IJC
International Journal of Cancer

Breast conserving therapy and mastectomy revisited: Breast cancer-specific survival and the influence of prognostic factors in 129,692 patients

Mirelle Lagendijk[1†], Marissa C. van Maaren[2,3†], Sepideh Saadatmand[4], Luc J.A. Strobbe[5], Philip M.P. Poortmans[6], Linetta B. Koppert[1], Madeleine M.A. Tilanus-Linthorst[1] and Sabine Siesling[2,3]

[1] Department of Surgical Oncology, Erasmus MC Cancer Institute, 3075 EA, Rotterdam, The Netherlands
[2] Department of Research, Netherlands Comprehensive Cancer Organisation, 3511 DT, Utrecht, The Netherlands
[3] Department of Health Technology & Services Research, MIRA Institute for Biomedical Technology and Technical Medicine, University of Twente, 7500 EA, Enschede, The Netherlands
[4] Department of Surgery, Maxima Medical Center, 5504 DB, Veldhoven, The Netherlands
[5] Department of Surgical Oncology, Canisius Wilhelmina Hospital, 6532 SZ, Nijmegen, The Netherlands
[6] Department of Radiation Oncology, Institut Curie, 26, Rue d'Ulm, 75248 Paris cedex 05, France

This large population-based study compared breast-conserving surgery with radiation therapy (BCT) with mastectomy on (long-term) breast cancer-specific (BCSS) and overall survival (OS), and investigated the influence of several prognostic factors. Patients with primary T1-2N0-2M0 breast cancer, diagnosed between 1999 and 2012, were selected from the Netherlands Cancer Registry. We investigated the 1999–2005 (long-term outcome) and the 2006–2012 cohort (contemporary adjuvant systemic therapy). Cause of death was derived from the Statistics Netherlands (CBS). Multivariable analyses, per time cohort, were performed in T1-2N0-2, and separately in T1-2N0-1 and T1-2N2 stages. The T1-2N0-1 stages were further stratified for age, hormonal receptor and HER2 status, adjuvant systemic therapy and comorbidity. In total, 129,692 patients were included. In the 1999–2005 cohort, better BCSS and OS for BCT than mastectomy was seen in all subgroups, except in patients < 40 years with T1-2N0-1 stage. In the 2006–2012 cohort, superior BCSS and OS were found for T1-2N0-1, but not for T1-2N2. Subgroup analyses for T1-2N0-1 showed superior BCSS and OS for BCT in patients >50 years, not treated with chemotherapy and with comorbidity. Both treatments led to similar BCSS in patients <50 years, without comorbidity and those treated with chemotherapy. Although confounding by severity and residual confounding cannot be excluded, this study showed better long-term BCSS for BCT than mastectomy. Even with more contemporary diagnostics and therapies we identified several subgroups that may benefit from BCT. Our results support the hypothesis that BCT might be preferred in most breast cancer patients when both treatments are suitable.

Large randomized controlled trials (RCTs) in the 1980s have shown equal survival for breast-conserving therapy (breast-conserving surgery plus radiation therapy, BCT) and mastectomy in early stage breast cancer.[1–4] Over recent years, however, multiple observational studies have challenged this equivalence, showing superior survival for patients treated with BCT compared to those treated with mastectomy.[5–10] The use of population-based observational studies in studying

Key words: breast cancer, breast cancer-specific survival, breast conserving therapy, mastectomy, radiation therapy, comorbidity, prognostic factors

Abbreviations: BCSS: breast cancer-specific survival; BCT: breast-conserving surgery with radiation therapy; CBS: the Statistics Netherlands; CI: confidence interval; DCIS: ductal carcinoma *in situ*; LCIS: lobular carcinoma *in situ*; NCR: Netherlands Cancer Registry; HER2: human epidermal growth factor receptor 2; HR: hazard ratio; ICD-10: International Statistical Classification of Diseases and Related Health Problems; ICD-O: International Classification of Diseases for Oncology; N: nodal stage; OS: overall survival; PMRT: post-mastectomy radiation therapy; RT: radiation therapy; T: tumor stage; TNM: tumor, node and metastasis

Additional Supporting Information may be found in the online version of this article.

[†]Both authors contributed equally to this manuscript.

Conflicts of Interest: The authors declare no conflicts of interest.

DOI: 10.1002/ijc.31034
History: Received 21 Apr 2017; Accepted 24 Aug 2017; Online 7 Sep 2017

Correspondence to: Marissa C. van Maaren, Netherlands Comprehensive Cancer Organisation, P.O. Box 19079, 3501 DB Utrecht, The Netherlands, Tel.: +31 88-2346000; E-mail: m.vanmaaren@iknl.nl

What's new?

While breast-conserving therapy (BCT) and mastectomy have long been considered equivalent in terms of survival in early-stage breast cancer, recent studies suggest BCT offers superior survival over mastectomy. The findings of this study support that idea, showing that breast cancer-specific survival and overall survival were greater for BCT than mastectomy in analyses of 129,692 patients diagnosed with breast cancer in The Netherlands between 1999 and 2012. Subgroup analyses revealed better survival for BCT in most instances, with survival being similar for BCT and mastectomy primarily among patients under age 50, patients without comorbidity, and those treated with chemotherapy.

treatment effects can be of additional value on outcomes obtained through RCTs. In these studies, treatment effects are evaluated in an unselected population making results more generalizable.[11]

A recent observational population-based study of van Maaren *et al.* showed favorable overall (OS), relative (RS) and distant metastasis-free survival for BCT compared to mastectomy in T1N0 stage breast cancer.[12] Investigating the prognostic factors for survival in primary breast cancer, Saadatmand *et al.* showed that BCT led to significantly higher OS and RS than mastectomy (with or without radiation therapy, RT) in a Dutch cohort diagnosed between 1999 and 2012.[13] However, both of these studies lacked information about breast cancer-specific deaths and comorbidity.

The aim of this study was to investigate the effect of BCT compared to mastectomy on breast cancer-specific survival (BCSS) and OS. The prognostic factors age, stage, hormonal receptor status, HER2 status, adjuvant systemic therapy and comorbidity are considered as a possible explanation for the previously reported survival differences between BCT and mastectomy. To identify patients that could possible benefit from BCT, subgroup analyses were performed evaluating these prognostic factors separately in relation to BCSS and OS.

