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CLINICAL INVESTIGATION **Breast**

EARLY-STAGE YOUNG BREAST CANCER PATIENTS: IMPACT OF LOCAL TREATMENT ON SURVIVAL

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Purpose: **In young women, breast-conserving therapy (BCT), *i.e.*, lumpectomy followed by radiotherapy, has been associated with an increased risk of local recurrence. Still, there is insufficient evidence that BCT impairs survival. The aim of our study was to compare the effect of BCT with mastectomy on overall survival (OS) in young women with early-stage breast cancer.**

Methods and Materials: **From two Dutch regional population-based cancer registries (covering 6.2 million inhabitants) 1,453 women <40 years with pathologically T1N0–1M0 breast cancer were selected. Cox regression survival analysis was used to study the effect of local treatment (BCT vs. mastectomy) stratified for nodal stage on survival and corrected for tumor size, age, period of diagnosis, and use of adjuvant systemic therapy.**

Results: **With a median follow-up of 9.6 years, 10-year OS was 83% after BCT and 78% after mastectomy, respectively (unadjusted hazard ratio [HR], 1.37; 95% confidence interval [CI], 1.09–1.72). In N0-patients, 10-year OS was 84% after BCT and 81% after mastectomy and local treatment was not associated with differences in OS (HR 1.19; 95% CI, 0.89–1.58; $p = 0.25$). Within the N1-patient group, OS was better after BCT compared with mastectomy, 79% vs. 71% at 10 years (HR 1.91; 95% CI, 1.28–2.84; $p = 0.001$) and in patients treated with adjuvant hormonal therapy (HR 0.34; 95% CI, 0.18–0.66; $p = 0.001$).**

Conclusions: **In this large population-based cohort of early-stage young breast cancer patients, 10-year OS was not impaired after BCT compared with mastectomy. Patients with 1 to 3 positive lymph nodes had better prognosis after BCT than after mastectomy.**

Breast cancer, Young age, Breast-conserving therapy, Mastectomy, Population-based cancer registry.

INTRODUCTION

In the Netherlands, 5% of all women diagnosed with breast cancer are younger than 40 years (1). Breast cancers in young women generally have a higher proportion of pathologic features associated with more aggressive tumor behavior, such as negative estrogen receptor, poor differentiation grade (Grade 3), and lymphovascular invasion (2, 3). However, even if these differences are accounted for, young age remains an independent risk factor associated with worse clinical outcome, after both breast-conserving therapy (BCT) and mastectomy (4–10). The risk of dying of breast cancer within 5 years of diagnosis in women aged younger than 35 with Stage I–IIb breast cancer has been reported to be 1.8-fold higher than in women aged 50 to 69 years (9).

Like older women, young women with early stage breast cancer are treated with either BCT or mastectomy. Young women have worse local control rates after BCT, compared with mastectomy (11–14). However, there is still controversy as to whether this difference in local control translates into inferior survival after BCT in young breast cancer patients (11, 12, 15). In this study, we investigated the effect of type of local treatment (BCT vs. mastectomy) on overall survival (OS) of women aged <40 years with early-stage breast cancer.

METHODS AND MATERIALS

Study population

Patients were selected from two Dutch population-based cancer registries (CR), including the Comprehensive Cancer Center North

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East and the Comprehensive Cancer Center Amsterdam, covering a population of approximately 6.2 million inhabitants (40% of the Dutch population).

The Dutch CR record data of all newly diagnosed malignancies. Notifications are obtained from the Pathology Automated Archives. Furthermore, additional data are received from the National Registry of Hospital Discharge Diagnoses, which accounts for up to 8% of new cases (16). Data are obtained from patient files and include identifying information and tumor characteristics. Topography and morphology are coded according to the International Classification of Diseases for Oncology. TNM classification is used for staging (International Union against Cancer 2002) (17). Moreover, data on treatment (type of surgery, radiotherapy, chemotherapy, and hormonal therapy) are gathered on regular basis within the CR. The quality of the Dutch cancer registries is high, and completeness is estimated to be over 95% (18). Data on mortality are derived from the Municipal Personal Records Database. In this study, last linkage was set on February 1, 2009. For most patients under study, the CR did not collect data on recurrent disease or distant metastases. Hormonal receptor status was not routinely assessed by the CR in the beginning of the study period and was therefore not considered as covariate.

