Breast Cancer Res Treat
DOI 10.1007/s10549-016-4012-8

EPIDEMIOLOGY

Breast-conserving therapy versus mastectomy in T1-2N2 stage breast cancer: a population-based study on 10-year overall, relative, and distant metastasis-free survival in 3071 patients

M. C. van Maaren[1] · L. de Munck[1] · J. J. Jobsen[2] · P. Poortmans[3] · G. H. de Bock[4] · S. Siesling[1,5] · L. J. A. Strobbe[6]

Received: 4 October 2016 / Accepted: 5 October 2016

Abstract

Purpose Our previous study demonstrated breast-conserving surgery with radiation therapy (BCT) to be at least equivalent to mastectomy in T1-2N0-1 breast cancer. Yet, 10-year survival rates after BCT and mastectomy with radiation therapy (MAST) in T1-2N2 breast cancer specifically have not been examined. Our study aimed to determine 10-year overall (OS), relative (RS), and distant metastasis-free survival (DMFS) in T1-2N2 breast cancer after BCT and MAST, stratified for T category.

Methods All women diagnosed with primary invasive T1-2N2 breast cancer in 2000–2004, treated with BCT or MAST, both with axillary dissection and RT, were selected from the Netherlands Cancer Registry. Ten-year OS and DMFS were estimated using multivariable Cox regression. Excess mortality ratios (EMR) were calculated to estimate RS, using life tables of the general population. OS and RS were determined on the whole cohort, and DMFS on the 2003 cohort with completed follow-up. Missing data were imputed.

Results Of 3071 patients, 1055 (34.4 %) received BCT and 2016 (65.7 %) MAST. BCT and MAST showed equal 10-year OS and RS. After stratification, BCT was significantly associated with improved 10-year OS [$HR_{adjusted}$ 0.82 (95 % CI 0.71–0.96)] and RS ($EMR_{adjusted}$ 0.81 (95 % CI 0.67–0.97]) in T2N2, but not in T1N2. Ten-year DMFS was equal for both treatments [$HR_{adjusted}$ 0.87 (95 % CI 0.64–1.18)] in the 2003 cohort (n = 594), which was representative for the full cohort.

Conclusion BCT showed at least equal 10-year OS, RS, and DMFS compared to MAST. These results confirm that BCT is a good treatment option in T1-2N2 breast cancer.

Keywords Breast cancer · Breast-conserving surgery · Mastectomy · Radiation therapy · Overall survival · Relative survival · Distant metastasis-free survival

Abbreviations

BCSS	Breast cancer-specific survival
BCT	Breast-conserving surgery with radiation therapy
CI	Confidence interval
DMFS	Distant metastasis-free survival
EMR	Excess mortality ratio
HR	Hazard ratio

Electronic supplementary material The online version of this article (doi:10.1007/s10549-016-4012-8) contains supplementary material, which is available to authorized users.

✉ M. C. van Maaren
M.vanMaaren@iknl.nl

[1] Department of Research, Netherlands Comprehensive Cancer Organisation, P.O. Box 19079, 3501 DB Utrecht, The Netherlands

[2] Department of Radiation Oncology, Medical Spectrum Twente, P.O. Box 50000, 7500 KA Enschede, The Netherlands

[3] Department of Radiation Oncology, Radboud University Medical Center, P.O. Box 9101, 6500 HB Nijmegen, The Netherlands

[4] Department of Epidemiology, University Medical Center Groningen, University of Groningen, P.O. Box 30001, 9700 RB Groningen, The Netherlands

[5] Department of Health Technology & Services Research, MIRA Institute for Biomedical Technology and Technical Medicine, University of Twente, P.O. Box 217, 7500 AE Enschede, The Netherlands

[6] Department of Surgical Oncology, Canisius Wilhelmina Hospital, P.O. Box 9015, 6500 GS Nijmegen, The Netherlands

Published online: 11 October 2016

MAST	Mastectomy with radiation therapy
RCT	Randomized controlled trial
RS	Relative survival
RT	Radiation therapy
T category	Pathologically staged tumor category (T1 = 0–2 cm, T2 = 2–5 cm)

Introduction

Randomized controlled trials (RCTs) have shown equal survival for breast-conserving surgery with radiation therapy (BCT) and mastectomy without post-operative radiation therapy (RT) [1–3]. These studies are conducted in the eighties, while treatments have been improved over time. Besides, RCT populations may not adequately reflect the real-life population [4]. Therefore, population-based studies, as long as they are properly designed, may increase our knowledge regarding treatment effects in daily practice. Our previous population-based study showed at least equal 10-year overall (OS), relative (RS), and distant metastasis-free survival (DMFS) for BCT compared to mastectomy (without RT) in T1-2N0-1 breast cancer [5], thereby confirming results of other studies [6–9]. Since N2 stage harbors a worse prognosis compared to N0-1 [10], and Dutch guidelines recommend RT for N2 [11], it is of importance to study treatment options in these patients specifically. However, no studies have been identified that investigated survival rates in T1-2N2 breast cancer distinctively. We investigated 10-year OS, RS, and DMFS in T1-2N2 breast cancer after BCT or MAST, both with RT, stratified for T category, on population-based data.

Methods

Patients

The study population was selected from the nationwide Netherlands Cancer Registry (NCR) [5]. All 3078 female patients diagnosed with primary invasive breast cancer (morphology codes 8500–8575, excluding Morbus Paget's) between 2000 and 2004, with pathologically staged T1-2N2M0 disease, treated with BCT or MAST, both with axillary dissection and RT, were included. Cases were allocated to one of the treatment groups according to the most extensive operation of the primary tumor. Patients treated in foreign or unknown hospitals ($n = 1$), with undifferentiated tumors ($n = 2$) or macroscopic residual tumor after surgery ($n = 4$) were excluded, leading to 3071 eligible cases. For patients diagnosed in 2003 ($n = 594$), an active follow-up was conducted registering all recurrences within 10 years after diagnosis.

Definitions and outcomes

Definitions used are in concordance with our previous study [5]. Primary outcomes, determined on the complete 2000–2004 cohort, were 10-year OS (cumulative probability of being alive, 10 years after diagnosis) and RS (observed survival of the patient population divided by the expected survival of the general population, matched by sex, age, and year of diagnosis). Follow-up was calculated from date of diagnosis to date of death. The secondary outcome was 10-year DMFS, determined on the 2003 cohort. DMFS was defined as being free from distant metastases 10 years after diagnosis, with distant metastases being defined according to the consensus-based event definitions for recurrence classification of Moossdorff et al. [12] and DATECAN guidelines [13]. Follow-up was calculated from date of last surgery of the primary tumor to date of event. Events that occurred within three months after the date of primary diagnosis were considered as synchronous with the primary tumor and were not counted as events.