Methods

Study population

In this study, all patients diagnosed between 1999 and 2012 with primary T1–2N0–2M0 breast cancer treated with BCT or mastectomy were selected from the population-based Netherlands Cancer Registry (NCR). Details on the NCR are described elsewhere.[12,13] In case of multiple breast surgeries, the most extensive surgery was used. T1–2N0–2M0 patients were included based on primary eligibility for both BCT and mastectomy. Patients with insufficient data for linkage of the NCR to the Statistics Netherlands (CBS) were excluded. Furthermore, patients who lacked information on type of surgery, clinical and pathological tumor stage or pathological nodal stage were excluded. Patients treated with primary (neoadjuvant) systemic therapy, breast-conserving surgery without RT, patients diagnosed with Paget's disease, ductal (DCIS) or lobular carcinoma *in situ* (LCIS) were excluded.

Procedures

Patient-, tumor-, and treatment-related characteristics were obtained from the NCR. Through linkage with the Municipal Personal Records database, data on vital status and date of death (if applicable) were obtained.

The cohort was divided into two prespecified consecutive time cohorts: the 1999–2005 cohort and the 2006–2012 cohort. The cohorts were chosen based on changes in the indication and type of systemic therapy available in daily practice, as described previously.[13] The 1999–2005 cohort was evaluated to interpret the long-term outcome following BCT versus mastectomy. The 2006–2012 cohort most closely resembles current breast cancer care in The Netherlands.

Tumor topography and morphology were coded according to the International Classification of Diseases for Oncology (ICD-O), 2nd (1999–2002)[14] or 3rd (2003–2012)[15] edition. Staging was coded according to the tumor, node and metastasis (TNM) classification system (International Union Against Cancer, 5th (1999–2002),[16] 6th (2003–2009)[17] or 7th (2010–2012)[18] edition). In case of lacking data regarding pathological tumor stage, we used clinical tumor stage (based on imaging and clinical examination). Nodal stage was based on pathological evaluation. Since the definition of N1 in the TNM classification system changed between the 5th and 6th editions, the number of positive lymph nodes was used to classify patients into N stages. Patients without lymph node involvement were classified as N0 and patients with 1–3 positive nodes as N1. Patients with >3 positive lymph nodes were classified as N2. Data on hormonal receptor status, HER2 status and multifocality were routinely registered for the 2006–2012 cohort, but not for the 1999–2005 cohort. Hormonal receptor status was considered positive in case of $\geq$10% nuclear staining of the estrogen receptor. Second primary breast cancer was defined as contralateral DCIS or invasive breast cancer.[19] Data on comorbidities were available in a subcohort from the south of The Netherlands. Comorbidities were registered at time of diagnosis. Due to a low number of patients with a known comorbidity status, no additional classifications could be made for number or severity of comorbidities. For all patients, cause of death (if applicable) was obtained through linkage to the CBS based on birthdate, date of death (if applicable) and (a history of) area code of residence. This is a mandatory registry that documents cause of death for all inhabitants of The Netherlands. Deaths were considered breast cancer-related if physicians reported "breast cancer" as a first, second or third cause of death. Medically trained,

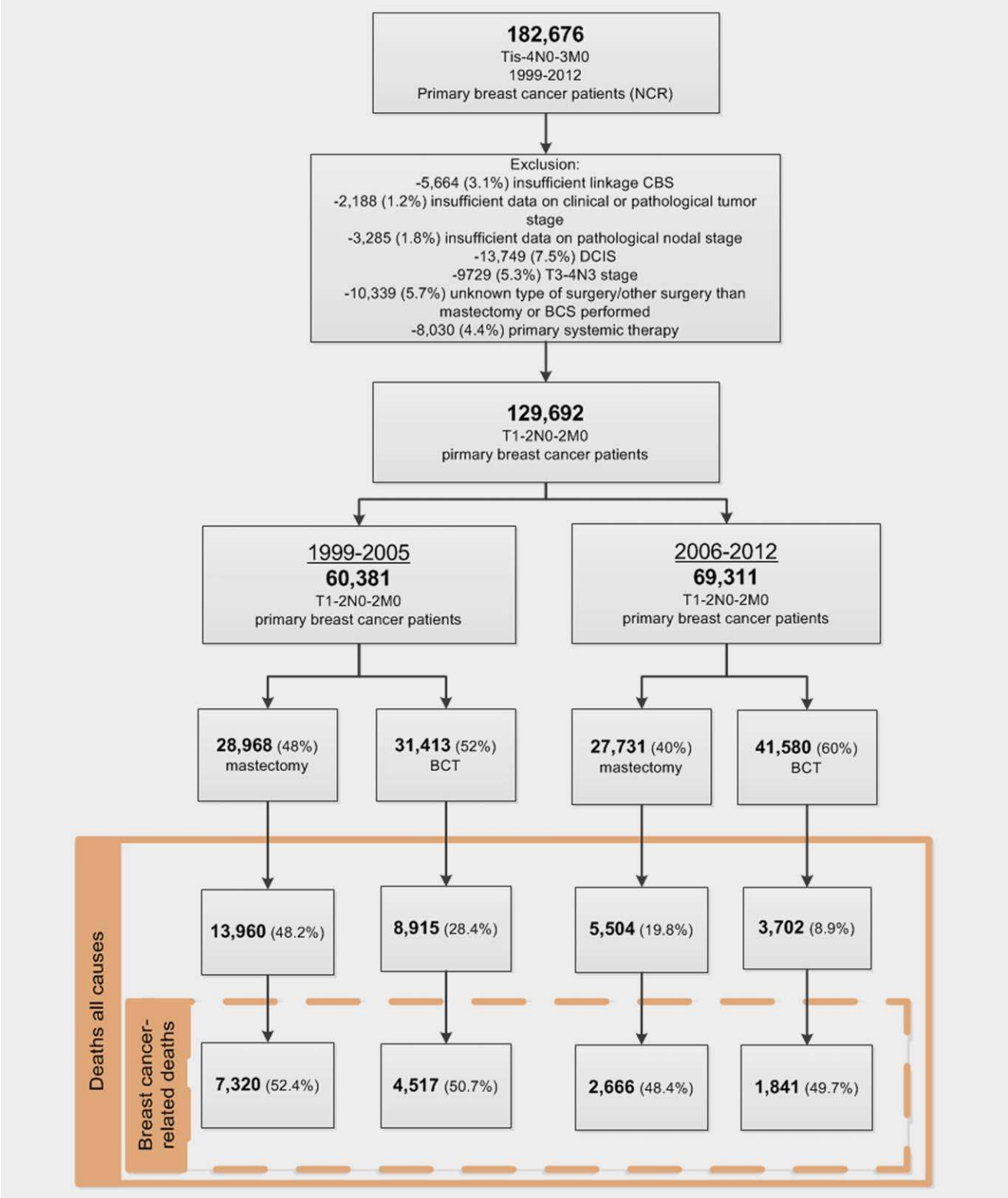

Figure 1. Flowchart of included patients and number of events for all cause and breast cancer-related deaths. [Color figure can be viewed at wileyonlinelibrary.com]

specialized personnel coded the cause of death based on the International Statistical Classification of Diseases and Related Health Problems, 10th revision (ICD-10).[18] Follow-up was calculated from date of diagnosis to the date of death. Patients were censored at date of breast cancer-related death (BCSS), all cause death (OS) or last date of observation (BCSS and