Female patients <40 years of age at diagnosis with invasive breast cancer pathologically ≤2 cm (pT1a–c), with up to 3 lymph node metastases (pN0-1) and treated with either BCT (breast-conserving surgery and radiotherapy) or mastectomy, with or without radiotherapy, between January 1989 and January 2005 were selected. We only included patients with small tumors, suitable for lumpectomy and up to 3 positive lymph nodes, because these patients are considered ideal for BCT (17). Choice of type of local treatment (BCT or mastectomy) was based on the surgeons' or patients' preferences (19, 20). Patients with distant metastatic (M1) disease, previous diagnosis of invasive cancer except nonmelanoma skin cancer, and patients treated with neoadjuvant therapy were excluded. The cohort was composed in accordance to privacy regulations of the Netherlands Cancer Registry.

Patient characteristics

Ultimately, the study population comprised 1,453 patients. Table 1 summarizes patient and tumor characteristics for both treatment groups (BCT or mastectomy), both overall and stratified for nodal stage. Median age was 36.5 (interquartile range, 33.8–38.4) years. Median follow-up was 9.6 (interquartile range, 5.9–14.3) years. Local treatment was BCT in 63% ($n = 909$) and mastectomy in 37% ($n = 544$) of the patients. Within the mastectomy group, 125 (23%) women received adjuvant radiotherapy. The majority of tumors (75%) were between 1 and 2 cm in diameter (pT1c), and 72% of patients had node-negative disease. Within the N0-group, both local treatment groups were well balanced on all characteristics. In the N1-group, the mastectomy group received more hormonal therapy than the BCT group (Table 1).

Treatment

Patients were treated according to the national guidelines at time of diagnosis. The guidelines for patients under 40 years of age are outlined below.

Local treatment consisted of wide tumor excision or quadrantectomy followed by radiotherapy to the whole breast with or without a boost to the tumor bed area, or a mastectomy. In cases of positive surgical margins or multifocality after mastectomy, surgery was followed by chest wall irradiation. Axillary staging consisted of axillary lymph node clearance, and, since the late 1990s, a sentinel node biopsy was followed by axillary clearance in case of a positive sentinel node.

Locoregional radiotherapy, consisting of irradiation of the draining nodal areas, such as axillary, supraclavicular, and internal mammary chain, was indicated in cases of positive apical lymph nodes and extensive extra nodal growth. From 1994 until 2003, internal mammary chain irradiation was indicated in medial located tumors in combination with 1 to 3 positive lymph nodes. After mastectomy, locoregional radiotherapy always included irradiation to the chest wall.

Table 1. Baseline characteristics of eligible patients according to local treatment ($n = 1,453$)

