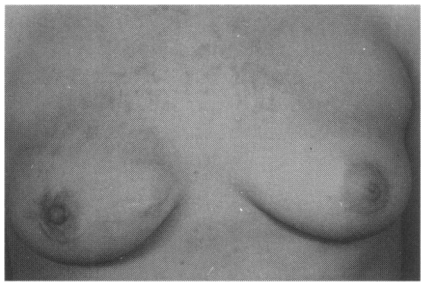

Figure 2 Wider angle view of same patient showing symmetry with the opposite breast. The scars have faded and there has been no clinically obvious capsular contracture after three years follow up

Treatment options

- no surgery; radiotherapy and/or hormone therapy (especially for the very eldery or unfit especially if oestrogen receptor+ve)
- excision of lesion ± axillary surgery (lumpectomy, tylectomy, wide local excision), plus radiotherapy, with or without chemotherapy and/or hormone therapy
- quadrantectomy ± axillary surgery, plus radiotherapy, with or without chemotherapy and/or hormone therapy
- mastectomy ± axillary surgery, plus radiotherapy, with or without chemotherapy and/or hormone therapy

Box 2

High-dose chemotherapy

Dose intensity, and to a lesser extent dose density, have emerged as important issues in attempts to achieve higher response rates. Four cycles of a high dose FEC regime (600 mg 5-fluorouracil, 60 mg epirubicin and 600 mg cyclophosphamide per metre^2) give higher responses rates when used as adjunctive therapy, than either the same total dose given over 6 months or a more standard CMF regimen over 6 months.[14] Increasing doses of single agent doxorubicin were also shown to increase the response rates in advanced disease but toxicity limited this approach.[15] The use of growth factors to stimulate bone marrow growth allows quicker marrow recovery and reduces both the total number and severity of neutropenic episodes. This has allowed the use of more intensive regimens. At about the same time the use of very high-dose chemotherapy with reinfusion of the patient's own bone marrow (extracted before chemotherapy) was applied to breast cancer patients. This bone marrow transplantation was developed for treatment of haematological malignancies and carried a treatment-related mortality of about 10%. This figure fell with better understanding of the technique and supportive therapy. It has largely been superseded by the use of peripheral stem cell harvesting. The administratioon of the growth factors referred to above causes release into the peripheral circulation of cells normally found only in the marrow. They can be collected and stored and have the ability to repopulate the marrow when reinfused. This has greatly improved the feasibility of giving very high doses of chemotherapy. The techniques were initially used in the treatment of advanced disease where responses were seen after all other treatments had failed and where prolongation of survival for up to two years has been reported.[16] More recently they have been advocated as adjunctive therapy for women at high risk of metastasis, defined as those having more than 10 axillary nodes involved.

The introduction of a new class of drugs which stabilise the cell microtubules, the taxoids, has given new therapeutic approaches. The active ingredient was initially derived from the bark of the Pacific Yew tree, although synthetic sources are now used, and the drug is in clinical trials. Early reports suggest it may be the most effective single agent in the treatment of breast cancer.[17] It has a different side-effect profile than normal chemotherapy drugs and work is ongoing to determine its most effective route of administration and dosages.

Clinical trials

During the 1980s, the results of clinical trials changed clinical practice. All available trial data were summarised and published as overviews, enabling data from smaller trials which did not achieve statistical significance on their own to be included. Large numbers of patients were therefore available for study and a limited number of subgroup analyses was also permissible. The world overviews in 1985,[18] 1990,[19] and 1995 (not yet published) have all demonstrated the benefit of adjuvant hormone therapy (essentially tamoxifen) for the over 50s. A smaller benefit was seen in the under 50s whereas the benefits of adjuvant chemotherapy were greater in the younger women. The use of ovarian ablation in the premenopausal group was shown to improve survival. The overviews have spawned further trials on the use of adjuvant hormonal treatment in younger women, the optimum duration of tamoxifen, and the use of tamoxifen as a preventative against the development of breast cancer in those at increased risk because of family history. The newer generation of aromatase inhibitors which are orally administered are about to be tested in the adjuvant setting. A study of the timing of surgery within the menstrual cycle is on-going, as are several studies on tamoxifen duration.

It has been estimated that only 5–10% of eligible patients are recruited into clinical trials. Various explantations have been proposed for this; although certainly many surgeons have a genuine problem with lack of time for talking to patients about studies, as well as completing case record forms (especially if the trial is to conform to the American FDA requirements). Data monitors and research staff will be essential personnel in a modern breast unit. Evidence of recruitment into clinical trials may well be a requisite of achieving cancer unit status as envisaged by the Calman report.

Genetics

Approximately 7% of breast cancers occur in individuals with multiple other family members with a history of breast cancer, some of whom may also have had ovarian cancer. There are rare hereditary conditions such as the Li Fraumeni syndrome (with a defect in the p53 gene) and the ataxis–telangectasia syndrome

where there is a predisposition to breast cancer. In addition, there are families with abnormalities of the long arm of chromosome 17 where the BRCA1 gene has been identified.[20] This is a complicated gene with many exons whose function is not clear. Once a defect has been identified for an individual, a similar abnormality can be screened for in relatives. Before taking such a test the relative needs counselling as the implications of a positive test are far-reaching. Prophylactic mastectomy with immediate reconstruction (with or without oophorectomy) has been advocated for some. The position of the insurance industry has yet to be clarified; if the AIDS-related loading of policies is an example it may well be that the act of taking a test renders the individual open to an increased premium (if the risk is accepted at all), whatever the result.

Training issues

In the UK, there are insufficient numbers of trained personnel to carry out breast work in all specialist units. To achieve such expertise in every breast unit will take many years and may never be appropriate for smaller units. Links between cancer units and centres will allow referral of individuals who need specialist input (such as flap reconstruction or high-dose chemotherapy). The shortage of individuals relates not just to surgeons but also to clinical and medical oncologists. The Calman report calls for the establishment of training programmes to meet this need; this will require an input of money which does not appear to be forthcoming. The Specialist Advisory Committee has provisionally outlined a surgical training programme with three levels of expertise. The first of these is a basic knowledge of diagnosis and treatment, while the second level encompasses all aspects of breast work other than advanced reconstruction and some other specialist techniques (level 3). The level 2 surgeon will have spent a year in a specialist uint and a year in a district hospital unit, will have presented the results of some research aspect of breast work, and will be the nucleus of the future cadre of breast surgeons. The breast surgical subgroup of the British Association of Surgical Oncology will be responsible for the training programmes and their implementation.

Future prospects

The organisational changes planned should allow greater equality of access and care in the future. The adoption of the British Association of Surgical Oncology quality standard guidelines and their audit will allow easy external inspection of how well a service is running. The increased use of multimodality care should lead to improved patient outcomes. Some surgeons worry that the numbers of patients referred will swamp their service; hopefully, with appropriate referral guidelines, appropriate investigation and sufficient help with data management, these fears will prove to be unjustified.

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