Table 1. Baseline characteristics ($n = 129,692$)

	1999–2005 (60,381)			2006–2012 (69,311)	
Treatment group	**Mastectomy ($n = 28,968$)**	**BCT ($n = 31,413$)**		**Mastectomy ($n = 27,731$)**	**BCT ($n = 41,580$)**
Median age (IQR)	62 (50–74)	57 (50–66)		61 (50–73)	59 (51–67)
Age					
<40	1,768 (6.1)	1,688 (5.4)		1,845 (6.7)	1,489 (3.6)
40–49	5,145 (17.8)	6,088 (19.4)		5,056 (18.2)	6,957 (16.7)
50–65	9,657 (33.3)	15,064 (48.0)		9,772 (35.2)	20,852 (50.1)
66–75	6,239 (21.5)	6,990 (22.3)		5,541 (20.0)	10,277 (24.7)
>75	6,159 (21.3)	1,583 (5.0)		5,517 (19.9)	2,005 (4.8)
Year of diagnosis					
1999	4,483 (15.5)	3,640 (11.6)	2006	3,883 (14.0)	5,552 (13.4)
2000	4,224 (14.6)	4,062 (12.9)	2007	3,981 (14.4)	5,806 (14.0)
2001	4,360 (15.1)	4,161 (13.2)	2008	4,082 (14.7)	5,710 (13.7)
2002	4,231 (14.6)	4,318 (13.7)	2009	4,160 (15.0)	5,649 (13.6)
2003	3,967 (13.7)	4,886 (15.6)	2010	3,916 (14.1)	5,885 (14.2)
2004	3,886 (13.4)	5,013 (16.0)	2011	3,972 (14.3)	6,327 (15.2)
2005	3,817 (13.2)	5,333 (17.0)	2012	3,737 (13.5)	6,651 (16.0)
Multifocality	NA	NA			
No				19,657 (70.9)	38,265 (92.00
Yes				7,699 (27.8)	2,836 (6.8)
Unknown				375 (1.4)	479 (1.2)
Tumor localization					
Outer quadrants	13,161 (45.4)	16,694 (53.1)		11,829 (42.7)	21,033 (50.6)
Inner quadrants	4,910 (16.9)	6,693 (21.3)		4,835 (17.4)	9,075 (21.8)
Central parts	2,719 (9.4)	1,617 (5.1)		2,436 (8.8)	2,448 (5.9)
Overlapping parts	7,521 (26.0)	5,926 (18.9)		8,166 (29.4)	8,462 (20.4)
Unknown	657 (2.3)	483 (1.5)		465 (1.7)	562 (1.4)
Tumor stage					
T1a	1,037 (3.6)	1,093 (3.5)		1,312 (4.7)	2,099 (5.0)
T1b	2,661 (9.2)	6,202 (19.7)		2,662 (9.6)	9,013 (21.7)
T1c	10,276 (35.5)	16,158 (51.4)		10,349 (37.3)	21,369 (51.4)
T2	14,994 (51.8)	7,960 (25.3)		13,408 (48.4)	9,099 (21.9)
Nodal stage					
N0	15,917 (54.9)	22,204 (70.7)		15,985 (57.6)	31,299 (75.3)
N1	9,855 (34.0)	7,826 (24.9)		9,082 (32.8)	9,028 (21.7)
N2	3,196 (11.0)	1,383 (4.4)		2,664 (9.6)	1,253 (3.0)
Morphology					
Ductal	22,160 (76.5)	25,750 (82.0)		21,474 (77.4)	35,114 (84.4)
Lobular	3,693 (12.7)	2,606 (8.3)		3,601 (13.0)	3,273 (7.9)
Other/unknown	3,115 (10.8)	3,057 (9.7)		2,656 (9.6)	3,193 (7.7)
Differentiation					
Grade 1	4,002 (13.8)	6,897 (22.0)		5,126 (18.5)	11,694 (28.1)
Grade 2	11,229 (38.8)	12,392 (39.4)		12,.347 (44.5)	17,704 (42.6)
Grade 3	9,318 (32.2)	8,018 (25.5)		8,854 (31.9)	10,583 (25.5)
Unknown	4,419 (15.3)	4,106 (13.1)		1,404 (5.1)	1,599 (3.8)

Table 1. Baseline characteristics ($n = 129,692$) (Continued)

	1999–2005 (60,381)		2006–2012 (69,311)	
Treatment group	**Mastectomy ($n = 28,968$)**	**BCT ($n = 31,413$)**	**Mastectomy ($n = 27,731$)**	**BCT ($n = 41,580$)**
Hormonal receptor status	NA	NA		
Negative			4,885 (17.6)	5,911 (14.2)
Positive			22,475 (81.0)	35,112 (84.4)
Unknown			371 (1.3)	557 (1.3)
HER2 status	NA	NA		
Negative			22,280 (80.30	35,884 (86.3)
Positive			4,233 (15.3)	4,166 (10.0)
Unknown			1,218 (4.4)	1,530 (3.7)
Axillary lymph node dissection				
No	6,956 (24.0)	15,930 (50.7)	14,296 (51.6)	32,098 (77.2)
Yes	22,012 (76.0)	15,483 (49.3)	13,435 (48.4)	9,482 (22.8)
Radiation therapy				
No	22,902 (79.1)	na	22,971 (82.8)	na
Yes	6,066 (20.9)	31413 (100.0)	4,760 (17.2)	41,580 (100.0)
Systemic therapy				
None	11,730 (40.5)	16,894 (53.8)	8,060 (29.1)	18,157 (43.7)
Endocrine therapy	4,151 (14.3)	4,126 (13.1)	3,432 (12.4)	4,578 (11.0)
Chemotherapy	8,017 (27.7)	5,504 (17.5)	7,853 (28.3)	9,092 (21.90
Chemotherapy & endocrine therapy	5,070 (17.5)	4,889 (15.6)	8,386 (30.2)	9,753 (23.5)
Contralateral BC				
No	26,809 (92.5)	29,318 (93.3)	26,323 (94.9)	40,261 (96.8)
Yes	2,159 (7.5)	2,095 (6.7)	1,408 (5.1)	1,319 (3.2)
Comorbidities				
No	5,229 (18.1)	6,969 (22.2)	2,963 (10.7)	5,687 (13.7)
Yes	2,176 (7.5)	2,239 (7.1)	2,154 (7.8)	3,479 (8.4)
NA	21,563 (74.4)	22,205 (70.7)	22,614 (81.5)	21,414 (78.0)

Abbreviations: BCT = Breast-conserving surgery plus radiation therapy; FU = follow-up; IQR = interquartile range; NA = not available; na = not applicable.

