Comparison of breast-conserving therapy with mastectomy for treatment of early breast cancer in community hospitals

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Although the results of clinical trials support breast-conserving therapy as a replacement for mastectomy in early breast cancer, the question remains whether these results apply in routine clinical practice. In the present analysis the breast cancer-specific survival and recurrence-free survival of 464 consecutive patients with breast tumours ≤3 cm across undergoing breast-conserving therapy were compared with a group of 459 patients with similar extent of disease and period of diagnosis undergoing mastectomy. All patients were treated in community hospitals in the south-eastern Netherlands. Median follow-up of both treatment groups was 6.2 years. After adjustment for the prognostic effects of age, tumour size, axillary nodal status and adjuvant systemic therapy, neither breast cancer-specific survival nor recurrence-free survival differed significantly between the breast-conserving therapy group and the mastectomy group. This finding indicates that in routine clinical practice breast-conserving therapy may be as effective as mastectomy.

Key words: breast cancer; breast-conserving therapy; mastectomy.

Introduction

The efficacy of breast-conserving therapy (BCT) and mastectomy in early breast cancer has been compared in several randomized clinical trials carried out during the seventies and early eighties.[1–3] All trials yielded similar survival rates for the two types of primary treatment. At subsequent consensus meetings and in various national, regional and institutional guidelines for treatment, BCT has been considered an appropriate method of primary therapy for the majority of women with stage I or II breast cancer. Nonetheless, substantial variation still exists in the proportion of women receiving BCT between hospitals and across regions.[4–7] In addition, especially older women have been reported to be less likely to receive BCT.[6–10] This may reflect the current uncertainties about selection criteria and the effectiveness of BCT in routine clinical practice.

In the south-eastern Netherlands, BCT was introduced into the treatment guidelines of the regional Breast Cancer Study Group in 1981. The area is exclusively served by community hospitals and one department of radiotherapy and characterized by a high and increasing incidence of early breast cancer.[11] Until 1991, the use of BCT increased gradually, although showing considerable variation between hospitals and being smaller in the elderly.[12] In a previous analysis of all patients treated with BCT between 1981 and 1987, survival and recurrence rates appeared to be comparable to those reported in literature.[13] In the current study we compared the breast cancer-specific survival and recurrence-free survival rate for BCT and mastectomy after a median follow-up of 6 years.

Patients and methods

Data were obtained from the population-based Eindhoven Cancer Registry, which serves a population of almost one million inhabitants in the south-eastern part of the Netherlands (7% of the Dutch population).[14] Data were collected by the cancer registry from copies of the pathologist's reports and from the medical records of eight community hospitals and the regional department of radiotherapy. Between 1981 and 1987, 482 patients with an invasive breast tumour ≤3 cm in diameter and post-surgical axillary nodal status N_0 or N_1 underwent BCT. During the same period 872 patients with breast cancer of the same stage had undergone modified radical mastectomy and from this group 500 patients were randomly selected: 150 from the period 1981–3 and 350 from the period 1984–7.

At the departments of surgery and the department of radiotherapy all medical records were screened for clinical events, including the site and date of any recurrence (local, regional or distant) and the date of death, up to June 1992. Information on the vital status was obtained from general

Table 1. Characteristics of patients according to primary treatment

Variable	Primary treatment	
	BCT ($n=464$)	Mastectomy ($n=457$)
Follow-up interval (years)		
Mean	6.2	6.2
Range	0.8–11.1	0.4–11.2
Age (years)		
≤ 45	144 (31%)	79 (17%)
46–65	251 (54%)	228 (50%)
≥ 66	69 (15%)	150 (33%)
Mean	51.6	58.3
Range	27–85	26–87
Period of primary treatment		
1981–3	127 (27%)	124 (27%)
1984–7	337 (73%)	323 (73%)
Tumour size (cm)		
≤ 2.0	380 (82%)	259 (57%)
2.1–3.0	84 (18%)	198 (43%)
Nodal status		
pN_0	346 (75%)	293 (64%)
pN_1	118 (25%)	164 (36%)
Adjuvant systemic therapy (Adj) according to nodal status		
pN_0 without Adj	342 (99%)	288 (98%)
pN_0 with Adj	4 (1%)	5 (2%)
pN_1 without Adj	44 (37%)	85 (52%)
pN_0 with Adj	74 (63%)	79 (48%)

practitioners and municipal registries. Four patients undergoing mastectomy and one patient undergoing BCT could not be traced after the date of primary treatment. Another 39 and 17 patients were excluded from the mastectomy group and the BCT group respectively: 25 and 10 with a previous breast tumour, nine and six with another previous malignancy and five and one respectively with synchronous bilateral breast cancer. Ultimately 921 patients were available for analysis, 464 with BCT and 457 with modified radical mastectomy (Table 1).

Guidelines for BCT and modified radical mastectomy were drawn up in 1981 by the regional Breast Cancer Study Group and adapted in 1983. Initially, all breast cancer patients with tumours ≤ 2 cm across at mammography were considered candidates for BCT, but in 1984 3 cm became the limit. Patients with relatively small breasts, diffuse microcalcifications on the mammogram, a tumour fixed to the muscles, or multiple breast tumours were supposed to undergo mastectomy. From 1981 until 1987 the proportion of patients with a tumour ≤ 2 cm who had BCT increased from 21% to 46%. The proportion of patients with tumours of 2–3 cm having BCT increased from less than 10% to 28%.