	N0					N1					All N				
	BCT ($n = 693$)		M ($n = 357$)			BCT ($n = 216$)		M ($n = 187$)			BCT ($n = 909$)		M ($n = 544$)		
Characteristic	*n*	(%)	*n*	(%)	*p* value*	*n*	(%)	*n*	(%)	*p* value*	*n*	(%)	*n*	(%)	*p* value*
Age at diagnosis (years)															
<35	231	(33.3)	128	(35.9)		77	(35.6)	71	(38.0)		308	(33.9)	199	(36.6)	
35–39	462	(66.7)	229	(64.1)	0.42	139	(64.4)	116	(62.0)	0.63	601	(66.1)	345	(63.4)	0.30
Period of diagnosis															
1989–1994	259	(37.4)	139	(38.9)		76	(35.2)	53	(28.3)		335	(36.9)	192	(35.3)	
1995–2000	213	(30.7)	104	(29.1)		60	(27.8)	61	(32.6)		273	(30.0)	165	(30.3)	
2001–2004	221	(31.9)	114	(31.9)	0.84	80	(37.0)	73	(39.0)	0.31	301	(33.1)	187	(34.4)	0.82
Pathological T stage															
1ab	173	(25.0)	106	(29.7)		39	(18.1)	45	(24.1)		212	(23.3)	151	(27.8)	
1c	520	(75.0)	251	(70.3)	0.10	177	(81.9)	142	(75.9)	0.14	697	(76.7)	393	(72.2)	0.06
Adjuvant chemotherapy															
No	544	(78.5)	280	(78.4)		34	(15.7)	22	(11.8)		578	(63.6)	302	(55.5)	
Yes	149	(21.5)	77	(21.6)	0.98	182	(84.3)	165	(88.2)	0.25	331	(36.4)	242	(44.5)	**0.002**†
Adjuvant hormonal therapy															
No	631	(91.1)	323	(90.5)		160	(74.1)	121	(64.7)		791	(87.0)	444	(81.6)	
Yes	62	(8.9)	37	(10.4)	0.76	56	(25.9)	66	(35.3)	**0.041**	118	(13.0)	100	(18.4)	**0.005**

Abbreviations: BCT = breast-conserving therapy; M = mastectomy.
* Estimated from chi-square analysis.
† Bold print indicates a p value <0.05.

In node-positive patients, all indications for locoregional irradiation were based on tumor characteristics acquired after primary surgery and had no influence on the surgeons' choice for either breast-conserving surgery or mastectomy.

In the 1980s and early 1990s, only node-positive patients were treated with adjuvant chemotherapy, generally consisting of cyclophosphamide, methotrexate, and 5-fluorouracil. Anthracycline-based chemotherapy was increasingly used from the mid-1990s. In the late 1990s, chemotherapy was also indicated for premenopausal, high-risk, node-negative patients, depending on tumor size, grade, and hormonal receptor status. Around 2001, adjuvant systemic treatment indications were expanded to patients aged ≤35 years, irrespective of their lymph node status or primary tumor characteristics.

Hormonal status was assessed routinely after 1998, and since then adjuvant hormonal therapy was added to chemotherapy in all hormone receptor-positive, node-positive patients and unfavorable node-negative patients (21, 22). In the Netherlands, trastuzumab as adjuvant treatment for breast cancer patients was introduced in 2005 and therefore not part of standard treatment in this cohort.

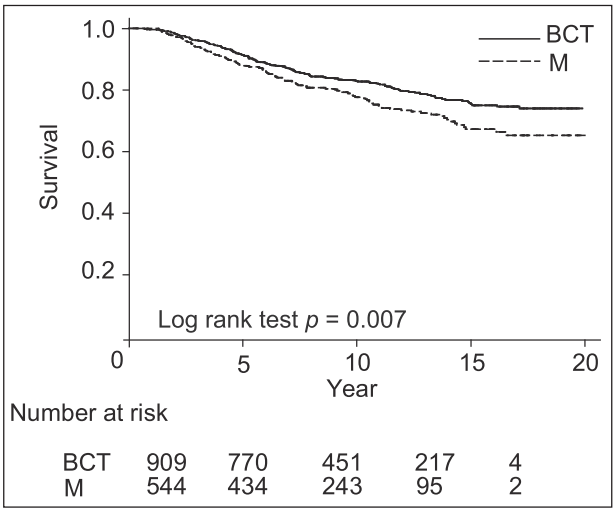

Fig. 1. Overall survival of patients after breast conserving therapy (BCT) or mastectomy (M) (unadjusted hazard ratio 1.37; 95% confidence interval, 1.09–1.72; $p = 0.007$).

Statistical analysis

Patient characteristics were described by local treatment and compared with the chi-square test. The unadjusted 5- and 10-year actuarial rates of OS were calculated using the Kaplan-Meier method, and both treatment groups were compared with the log-rank test.

