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Original Paper

Safe Selection Criteria for Breast Conservation Without Radical Excision in Primary Operable Invasive Breast Cancer

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In a previous series from this unit of 263 women with primary operable breast cancer treated by macroscopic lumpectomy and breast irradiation, local recurrence was high. An audit at a median follow up of 36 months showed 56 (21%) ipsilateral breast recurrences. Eighteen of these recurrences were aggressive and uncontrolled. Multivariate analysis shows patient age, lymphovascular invasion, tumour size and nodal status to be predictive of local recurrence (Locker AP, *et al.*, *Br J Surgery* 1989, 76, 890–894). New selection criteria for breast conservation were defined based on these data and also on securing an adequate clear margin of excision. In a subsequent prospective series of 275 women fulfilling these criteria, 6 women (2.2%) developed ipsilateral breast recurrence at the same median follow up of 36 months. In none was this uncontrolled and aggressive. Breast conservation, without radical excision, is safe as long as the selection criteria described are followed.

Key words: breast cancer, treatment, breast conservation, local recurrence
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INTRODUCTION

BREAST CONSERVATION is an alternative to mastectomy for the treatment of primary operable breast cancer. Several studies have shown no survival disadvantage for breast conservation against conventional mastectomy [1–3] and none is to be anticipated. Therefore, the possibility that local (in breast) recurrence is higher has to be investigated.

Veronesi and associates [4] have shown that very low rates of local recurrence (3% at 10–17 years follow up) can be achieved by using very wide excision (quadrantectomy) followed by radiotherapy for small tumours. The same author has subsequently reported trials which show a higher rate of recurrence when excision was less radical (7% versus 2.2% at 3–5 years follow up) [5] or if postoperative radiotherapy was omitted (8.8% versus 0.3% at 39 months follow up) [6]. Attention has now turned towards establishing the optimum surgical resection/radiotherapy combination which minimises local recurrence without compromising acceptable cosmesis.

The frequency of local breast recurrence in our original series prompted a review of Nottingham's breast conservation protocol; of particular interest were clinical and pathological features that might be used to advise against breast conservation. The intention was a protocol allowing acceptable cosmesis without compromising adequate surgical excision.

This publication then describes an audit with completion of the audit loop. New selection criteria have been established and their effectiveness demonstrated. This method of progression through audit is complementary to the use of randomised clinical trials.

PATIENTS AND METHODS

Local recurrence is defined as tumour in the skin or parenchyma of the treated breast, irrespective of distance from the initial excision site; thus no attempt is made to distinguish between recurrent tumour and a new primary breast cancer. Recurrence is considered uncontrolled if unsalvageable by conversion to mastectomy or if disease on the chest wall persists despite mastectomy. Regional recurrence is not considered in this paper.

Following breast conservation, clinical review was 3-monthly to 18 months and 6-monthly thereafter. Women received mammography of the treated breast 6-monthly for 3 years and thereafter annual mammography until age 70 years. Mammography of the contralateral breast was performed every 2 years. Clinical examination or mammography suggestive of a local recurrence was investigated initially by aspiration cytology. All recurrences documented here were confirmed histologically.

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Original retrospective study group

Between 1979 and 1986, women aged ≤70 years with primary operable invasive breast cancer (≤5 cm on clinical measurement) were offered surgery with breast conservation followed by intact breast irradiation. 263 women received lumpectomy and double node biopsy (low axillary, and high axillary or internal mammary [7]). At surgery, macroscopic clearance of the tumour was obtained, but no attempt was made to ensure clear histological excision margins.

Postoperatively, whole breast irradiation of 45 Gy with a 15 Gy boost to the tumour bed was given over 6 weeks in divided fractions using a 4 or 6 Mv linear accelerator. No women received adjuvant systemic therapies.

At initial review, with a minimum follow up of 1 year (median 3 years), 56 patients had developed a local recurrence. In 18, local recurrence was aggressive and uncontrolled.

A multivariate analysis was used to define factors independently predicative of local recurrence [8]. The most important factors in the prediction of local recurrence were tumour size, the presence of lymphovascular invasion and patient age less than 50 years. Using this analysis and considering the data then currently available, new criteria defining patient suitability for breast conservation were drawn up.