According to the guidelines, breast-conserving surgery involved a wide local excision of the tumour with an attempted margin of at least 1 cm of healthy tissue. Mastectomy was supposed to be of the modified radical type, according to the method of Patey or Madden. Both types of surgery included axillary dissection. All patients who underwent breast-conserving surgery received total breast irradiation, usually 50 Gy within 5 weeks with an additional booster dose of 14–15 Gy to the tumour bed. Of the mastectomy patients 52% underwent irradiation.

Adjuvant systemic therapy was recommended only for axillary node-positive patients, regardless of the type of surgery. Chemotherapy (six cycles of cyclophosphamide, methotrexate and fluorouracil) was indicated for pre-menopausal patients and hormonal therapy (tamoxifen) for post-menopausal patients with oestrogen receptor-positive tumours.

Breast cancer-specific survival and recurrence-free survival, calculated from the date of BCT or mastectomy, were used as endpoints in this study. Breast cancer-specific survival was based on death due to, or in the presence of, distant recurrence. Patients dying without distant recurrence and patients still living at the date of the last follow-up were considered as censored. To determine recurrence-free survival each first recurrence (local, regional or distant) was scored as an event. Patients without tumour recurrence were considered withdrawn alive at the date of last follow-up or death. Local recurrence was defined as pathologically confirmed tumour growth in the preserved breast after BCT or in the chest wall after mastectomy, regional recurrence as pathologically confirmed tumour growth in lymph nodes in the ipsilateral axilla and/or infraclavicular fossa and/or parasternal lymph nodes; clinically confirmed relapse of breast cancer in any other location was considered as distant recurrence.

The life-table method was used to perform the survival analysis.[15] To compare breast cancer-specific and recurrence-free survival in the BCT group and the mastectomy group the Cox proportional hazards model was used to adjust for the influence of the following prognostic factors: age, tumour size, axillary nodal status and adjuvant systemic therapy.[16] The resulting model parameters were converted to relative risks.

Results

The median follow-up time was 6.2 years for both treatment groups (Table 1). Between the BCT group and the mastectomy group there were significant differences in age, tumour size, and nodal status (χ^2: $P<0.001$) (Table 1). Node-positive patients in the BCT group were more likely to receive adjuvant systemic therapy (χ^2: $P<0.001$): 63% of the node-positive patients in the BCT group received any form of adjuvant systemic therapy vs 48% in the mastectomy group (Table 1). Of all node-negative patients only nine received adjuvant systemic therapy.

A total of 198 patients died (21%), 84 after BCT and 114 after mastectomy. Of all deaths 125 were breast cancer-related: 60 after BCT and 65 after mastectomy. At 7 years the breast cancer-specific survival rates were 84% (95% CI: 80–88) for BCT patients and 86% (95% CI: 82–90) for those treated with mastectomy (Fig. 1). Adjuvant systemic therapy and nodal status were combined to one variable consisting of three categories when included into the multivariate Cox model. After adjustment for the potentially confounding effect of age, tumour size and the combined variable of nodal status and adjuvant systemic therapy, the relative risk for death due to breast cancer for the BCT group compared to the mastectomy group was 1.09 ($P=0.67$) (Table 2). Node-positive patients with adjuvant systemic therapy were

found to have a reduced relative risk of dying from breast cancer compared with node-positive patients without systemic therapy (RR = 0.48; $P = 0.006$) (Table 2).

Tumour recurrence was detected in 104 BCT patients and in 119 mastectomy patients (Table 3). At 7 years, the actuarial recurrence-free survival rates were 77% (95% CI: 73–81) for the BCT group and 71% (95% CI: 67–76) for the mastectomy group (Fig. 1). After adjustment for age, tumour size and the combined variable of nodal status and adjuvant systemic therapy, the relative risk for recurrence for the BCT group compared to the mastectomy group was 0.96 ($P = 0.75$) (Table 2). The recurrence risk was halved for node-positive patients who received adjuvant systemic therapy, compared to node-positive patients without adjuvant systemic therapy ($P = 0.001$) (Table 2).
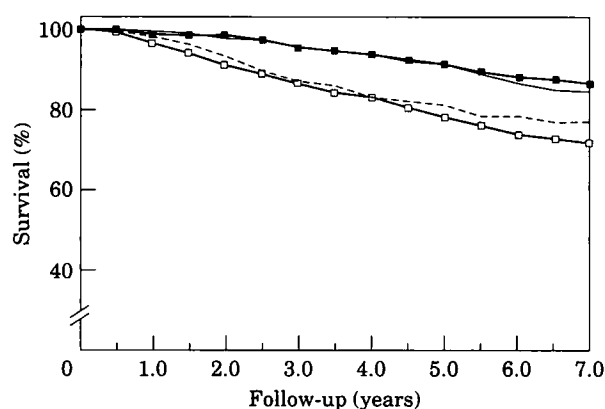

Fig. 1. Life table analysis. Breast cancer-specific survival (BC) and recurrence-free survival (RFS) after breast-conserving therapy (BCT) and mastectomy. (——— = BC + BCT; —■— = BC + mastectomy; – – – = RFS + BCT; —□— = RFS + mastectomy.)