OS). The follow-up for both registries was complete until December 31st, 2015.

Study outcomes

The primary outcome was BCSS, the secondary outcome was OS. We compared BCT with mastectomy on both survival outcomes for the two cohorts separately: the 1999–2005 cohort and the 2006–2012 cohort.

Statistical analysis

For both the 1999–2005 and 2006–2012 cohorts, patient-, tumor- and treatment-related characteristics were compared between the treatment groups using the Pearson's X^2 or Mann-Whitney U tests. The Kaplan-Meier method was used to estimate crude BCSS, and the log-rank test was used to compare treatment groups. Hazard ratios (HR) with 95% confidence intervals (CIs) of BCT and mastectomy on both BCSS and OS were estimated using multivariable Cox proportional hazard analyses. These analyses were performed overall, and separately for the T1–2N0–1 stages (T1abN0, T1cN0, T1N1, T2N0, T2N1) and T1–2N2 stages. In addition, the T1–2N0–1 stages were further stratified according to age (<40, 40–49, 50–65, 66–75, >75 years), hormonal receptor status (negative, positive), HER2 status (negative, positive), adjuvant systemic therapy administered (none, chemotherapy, endocrine therapy, both chemotherapy and endocrine therapy) and comorbidity at time of diagnosis (yes/no). In multivariable analyses, we adjusted for all potential confounding variables available for the specific time cohorts. The subgroup of patients < 40 years had too few events to study all potential confounding variables. For this subgroup, it was decided to use the most important prognostic factors based on foreknowledge (indicated in the legends of the figures). We tested the proportional hazard assumption by plotting all coefficients over time and inspecting these for consistency. No violations were found. All statistical tests were

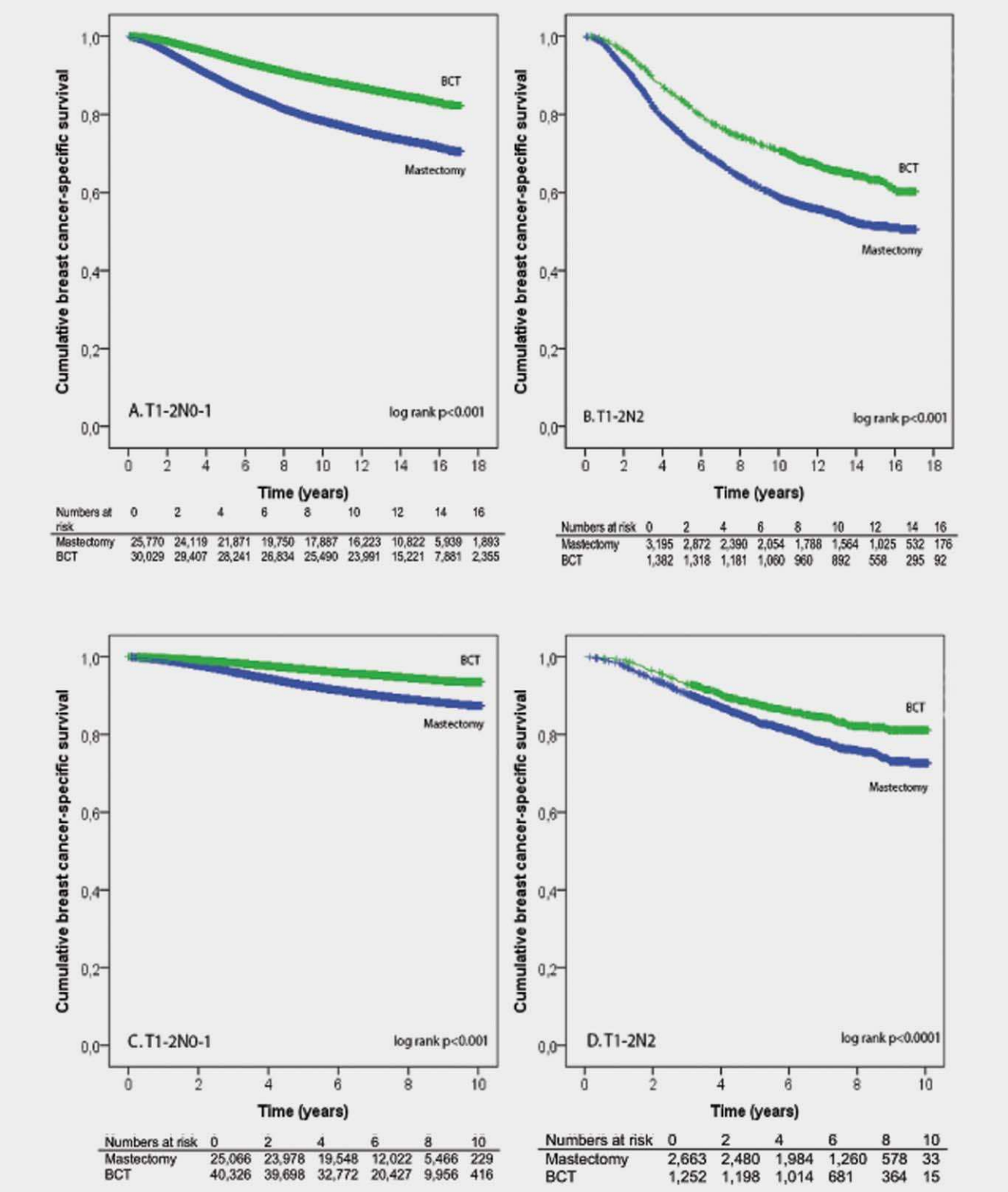

Figure 2. Kaplan-Meier curves for BCSS in the 1999–2005 cohort for (*a*) T1–2N0–1 and (*b*) T1–2N2, in the 2006–2012 cohort for (*c*) T1–2N0–1 and (*d*) T1–2N2 patients. [Color figure can be viewed at wileyonlinelibrary.com]

two-sided and a p values < 0.05 was considered to be statistically significant. All analyses were performed in SPSS Statistics for Windows (version 21.0) (IBM Corp, Armonk, NY).

