Surgical management of breast cancer

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Introduction

Breast cancer is largely a disease of the aged as about 60% of women with newly diagnosed cancer are 65 years and above [1]. This important point is made as there is clear evidence of less adequate surgical treatment in older women, even though the principles of surgical treatment have been well documented in younger women. Reasons for the under-treatment of older women are related to surgeon and oncologists perception of co-morbidities and assumptions about older women's attitudes to quality of life. A further problem is that clinical trials generally exclude older women. This aspect of the surgical management will be reinforced in this paper, as surgeons can easily modify practice to give the same benefits of treatment to the older (the majority of) patients with operable breast cancer. This is particularly true when newer less invasive managements such as sentinel node biopsy are now available. Changing practice in this way would be more beneficial than altering the mastectomy to breast conservation ratio by a few percent in younger women.

Treatment of operable disease

The optimum surgical treatment of operable breast cancer is well established. The principles of therapy are based on several important randomized trials carried out in the last 25 years, although these were mostly carried out in women below the age of 70 years [2–5]. For tumours smaller than 3–4 cm, breast-conserving wide-tumour excision and axillary dissection is appropriate, although the size cut-off depends on breast size and patient preference. The option of breast conservation should be offered to all patients with tumours deemed suitable for breast-conserving therapy. Initially wide excisions were performed by excising a whole quadrant of the breast together with the overlying skin, but this was associated with a higher proportion of poor cosmetic results. Increasing patient expectations of a good result allied to increased sophistication of breast-conserving techniques has resulted in a reduction in the volume of tissue removed without increase in local recurrence. This has been achieved by earlier diagnosis resulting in smaller tumour sizes, so that a cylinder of tissue can be removed down to the pectoral fascia, but without removing overlying skin (unless it is involved by tumour). An essential requirement is that the surgeon obtains clear margins and specimen radiography may help to show any close margins at the time of primary surgery. Many studies have shown unequivocally that wide local excision must be accompanied by radiotherapy to the breast to achieve good local control of around 5–10% over 10 years [6,7].

Traditionally larger tumours have been treated by total mastectomy, but increasingly, preliminary neoadjuvant therapy allied to oncoplastic surgical techniques is also allowing larger tumour sizes to be treated with breast conservation. Tumour reduction of around 50–70% is possible in many cases and the reduction is best monitored by ultrasound or MRI examinations. Total pathological response in adjuvant therapy is only achieved in 10% or less of patients and thus surgery of some sort is required in most patients in order to gain satisfactory local control.

For larger tumours without evidence of metastatic disease unsuitable for neoadjuvant therapy, total mastectomy with axillary dissection is still the surgical treatment of choice. Halsted radical mastectomy is seldom required in European and US practice, although it is still used in many parts of the World where late presentation of breast cancer is common. These treatments are based on sound high-level evidence from meta-analyses of large RCTs, but the therapy of elderly breast cancer is much less evidence-based, as women over 65 have generally been excluded from many trials. Some trials have been conducted to answer the question of best surgical therapy for the elderly patient.

The Cancer Research UK Breast Cancer Trial Group conducted a RCT for women over 70 years of age with operable breast cancer. Of 455 patients,

from 27 hospitals in the UK, 225 were randomized to surgery + tamoxifen and 230 to receive tamoxifen alone. Local control at a median FU of 12 years was better when surgery was combined with tamoxifen. Fifty seven patients randomized to surgery and 141 to tamoxifen alone progressed. The hazard ratio (HR) for local progression for tamoxifen as compared to mastectomy was 17.24; 95%CI: 6.4–47.6 and for tamoxifen compared to BCT, 5.99; 95%CI: 4.12–8.7. The risk of local progression was greater in the BCT arm compared to mastectomy (HR = 2.98; 95%CI: 1.06–8.39). The 5-year risk of local progression was 8% after mastectomy, 18% after breast conservation and 64% in women who had tamoxifen alone.

The 10-year survival was 37.7% for surgery + tamoxifen and 28.8% for tamoxifen alone. Primary tamoxifen therapy is inferior to mastectomy and breast-conserving surgery in achieving local control. Among patients randomized to surgery plus tamoxifen, the risk of local progression was greater in those who had breast conservation than in those who had a mastectomy [8].