Criteria for breast conservation applied to the new prospective study group

1. *Pre-operative assessment.* The cancer should not measure >3 cm on either clinical examination or mammography. Mammography should show no suggestion of multifocal disease.

2. *Surgery.* The intention was lumpectomy with a macroscopic margin at operation of approximately 1 cm but not a radical operation such as quadrantectomy or segmentectomy. Anteriorly, only if there was skin fixity was it our practice to take an ellipse of skin with the specimen. Dissection posteriorly is carried out down to the pectoral fascia so that a cylinder of tissue is excised around the tumour from the subcutaneous plane to the pectoral fascia.

3. *Macroscopic inspection of margins and specimen X-ray.* At the time of resection, margins were inspected with the naked eye. The specimen was carefully orientated and marked with ties in three axes. Specimen radiography was performed at the time of surgery to gain information about the circumferential margins. If the margin of clearance on the specimen X-ray appeared to be <1 cm, re-excision of that margin was carried out at the same operation. Resection margins of the fresh surgical specimen were painted with ink to permit their histological evaluation.

4. *Postoperative histological assessment.* (i) The circumferential margins were examined. Superficial (subcutaneous) and deep margins were disregarded, as the dissection had already been taken as far as possible in these two directions (see above). If the other criteria for conservation were fulfilled but a histological margin of clearance (for either invasive or *in situ* carcinoma) was <0.5 cm, re-excision of that margin was advised. If several margins were involved, the patient was usually advised conversion to simple mastectomy. The presence of apparent extensive carcinoma *in situ* was not used as a criterion, but margins had to be clear of *in situ* disease as well as invasive.

(ii) A search was made for lymphovascular invasion (LVI) in and around the tumour. In the absence of LVI, all women were considered suitable to continue with conservative treatment as long as the criteria described above were met. If LVI was detected, women aged 50 years and over were considered suitable to continue with breast conservation and proceeded to radiotherapy; younger women with LVI were considered suitable only if their tumours were small (≤1 cm). In those failing to fulfil these criteria, conversion to simple mastectomy was advised.

5. *Postoperative radiotherapy and adjuvant therapy.* (i) Whole breast irradiation was given to those women who fulfilled the criteria. At first, radiotherapy was as used for the earlier patients. Since 1989 there has been a change, but one that we would not expect to have made a major impact on tumour control. We now participate in EORTC Trial 22881 and give radiotherapy according to the protocol of this trial, which is as follows. Where tumours are completely excised (as all of ours are), patients are randomised giving informed consent between two radiotherapy arms. All patients receive 50 Gy in 25 fractions to the whole breast, one arm receives no further treatment the other receives a boost of 16 Gy in eight fractions to the tumour bed. The technique by which the boost is delivered is at the discretion of the individual radiotherapist. Of course, many patients do not wish to participate in this trial and for these since 1989, we have been using a standard treatment of 50 Gy in 25 fractions to the whole breast with no boost.

(ii) Selected women in this group have received adjuvant therapies. Need for axillary radiotherapy was dependent upon node biopsy positivity and poor histological grade. Selection for adjuvant systemic therapy was determined by using the Nottingham Prognostic Index [9]. Women with a good prognostic score and only a 10% chance of dying from breast cancer by 15 years did not receive adjuvant systemic therapy. Premenopausal women with poor or moderate prognostic scores received adjuvant hormone therapy or adjuvant cytotoxic therapy with CMF (cyclophosphamide, methotrexate and 5-fluorouracil for 6 weeks at monthly intervals) depending upon their ERICA score (oestrogen receptor–immunocytochemical assay) [10].

Prospective study group (Figure 1)

Between January 1988 and December 1992, 840 women aged ≤70 years have been diagnosed with primary operable invasive breast cancer (≤5 cm in diameter). Of these 42 (5%) had tumours of >3 cm and were not offered breast conservation. 3 of these women had large breasts with tumours situated in the upper outer quadrant, and it was possible to perform a quadrantectomy without adversely affecting cosmesis. 798 women were offered treatment with breast conservation or mastectomy and 372 chose the latter.