Statistical analysis

For both the 2000–2004 cohort and the 2003 cohort, patient-, tumor-, and treatment-related characteristics were summarized and compared between treatment groups using the χ^2, Fisher's exact or Wilcoxon rank sum test. Missing data, which were regarded as missing at random, were imputed as described previously [5]. Distributions of original and imputed data were compared (Online Resource 1), whereafter imputed datasets were used for multivariable analyses.

Unadjusted 10-year OS (2000–2004 cohort) and DMFS (2003 cohort) were estimated using the Kaplan–Meier method, and treatment groups were compared with the log-rank test. Multivariable Cox proportional hazard analysis was performed to correct for confounding and estimate hazard ratios (HRs) with 95 % confidence intervals (CIs) for 10-year OS, RS, and DMFS. Ten-year RS is estimated by calculating excess mortality ratios (EMRs) with 95 % CIs using the Ederer II method [14]. Expected survival was based on life tables of the Dutch population. Age standardization was performed [15]. All analyses were stratified for T category.

In the multivariable analyses, potential confounding variables differing between treatment groups ($p < 0.1$) and considerably contributing to the outcome in univariable analysis ($p < 0.1$), were included in the model. Manual backward selection ($p < 0.1$) was used to remove non-significant variables. The proportional hazards assumption was tested by the observation of scaled Schoenfeld residuals over time. Model fits were tested graphically by

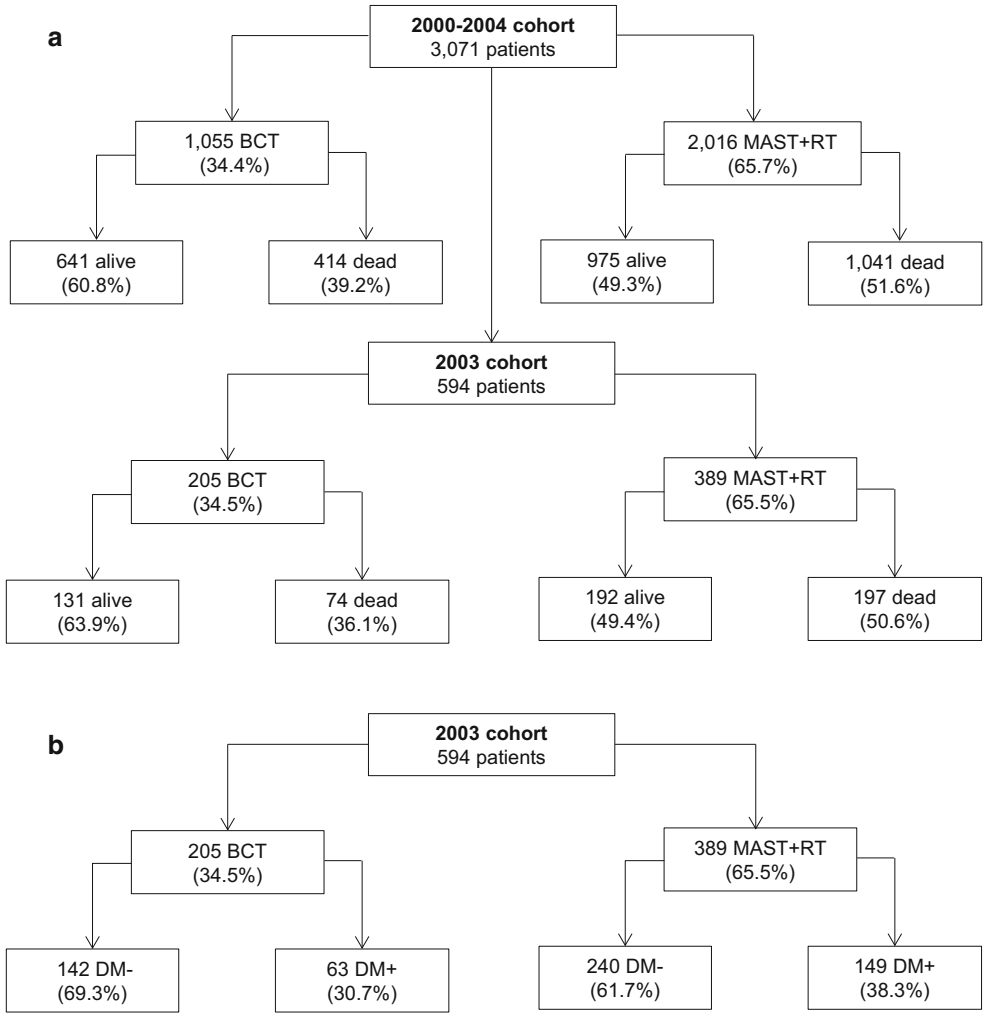

Fig. 1 Consort diagram of included patients. **a** shows the two cohorts with numbers and percentages of patients alive and patients died, specified for primary surgery. **b** shows the 2003 subcohort including numbers and percentages of patients experiencing a distant metastasis and patients free of distant metastases, specified for primary surgery, after 10 years of follow-up. *MAST* mastectomy with post-operative radiation therapy; *BCT* breast-conserving surgery with post-operative radiation therapy; *DM* + distant metastasis; *DM* − absence of distant metastasis

observation of Cox–Snell residuals. No deviations were found. All statistical tests were two-sided. To adjust for multiple testing (OS and RS) in the 2000–2004 cohort, Bonferroni correction was used and a p value of $0.05/2 = 0.025$ was considered statistically significant. In the 2003 cohort, a p value <0.05 was considered statistically significant. All analyses were performed in STATA® 13.1 (StataCorp LP).

Results

Eventually, the 2000–2004 cohort included 3071 patients, of which 1055 patients (34.4 %) received BCT and 2016 patients (65.7 %) received MAST. The 2003 cohort included 594 patients, of which 205 patients (34.5 %) received BCT and 389 patients (65.5 %) received MAST (Fig. 1).