Results

The final study population consisted of 129,692 patients: 60,381 patients in the 1999–2005 cohort and 69,311 in the

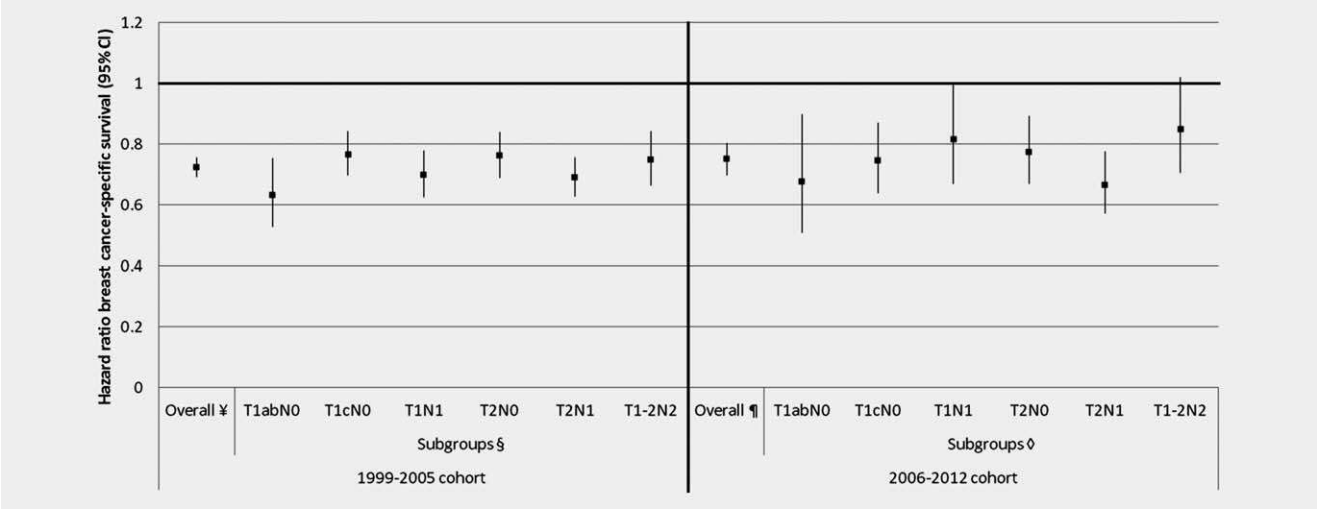

Figure 3. Hazard ratios of breast-conserving therapy compared to mastectomy on BCSS for both cohorts, overall and specified for T and N stage. "T" indicates the tumor stage. "N" indicates the nodal stage. ¥Corrected for age, year of diagnosis, tumor stage, nodal stage, morphology, differentiation grade, axillary lymph node dissection, systemic therapy and contralateral breast cancer. §Corrected for age, year of diagnosis, morphology, differentiation grade, axillary lymph node dissection, systemic therapy and contralateral breast cancer. ¶Corrected for age, year of diagnosis, tumor stage, nodal stage, morphology, differentiation grade, axillary lymph node dissection, systemic therapy, contralateral breast cancer, hormonal receptor status, HER2 status and multifocality. ◇Corrected for age, year of diagnosis, morphology, differentiation grade, axillary lymph node dissection, systemic therapy, contralateral breast cancer, hormonal receptor status, HER2 status and multifocality.

2006–2012 cohort. Figure 1 presents the patient selection and division as described in the methods. In the 1999–2005 cohort, 52% of the patients was treated with BCT, compared to 60% in the 2006–2012 cohort. Baseline characteristics according to type of surgery for both cohorts are shown in Table 1 and Supporting Information Table S1. In the 1999–2005 cohort, the median age at diagnosis was 57 and 62 years in the BCT and mastectomy group, respectively. In the 2006–2012 cohort, the median age at diagnosis was 59 and 61 years for the BCT and mastectomy group, respectively. Characteristics of the subcohort with known comorbidity status are similar to the entire cohort, indicating its representativeness (Supporting Information Table S2). Information on adjuvant systemic therapy for both cohorts in the T1–2N0–1 stages is shown in Supporting Information Tables S3 and S4.

Breast cancer-specific and overall survival in the 1999–2005 cohort

In the BCT group, 8,915 out of 31,413 (28.4%) patients died, of whom 4,517 (50.7%) died due to breast cancer. In the mastectomy group, 13,960 out of 28,968 (48.2%) patients died, of whom 7,320 (52.4%) died due to breast cancer (Fig. 1). Median follow-up duration was 12.0 and 11.2 years for the BCT and mastectomy group, respectively.

Kaplan-Meier analysis and the log-rank test showed significantly higher crude BCSS for BCT compared to mastectomy in T-2N0–1 and T1–2N2 stage (Fig. 2). Overall, adjusted HRs for both BCSS [0.72 (95% CI: 0.69–0.76, $p < 0.0001$)] and OS [0.74 (95% CI: 0.71–0.76, $p < 0.0001$)] were higher for BCT than mastectomy. These results remained significant after stratification by T and N stage (Fig. 3 and Supporting Information Table S5). Further stratification in T1–2N0–1 stage breast cancer for age category, systemic therapy and comorbidity showed similar superior survival for the BCT group (Fig. 4 and Supporting Information Table S6).

Breast cancer-specific and overall survival in the 2006–2012 cohort

In the BCT group, 3,702 out of 41,580 (8.9%) died, of whom 1,841 (49.7%) died due to breast cancer. In the mastectomy group, 5,504 out of 27,731 (19.8%) patients died, of whom 2,666 (48.4%) died due to breast cancer (Fig. 1). Median follow-up duration was 6.0 and 5.9 years for the BCT and mastectomy group, respectively. Kaplan-Meier analysis accompanied by log-rank testing showed significantly superior crude BCSS for BCT compared to mastectomy in both the T1–2N0–1 and T1–2N2 stages (Fig. 2).

After correction for confounding, adjusted BCSS and OS were superior for BCT compared to mastectomy in the entire cohort [0.75 (95% CI: 0.70–0.80, $p < 0.0001$)] and [0.67 (95% CI: 0.64–0.71, $p < 0.0001$)], respectively. This remained significant in the T1–2N0–1 stages (Fig. 3 and Supporting Information Table S5) but not in the T1–2N2 stages (Fig. 3 and Supporting Information Table S5).