Because significant interaction was present between local treatment and nodal stage, we analyzed the data for node-negative and node-positive patients separately.

Multivariate analysis was performed using the Cox proportional hazard model to study the effect of local treatment (BCT or mastectomy) on OS. In the analysis, we corrected for pathological tumor size (pT1ab/T1c), age at diagnosis (< 35/35-39), adjuvant chemotherapy (no/yes), adjuvant hormonal therapy (no/yes), and period of diagnosis (1989–1994/1995–2000/2001–2004). In general, these time periods corresponded with changes in systemic therapy guidelines. The OS was calculated as the interval between pathological diagnosis and date of death.

Because of the relatively young age of the cohort, we report OS and not only breast cancer–related deaths. In this way, we take potential treatment related long-term toxicity deaths into account.

Model fit was evaluated using residual-based graphical methods and goodness-of-fit statistics. All tests were two-sided, and a p value <0.05 was considered statistically significant. Interaction with local treatment was tested and for the interaction terms significance was set on 0.1. Analyses were performed using the STATA software package, version 10.1 for Windows (Stata Corporation LP, College Station, TX).

RESULTS

Overall survival

The 10-year actuarial OS rate was 83% in the BCT group vs. 78% in the mastectomy group (log-rank test $p = 0.007$; unadjusted hazard ratio [HR] 1.37; 95% confidence interval [CI], 1.09–1.72; Figure 1). In total, 302 (21%) patients died during follow-up (Table 2). Patients without lymph node metastasis had a significantly better 10-year survival than node-positive patients (log-rank test $p < 0.001$; unadjusted HR 1.55; 95% CI, 1.22–1.96), 83% and 75%, respectively.

Because a significant interaction was present between local treatment and nodal stage ($p = 0.099$), we analyzed the data for node-negative and node-positive patients separately (Fig. 2A and 2B). Events and actuarial OS rates for both subgroups are presented in Table 2. In patients without lymph node metastases, no significant difference was seen in OS between treatment groups (log-rank test $p = 0.26$; unadjusted HR 1.18; 95% CI, 0.88–1.57). In node-positive disease, patients with mastectomy had a significantly worse OS outcome (log-rank test $p = 0.014$; unadjusted HR 1.62; 95% CI, 1.10–2.40) compared with patients who had BCT.

The stratified multivariate analysis of OS in node-negative patients is shown in Table 3. Local treatment was not associated with OS in this subgroup (HR 1.19; 95% CI, 0.89–1.58; $p = 0.247$). Women diagnosed and treated in the period 2000–2004 had significantly better survival than patients diagnosed before 1994 (HR 0.56; 95% CI, 0.33–0.96; $p = 0.034$; overall $p = 0.053$).

The effect of local treatment in patients with positive lymph nodes is shown in Table 4. In node-positive patients, mastectomy was independently associated with worse OS (HR 1.91; 95% CI, 1.28–2.84; $p = 0.001$). Furthermore, patients treated with adjuvant hormonal therapy had better OS than patients without hormonal therapy (HR 0.34; 95% CI, 0.18–0.66; $p = 0.001$).

In total, 6.9% of patients developed contralateral breast cancer as first event and 4.1% of the patients developed a non-breast-cancer malignancy. Excluding these second cancer cases from the analysis did not alter the OS results (data not shown).

