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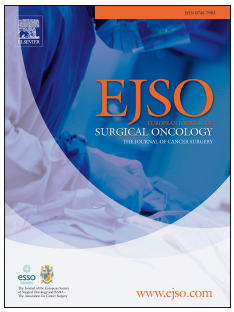

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Title

Should patients with early breast cancer still be offered the choice of breast conserving surgery or mastectomy?

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Abstract

Breast conserving therapy (BCT) for breast cancer aims to achieve long-term local disease control with reduced local morbidity. BCT has similar long-term survival outcomes to mastectomy in patients with early breast cancer and recent studies have reported similar rates of recurrence compared with mastectomy. An increasing number of studies have shown improved overall survival among women treated with BCT regardless of cancer phenotype compared with mastectomy. Despite BCT being at least equivalent in outcome to mastectomy many women with small breast cancers continue to be treated by mastectomy and several studies in the last decade have shown a trend of increasing numbers of unilateral and bilateral mastectomies. The advent of increasingly effective neoadjuvant treatment has allowed even more women to have breast conservation. Not only has neoadjuvant therapy been shown to increase the rates of BCT, it does so without increasing in breast recurrence rates. Patients who are suitable for BCT should be advised that BCT is the best treatment option for them. They should be informed that not only does it confer at least equivalent survival and local recurrence rates but that compared with mastectomy it has the advantages of less complications, better quality of life and many less operations if reconstructive surgery is performed. It may no longer be appropriate to offer women suitable for BCT the choice of mastectomy or BCT.

Introduction

Breast conserving therapy (BCT) consists of breast conserving surgery and whole breast radiotherapy and aims to achieve long-term local disease control with minimum local morbidity. Almost two thirds of screen detected cancers and the majority of women presenting to symptomatic breast clinics have early breast cancers that are suitable for BCT. There are a number of advantages of BCT for women with early breast cancer who do not have a genetic mutation predisposing to breast cancer. For the majority BCT produces an acceptable cosmetic result (1) and is associated with lower levels of psychological morbidity, notably less anxiety and depression and improved body image, sexuality and self-esteem, compared with mastectomy (2, 3). Two systematic reviews performed many years ago showed equivalence in terms of disease outcome for BCT and mastectomy (4, 5). Local control is important and has an influence on overall survival with local failure being a risk factor for the development of metastatic disease (6, 7). An initial review of 6 randomised trials noted similar rates of local recurrence comparing BCT and mastectomy and even in 1997 it was evident to the authors that ”particularly for node-positive patients, BCT may confer a relative survival advantage over mastectomy. In particular, mastectomy without adjuvant radiation appears to be inferior to BCT for node-positive patients” (5). A subsequent analysis did report a higher locoregional recurrence rate for BCT in 4 of the 6 trials (8). Local recurrence rates following BCT have fallen over time as a result of better imaging, more attention to margins, and more effective and longer durations of systemic therapy so that although local recurrence was at one time considered more common after BCT than mastectomy, this no longer appears true (9). Current practice is to aim for at least microscopically disease-free margins. There is ongoing debate about how much breast tissue should be removed and what constitutes a clear margin. A meta-analysis of 33 studies showed that positive margins conferred an odds ratio of ipsilateral breast tumour recurrence

of 2.44 and close margins had an odds ratio of 1.74, which were both significant compared to negative margins (10). When looking at different threshold for negative margins 1mm was as good as wider margins. The data on >0mm were insufficient and there were minimal data on this margin included in the meta-analysis (10). For this reason the most commonly used negative margin in the UK is 1mm. What is clear from the meta-analysis is that wider margins will not reduce local recurrence but wider margins impact negatively on cosmetic outcome.

The rates of in breast tumour recurrence are now very similar to the rates of local recurrence seen after mastectomy alone even in young women (11). Although young age at diagnosis is associated with increased rates of in breast tumour events in part because young women have higher grade and triple negative cancers these same women and cancer types are associated with an increased rate of recurrence after mastectomy. A recent review showed equivalence between BCT and mastectomy in local regional control in young women (11).