Patient-, tumor-, and treatment-related characteristics

In general, patients in the BCT group more often had small, ductal, unifocal, well-differentiated, and hormone receptor-positive tumors localized in the outer quadrants of the breast, compared to patients in the MAST group. Patients over 79 years were less often treated with BCT. Patients treated with BCT more frequently received a combination of hormonal therapy and chemotherapy, compared to patients treated with MAST (Table 1). Characteristics of

Table 1 Baseline characteristics of T1-2N2 stage breast cancer patients according to type of surgery ($n = 3071$)

Characteristics	MAST			BCT		
	Overall ($n = 2016$)	T1N2 ($n = 543$)	T2N2 ($n = 1473$)	Overall ($n = 1055$)	T1N2 ($n = 504$)	T2N2 ($n = 551$)
Year of diagnosis[a,b,c]						
2000	365 (18.1)	89 (16.4)	276 (18.7)	189 (17.9)	99 (19.6)	90 (16.3)
2001	407 (20.2)	102 (18.8)	305 (20.7)	206 (19.5)	113 (22.4)	93 (16.9)
2002	439 (21.8)	115 (21.2)	324 (22.0)	191 (18.1)	81 (16.1)	110 (20.0)
2003	402 (19.9)	126 (23.2)	276 (18.7)	211 (20.0)	94 (18.7)	117 (21.2)
2004	403 (20.0)	111 (20.4)	292 (19.8)	258 (24.5)	117 (23.2)	141 (25.6)
Age[a,b,c]						
<40	204 (10.1)	57 (10.5)	147 (10.0)	93 (8.8)	41 (8.1)	52 (9.4)
40–49	549 (27.2)	134 (24.7)	415 (28.2)	289 (27.4)	129 (25.6)	160 (29.0)
50–59	509 (25.3)	143 (26.3)	366 (24.9)	348 (33.0)	181 (35.9)	167 (30.3)
60–69	329 (16.3)	96 (17.7)	233 (15.8)	184 (17.4)	92 (18.3)	92 (16.7)
70–79	271 (13.4)	83 (15.3)	188 (12.8)	119 (11.3)	52 (10.3)	67 (12.2)
>79	154 (7.6)	30 (5.5)	124 (8.4)	22 (2.1)	9 (1.8)	13 (2.4)
SES						
Low	619 (30.7)	170 (31.3)	449 (30.5)	314 (29.8)	143 (28.4)	171 (31.0)
Medium	793 (39.3)	209 (38.5)	584 (39.7)	423 (40.1)	205 (40.7)	218 (39.6)
High	604 (30.0)	164 (30.2)	440 (29.9)	318 (30.1)	156 (31.0)	162 (29.4)
Hospital volume (patients per year)[a]						
0–49	388 (19.3)	107 (19.7)	281 (19.1)	218 (20.7)	107 (21.2)	111 (20.2)
50–99	885 (43.9)	253 (46.6)	632 (42.9)	435 (41.2)	206 (40.9)	229 (41.6)
100–149	461 (22.9)	116 (21.4)	345 (23.4)	223 (21.1)	107 (21.2)	116 (21.1)
>149	282 (14.0)	67 (12.3)	215 (14.6)	179 (17.0)	84 (16.7)	95 (17.2)
Region[a,b,c]						
A	262 (13.0)	66 (12.2)	196 (13.3)	161 (15.3)	78 (15.5)	83 (15.1)
B	171 (8.5)	45 (8.3)	126 (8.6)	60 (5.7)	23 (4.6)	37 (6.7)
C	135 (6.7)	35 (6.5)	100 (6.8)	79 (7.5)	41 (8.1)	38 (6.9)
D	352 (17.5)	104 (19.2)	248 (16.8)	234 (22.2)	116 (23.0)	118 (21.4)
E	207 (10.3)	41 (7.6)	166 (11.3)	98 (9.3)	48 (9.5)	50 (9.1)
F	303 (15.0)	83 (15.3)	220 (14.9)	124 (11.8)	59 (11.7)	65 (11.8)
G	284 (14.1)	73 (13.4)	211 (14.3)	161 (15.3)	83 (16.5)	78 (14.2)
H	108 (5.4)	36 (6.6)	72 (4.9)	71 (6.7)	35 (6.9)	36 (6.5)
I	194 (9.6)	60 (11.1)	134 (9.1)	67 (6.4)	21 (4.2)	46 (8.4)
Lateralization[a,b]						
Left	1098 (54.5)	313 (57.6)	785 (53.3)	540 (51.2)	255 (50.6)	285 (51.7)
Right	917 (45.5)	230 (42.4)	687 (46.7)	515 (48.8)	249 (49.4)	266 (48.3)
Unknown	*1 (0.1)*		*1 (0.1)*			
Sublocalization[a,b,c]						
Outer quadrants	1004 (50.8)	269 (50.6)	735 (50.9)	652 (63.1)	307 (62.7)	345 (63.4)
Inner quadrants	237 (12.0)	66 (12.4)	171 (11.8)	151 (14.6)	77 (15.7)	74 (13.6)
Central portion	188 (9.5)	42 (7.9)	146 (10.1)	49 (4.7)	24 (4.9)	25 (4.6)
Overlapping lesions	547 (27.7)	155 (29.1)	392 (27.2)	182 (17.6)	82 (16.7)	100 (18.4)
Unknown	*40 (2.0)*	*11 (2.0)*	*29 (2.0)*	*21 (2.0)*	*14 (2.8)*	*7 (1.3)*
Histological tumor type[a,c]						
Ductal	1619 (80.3)	448 (448)	1171 (79.5)	900 (85.3)	429 (85.1)	471 (85.5)
Lobular	253 (12.6)	62 (62)	191 (13.0)	84 (8.0)	38 (7.5)	46 (8.4)
Other	144 (7.1)	33 (33)	111 (7.5)	71 (6.7)	37 (7.3)	34 (6.2)