This gave 426 women (53%) in whom the initial therapeutic operation was wide local excision. 36 of these women (8%) failed the postoperative histological criteria (Table 1) and were advised to undergo mastectomy (all accepted the advice). 115 of the women having wide local excision of tumours ≤2 cm and of low grade or special histological types were excluded from this study because of entry into a separate study of surgery without postoperative whole breast irradiation. Therefore, 275 women, median age 53 years (range 24–70), proceeded to radiotherapy. 28 (10%) of these women required re-excision of one or more margin to achieve the necessary 0.5 cm clearance around the tumour.

128 (47%) of the 275 women in the study group had Nottingham Prognostic Index (NPI) scores in the good prognostic

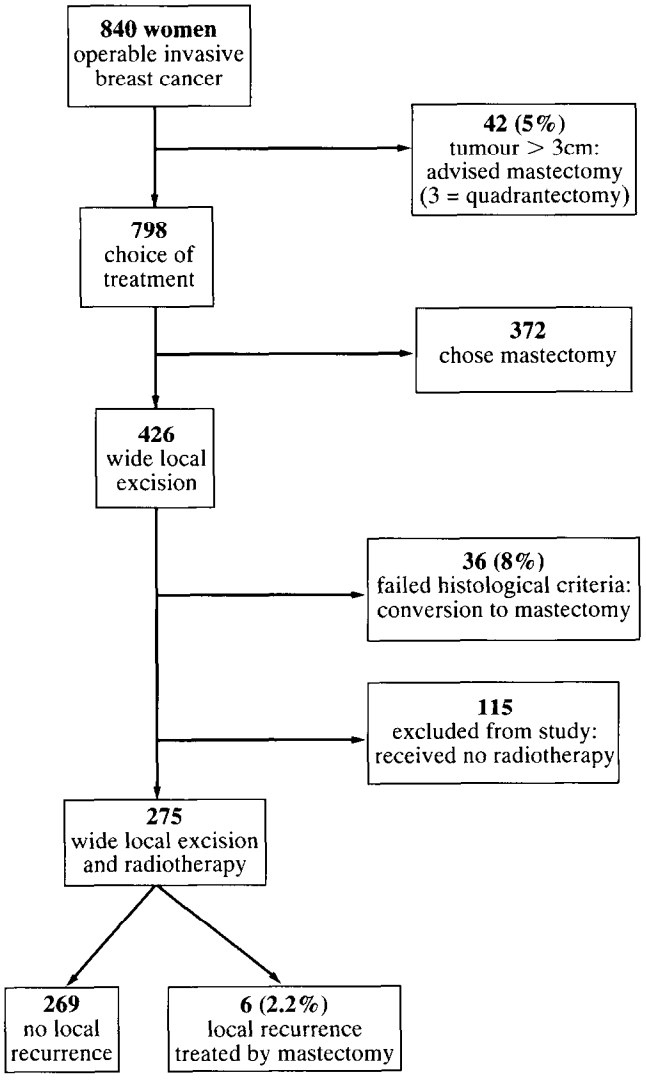

Figure 1. Treatment of women with primary operable breast cancer at Nottingham City Hospital 1988–1992.

Table 1. *Women advised conversion to mastectomy for failing post-operative histological criteria* (n = 36)

	n
Involved excision margins	18
Vascular invasion present (<50 years, >1 cm tumour)	6
Involved excision margins and vascular invasion	12

range; these women received no postoperative adjuvant treatments. 81 (29%) postmenopausal women with NPI scores in the moderate and poor groups received Tamoxifen 20 mg for 5 years. 46 (17%) premenopausal women with NPI scores in the moderate and poor groups had oestrogen receptor (ER) negative tumours and received 6 months of postoperative adjuvant CMF; 20 (7%) women with ER positive tumours received postoperative adjuvant goserelin.

RESULTS

Audit of the prospective study group, at a median follow up of 36 months (range 15–69), showed that 6 of the 275 women (2.2%) had local recurrence in the treated breast. In none had the disease been uncontrollable. All local recurrences were managed by conversion to mastectomy and these women remain free of local disease. One of the 6 women presented with local recurrence after the development of distant metastases. Local recurrence was at the excision site and resembled the original tumour histologically in 4 cases. In 2 women the recurrence was elsewhere in the breast and probably represented a second primary tumour, since histological grade and type were different.