DISCUSSION

In this population-based analysis among young women with early-stage breast cancer, OS was not impaired after BCT compared with mastectomy. In node-positive patients, OS was better, even after correction for other prognostic

Table 2. Patient follow-up and events stratified for nodal stage (n = 1,453)

	N0		N1		all N	
Characteristic	BCT	M	BCT	M	BCT	M
Patients, *n* (%)	693 (66.0%)	357 (34.0%)	216 (53.6%)	187 (46.4%)	909 (62.6%)	544 (37.4%)
Age at diagnosis (years)						
Median	36.5	36.4	36.9	36.5	36.6	36.4
ICR	33.9–38.5	33.8–38.2	33.4–38.7	33.8–38.3	33.9–38.5	33.8–38.2
Follow-up (years)						
Median	10.0	9.8	9.6	7.0	9.9	8.9
ICR	6.4–14.8	6.3–14.6	5.5–14.8	4.6–11.4	6.1–14.8	5.7–13.6
10-year OS						
At risk at 10 years	346	176	105	67	451	243
OS	84%	81%	79%	71%	83%	78%

Abbreviations: BCT = breast-conserving therapy; M = mastectomy; ICR = interquartile range; OS = overall survival.

factors. To our knowledge, this is the largest published series comparing mastectomy to BCT in young breast cancer patients (aged <40 years) who are ideal candidates (pT1N0–1M0) for BCT.

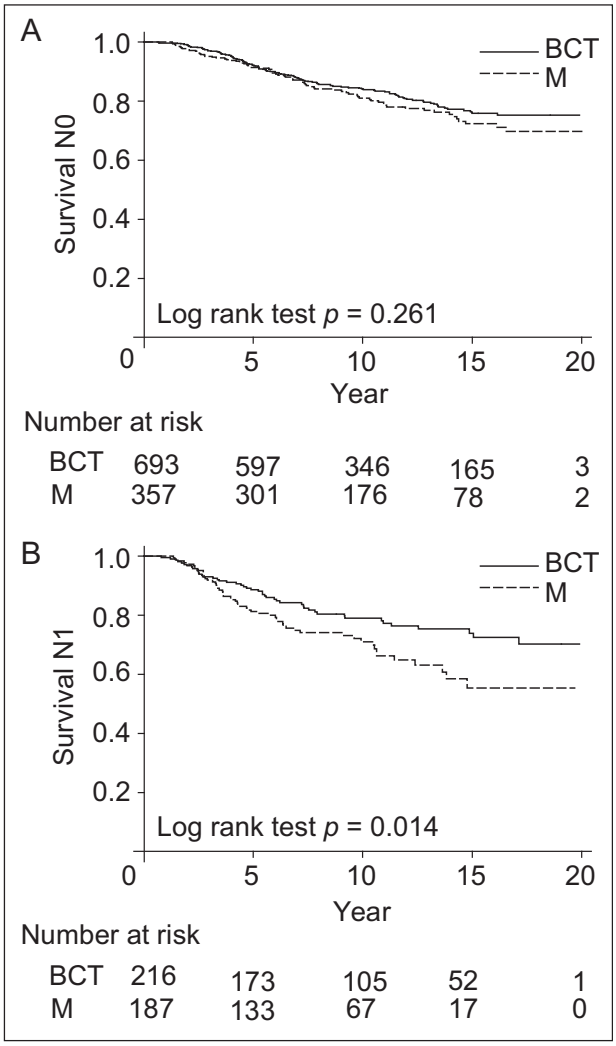

Fig. 2. Overall survival of patients after breast conserving therapy (BCT) or mastectomy (M) in node-negative patients (A); (unadjusted hazard ratio 1.18; 95% confidence interval, 0.88–1.57; p = 0.26) and node-positive patients (B); (unadjusted hazard ratio 1.62; 95% confidence interval, 1.10–2.40; p = 0.014).

The overall actuarial 10-year OS rate was 83% in the BCT group vs. 78% in the mastectomy group. These OS rates and the difference between BCT and mastectomy are comparable to other long-term outcomes from retrospective series. In women 35 years and younger with Stage I–III disease, Beadle *et al.* (23) described 10-year OS rates of 80% and 59% for BCT and mastectomy, respectively. In a favorable subset-analysis among Stage I young breast cancer patients, <40 years, considered ideal candidates for BCT, breast-cancer-specific survival (BCSS) at 10 years was 91% in the BCT group vs. 86% after mastectomy (15).