Table 1 continued

Characteristics	MAST			BCT		
	Overall ($n = 2016$)	T1N2 ($n = 543$)	T2N2 ($n = 1473$)	Overall ($n = 1055$)	T1N2 ($n = 504$)	T2N2 ($n = 551$)
Differentiation[a,b]						
Grade I	136 (7.9)	52 (11.2)	84 (6.7)	110 (12.0)	68 (16.0)	42 (8.5)
Grade II	707 (41.1)	200 (43.0)	507 (40.4)	383 (41.8)	187 (44.0)	196 (39.8)
Grade III	876 (51.0)	213 (45.8)	663 (52.9)	424 (46.2)	170 (40.0)	254 (51.6)
Unknown	*297 (14.7)*	*78 (14.4)*	*219 (14.9)*	*138 (13.1)*	*79 (15.7)*	*59 (10.7)*
Tumor size (mm)[a,b,c]						
Median (IQR25–75)	25 (20–35)	17 (14–19)	30 (25–38)	21 (16–25)	16 (14–18)	25 (23–30)
Unknown	*798 (39.6)*	*207 (38.1)*	*591 (40.1)*	*379 (35.9)*	*194 (38.5)*	*185 (33.6)*
Number of positive nodes[a,b,c]						
Median (25–75 %)	6 (4–7)	5 (4–7)	6 (4–7)	5 (4–7)	5 (4–6)	5 (4–7)
Unknown (%)	*14 (0.7)*	*2 (0.4)*	*12 (0.8)*	*5 (0.5)*	*2 (0.4)*	*3 (0.5)*
Multifocality[a,b,c]						
Yes	251 (27.8)	85 (33.6)	166 (25.5)	41 (8.5)	22 (9.9)	19 (7.3)
No	653 (72.2)	168 (66.4)	485 (74.5)	441 (91.5)	201 (90.1)	240 (92.7)
Unknown	*1112 (55.2)*	*290 (53.4)*	*822 (55.8)*	*573 (54.3)*	*281 (55.8)*	*292 (53.0)*
Hormone receptor status[a,b]						
ER and PR +	479 (58.4)	137 (58.1)	342 (58.6)	311 (67.6)	150 (70.1)	161 (65.5)
ER or PR+	148 (18.1)	45 (19.1)	103 (17.6)	70 (15.2)	30 (14.0)	40 (16.3)
ER and PR −	193 (23.5)	54 (22.9)	139 (23.8)	79 (17.2)	34 (15.9)	45 (18.3)
Unknown	*1196 (59.3)*	*307 (56.5)*	*889 (60.4)*	*595 (56.4)*	*290 (57.5)*	*305 (55.4)*
(Neo-)adjuvant systemic therapy[a,b,c]						
No	107 (5.3)	24 (4.4)	83 (5.6)	41 (3.9)	19 (3.8)	22 (4.0)
Hormonal therapy	489 (24.3)	141 (26.0)	348 (23.6)	199 (18.9)	98 (19.4)	101 (18.3)
Chemotherapy	534 (26.5)	142 (26.2)	392 (26.6)	260 (24.6)	127 (25.2)	133 (24.1)
Both	886 (44.0)	236 (43.5)	650 (44.1)	555 (52.6)	260 (51.6)	295 (53.5)

Numbers are *n* (%) unless otherwise specified

MAST mastectomy with post-operative radiation therapy; *BCT* breast-conserving surgery with post-operative radiation therapy; *SES* social economic status, *ER* estrogen receptor, *PR* progesterone receptor

* significant difference between the treatment groups ($p < 0.1$). [a] significant difference between treatment groups in overall analysis, $p < 0.1$; [b] significant difference between treatment groups in T1N2 analysis, $p < 0.1$; [c] significant difference between treatment groups in T2N2 analysis, $p < 0.1$

the 2003 subcohort (Online Resource 2) were comparable with those of the entire 2000–2004 cohort, indicating its representativeness.

Association of type of surgery and 10-year overall and relative survival in the 2000–2004 cohort

In the total 2000–2004 cohort, 1464 deaths were identified. In the BCT group, 414 patients (39.2 %) died, compared to 1041 (51.6 %) in the MAST group (Fig. 1a). Median follow-up was 10.5 years.

Kaplan–Meier analysis showed significantly improved unadjusted 10-year OS for BCT compared to MAST in the overall cohort, as well as in T1N2 and T2N2 separately (Fig. 2a, c, d). T2N2 had worse prognosis compared to T2N1 (Fig. 2b). Unadjusted 10-year RS showed a similar pattern (Fig. 3). Estimates remained similar after stratification for T category. After adjustment for confounders, the overall $HR_{adjusted}$ for 10-year OS was 0.88 (95 % CI 0.77–0.99). After stratification, the $HR_{adjusted}$ was 0.83 (95 % CI 0.68–1.01) in T1N2 and 0.82 (95 % CI 0.71–0.96) in T2N2, indicating a significant difference in favor of BCT in T2N2, although estimates are similar to T1N2 (Table 2). No significant difference was found between BCT and MAST for overall 10-year RS $EMR_{adjusted}$ 0.89 (95 % CI 0.75–1.04). After stratification, the $EMR_{adjusted}$ was 0.81 (95 % CI 0.62–1.05) in T1N2 and 0.81 (95 % CI 0.67–0.97) in T2N2, revealing a statistically significant difference favoring BCT over MAST in T2N2 (Table 2).