Professor RW Blamey and his group reported the results of a trial comparing tamoxifen alone with wedge mastectomy for women above age 70. They randomised 135 women with operable <5 cm tumours, 68 to the tamoxifen (20 mg b.d.) group and 67 to the mastectomy arm. Those women developing local recurrence or progression in the tamoxifen arm underwent wedge mastectomy later. In the wedge mastectomy group local recurrences were treated with further excision or radiotherapy and if tumour recurred again, patients were given tamoxifen. The mortality from metastatic breast cancer was 10% in the tamoxifen and 15% in the mastectomy group. In the mastectomy group 70% remained alive and free of recurrence at 24 months, compared with 47% in the tamoxifen group. Authors concluded that since many patients in tamoxifen arm eventually required surgery, optimum treatment should include surgery and tamoxifen [9].

This issue was also evaluated by EORTC 10851 multicentre trial [10]. Women above 70 years with operable breast cancer were randomized to either MRM (82 cases) or tamoxifen – 20 mg daily (82 cases). Tamoxifen was given until death or relapse. The median follow-up was for 11.7 years for MRM and 10.2 years in the tamoxifen group. Eleven percent of women in the MRM arm and 62% in the tamoxifen group developed locoregional progression, the difference being highly significant (p < 0.001). The risk of distant progression was noted in 20% of MRM and 23% of those getting tamoxifen alone (p = 0.654).

For overall survival, the modified logrank test gave a p = 0.001, rejecting the null hypothesis of non-equivalence, thus indicating that the two groups are similar in terms of overall survival.

The GRETA trial (Mustacchi et al. [11]) reported the results of a multicentre RCT on tamoxifen alone versus surgery followed by adjuvant tamoxifen in elderly women. Between 1987 and 1992, women above 70 with operable breast cancer were randomized – 239 to surgery + tamoxifen (20 mg/day) and 235 to tamoxifen alone. The tamoxifen was given for 5 years. At a median follow-up of 80 months 274 patients have died, there is no difference between the two groups as regards the overall and breast cancer survival. Local progression was noted in 27 cases in surgery group and 106 in the tamoxifen alone group. They concluded that minimal surgery followed by tamoxifen appears to be the appropriate therapy for older women as compared to tamoxifen alone.

In the EORTC 10850 multicentre study [12], 236 women above 70 years with operable breast cancer were randomized to either modified radical mastectomy (MRM; n = 120) or wide excision + tamoxifen (WLE + tam; n = 116). No other adjuvant therapy was given. The tamoxifen group received 20 mg daily till death or relapse. The median follow-up period was 10.9 years for the mastectomy and 10.4 years for the WLE + tamoxifen. Women experienced locoregional recurrences in 16% in the MRM arm versus 26% in the WLE + tamoxifen group. Distant relapse was observed in 28% in MRM and only 13% in WLE + tamoxifen group. There was a higher risk of local relapse and significantly reduced risk of distant relapse in the WLE + tamoxifen arm. The multivariate Cox's modeling revealed no treatment effect according to time to progression (HR = 0.89; P = 0.06). In terms of overall survival all predictors except for age were removed. A model with age showed that the patients in the most elderly group had the highest mortality hazard.

Truong et al. [13] have reported an overview of the literature on BCT in elderly women with early breast cancer. They found a paucity of prospective data and numerous retrospective series of diverse treatments with conflicting results. Their observation supports BCT + postoperative RT as the standard of care for the elderly.

Crowe and co-workers [14] reported the outcome of modified radical mastectomy in a group of 1353 women (age range 22-75). The hazard ratio for death was similar in all three age groups (<45, 46–65 and >65). These data demonstrate that older women can

achieve similar results as younger ones, provided they are treated adequately.

