Eur J Cancer Clin Oncol, Vol. 24, No. 1, pp. 73–76, 1988.
Printed in Great Britain

0277–5379/88$3.00+0.00
Pergamon Journals Ltd.

Surgery in the Management of Early Breast Cancer: a Review

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INTRODUCTION

SURGERY still has a central role in the management of breast cancer. There has been a shift away from mastectomy towards breast conservation and this trend has continued and increased in recent years. A surgeon who is treating patients with breast cancer probably will have several objectives including potential cure of the disease, local control of malignancy and accurate staging, achieved when possible with minimal physical and psychological morbidity. However, these various aims may have different priorities depending upon the age of the patient, the type of tumour and possible co-existence of other diseases. Finally, the availability of other disciplines such as nuclear medicine, radiotherapy and medical oncology may also determine treatment schedules. This review will examine surgical options for various sub-types of breast cancer and assess the current role of mastectomy in the management of the disease.

ELDERLY WOMEN

Almost all controlled trials of treatment for operable breast cancer have excluded women over the age of 70 years. This is an arbitrary cut-off. In the United Kingdom one third of patients with breast cancer are aged over 70 years. [1]. These patients do not have more or less aggressive tumours than younger women but are more likely to die of intercurrent disease [2]. Mastectomy in this age group may carry a mortality rate of up to 5%, among those originally deemed fit for surgery [3]. Prolonged radiotherapy may impose too great a burden for older patients and few clinicians would use cytotoxic chemotherapy. For these reasons endocrine therapy has been widely used in this age group. Tamoxifen has emerged as a subjectively acceptable treatment for primary breast cancer in the elderly [4, 5], but no prospective randomized studies have yet evaluated it. The EORTC is running two parallel controlled trials. In the first one, patients are randomized to either modified radical mastectomy or to tumourectomy followed by tamoxifen 20 mg daily. In the other trial patients are treated by either modified radical mastectomy or by tamoxifen alone without excision of the tumour. A pilot study of the first trial has been running at Guy's Hospital for three and a half years. So far there has been a 15% local relapse rate among those treated by tumourectomy and tamoxifen. Recurrence within the breast does not appear to be related to completeness of tumour excision nor to steroid receptor positivity or negativity, although most patients who relapsed locally had ER levels at the lower end of the range. Studies in which tamoxifen was used, without tumourectomy, have indicated that a local relapse rate of 40% can be expected. It is yet to be determined whether this is followed by an increased mortality rate.

HISTOLOGY

The histological type of breast cancer does not often influence management. At present the majority of patients with infiltrating carcinomas tend to be lumped together, but it is possible that certain sub-types with a better prognosis, such as tubular or mucoid carcinoma, might be treated less aggressively although this has not yet been prospectively examined.

Non-infiltrating carcinomas certainly warrant more attention. The more common variant ductal carcinoma *in situ* (DCIS) will increase in frequency as screening becomes more universally available [6]. Where DCIS has been diagnosed on a biopsy specimen, subsequent wider excision will show residual disease in one-third of patients, with an infiltrating carcinoma co-existent in 16% [7]. Total mastectomy reveals multi-centric DCIS in another

one-third of cases. Is it therefore necessary to carry out a mastectomy because of this? What happens if clearance of the primary lesion has been achieved? Is this affected by external radiotherapy? These questions are currently being addressed in two controlled trials, one run by the NSABP which compares wide excision and axillary clearance with wide excision and axillary clearance plus external radiotherapy. The other is being carried out by the EORTC and after histological confirmation of clearance in a wide excision specimen, patients are being randomized to either observation alone or to receive external radiotherapy to the breast, without boost to the primary site and without any surgical or radiotherapeutic treatment of the axilla [8]. However, it is likely that this study will only yield information about tumour-forming and microfocal types of DCIS. Those patients with more diffuse DCIS will be excluded from the trial because of the histopathological criteria for clear margins in the wide excision or quadrantectomy specimen.

Lobular carcinoma *in situ* (LCIS), presents a different problem. LCIS is a histological marker of an unstable pre-malignant breast epithelium with a propensity for bilateral development of subsequent infiltrating carcinoma in up to one-third of patients after long-term follow-up [9–11]. The condition is predominantly diagnosed in premenopausal women, who will not accept the offer of bilateral mastectomy as a potentially curative procedure. At present most of these patients are treated by careful follow-up alone. They do provide a high-risk group and may form a suitable cohort for trials of preventive treatment by endocrine manipulation. This is being tested by the EORTC in a new trial in which patients with LCIS are randomized to observation alone or to receive tamoxifen 20 mg once daily for 5 years.

CONSERVATION TRIALS

Returning to the major problem, that is infiltrating breast cancer in women up to the age of 70, what has been learnt from previous trials? First, local treatment is important. Inadequate primary therapy is responsible for increased local recurrence, distant recurrence and death. In the first Guy's Hospital trial comparing wide excision and radical mastectomy in women aged over 50 with operable breast cancer (N_0 and N_1), patients with clinically involved axillae developed more loco-regional and distant metastases when treated by wide excision and radiotherapy [12]. In the second study which included only N_0 cases, but of any age, there were more local recurrences within the conservatively treated group. This was followed by more distant recurrences and a significantly diminished survival [13].

The NSABP trial, B-06, which included patients with tumours up to 4 cm in diameter, has also demonstrated that sub-optimal treatment will lead to increased local recurrence [14]. The study compared three treatment arms, total mastectomy and axillary clearance, segmental mastectomy and axillary clearance with external radiotherapy, and segmental mastectomy with axillary clearance alone. By 5 years actuarial follow-up, 30% of patients treated by segmental mastectomy had developed local recurrence. This was despite histological confirmation of tumour clearance being a prerequisite for breast conservation. This increased local recurrence rate has not yet been followed by an effect on survival. In addition the psychological morbidity associated with a 30% local relapse rate has not yet been measured. However, at this time of follow-up there is no difference between the local and distant recurrence rates of patients treated by segmental mastectomy plus radiation or those treated by total mastectomy.