Additional stratification within the T1–2N0–1 group showed superior BCSS and OS for patients >50 years, with comorbidity, without adjuvant systemic therapy and those treated with endocrine therapy only (Fig. 4 and Supporting Information Table S6). This superior outcome was present irrespective of hormonal receptor and HER2 status. No significant difference in BCSS was found between BCT and

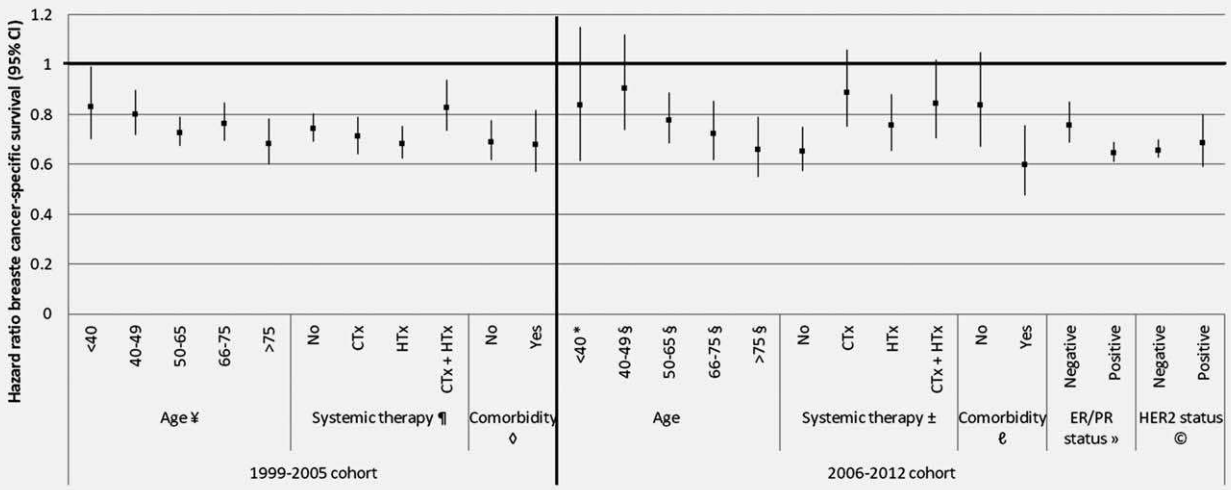

Figure 4. Hazard ratios of breast-conserving therapy compared to mastectomy on BCSS in T1–2N0–1 stage breast cancer, specified for predefined prognostic factors. Comorbidity was available for a subcohort of 28,871 patients. "T" indicates the tumor stage. "N" indicates the nodal stage. NA = not available. #Only one region in the South of The Netherlands. ¥Corrected for year of diagnosis, tumor stage, nodal stage, morphology, differentiation grade, axillary lymph node dissection, systemic therapy and contralateral breast cancer. ¶Corrected for year of diagnosis, tumor stage, nodal stage, morphology, differentiation grade, axillary lymph node dissection and contralateral breast cancer. ◇ Corrected for age, year of diagnosis, tumor stage, nodal stage, morphology, differentiation grade, axillary lymph node dissection, systemic therapy and contralateral breast cancer. *Corrected for year of diagnosis, tumor stage, nodal stage, differentiation grade, systemic therapy, contralateral breast cancer, hormonal receptor status and HER2 status. **Corrected for year of diagnosis, tumor stage, nodal stage, differentiation grade, systemic therapy, contralateral breast cancer, hormonal receptor status and HER2 status. §Corrected for year of diagnosis, tumor stage, nodal stage, morphology, differentiation grade, axillary lymph node dissection, systemic therapy, contralateral breast cancer, hormonal receptor status, HER2 status and multifocality. ±Corrected for age, year of diagnosis, tumor stage, nodal stage, morphology, differentiation grade, axillary lymph node dissection, contralateral breast cancer, hormonal receptor status, HER2 status and multifocality. ℓ Corrected for age, year of diagnosis, tumor stage, nodal stage, morphology, differentiation grade, axillary lymph node dissection, systemic therapy and contralateral breast cancer, hormonal receptor status, HER2 status and multifocality. » Corrected for age, year of diagnosis, tumor stage, nodal stage, morphology, differentiation grade, axillary lymph node dissection, systemic therapy and contralateral breast cancer, HER2 status and multifocality. © Corrected for age, year of diagnosis, tumor stage, nodal stage, morphology, differentiation grade, axillary lymph node dissection, systemic therapy and contralateral breast cancer, hormonal receptor status and multifocality.

mastectomy in patients <50 years, patients without comorbidity and patients treated with adjuvant chemotherapy (Fig. 4 and Supporting Information Table S6). With regard to OS, no significant differences between treatments were found in patients aged < 40, and those treated with adjuvant chemotherapy (Fig. 4 and Supporting Information Table S6).

Discussion

BCT showed roughly 25% better BCSS and OS than mastectomy after correction for all identifiable confounders. Superior survival for BCT was seen both after long-term follow-up (1999–2005 cohort) and in the era of more contemporary adjuvant systemic therapy (2006–2012 cohort). In the 1999–2005 cohort, BCT showed superior BCSS in all subgroups based on age, stage, adjuvant systemic therapy and comorbidity. In the 2006–2012 cohort, BCT showed superior BCSS for all T1–2N0–1 staged patients > 50 years, and the effect was even seen in patients with comorbidity. In patients treated with chemotherapy, irrespective of hormonal and HER2 receptor status, BCT was similar to mastectomy.

Our results further support the hypothesis that BCT might be the preferred choice for breast cancer patients when both BCT and mastectomy are suitable treatment options.[5–10,12] A previous observational study that also investigated survival outcomes following both types of surgery hypothesized that the prognostic advantage of BCT over mastectomy may be related to the effects of RT as a component of BCT while early stage mastectomy patients in general receive no RT5. This explanation is partly supported by the results of our study, as the survival differences were most pronounced in the subgroups where a lower percentage of patients was treated with RT in the mastectomy group, while all patients in the BCT group received RT. Since patients with N1 stage were more often treated with adjuvant systemic therapy, survival differences between BCT and mastectomy can also be influenced by the use of adjuvant systemic therapy. In the most recent cohort, we found a larger benefit of BCT for T1N0 patients as compared to T1N1 stage. This might be explained by an increased utilization rate of RT after mastectomy for N1 disease over time, following the publication of level 1 evidence supporting PMRT for patients with limited nodal involvement as well.[20] In that case, the benefit of RT for N1 disease after mastectomy could have blurred the benefit of BCT. In contrast, we observed a larger benefit of BCT for T2N1 stage as compared to T2N0 stage. Importantly, these patients are more likely to receive adjuvant systemic