Node-negative patients diagnosed after 2000 had better OS than patients treated before 1994 (HR 0.56; 95% CI, 0.33–0.96; p = 0.034, overall p = 0.053). By including period of diagnosis in our analysis, we tried to adjust for changes in systemic treatment over time. Because of guideline changes, more patients received a combination of both adjuvant

Table 3. Multivariate Cox regression survival analysis stratified for nodal stage

Node-negative patients (n = 1,050)				
Characteristic	*n*	HR	(95% CI)	*p* value
Age at diagnosis (y)				
<35	359	1		
35–39	691	0.84	(0.63–1.12)	0.24
Period of diagnosis				
1989–1994	398	1		0.053
1995–2000	317	1.07	(0.78–1.47)	0.66
2001–2004	335	**0.56**	**(0.33–0.96)**	**0.034***
Local treatment				
BCT	693	1		
M	357	1.19	(0.89–1.58)	0.25
Pathological T stage				
1ab	279	1		
1c	771	1.01	(0.73–1.38)	0.97
Adjuvant chemotherapy				
No	824	1		
Yes	226	0.89	(0.53–1.50)	0.66
Adjuvant hormonal therapy				
No	954	1		
Yes	96	0.46	(0.16–1.33)	0.15

Abbreviations: BCT = breast-conserving therapy; CI = confidence interval; HR = hazard ratio; M = mastectomy.

* Bold print indicates a p value <0.05.

Table 4. Multivariate Cox regression survival analysis stratified for nodal stage

Node-positive patients (n = 403)				
Characteristic	n	HR	(95% CI)	p value
Age at diagnosis (years)				
<35	148	1		
35–39	255	0.68	(0.46–1.01)	0.056
Period of diagnosis				
1989–1994	129	1		0.37
1995–2000	121	0.73	(0.45–1.18)	0.20
2001–2004	153	1.03	(0.58–1.83)	0.93
Local treatment				
BCT	216	1		
M	187	**1.91**	**(1.28–2.84)**	**0.001***
Pathological T stage				
1ab	84	1		
1c	319	1.25	(0.75–2.09)	0.39
Adjuvant chemotherapy				
No	56	1		
Yes	347	0.70	(0.42–1.17)	0.18
Adjuvant hormonal therapy				
No	281	1		
Yes	122	**0.34**	**(0.18–0.66)**	**0.001**

Abbreviations: BCT = breast-conserving therapy; CI = confidence interval; HR = hazard ratio; M = mastectomy.

* Bold print indicates a p value <0.05.

hormonal therapy and chemotherapy in the period after 2000. An improvement in outcome in node-negative patients by period of diagnosis was also observed in the study by van der Sangen *et al.* (24). There were no differences in the choice of local treatment in the different periods (data not shown). In our study, no relation was found between local treatment and OS among patients with node-negative disease.

In the node-positive (1 to 3 positive lymph nodes) patients, OS rate was better in patients after BCT compared with mastectomy, similar to the results of Beadle *et al.* (23), who found mastectomy to be predictive of inferior OS (81% vs. 63% at 10 years) in 296 Stage II patients. The analysis of Surveillance, Epidemiology, and End Results data showed that radiotherapy was independently associated with improved OS in patients with Stage II breast cancer with 1–3 positive lymph nodes. At 10 years, BCSS was 88% for pT1 patients after BCT compared with 84% after mastectomy without radiotherapy ($p < 0.001$) (25). In this study, we have found a similar advantage favoring BCT in a population of young women with Stage IIa (excluding T2N0) breast cancer.