Table 2. Results of multivariate analysis of breast cancer-specific survival and recurrence-free survival ($n = 921$)

Factor	Breast cancer-specific survival RR (95% confidence limit)	Recurrence-free survival RR (95% confidence limit)
Primary treatment		
Mastectomy*	1	1
BCT	1.09 (0.74–1.57)	0.96 (0.73–1.26)
Age group (years)		
≤45*	1	1
46–65	0.77 (0.51–1.16)	0.83 (0.60–1.13)
≥66	0.77 (0.45–1.31)	0.64 (0.42–0.96)
Tumour size (cm)		
≤2.0*	1	1
2.1–3.0	1.40 (0.94–2.06)	1.59 (1.19–2.10)
Nodal status and adjuvant systemic therapy (Adj)		
pN₁ without Adj*	1	1
pN₁ with Adj	0.48 (0.28–0.81)	0.50 (0.34–0.73)
pN₀†	0.29 (0.19–0.44)	0.34 (0.25–0.46)

RR: Relative risk as compared to reference category.
* Reference category; † including nine patients with adjuvant systemic therapy.

Table 3. Site of first recurrence in both treatment groups

	Primary treatment			
	BCT		Mastectomy	
Type of first recurrence	n	(%)	n	(%)
Local	27	(26)	15	(13)
Regional	9	(9)	13	(11)
Distant	63	(61)	85	(71)
Local and regional	1	(1)	2	(2)
Local and distant	1	(1)	1	(1)
Regional and distant	3	(3)	3	(3)
Total	104	(100)	119	(100)

Twenty-seven recurrences occurred in the preserved breast in the BCT group, as the first site of failure, and 15 in the chest wall in the mastectomy group (Table 3). The actuarial local recurrence rates at 7 years were 7.6% (95% CI: 4.8–10.4) and 5.3% (95% CI: 2.9–7.7) respectively. Distant metastases developed in 10 of the 27 patients with local recurrence after BCT, and at the time of analysis six of these had died with disseminated disease. Of the 15 patients with chest wall recurrence after mastectomy six developed distant metastases, of whom five died, four with and one without disseminated disease.

Discussion

Six major prospective randomized trials have now shown equivalent survival in comparisons of breast-conserving surgery and radiotherapy with mastectomy.[17-22] Our study group was derived from community hospitals, and in contrast to most trial populations older patients were also included. The results indicate that the efficacy achieved in trial centres may be reproduced in routine clinical practice.

We do not think that the non-random assignment of primary treatment has biased our results substantially. To prevent confounding by indication for primary treatment, the study was restricted to patients with a well-defined stage of early breast cancer. The possible confounding effects of age, tumour size, nodal status and adjuvant systemic therapy were eliminated in the multivariate analysis. The smaller proportion of node-positive patients with adjuvant systemic therapy in the mastectomy group is largely explained by the greater proportion of post-menopausal patients in this group and the regional guidelines concerning adjuvant systemic therapy. According to these guidelines post-menopausal patients with an oestrogen receptor-negative tumour were supposed not to receive tamoxifen. During the study period less than 10% of the post-menopausal patients with an oestrogen receptor-negative tumour received tamoxifen, whereas the proportion of node-positive women with oestrogen receptor-positive tumours increased from 50% to 80% between 1984 and 1987.[12] Currently, tamoxifen is given irrespective of the oestrogen receptor status of the tumour.

Even after multivariate analysis the possibility remains of confounding by factors which have not been documented in the cancer registry. Several relative contraindications for

the use of BCT, such as the presence of vascular invasion, extensive intraductal component or margin involvement, have not been taken into account, because information was not available at that time. However, these factors may have had only a slight effect on the results. First, patients were diagnosed before 1988, when knowledge of the pathophysiology of local recurrence and many of the risk factors for local recurrence after BCT was still limited. Second, most of the independent risk factors for relapse in the conserved breast are local features, which may not have any prognostic significance for breast cancer-specific survival. And in view of the low local recurrence rate after BCT in this study, local tumour characteristics could only have exerted a small influence on recurrence-free survival.

Though not the central aim of this analysis, we observed a significantly reduced risk of recurrence and death from breast cancer in node-positive patients receiving adjuvant systemic therapy. Such risk reductions are consistent with results from trials.[23] Numbers were too small to perform a separate analysis of the expected impact of adjuvant systemic therapy on the local recurrence rate.[3,24-26] Another indirect finding was the better recurrence-free survival of patients ≥ 66 years compared to patients ≤ 45 years.

Though based on a non-randomized study, our findings indicate that BCT can be applied adequately in routine practice according to current standards. No significant differences were observed in the breast cancer-specific survival and recurrence-free survival between patients with early breast cancer who were selected for either BCT or mastectomy in the community hospitals in south-eastern Netherlands.

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