therapy. The interplay between systemic therapy and RT is very complex,[21] resulting in the fact that the possible benefit of RT is not always more pronounced in N0 stage compared to N1 stage. To make sure that the lateralization of the tumor did not affect the survival estimates, we conducted a sensitivity analyses in which we stratified the analyses by lateralization (left or right). This did not change the results (data not shown). From previous studies we know that adjuvant systemic therapy largely influences survival rates.[22,23] In the 1999–2005 cohort, the superior effect of BCT remained after stratification for use and type of adjuvant systemic therapy. However, in the 2006–2012 cohort, BCT and mastectomy showed similar BCSS and OS in patients treated with chemotherapy and similar BCSS for patients treated with both chemotherapy and endocrine therapy. We hypothesize that especially the contemporary chemotherapy regimens diminish the survival advantage of BCT over mastectomy. Similar BCSS and OS for BCT and mastectomy in patients < 50 years in the 2006–2012 cohort support this hypothesis, since in both cohorts over 80% of the patients < 40 and over 60% of the patients 40–49 years received chemotherapy (Supporting Information Tables S3 and S4). In the current era of personalized medicine, targeted therapy plays an important role in treatment strategies. Targeted therapy is in our analyses included in the chemotherapy variable, since in The Netherlands, it is given simultaneously with chemotherapy in HER2 positive patients. In this way, we avoided collinearity in the multivariable analysis. However, by doing this we were not able to investigate the direct effect of targeted therapy alone, a indirect analysis, stratifying for HER2 status, showed the advantage of BCT over MAST in both HER2 positive and negative patients (Supporting Information Table S6). The result that BCT and mastectomy lead to similar survival outcomes in patients < 40 years is supported by other observational studies that reported minor survival differences between BCT and mastectomy in patients < 40 years.[24–26] In the T1–2N2 stages we also observed similar BCSS for BCT and mastectomy. This may be explained by the fact that 83.8% and 70.2% of these patients received adjuvant systemic therapy, in the BCT and mastectomy group, respectively. However, it may also be explained by the use of post-mastectomy radiation therapy (PMRT), since 85.7% of the patients in the mastectomy group had undergone PMRT (data not shown). For patients with comorbidity, a large survival advantage for BCT compared to mastectomy was observed in both cohorts. For the cohort with known comorbidity status, the baseline characteristics and the proportion of BCT was approximately similar to the entire cohort, making this subcohort representative. These results confirm that BCT is safe and possibly the preferred option even in patients with comorbidity when both treatments are suitable. In patients without comorbidity, we did not find a significant difference between BCT and mastectomy on BCSS in the 2006–2012 cohort, but we did find improved long-term BCSS for BCT compared to mastectomy in the 1999–2005 cohort. The fact we did not find a significant difference between BCT and mastectomy in patients without comorbidities in the 2006–2012 cohort may be explained by the age distributions. Patients without comorbidities are generally younger than patients with comorbidities (as is also seen in our data). In patients < 50 years we did not observe survival differences after BCT and mastectomy, while we did find increased BCSS for BCT compared to mastectomy in patients > 50 years.

The similar BCSS after BCT or mastectomy in patients without comorbidity confirms results of large RCTs.[1–4] It is expected that participants in RCTs are mainly patients without comorbidity and thus this subgroup probably best resembles patients studied in these RCTs.

A possible explanation for the differences in BCSS between the two time cohorts, apart from the difference in the applied chemotherapy regimens, is the length of follow-up. Recurrence peaks (including local/locoregional recurrences and distant metastases) are described to occur 2, 5 and 9 years after diagnosis.[2–29] Since the 2006–2012 cohort had a median follow-up of 7 years, this cohort may have had too short follow-up to reveal the effect of BCT and mastectomy after 7 years. Another explanation is the fact that diagnostic procedures and treatments (surgery, RT and adjuvant systemic therapy) have improved over time, which may have influenced the generalizability of the treatment effects. However, this is largely obviated by analysis of the two time cohorts separately. Of note, the aim of this study was to investigate the effect of BCT compared to mastectomy after long-term follow-up, and in the era of more contemporary diagnostics and adjuvant treatment, and not to compare the two cohorts over time by itself.

Major strengths of this study are its population-based character, the large number of patients, the availability of data on cause of death, stratification for age, stage, hormonal and HER2 receptor status, adjuvant systemic therapy and comorbidity. By linking the NCR registry to the CBS registry – both covering the entire population – data on cause of death could be collected for almost all deceased patients. The population-based character increases the generalizability of the results and is therefore of additional value to results that are obtained through large RCTs, in which selected populations are studied.[30] Since age, stage, hormonal and HER2 receptor status, adjuvant systemic therapy and comorbidity are considered to be the most important variables that could potentially bias the analysis for survival differences between BCT and mastectomy, the stratified analyses gave more insight in treatment effects for these specific subgroups. As a result, we were able to identify subgroups that would benefit the most from BCT. A limitation of this study is that comorbidity status was only known for a relatively small percentage of patients, resulting in a low number of events, disabling us from doing stratified analyses within the group of patients with comorbidity. Although data on comorbidity was only available for a subcohort of patients, this subcohort had similar baseline characteristics and was thus considered

representative for the entire cohort. Another limitation of this study is its observational design, in which confounding by severity and residual confounding cannot be excluded. Furthermore, a causal relationship explaining the superior outcome for BCT cannot be confirmed based on observational studies only. In this study, patients were treated with BCT or mastectomy with or without RT. Since patients treated with PMRT may have a poorer prognosis compared to patients treated with mastectomy only, we might have created confounding by severity. To largely overcome this problem, we performed a subanalysis in T1–2N0–1 breast cancer excluding patients treated with RT following mastectomy (PMRT). This led to similar favorable BCCS and OS rates for BCT compared to mastectomy in all T and N stages (data not shown). There is a considerable debate with regard to the value of observational studies in the evaluation of treatment outcome as compared to randomized trials. Population-based observational studies may increase our knowledge concerning treatment effects in daily practice. Although these studies can be extremely informative, results have to be interpreted with care and residual confounding is unavoidable. For sufficient interpretation of treatment decisions, the current leading national guidelines should be considered. Another limitation is the lack of data on the extent of RT. A discrimination between local or locoregional RT was not registered and could therefore not be analyzed. Furthermore, we lacked data on comorbidities occurring during follow-up.

Clinical impact

Within this cohort, the superior survival of BCT compared to mastectomy in T1–2N0–1 breast cancer is confirmed. We identified several subgroups that benefit most from BCT. Importantly, superior BCSS for BCT was observed in patients >50 years and patients with comorbidity at diagnosis. Therefore, for older patients and patients with comorbidity it is no longer an argument to prefer mastectomy over BCT. However, in case of an expected inferior aesthetic outcome following BCT, or a contra-indication for RT, mastectomy may still be the best treatment option. These results could add as an additional argument for BCT in shared (surgical) decision-making when both treatments are suitable options.