The decision to have mastectomy has been based first on the belief that mastectomy decreases local recurrence rates compared with BCT and second because of the fear of annual mammograms and recall for further treatment. Given that recurrence rates are the same, recall rates after BCT are now very low and with newer studies showing improved survival for BCT the aim of this review is to detail what is known about the outcomes of these two surgical approaches and to answer the question, whether there is any specific group of women where BCT is not a better option than mastectomy?

Comparing survival with BCT and Mastectomy

Although randomised controlled trials comparing BCT with mastectomy performed many years ago for early stage breast cancer showed equivalence in overall survival (12-17), and recurrence rates after BCT have fallen dramatically since these randomised trials both for mastectomy and in particular for BCT (9), there continues to be a high and increasing mastectomy rate (18). One potential reason for this increase has been the increasing use of MRI (19, 20), although, in the USA there are other reasons why there has also been an increase in mastectomies for both women with invasive and *in situ* disease (18). One reason for this increase is improvements in reconstructive techniques, and a reported reduction in anxiety of long term follow-up after mastectomy because of a perceived lower rate of recurrence and the avoidance of follow up mammography. The evidence of higher local recurrence rates following BCT in patients with certain tumour phenotypes has added to this (21, 22). Recurrence rates in these women are however also increased to a similar degree after mastectomy (23). Using tumour phenotype to decide surgery is not therefore supported by evidence.

A number of recent studies have cast doubt on the equivalence in outcomes of mastectomy and BCT and have raised the issue of whether women with early breast cancer suitable for BCT should any longer be offered the choice of mastectomy or BCT. A series of studies from various different countries have reported outcomes related to the type of surgery performed including breast cancer specific and overall survival in women with stage I–II breast cancer. The aim of these studies was to determine the influence of surgery type on long-term outcomes for early stage disease (24). One large cohort study from California consisted of 112,154 women, of whom 61,771 (55%) were treated by BCT and 50,383 (45%) by

mastectomy without radiation. At a median follow up time of 110.6 months, women undergoing BCT had a significantly improved overall (HR = 0.81, 95% CI 0.80-0.83) and breast cancer disease specific survival (HR = 0.85, 95% CI 0.78-0.91) when compared to women treated with mastectomy. The disease specific survival benefit for BCT compared to mastectomy was somewhat greater among women age ≥ 50 with HR-positive disease (HR =0.86, 95% CI 0.82-0.91) than among women age <50 with HR-negative disease (HR = 0.88, 95% CI 0.79-0.98); although the benefit of BCT was significant in all ages and subgroups analysed. This study concluded that in patients with early stage breast cancer, BCT resulted in significantly improved disease specific survival compared with mastectomy. These data provide confidence that BCT is an effective alternative to mastectomy for early stage disease regardless of age, HR status and cancer phenotype (24). The better outcomes for BCT persisted after adjusting for tumour grade, proportion of positive nodes, race, socioeconomic status, tumour size, age at diagnosis, and year of diagnosis (24). A number of other recent studies have provided supportive evidence of better outcomes for BCT compared to mastectomy. In a population based study from the Netherlands, in women treated between 2006 and 2012, BCT conferred a survival advantage in a group of 173,797 patients compared with mastectomy following correction for stage, age, and adjuvant therapies (HR 0.87 95% CI 0.81-0.93 p<.001) (25). A further study conducted in Norway included 9547 women aged 50-69 years diagnosed with primary invasive breast cancer without distant metastasis, who underwent either BCT or mastectomy between 2005 and 2011. Women treated with BCT had more favourable tumour characteristics compared to women treated with mastectomy. Adjusted analyses revealed a 1.7 (95% CI 1.3-2.4) greater risk of breast cancer death amongst women who underwent mastectomy compared with BCT (26). This study showed a better survival from BCT in screen detected, interval and symptomatic cancers. A second Norwegian study of 13,015 women with invasive, early-stage breast cancer treated over a ten