4 of the 42 women with tumours >3 cm advised against breast conservation developed local recurrence. 3 of the 36 women advised to have conversion to mastectomy developed flap recurrence. Overall, 7 of 78 (9%) advised not to have breast conservation developed local recurrence. 31 of the 372 (8%) women choosing mastectomy as primary treatment developed flap recurrence. None of the patients treated by mastectomy have developed uncontrollable local recurrence.

DISCUSSION

Breast conservation should show no survival disadvantage compared to mastectomy because survival is dependent on the presence of distant metastases; no survival disadvantage has been demonstrated in randomised trials [1–3]. Debate centres on case selection and in establishing the optimum surgical/radiotherapy combination which minimises local recurrence without compromising acceptable cosmesis.

Veronesi and associates [4] and Bartelink and associates [11] report 5-year local recurrence rates of less than 5%. Others [12, 13], including ourselves [8] have experienced higher rates. Such differences result, in part, from varied patient selection (particularly relating to tumour size), the extent of surgical clearance, differing postoperative radiotherapy regimes, the inclusion/exclusion in the results of local recurrence developing after the emergence of other systemic metastases, differing definition of 'local recurrence', varying length of follow up and possibly the use of adjuvant systemic therapies. Very low local recurrence rates can be achieved with radical local excision of small tumours [4], but only at the expense of cosmesis [5]. With less radical excision, cosmesis is improved but local recurrence rises [5]. In such patients, clinical and pathological features predictive of local recurrence become important for patient management.

There are many publications reporting factors associated with local recurrence after breast conservation [14–19], but to our knowledge only our previous paper [8] laid down criteria for acceptance for breast conservation based upon a combination of the factors selected by multivariate analysis. It is of notable interest that the same factors emerged as predictive of recurrence after lumpectomy in the series reported by Fourquet and associates [14] and by Kurtz and associates [19].

In many publications [13, 17, 18], tumour size did not predict for local recurrence but frequently these series placed an upper limit on size for acceptance for breast conservation. In the original Nottingham series, tumours of up to 5 cm were accepted for treatment and size was of predictive significance for local recurrence. It is probable that this was, in part, due to larger tumours being less likely to be fully excised. For this reason, breast conservation is no longer advised at our unit if the primary tumour measures >3 cm. Our policy of a 1-cm macroscopic margin of clearance would compromise cosmesis in women with tumours >3 cm. Women excluded because of tumours clinically or mammographically >3 cm diameter form only 5% of women with primary operable breast cancer (≤5 cm) in our series. In a

small proportion of such women who had large breasts with tumours situated in the upper outer quadrant, it was possible to perform a more radical excision (quadrantectomy) without compromising cosmesis.

Macroscopic lumpectomy with no attempt at histological clearance of invasive disease can be regarded as inadequate surgery; Fourquet and associates [14] and Kurtz and associates [19] demonstrated the importance of clear margins. The original Nottingham series was a retrospective analysis; no margin was aimed for and assessment of adequate clearance had not, therefore, routinely been made as part of the treatment protocol at that time. Retrospective assessment was frequently not possible from the available archival blocks. As such, this variable was not included in the multivariate analysis. Our present policy is to orientate carefully and mark all excision specimens. If histological clearance of either *in situ* or invasive disease is <0.5 cm then re-excision is performed.

The issue of margin clearance is closely related to the topic of surrounding extensive intraduct carcinoma (EIC). Although there is the difficulty of a consistent definition of 'extensive', the presence of EIC is frequently reported as a factor predictive of local recurrence, especially in premenopausal women [16, 17, 19]. It is likely to be a predictor of local recurrence by virtue of the fact that it is a marker of residual disease; in those centres performing 'very wide' local excision, its value as a predictor of local recurrence is reduced. Schnitt and associates [20] have recently reported that the importance of EIC as a marker of risk of local recurrence is directly related to the margins of excision. In 30 patients with EIC-positive tumours treated by breast conservation, the 5-year local recurrence rate was 50% when margins were more than focally positive, but 0% when margins were negative or close.