The Milan trial comprised 701 patients with tumours less than 2 cm in diameter (measured radiologically or pathologically), and compared QUART (quadrantectomy, axillary clearance and external radiotherapy) with a Halsted mastectomy [15]. The 8 year results for this trial show similar results for the QUART and Halsted groups with disease-free survival of 80% and 77% respectively and with an overall survival of 85% and 83% [16].

The EORTC has carried out a controlled trial which included patients with tumours up to 5 cm in diameter who were treated by either radical mastectomy or with tumourectomy, axillary clearance, iridium implant and external radiotherapy. The encouraging early results were presented at this conference (see Workshop Report by E. van de Schueren and J.A. van Dongen).

The emerging message is that breast conservation techniques can achieve similar results to mastectomy for the treatment of tumours up to 4–5 cm in diameter. The next question to be asked is whether these techniques can be improved in terms of cosmesis, morbidity and general applicability for hospitals without specialized radiotherapy facilities.

TREATMENT OF THE AXILLA

The majority of breast conservation trials have included axillary clearance, in part because this information was used to determine entry to concomitant adjuvant treatment trials. However, is it necessary to clear the axilla surgically? The advantages of clearance are the completeness of information on axillary nodal status, the potential for cure in a few patients and because it is then unnecessary to irradiate the axilla. The staging information is very important, with recurrence rates being directly related to the number of involved nodes [17]. In addition, knowledge of the presence

or absence of extra capsular spread may help in grouping patients over 40 into three subgroups with different prognoses at 10 years [18]. Against this the procedure may sometimes produce lymphoedema, and minor or moderate scapulo-humeral degenerative conditions and will usually be associated with some sensory loss due to division of the intercostobrachial nerve. Finally, axillary clearance is unnecessary in approximately one half of patients who will have no nodal metastases. Until either magnetic resonance imaging (MRI) scanning or labelled monoclonal antibody images have been refined so that the incidence of false-negativity is almost zero, it will still be necessary to carry out this procedure if complete axillary information is required. It could be argued for postmenopausal women where a non-toxic adjuvant treatment exists which may work in node negative patients, that axillary nodal state is unnecessary. Nevertheless axillary radiotherapy will again mean overtreatment of 50% of cases. Leaving the axilla untreated, even where there is no clinical evidence of nodal metastases, will result in an increased local recurrence rate, which might eventually affect survival [19]. There is now general agreement that a combination of surgical clearance and radiotherapy will lead to an unacceptably high rate of lymphoedema [20].

DETECTION OF RECURRENCE AFTER BREAST CONSERVATION

Early assessment of local recurrence in patients with breasts treated by surgery and radiotherapy is a very difficult exercise. As has also been attempted with breast cancer screening it would be invaluable if a high-risk group could be identified. There have been attempts to do this using criteria such as completeness of primary excision, tumour grade and presence of intra-ductal carcinoma within the specimen [21], but these have not been shown to be consistent risk factors [22]. This work needs extension but it may be very difficult to identify those 1–2% of patients who will annually develop either local recurrence or a new primary breast carcinoma.

Neither clinical, mammographic nor ultrasonic examination have been shown to be of great value in detection of recurrence within the breast. It is hoped that the new generation of scans using MRI may prove to be of use.

TREATMENT OF RECURRENCE

Of patients developing recurrence within the breast after conservation treatment, possibly one fifth will have synchronous distant metastases [23]. Late recurrence may represent a new primary and thus carry a similar prognosis and be treatable by mastectomy [22]. However, patients with early recurrence after adequate radiotherapy may represent those with more aggressive disease and to achieve local control by salvage mastectomy it may be necessary to carry out a procedure with wide excision of skin and replace the deficit using either a latissimus dorsi or rectus abdominus flap [24]. Rarely it may be necessary to combine this with chest wall resection to ensure local control.

INDICATIONS FOR MASTECTOMY

Some surgeons still feel that mastectomy is the most effective local treatment for tumours greater than 2 cmd because the trials are not mature enough for conclusions on long-term survival. Nevertheless it is encouraging that differences in local relapse rates have not been seen when the newer techniques using excision, axillary clearance and radiation have been compared with mastectomy. By this time of follow-up for the Guy's wide excision studies, the patients treated with breast conservation had developed more local recurrences than those treated with mastectomy.

At present, there is no evidence from controlled trials that patients with tumours greater than 5 cmd can be safely treated by breast conservation; thus mastectomy should be the treatment choice for such operable lesions. Another indication is the presence of multifocal infiltrating carcinoma, and also proven multifocal ductal carcinoma *in situ*. Clinical signs of unsuitability for breast conservation include localized peau d'orange and localized skin infiltration or ulceration over the primary. Although these are T4 lesions, some of the patients may have operable disease which can be locally controlled by mastectomy.

Mastectomy will continue as the major salvage therapy following local relapse after breast irradiation, or operable breast recurrence in elderly women who had received tamoxifen as primary therapy. The indications for mastectomy are not absolute: there will undoubtedly be change, with a reduction in the number of patients deemed to require radical surgery.

CONCLUSION

Safety of breast conservation techniques for selected patients has now been demonstrated. The aim of surgery will be to refine these techniques and reduce morbidity, to study applications for other groups of patients with breast cancer and to develop improved techniques for the detection of recurrent disease within the conserved breast.

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