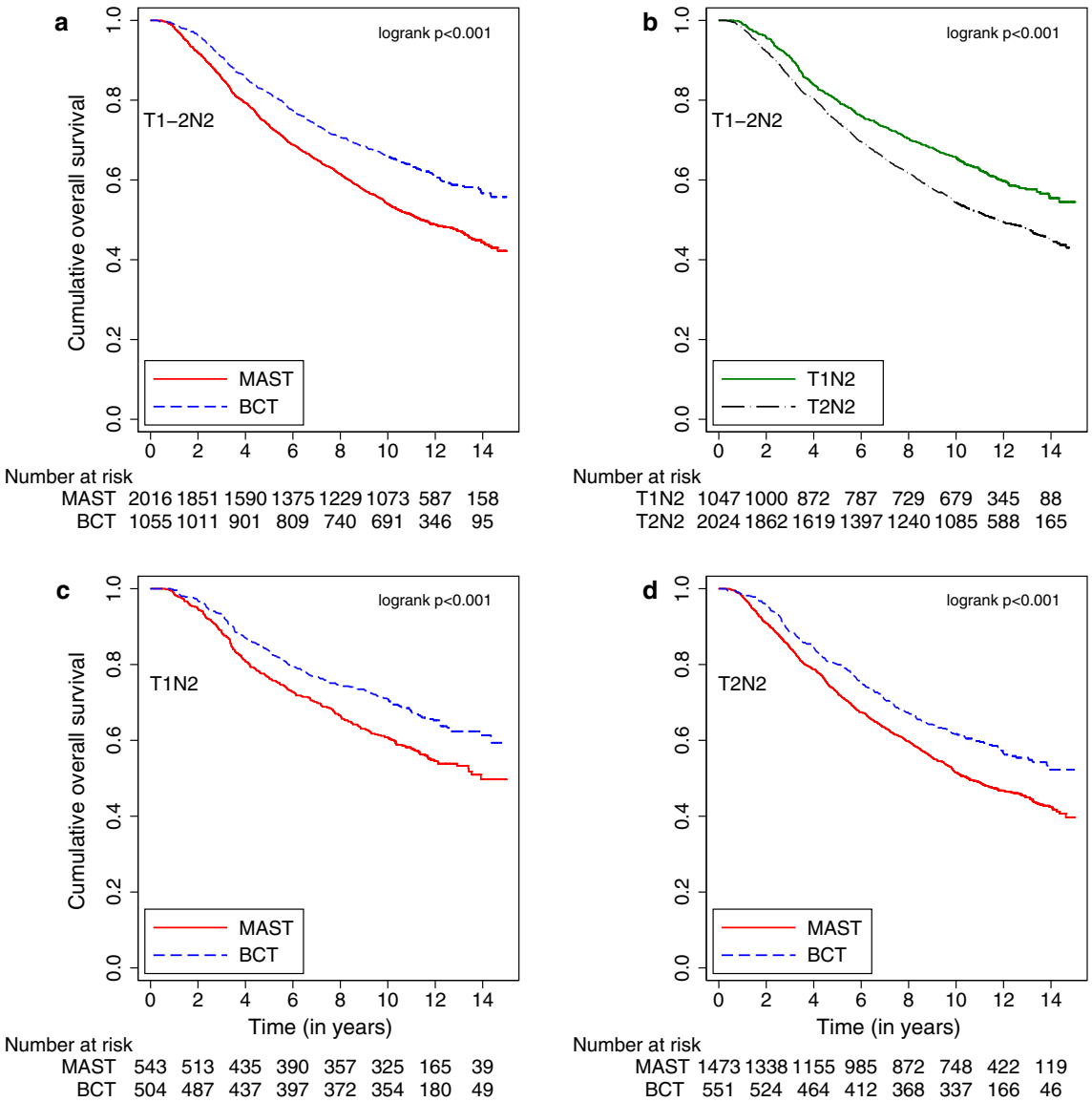

Fig. 2 Cumulative 10-year overall survival in T1-2N2 stage breast cancer patients in the 2000–2004 cohort ($n = 3071$). **a** Cumulative 10-year overall survival in the whole cohort, specified for type of primary surgery; **b** Cumulative 10-year overall survival of the whole cohort, specified for T and N stage; **c** Cumulative 10-year overall survival of the T1N2 subgroup, specified for type of primary surgery; **d** Cumulative 10-year overall survival of the T2N2 subgroup, specified for type of primary surgery. *MAST* mastectomy with post-operative radiation therapy; *BCT* breast-conserving surgery with post-operative radiation therapy

Association of type of surgery and 10-year distant metastasis-free survival in the 2003 cohort

In the 2003 cohort, 63 patients (30.7 %) experienced a distant metastasis in the BCT group, and 74 patients (36.1 %) died. In the MAST group, 149 patients (38.3 %) experienced a distant metastasis, and 197 patients (50.6 %) died (Fig. 1a, b). Median follow-up times to first distant metastasis and death were 8.1 and 11.1 years, respectively.

Kaplan–Meier analysis showed increased 10-year DMFS for BCT compared to MAST (Fig. 4a). Ten-year DFMS was higher for T1N2 than T2N2 (Fig. 4b). In T1N2, 10-year DMFS was not significantly different between BCT and MAST (Fig. 4c), while BCT showed significantly better 10-year DMFS compared to MAST in T2N2 (Fig. 4d). After correction for confounders, the overall $HR_{adjusted}$ was 0.87 (95 % CI 0.64–1.18). After stratification, the HRs were 1.15 (95 % CI 0.69–1.93) and 0.75 (95 % CI 0.51–1.11) in T1N2 and T2N2, respectively, indicating no significant difference in 10-year DMFS after BCT or MAST (Table 3).

Additional analyses demonstrated a large recurrence peak 2 years after diagnosis, followed by two smaller peaks around 5 and 9 years after diagnosis, especially in T2N2 (Online Resource 3).