After histological review, the suitability of the individual to continue with breast conservation is decided. Only 8% of women initially considered suitable for and choosing conservation were excluded from this treatment by our criteria applied after the initial operation. In our original series and in other reports, young age [8, 14, 15, 19] and LVI [8, 14] are powerful predictors of local recurrence, especially of the uncontrolled type. Allowance for young age may also allow for EIC (see previous paragraph).

Of particular concern in the original series were the cases of uncontrolled, aggressive recurrence, unsalvageable by conversion to mastectomy. Although 15 of the 18 uncontrolled local recurrences have synchronous evidence of progressive widespread disease and a dismal prognosis, the aim of treatment of the primary disease includes preventing local recurrence even in these women with advanced disease. These more aggressive local recurrences have been reported after breast conservation in other series. In the National Surgical Adjuvant Breast Project (protocol 6), 14% of the local recurrences seen were described as 'inflammatory', affecting not only the same quadrant as the index cancer, but also diffusely extending into other quadrants [21]. Stotter and associates [15] reported from the MD Anderson Hospital, U.S.A., that 8 of 51 breast recurrences were of an advanced nature involving both the breast and chest wall. The experience of both series mimics ours in that these recurrences developed soon after initial surgery and appeared suddenly despite adequate follow up, and were not the result of neglect of more readily treatable disease. 17 of the 18 women in our original study group were under the age of 50 years, a group that show a preference for treatment with breast conservation [22]. 9 had definite LVI at their initial operation; a percentage much higher than that for controlled local recurrence.

The change in the radiotherapy policy between our two series probably means that the majority of patients are receiving slightly less radiotherapy than in the earlier study. This change is, therefore, unlikely to be contributing to the reduction we have seen in local recurrence. Our original and prospective series differ in that no patient in the earlier series received postoperative systemic adjuvant therapies. More recently, the use of postoperative adjuvant systemic therapy was considered in selected patients. Whether such adjuvant therapy decreases local recurrence rates in the conserved breast and by how much is not yet known. Data from the Danish Cooperative Breast Group suggests that local treatments, rather than systemic, are the major influence with regard to local recurrences [23]. In a recent retrospective study, Haffty and associates [24] reported a significant reduction in local relapse after breast conservation in patients receiving adjuvant systemic chemotherapy. There was also a statistically non-significant trend towards a lower relapse rate in women receiving adjuvant Tamoxifen. The International Breast Cancer Study Group have reported a significant reduction in local relapse at 10 years in women receiving various systemic adjuvant therapies after total mastectomy and axillary clearance [25]. From a pragmatic viewpoint, whatever the effects of adjuvant treatments, the data from our prospective series shows that adopting the Nottingham protocol in its entirety results in a very acceptable local recurrence rate, while disqualifying few patients from this form of treatment.

The new criteria derived from the previous audit of our own practice [8] have now been used for over 5 years. The present paper closes the audit loop by applying the selection criteria to a new series and then re-auditing to assess benefit. It has resulted in a local recurrence rate as low as any reported. Perhaps more important is the complete disappearance of the distressing complication of uncontrolled local recurrence, the majority of which presented within 2 years of treatment. In the group treated since the protocol change, the median survival is now 36 months; it is likely, therefore, that this is a real gain. It is of note that in the women who failed to meet the new criteria for breast conservation, treatment including mastectomy has not been followed by the appearance of this distressing complication.

We do not favour the operation of radical excision (quadrantectomy) because the major advantage of breast conservation over mastectomy is better cosmesis. Ending up with a poor cosmetic result after conservative surgery seems illogical. In this publication, cosmesis after surgery and radiotherapy has not been objectively assessed. Such an assessment is currently ongoing [26]. The early results are available in 63 patients treated since 1988 and reviewed a minimum of 3 years post surgery. Eighty per cent of these women were judged to have an excellent/good cosmetic result at clinical review. Ninety six per cent were satisfied with the cosmetic result and 56% were highly satisfied.

Our criteria for the selection and management of patients for breast conservation have made the procedure of breast conservation, using a cosmetically favourable surgical approach with conventional radiotherapy, a safe option for the majority of women with operable invasive breast cancers. The selection criteria exclude only a small proportion of women (9% of all women treated) and allow breast conservation without radical excision.

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