year period when the outcomes for BCT and mastectomy were considered to be equal (27). BCT and mastectomy was compared in five subcohorts. Analyses were stratified into T1N0M0, T2N0M0, T1N1M0, T2N1M0, and age groups (<50, 50–69, ≥70). Women who underwent mastectomy had a hazard ratio of 1.64 (95% CI 1.43-1.88) for breast cancer death compared with women who underwent BCT after adjusting for the year of diagnosis, age at diagnosis, stage, histology, and grade. Outcome was better for BCT in all 5 cohorts. The authors concluded that survival was better or at least equivalent for BCT compared with mastectomy in all stages, surgical subcohorts, and age groups. Any advantage in outcome could not be attributed to differences in tumour biology (27). A US study investigated 132,149 patients treated over a ten year period from the SEER database, BCT was used to treat 70% of patients, mastectomy alone was used to treat 27% of patients, and mastectomy with radiation was used in 3% of patients. The 5-year breast cancer-specific survival rates for patients who underwent BCT, mastectomy alone, or mastectomy with radiation were 97%, 94%, and 90%, (P < .001); the 10-year breast cancer-specific survival rates were 94%, 90%, and 83%, respectively (P < .001). Multivariate analysis showed that women undergoing BCT had a significantly better survival rate compared to those undergoing mastectomy alone (hazard ratio, 1.31; 95% CI 1.25-1.39 P < .001) or mastectomy with radiation (hazard ratio, 1.47; 95% CI 1.34-1.61 P < .001). When stratified using propensity score, the effect of treatment on survival remained largely unchanged (28). The most recent study from the Netherlands presented at San Antonio also reported significantly better overall survival for BCT compared with mastectomy (HR=0.79 95% CI 0.75-0.83) (29).

Findings have also been reported for specific breast cancer subtypes. In a study of 1242 consecutive patients with triple negative breast cancer treated over ten years at a single institution, the 5-year risk of locoregional recurrence was 4.7 % in women with T1-2N0

disease. 448 of this cohort with T1, T2N0 cancer had BCT, and 198 had Mastectomy but no radiotherapy. BCT was as effective as mastectomy both for local and distant control (30). In another study of T1-2N0 triple negative breast cancers, women treated by mastectomy without radiotherapy had a significantly increased risk of locoregional recurrence compared with those treated with BCT (31). A series of studies have included data on women with triple negative breast cancers and these were combined in a meta-analysis presented at San Antonio in 2015. In the total cohort there were 37,207 patients. The 10-year OS was 76.8% after BCT and 59.7% after mastectomy. In a sub cohort, 11.0% of the patients experienced distant metastases (DM) after BCT compared to 14.7% after mastectomy ($p<0.001$). Regional recurrences (RR) were diagnosed in 2.1% of patients treated with BCT and in 4.0% of patients treated with mastectomy ($p<0.001$). The percentage who developed local recurrences (LR) did not differ between treatment groups (29). Overall the rate of locoregional recurrence was 39% less with BCT (HR = 0.61, 95% CI 0.41-0.90) and overall survival was 43% better with BCT (HR = 0.57, 95% CI 0.31-1.02 $p=0.012$). The conclusion of this analysis was that for women with triple negative breast cancer who are not gene mutation carriers, BCT appears a better option than mastectomy.

There is thus an increasing number of studies that have suggested that women treated with BCT may have a better breast cancer-specific survival and a lower risk of dying from breast cancer than women treated with mastectomy, independent of tumour characteristics. These reports importantly include all cancer phenotypes. They are in the main observational studies and some of the difference in outcomes is likely to be due to selection bias, however in the US studies many patients with small low risk cancers choose mastectomy, so it is difficult to explain the differences in outcome based purely on mastectomy patients having higher risk disease.

Not only are there potential survival advantages for BCT compared with mastectomy, but the rate of surgical complications and economic burden particularly with brachytherapy is better for BCT (32). Mastectomy has twice the rate of complications compared with BCT, and is a much less cost effective option than BCT particularly when mastectomy is combined with breast reconstruction. Another advantage of BCT is that it may allow patients to avoid axillary dissection if they are node positive on sentinel node biopsy and fulfil the ACOSOG Z-0011 criteria. After BCT ACOZOG Z-0011 showed that patients with 1 or 2 positive sentinel nodes do not get either a reduction in locoregional recurrence or a survival advantage by having an axillary node dissection (33).

Can BCT rates be increased even further with Neoadjuvant Therapy?