Radiotherapy has shown to improve OS after mastectomy and adjuvant systemic therapy (26), yet there is still debate as to whether this applies to all node-positive patients (27). In a subgroup analysis of the Danish Breast Cancer Cooperative Group b and c trials in patients with 1 to 3 positive lymph nodes, postmastectomy radiotherapy improved the absolute 15-year OS with 9% (relative risk reduction of 17%) (28). In the British Columbia trial, the 20-year BCSS improved by 15% in irradiated patients, the relative risk reduction was 23% and 24% in patients with 1 to 3 and ≥4 positive lymph nodes, respectively (29). MacDonald *et al.* (30) showed in a recent retrospective analysis an 18% absolute 10-year OS gain after chest wall irradiation compared with no irradiation in Stage II patients after mastectomy (30). These studies show a beneficial role of postmastectomy radiotherapy in Stage II patients. The difference we found in survival between the mastectomy and the BCT group might reflect the beneficial effect of radiotherapy, which was given to all BCT patients. Involvement of 1 to 3 lymph nodes was not an indication for postmastectomy radiotherapy in this study.

In our population, all patients received radiotherapy after breast-conserving surgery, which was not the case after mastectomy. Although it was possible to identify the patients receiving postmastectomy radiotherapy, it was not possible to distinguish in the breast-conserved group which patients received additional regional radiotherapy. Patients receiving regional radiotherapy would represent an unfavorable group, which cannot be accounted for in the BCT group. To prevent a selection bias and in the knowledge that the indication for locoregional irradiation was based on postsurgery findings, we did not include postmastectomy irradiation in our comparison between BCT and mastectomy. The OS of patients receiving postmastectomy radiotherapy, which was a prognostically unfavorable group, was equivalent to that of the patients undergoing mastectomy without radiotherapy (data not shown). Beadle *et al.* (23) showed that in patients with Stage II disease, after BCT and postmastectomy radiotherapy, the OS was the same, despite higher locoregional recurrence rates after BCT. Furthermore, the difference in locoregional recurrence rates after mastectomy with or without adjuvant radiotherapy translated in a survival advantage favoring the postmastectomy radiotherapy. This shows that the impact of locoregional recurrences on survival is different after BCT compared with mastectomy.

In this study, we evaluated survival regardless of local recurrence. Moreover, the number of local recurrences after BCT is expected to be higher than after mastectomy (7, 11–14, 24, 31). Even with the higher expected local recurrence rate, BCT resulted in a survival advantage over mastectomy in patients with 1 to 3 positive nodes. This suggests that OS differences in this lymph node–positive population are truly affected by choice of treatment.

Adjuvant hormonal therapy did significantly affect OS in node-positive patients. Similar results have been reported in a large meta-analysis of the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) (32), in which adjuvant hormonal therapy yielded significantly better survival in women 50 years and younger.

Limitations of this study are the retrospective design, which bears a risk of selection bias and the lack of information on other known prognostic factors, such as differentiation grade and receptor status. However, it is unlikely that these tumor-related prognostic factors have contributed to the choice of surgical procedure because at the time the women in this study were treated, these factors were assessed postoperatively and not taken into account for the type of surgery. Furthermore, to limit an eventual selection

bias by the surgeon, only tumors with a maximum diameter of 2 cm were included. For most tumors 2 cm and smaller, breast size would not be a factor accounting for the type of surgery. Choice of surgery in this population was based on surgeons' or patients' preferences, with large variations between regions and hospitals (19, 20). Multifocality, which is a risk factor for local recurrence (33–35), cannot be excluded as cause of selection bias but would, at the most, result in impaired results for the BCT group. In addition, because the CR did not gather data on prognostic factors and disease-related events, the impact of these events on OS could not be investigated. The node-positive mastectomy patients received significantly more adjuvant hormonal therapy compared with the BCT group, which at the least would benefit the mastectomy group.

In conclusion, in this large cohort of young, early-stage breast cancer patients, 10-year OS was not impaired after BCT compared with mastectomy. In patients with 1 to 3 positive lymph nodes, OS was better after BCT compared with mastectomy. Consequently, the study results do not justify withholding BCT from women younger than 40 years with early-stage breast cancer and adds on the mounting evidence in favor of radiotherapy for patients with 1 to 3 lymph nodes regardless of primary surgical treatment.

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