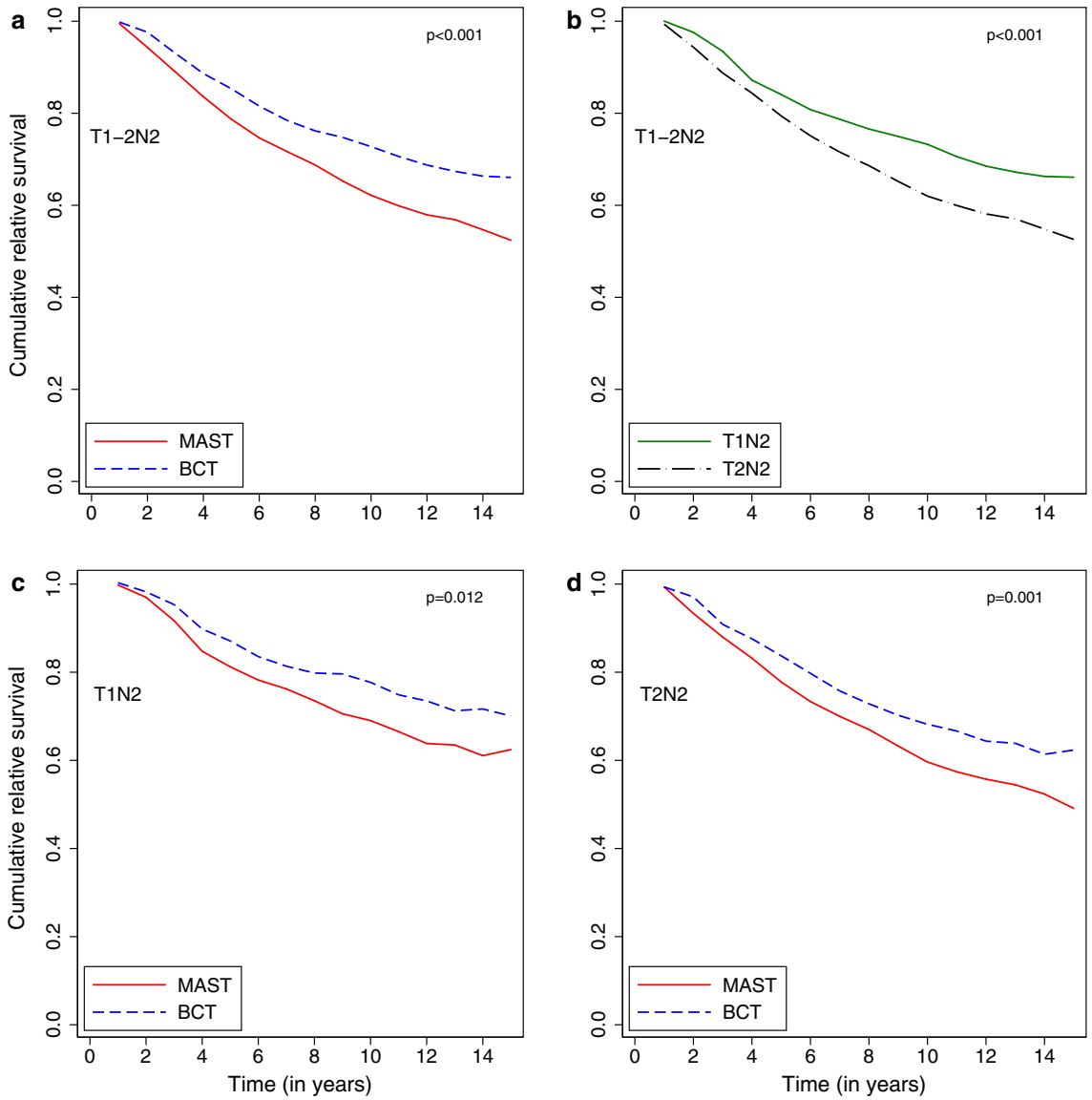

Fig. 3 Cumulative 10-year relative survival in T1-2N2 stage breast cancer patients in the 2000–2004 cohort ($n = 3071$). **a** Cumulative 10-year relative survival in the whole cohort, specified for type of primary surgery; **b** Cumulative 10-year relative survival of the whole cohort, specified for T and N stage; **c** Cumulative 10-year relative survival of the T1N2 subgroup, specified for type of primary surgery; **d** Cumulative 10-year relative survival of the T2N2 subgroup, specified for type of primary surgery. *MAST* mastectomy with post-operative radiation therapy; *BCT* breast-conserving surgery with post-operative radiation therapy

Discussion

To our knowledge, this is the first population-based study demonstrating at least equal 10-year OS, RS, and DMFS for BCT and MAST in T1-2N2 breast cancer. After stratification, T1N2 showed no significant difference between treatment groups regarding 10-year OS, RS, and DMFS. However, T2N2 showed significantly improved 10-year OS and RS after BCT, while 10-year DMFS was not significantly different between BCT and MAST.

The finding that OS and RS are significantly improved after BCT compared to MAST in T2N2 (and borderline significant in T1N2) might be interesting in light of our previous publication [5], where we found increased OS, RS, and DMFS after BCT compared to mastectomy (without RT) in T1N0 disease. Taking the limitations of observational studies into account, we postulated that RT might have played a role in this survival advantage, considering that these patients were barely treated with adjuvant systemic therapy. Since the current study population is treated with RT, and largely treated with systemic therapy, we would not expect survival differences. The difference between percentage of distant metastases (assuming this represents breast cancer-specific mortality) and dead due to

Table 2 Hazard ratios and excess mortality ratios of breast-conserving therapy versus mastectomy on 10-year overall and relative survival in T1-2N2 stage breast cancer patients in the 2000–2004 cohort ($n = 3071$)

	Mortality					Relative			
	Crude			Adjusted		Crude		Adjusted	
	n	HR (95 % CI)	*p* value	HR (95 % CI)	*p* value	EMR (95 % CI)	*p* value	EMR (95 % CI)	*p* value
Overall cohort[a]									
MAST	2016	1		1		1		1	
BCT	1055	0.69 (0.61–0.77)	**<0.001**	0.88 (0.77–0.99)	0.041	0.71 (0.62–0.83)	**<0.001**	0.89 (0.75–1.04)	0.148
Subgroups									
T1N2[b]									
MAST	543	1		1		1		1	
BCT	504	0.71 (0.59–0.87)	**<0.001**	0.83 (0.68–1.01)	0.060	0.77 (0.60–1.00)	0.051	0.81 (0.62–1.05)	0.107
T2N2[c]									
MAST	1473	1		**1**		1		1	
BCT	551	0.73 (0.63–0.84)	**<0.001**	0.82 (0.71–0.96)	**0.010**	0.76 (0.64–0.91)	**0.004**	0.81 (0.67–0.97)	**0.023**

p values depicted in bold are considered significant ($p < 0.025$)

MAST mastectomy with post-operative radiation therapy; *BCT* breast-conserving surgery with post-operative radiation therapy; *HR* hazard ratio; *CI* confidence interval; *n* number of patients; *EMR* excess mortality ratio

[a] Corrected for year of diagnosis, age, social economic status, region, lateralisation, sublocalisation, histological tumor type, differentiation grade, tumor size (mm), number of positive lymph nodes, hormone receptor status, adjuvant systemic therapy

[b] Corrected for age, region, differentiation grade, number of positive lymph nodes

[c] Corrected for age, sublocalisation, number of positive lymph nodes, adjuvant systemic therapy

all causes was larger in the MAST than in the BCT group, indicating that more patients in de MAST group died due to other causes. This might explain our finding that OS and RS were improved, but DMFS was equal for BCT compared to MAST.

Our results are in concordance with the study of Chen et al., that showed equal OS for BCT and MAST, both with RT, in T1-2N2-3 patients [9]. However, they did not stratify the analysis for every T and N category, thereby masking a possible benefit of BCT in the T2 category, as we see in our data. The results are somewhat contrary to the findings of Fisher et al., who showed a significantly higher 5-year all cause [$HR_{adjusted}$ 1.57 (95 % CI 1.12–2.21)] and breast cancer-specific [$HR_{adjusted}$ 1.60 (95 % CI 1.09–2.35)] mortality after MAST compared to BCT in stage III breast cancer [6]. However, this is likely to be explained by a different patient population, a shorter follow-up, lack of stratification, and slightly different outcomes, making these studies difficult to compare. In addition, stage III breast cancer includes tumors larger than five centimeters with more than 10 involved lymph nodes. These tumors are often considered as contraindication for BCT [11] and are known to confer poor prognosis [10, 16]. As these patients are expected to be treated with MAST rather than BCT, the study might have suffered from excessive confounding by severity, leading to biased estimates [17]. Another difference with the study of Fisher et al. relates to the use of breast cancer-specific survival (BCSS). We calculated RS and DMFS as a proxy for BCSS, due to lacking data on cause of death. Interestingly, additional analysis on our data showed that 94.3 % of all deceased patients were diagnosed with a distant metastasis, indicating that DMFS might be a reasonable measure for BCSS (data not shown). Furthermore, we were able to account for a longer follow-up.