A strong consensus has prevailed that by the time breast tumour is palpable, dissemination has already occurred and local treatment can only provide local control. Surgery cannot influence development of metastases. Data from the Oxford overview now challenge this belief, as more thorough excision of the cancer resulted in a small gain in mortality (EBCTCG, in press). Surgical intervention trials suggest that the extent of surgery may reduce the rate of distant metastasis and mortality from breast cancer, thus local treatment offers more than local control and may impede the metastatic process.

Management of the axilla

The drive to reduce the morbidity of surgery has now extended to the management of the axilla, as less invasive procedures are being utilized to reduce the morbidity of axillary surgery in the node negative patient. This move has been made possible by the development of sentinel node biopsy pioneered by Dr Morton in the USA. Studies have shown that this technique utilizing a combination of radioisotope and blue dye can detect a negative axillary status with an accuracy of around 96% of true negative axillas, and can spare women the morbidity of a full axillary clearance. Several randomized trials have recently shown a significantly higher quality of life after sentinel node biopsy compared with conventional axillary clearance. This technique will become the standard of care for most women with early breast cancer in the near future. The best treatment for women with a positive sentinel node remains an unresolved question and the EORTC AMAROS trial is currently examining the use of complete axillary clearance against axillary radiotherapy in a randomized trial.

Post mastectomy breast reconstruction

There has been a major growth in interest in breast reconstruction following mastectomy. Around 20% of women undergoing mastectomy will opt for breast reconstruction either as an immediate or delayed procedure. Despite much research there is still no consensus on whether immediate or delayed reconstruction is better in terms of cosmesis or quality of life. It must be said however that the quality of research in most studies is poor, perhaps contributing to the indefinite conclusions on these questions. Currently many techniques are available ranging

from simple insertion of a subpectoral prosthesis to a major myocutaneous flap reconstruction using a microvascular anastomosis.

In general, the myocutaneous reconstructions produce superior results, especially in older women where ptosis of the opposite breast is usual. Frequently surgery is necessary on the normal opposite breast to achieve symmetry and any breast unit offering routine breast reconstruction must be able to offer also correctional surgery on the opposite breast for symmetrisation. These developments in so-called oncoplastic surgery have been pioneered in Europe by a small group of highly dedicated oncoplastic surgeons who have described several new techniques for the solution of challenging cosmetic problems, while retaining the correct principles of surgical oncology for the management of the tumour.

Adjuvant therapies post surgery are discussed by Dal Lago et al. [15] in this supplement.

Treatment of advanced disease

Patients with locally advanced disease need evaluation by a combined breast care team and should be offered good local control by limited surgery and radiation followed by tamoxifen and chemotherapy. Women presenting with a fungating or bleeding ulcerated tumour should not be denied the benefit of limited surgical ablation and coverage of the defect with a myocutaneous flap. These rescue operations are particularly useful where there has been a history of slow growth of the tumour over many years. Palliative hemostatic fractions of radiation may help arrest bleeding. Women with dissemination of cancer need systemic chemoendocrine administration.

Prognostic factors in elderly breast cancer

Ian Fentiman in an editorial in a recent issue of British Journal of Surgery [1] pointed out that 60% of deaths from breast cancer occurred in women of 65 and above because of late diagnosis and treatment.

The outcome of the elderly patients and the post treatment quality of life has been studied by a number of authors. Age has been considered an important determinant of the type of the treatment and hence the outcome. In the CRUK trial, age and tumour size were found to predict mortality independently. Data from six regional National Cancer Institute Surveillance Epidemiology End Result (SEER) Cancer registries evaluated population-based random samples of 1800 patients in the age group of 55 and above. Seventy-three percent of the women presented with stage

I&II breast cancer, 10% with III&IV and 17% did not have stage assignment. Of the 1017 cases with stage I&II, node negative disease 95% of women received therapy in agreement with NIH consensus. Patients in older age groups were less likely to receive therapy according to the consensus statement. Women ≥70 years were significantly less likely to receive axillary lymph node dissection. Diabetes, renal failure, stroke, liver disease and history of smoking where significant predictors of early mortality in a statistical logistic regression model that included age and disease stage. These authors concluded that patient care decision making occurs in context of age and other co-morbid conditions. Co-morbidity in older patients results in less axillary dissections. As a result information on axillary node is not available in many elderly patients. Breast cancer was the underlying cause of death in 51% and heart disease in 17%. The number of women getting breast-conservation therapy is also reduced and co-morbidity also increases the risk of death from breast cancer [16].