Conclusion

BCT is the preferred treatment option in T1–2N0–1 stage breast cancer. Subgroups that may benefit most from BCT (when both treatments are suitable) are patients > 50 years, patients with comorbidity and those not treated with chemotherapy, irrespective of hormonal or HER2 receptor status. We confirmed this both after long-term follow-up and in the era of modern diagnostics and adjuvant systemic therapy.

Acknowledgements

The authors thank The Netherlands Cancer Registry for providing the data, as well as the registration clerks for their effort in gathering the data in The Netherlands Cancer Registry.

References

1. Veronesi U, Cascinelli N, Mariani L, et al. Twenty-year follow-up of a randomized study comparing breast-conserving surgery with radical mastectomy for early breast cancer. *N Engl J Med* 2002;347:1227–32.
2. Litiere S, Werutsky G, Fentiman IS, et al. Breast conserving therapy versus mastectomy for stage I-II breast cancer: 20 year follow-up of the EORTC 10801 phase 3 randomised trial. *Lancet Oncol.* 2012;13:412–9.
3. Fisher B, Anderson S, Bryant J, et al. Twenty-year follow-up of a randomized trial comparing total mastectomy, lumpectomy, and lumpectomy plus irradiation for the treatment of invasive breast cancer. *N Engl J Med* 2002;347:1233–41.
4. Early Breast Cancer Trialists' Collaborative Group. Effect of radiotherapy after breast-conserving surgery on 10-year recurrence and 15-year breast cancer death: meta-analysis of individual patient data for 10,801 women in 17 randomised trials. *Lancet* 2011;378:1707–16.
5. Onitilo AA, Engel JM, Stankowski RV, et al. Survival comparisons for breast conserving surgery and mastectomy revisited: Community experience and the role of radiation therapy. *Clin Med Res* 2015;13:65–73.
6. Hwang ES, Lichtensztajn DY, Gomez SL, et al. Survival after lumpectomy and mastectomy for early stage invasive breast cancer: the effect of age and hormone receptor status. *Cancer* 2013; 119:1402–11.
7. Hartmann-Johnsen OJ, Karesen R, Schlichting E, et al. Survival is better after breast conserving therapy than mastectomy for early stage breast cancer: a registry-based follow-up study of norwegian women primary operated between 1998 and 2008. *Ann Surg Oncol* 2015;22:3836–45.
8. Fisher S, Gao H, Yasui Y, et al. Survival in stage I-III breast cancer patients by surgical treatment in a publicly funded health care system. *Ann Oncol* 2015;26:1161–9.
9. Chen K, Liu J, Zhu L, et al. Comparative effectiveness study of breast-conserving surgery and mastectomy in the general population: a NCDB analysis. *Oncotarget.* 2015;6:40127–40.
10. Agarwal S, Pappas L, Neumayer L, et al. Effect of breast conservation therapy vs mastectomy on disease-specific survival for early-stage breast cancer. *JAMA Surg.* 2014;149:267–74.
11. Chavez-MacGregor M, Giordano SH. Randomized clinical trials and observational studies: is there a battle?. *J Clin Oncol* 2016;34:772–3.
12. van Maaren MC, de Munck L, de Bock GH, et al. 10 year survival after breast-conserving surgery plus radiotherapy compared with mastectomy in early breast cancer in the Netherlands: a population-based study. *Lancet Oncol.* 2016;17: 1158–70.
13. Saadatmand S, Bretveld R, Siesling S, et al. Influence of tumour stage at breast cancer detection on survival in modern times: population based study in 173,797 patients. *BMJ* 2015; 351:h4901.
14. Percy C, Van Holten V, Muir C. *International classification of diseases for oncology*. 2nd edn. Geneva: World Health Organization, 1990.
15. Fritz ACP, A. Jack *International classification of diseases for oncology*, 3rd edn. Geneva: World Health Organization, 2000.
16. Sobin LH, Fleming ID. *TNM classification of malignant tumors*. New York: Wiley, 1997.
17. Sobin LH, Wittekind C. *TNM classification of malignant tumours*. New York: Wiley, 2002.
18. Sobin LH, Gospodarowicz M, Wittekind C. *TNM classification of malignant tumors*. New York: Wiley, 2009.
19. World Health Organization. International statistical classification of diseases and related health problems, Geneva, Switzerland: World Health Organization, vol. 2, 2016.
20. Early Breast Cancer Trialists' Collaborative Group. Effect of radiotherapy after mastectomy and axillary surgery on 10-year recurrence and 20-year breast cancer mortality: meta-analysis of individual patient data for 8135 women in 22 randomised trials. *Lancet* 2014;383:2127–35.
21. Poortmans P. Postmastectomy radiation in breast cancer with one to three involved lymph nodes: ending the debate. *Lancet* 2014;383:2104–6.
22. Early Breast Cancer Trialists' Collaborative Group. Polychemotherapy for early breast cancer: an overview of the randomised trials. *Lancet* 1998;352:930–42.
23. Early Breast Cancer Trialists' Collaborative Group. Tamoxifen for early breast cancer: an overview of the randomised trials. *Lancet* 1998; 351:1451–67.
24. Ye JC, Yan W, Christos PJ, et al. Equivalent survival with mastectomy or breast-conserving

surgery plus radiation in young women aged < 40 years with early-stage breast cancer: a national registry-based stage-by-stage comparison. *Clin Breast Cancer* 2015;15:390–7.
25. Vila J, Gandini S, Gentilini O. Overall survival according to type of surgery in young (</=40 years) early breast cancer patients: a systematic meta-analysis comparing breast-conserving surgery versus mastectomy. *Breast* 2015;24:175–81.
26. Frandsen J, Ly D, Cannon G, et al. In the modern treatment era, is breast conservation equivalent to mastectomy in women younger than 40 years of age? a multi-institution study. *Int J Radiat Oncol Biol Phys* 2015;93: 1096–103.
27. Yin W, Di G, Zhou L, et al. Time-varying pattern of recurrence risk for Chinese breast cancer patients. *Breast Cancer Res Treat* 2009;114:527–35.
28. Witteveen A, Vliegen IMH, Sonke GS, et al. Personalisation of breast cancer follow-up: a time-dependent prognostic nomogram for the estimation of annual risk of locoregional recurrence in early breast cancer patients. *Breast Cancer Res Treat* 2015;152:627–36.
29. Jatoi I, Tsimelzon A, Weiss H, et al. Hazard rates of recurrence following diagnosis of primary breast cancer. *Breast Cancer Res Treat* 2005;89: 173–8.
30. Hershman DL, Wright JD. Comparative effectiveness research in oncology methodology: observational data. *J Clin Oncol* 2012;30:4215–22.