A main advantage of this study is its population-based character, including a large number of potential confounding variables. This, along with the use of a well-defined patient population, minimizes the chance on residual confounding. Another strength of this study is 10-year follow-up. Since recurrence peaks have been described to occur approximately 2, 5, and/or 9 years after diagnosis [18, 19] (which is also seen in our data), we were able to account for distant recurrences over long term. An additional strong point of this study is the use of exact (up to 1 mm) tumor size and exact number of positive lymph nodes. Since every centimeter in tumor size is associated with an ±10 % increase in 15-year mortality [16], dichotomization of tumor size may have a large impact on the outcome. Furthermore, N2 encompasses four to nine positive lymph nodes. As increasing number of positive nodes is associated with worse outcomes [20], we may have averted the possibly large impact of number of positive nodes on survival.

Alternatively, this study has several limitations. As this study is observational, confounding by severity and

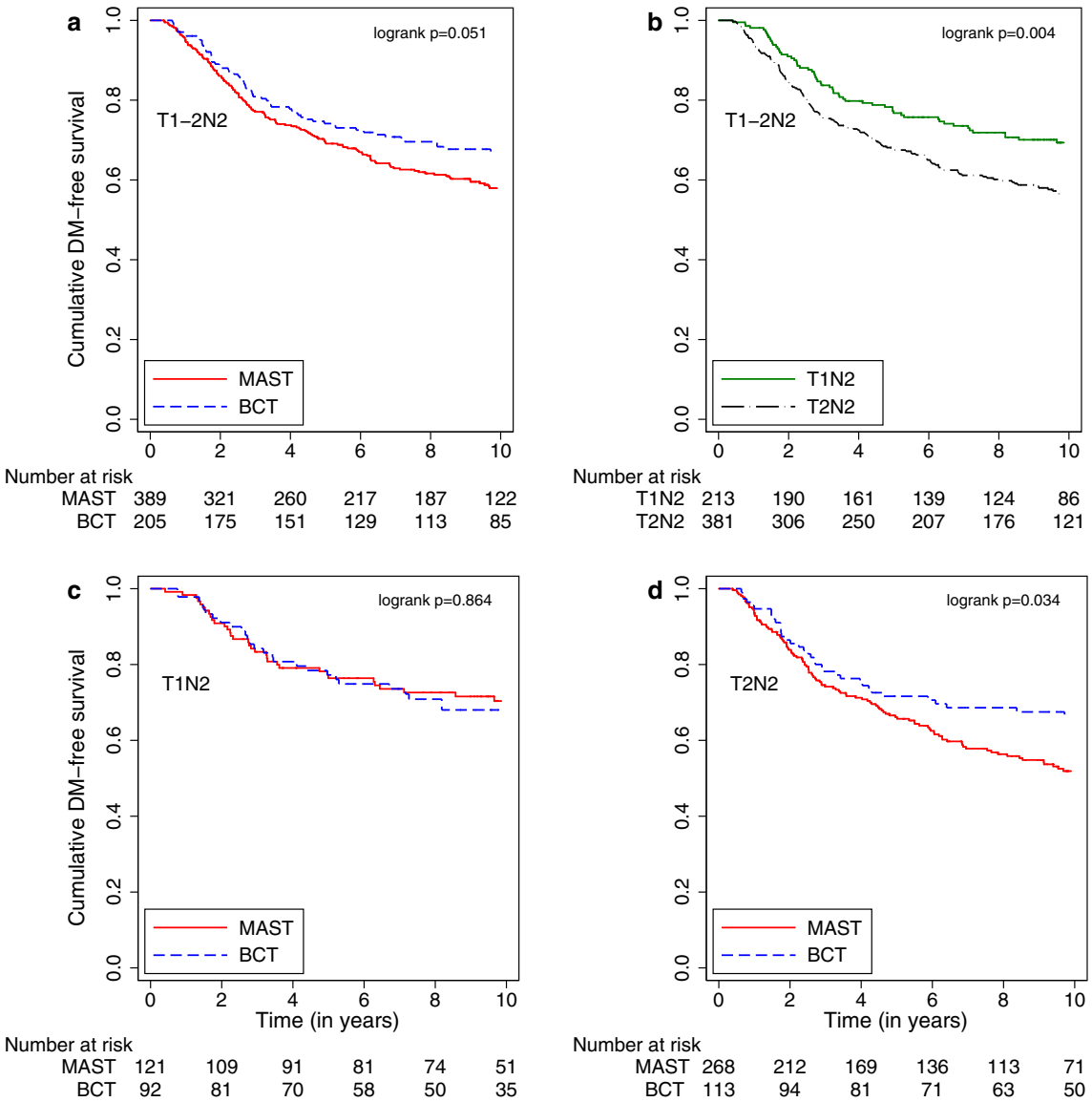

Fig. 4 Cumulative 10-year distant metastasis-free survival in T1-2N2 stage breast cancer patients in the 2000–2004 cohort ($n = 3071$). **a** Cumulative 10-year distant metastasis-free survival in the whole cohort, specified for type of primary surgery; **b** Cumulative 10-year distant metastasis-free survival of the whole cohort, specified for T and N stage; **c** Cumulative 10-year distant metastasis-free survival of the T1N2 subgroup, specified for type of primary surgery; **d** Cumulative 10-year distant metastasis-free survival of the T2N2 subgroup, specified for type of primary surgery. *MAST* mastectomy with postoperative radiation therapy; *BCT* breast-conserving surgery with postoperative radiation therapy; *DM* distant metastasis-free survival

residual confounding cannot be ruled out, and results have to be interpreted with care. There is a lot of debate in terms of the battle between RCTs and observational studies. A recently published article compares the effect of RT after breast surgery estimated from RCTs (EORTC) with the effect estimated from observational data (SEER registry), concluding that observational studies provide less trustful estimates compared to RCTs [21]. However, since RCTs comparing BCT and MAST are all conducted in the eighties, and do not reflect the real-world population regarding age and comorbidities [4], these results cannot directly be extrapolated to the entire breast cancer population. Our population-based observational study design reflects the real-world, which contributes to our understanding of the daily practice. As long as the research is of good quality and strengths and limitations of generated data are acknowledged, observational study designs can provide valid and important knowledge, as is confirmed by an editorial accompanying the above-discussed article [22].