Quality of life issues

The impact of the diagnosis of breast cancer and the effect of different therapeutic modalities has been addressed by a number of authors. Kroenke et al. [17] from Harvard School of Medicine and Harvard School of Public Health, reported changes in physical and psychological functions before and after breast cancer by age at diagnosis. From 122,969 women from the Nurses' Health Study (NHS) and NHS2 of age 29–71 years, who responded to a pre- and post-functional status assessments were included; 1082 women were diagnosed with breast cancer between 1992 and 1997. Functional status was assessed using Short Form SF-36. Mean change in health-related quality of life (HRQol) scores was computed. Compared with women ≤40 years without breast cancer, women with breast cancer experienced a functional decline. Young women who developed breast cancer experienced the largest decline in HRQol as compared with older women in multiple domains such as physical roles, bodily pain, social functioning and mental health. Much of the decline in HRQol was age related (age ≥65 years).

In a retrospective chart review study from Italy on 1724 cases (median age 61, range 17–89) treated in 63 hospitals, 541 (38%) were over treated. More than 2/3 of these inappropriate surgical procedures were unnecessary Halsted Mastectomy. There was considerable geographical variation in the rate of appropriateness (range 52–88%). The authors suggested

an urgent need of technology transfer to promote more appropriate surgical care and increase patient participation [18]. The same authors in another report on the same subjects (1724 cases) showed that elderly patients were less likely to have intensive diagnostic work-up, greater use of radical surgery and less use of limited surgery independently of their overall health status. The presence of one or more co-existent diseases was associated with a failure to undergo axillary clearance and a lower utilization of conservative surgery independent of age. The authors recommend the development of practice guidelines and their implementation to improve the quality of care [19].

Currently, the average life expectancy of a 75-year-old is 12 years (17 years if she is healthy), and that of an 85-year-old is 6 years (9 years if she is healthy). Due to paucity of good evidence-based data, there is considerable controversy about what constitutes appropriate care for older women. More than one quarter (27%) of breast-cancer deaths in 2001 in the USA were in the age group of 80 years and older. Although patient health status, patient and family preferences and support, and patient–physician interactions explain in part, age-related treatment variations, age alone remains an independent risk factor for less than definitive breast cancer care.

A similar study from Quebec, Canada, assessed the variation in care with age. Herbert-Croteau et al. [20] selected a stratified random sample of 1174 women from new cases of node negative breast cancer of age 50 or above. Women over 70 were less likely to receive definitive locoregional treatment than younger women (48–83%; p < 0.0001). Older women were less likely to receive breast-conserving surgery (76% vs 86%; p < 0.0001) and radiotherapy (54% vs 90%; p < 0.0001), axillary dissection (55% vs 86%; p < 0.0001), or receive chemotherapy (1.2% vs 13%; p < 0.0001). Tamoxifen was given equally to both groups (66% vs 64%; p = 0.41). Adjusting for comorbidity and other disease characteristics, age remained the strong determinant of definitive therapy (odds ratio 0.14, 95%CI: 0.12–0.18, for age ≥70 vs age 50–69 years). The authors complained that elderly women receive less aggressive surgical therapy independent of comorbidity.

Recommendations

The present knowledge base supports the following general guidelines for breast cancer:

<4 cm tumour, → BCT + axillary dissection +
ER+ve   RT + Tamoxifen or aromatase inhibitors.

<4 cm tumour, → BCT + axillary dissection +
ER−ve   RT + chemotherapy.

>4 cm tumour, → Modified radical mastectomy +
ER+ve   RT + Tamoxifen or aromatase inhibitors.
Alternative of neoadjuvant hormone or chemotherapy to allow breast conservation in some patients.

>4 cm tumour, → Modified radical mastectomy +
ER−ve   RT + chemotherapy, consider Herceptin.
Alternative of neoadjuvant chemotherapy.

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