A major benefit of neo-adjuvant chemotherapy is its potential to increase the rate of breast conservation, a procedure known to be associated with less morbidity and improved body image compared with complete breast removal (34). A systematic review and meta-analysis considered fourteen studies that randomised 5500 women (35). This review demonstrated that neoadjuvant chemotherapy results in survival rates at least equivalent to those associated with adjuvant chemotherapy. In the neoadjuvant group, the mastectomy rate was lower (relative risk 0·71) and when BCT was performed, this was without a significant increase in local recurrence (hazard ratio 1·12). Importantly there were significantly less infective episodes with neoadjuvant compared with adjuvant chemotherapy and there was no increase in surgical complications with NAC (35). Performing mastectomy with reconstruction, can delay chemotherapy in some patients, and delay has been reported in at least 3 major series that have investigated whether breast reconstruction delays adjuvant chemotherapy (36). In patients considering mastectomy and reconstruction, giving chemotherapy first has the advantage of allowing consideration of options and planning surgery if a complex

reconstruction is to be performed. Neoadjuvant endocrine therapy has also been shown to increase the rates of BCT without increasing local recurrence (37).

Are there any contraindications to BCT?

Multifocal or multicentric cancers have been considered a contraindication to BCT but this is based on a small number of patients in a small number of observational studies performed over 2 decades ago. An emerging body of evidence indicates BCT is a viable for many such patients. Acceptable local recurrence rates can be obtained providing that all margins of excision are clear of disease independent of the number of cancers in the breast (38). One recent study involving 19000 women compared local recurrence rates after mastectomy or breast-conserving surgery for multifocal/multicentric versus unifocal breast cancer, and in the multivariate analysis, although there was an increased risk of local relapse in the multifocal/multicentric group in the mastectomy group, this was not observed in the BCT group (39). BCT is also an option for patients with central cancers and large areas (>4cm) of DCIS when combined with a therapeutic mammoplasty (40)

Mastectomy a poor operation

One issue with mastectomy is that it does not remove all breast tissue. In a series of 206 women who underwent mastectomy biopsy samples were taken from skin flaps. In 76.2 % of the specimens, one or more biopsy samples showed breast tissue was present. The findings of breast tissue on mastectomy flaps were found diffusely across the superficial dissection surface of the specimen (41).

Whole breast radiotherapy treats all the skin and lymphatics under the skin whereas in mastectomy patients who do not have chest wall radiation any disease in lymphatics is targeted only by the systemic therapy. Not only does a mastectomy leave breast tissue behind

but it can have major psychological effects on women. One quality of life study performed in 990 women compared long-term quality of life between breast cancer patients treated by BCT or mastectomy. Mastectomy patients had significantly lower body image, and sexual functioning scores and their lives were more disrupted than BCT patients. Emotional and social functioning and financial and future health worries were significantly worse for younger patients after mastectomy. Patients ≥70 years of age also reported higher body image and lifestyle scores when treated with BCT (42). What is not widely appreciated is that patients undergoing mastectomy and axillary dissection have a significantly higher rate of lymphoedema compared with patients having BCT (RR=1.42; 95% CI 1.15-1.76) (43). Chronic pain is also much more common after mastectomy than BCT and is a particular issue in women undergoing a contralateral prophylactic mastectomy (44).

Conclusions

The proponents of a more consumerist approach to healthcare assert the positive benefits of active participation in treatment decision making BUT any benefits of patient involvement in choosing treatment are not well supported by firm data (45). Giving patients a choice of treatments indicates that the two choices are equal. Increasing evidence indicates that BCT is a superior option for patients with early operable breast cancer and that patients treated by BCT have better outcomes. BCT is associated with survival which is at least as good, and from recent studies may be better than mastectomy and patients can keep their own breast with intact sensation, which results in less morbidity and less surgical complications, all of which ultimately leads to a potentially better quality of life. It no longer seems logical to offer all patients with early breast cancer, who are not gene carriers, the option of BCT or mastectomy. Such patients should be advised that BCT is their optimal treatment. ~~Any peace~~

~~of mind that patients report after mastectomy is not based on evidence and BCT appears optimal treatment for most women with early breast cancer.~~

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