A restriction of this study is the low number of events in the 2003 cohort. It remains uncertain whether a larger population would reveal more accurate estimates. Another

Table 3 Hazard ratios of breast-conserving therapy versus mastectomy on 10-year distant metastasis-free survival in T1-2N2 stage breast cancer patients in the 2003 cohort ($n = 594$)

	Crude			Adjusted	
	n	HR (95 % CI)	*p* value	HR (95 % CI)	*p* value
Overall cohort[a]					
MAST	389	1		1	
BCT	205	0.75 (0.56-1.00)	0.052	0.87 (0.64–1.18)	0.374
Subgroups					
T1N2[b]					
MAST	121	1		1	
BCT	92	1.04 (0.63–1.73)	0.864	1.15 (0.69–1.93)	0.588
T2N2[c]					
MAST	268	1		1	
BCT	113	0.67 (0.46–0.97)	**0.035**	0.75 (0.51–1.11)	0.152

p values depicted in bold are considered significant ($p < 0.05$)

MAST mastectomy with post-operative radiation therapy; *BCT* breast-conserving surgery with post-operative radiation therapy; *HR* hazard ratio; *CI* confidence interval; *n* number of patients

[a] Corrected for age, sublocalisation, differentiation grade, number of positive lymph nodes, adjuvant systemic therapy

[b] Corrected for age

[c] Corrected for age, sublocalisation, differentiation grade, number of positive lymph nodes

limitation is the presence of missing data. However, to prevent exclusion of observed data from patients that have one missing variable, multiple imputation may be favored over complete case analysis. This is shown to result in equivalent, but more precise, effect estimates as obtained with complete case analysis [23]. We compared imputed analyses with complete case analyses. Indeed, estimates were similar (data not shown). Another restriction is lacking data on HER2 status. In 2000–2004, HER2 was not routinely determined, neither it was used in decision making regarding targeted therapy. This may affect the generalizability of the results to the current setting. Furthermore, since primary systemic therapy was only incidentally used in the studied patient groups (2000–2004), survival may be different in more recent, stage-wise comparable, populations.

In clinical practice, patients with four or more positive lymph nodes used to be more often treated with MAST than with BCT (as is also seen in our data), although this might evolve following the introduction of primary systemic therapy. Our results confirm at least equal survival for BCT compared to MAST. Considering the superior cosmetic aspects after BCT alongside the psychological impact following MAST, BCT might be favored over MAST when both treatments are suitable options. Many patients still choose for MAST, primarily due to fear of recurrent cancer, access to immediate reconstruction, and use of MRI [24]. However, post-mastectomy RT has been associated with high surgical complication rates and implant loss among patients who underwent immediate reconstruction [25]. Therefore, if appropriate, patients should be offered both treatment options, in which risks and benefits need to be addressed in the light of a proper shared decision-making process.

Conclusion

These results demonstrate at least equal 10-year OS, RS, and DMFS after BCT as compared to MAST in T1-2N2 breast cancer patients. Based on these results, BCT is a good treatment option when feasible and appropriate.

Acknowledgments We thank the Netherlands Cancer Registry for providing the data, and we thank the registration clerks for their effort in gathering data in the Netherlands Cancer Registry.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical standards This study complies with the current laws in the Netherlands.

References

1. Fisher B, Anderson S, Bryant J, Margolese RG, Deutsch M, Fisher ER, Jeong JH, Wolmark N (2002) 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 347(16):1233–1241
2. Veronesi U, Cascinelli N, Mariani L, Greco M, Luini A, Aguilar M, Marubini E (2002) Twenty-year follow-up of a randomized

study comparing breast-conserving surgery with radical mastectomy for early breast cancer. N Engl J Med 347(16):1227–1232
3. Van Dongen JA, Voogd AC, Fentiman IS, Legrand C, Sylvester RJ, Tong D, van der Schueren E, Helle PA, van Zijl K, Bartelink H (2000) Long-term results of a randomized trial comparing breast-conserving therapy with mastectomy: European Organization for Research and Treatment of Cancer 10801 trial. J Natl Cancer Inst 92(14):1143–1150
4. Hershman DL, Wright JD (2012) Comparative effectiveness research in oncology methodology: observational data. J Clin Oncol 30(34):4215–4222
5. van Maaren MC, de Munck L, de Bock GH, Jobsen JJ, van Dalen T, Linn SC, Poortmans P, Strobbe LJ, Siesling S (2016) 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. doi:10.1016/S1470-2045(16)30067-5
6. Fisher S, Gao H, Yasui Y, Dabbs K, Winget M (2015) Survival in stage I-III breast cancer patients by surgical treatment in a publicly-funded healthcare system. Ann Oncol 26(6):1161–1169
7. Hofvind S, Holen A, Aas T, Roman M, Sebuodegard S, Akslen LA (2015) Women treated with breast conserving surgery do better than those with mastectomy independent of detection mode, prognostic and predictive tumor characteristics. Eur J Surg Oncol 41(10):1417–1422
8. Onitilo AA, Engel JM, Stankowski RV, Doi SA (2014) Survival comparisons for breast conserving surgery and mastectomy revisited: community experience and the role of radiation therapy. Clin Med Res 13(2):65–73
9. Chen K, Liu J, Zhu L, Su F, Song E, Jacobs LK (2015) Comparative effectiveness study of breast-conserving surgery and mastectomy in the general population: a NCDB analysis. Oncotarget 6(37):40127–40140
10. Fisher B, Bauer M, Wickerham DL, Redmond CK, Fisher ER, Cruz AB, Foster R, Gardner B, Lerner H, Margolese R et al (1983) Relation of number of positive axillary nodes to the prognosis of patients with primary breast cancer. An NSABP update. Cancer 52(9):1551–1557
11. NABON (2016). Dutch guideline breast cancer (Landelijke richtlijn mammacarcinoom). http://www.oncoline.nl/mammacarcinoom. Accessed 19 May 2016
12. Moossdorff M, van Roozendaal LM, Strobbe LJ, Aebi S, Cameron DA, Dixon JM, Giuliano AE, Haffty BG, Hickey BE, Hudis CA et al (2014) Maastricht delphi consensus on event definitions for classification of recurrence in breast cancer research. J Natl Cancer Inst 106(12):dju288
13. Gourgou-Bourgade S, Cameron D, Poortmans P, Asselain B, Azria D, Cardoso F, A'Hern R, Bliss J, Bogaerts J, Bonnefoi H et al (2015) Guidelines for time-to-event end point definitions in breast cancer trials: results of the DATECAN initiative (definition for the assessment of time-to-event endpoints in cancer trials). Ann Oncol 26(5):873–879
14. Hakulinen T, Seppa K, Lambert PC (2011) Choosing the relative survival method for cancer survival estimation. Eur J Cancer 47(14):2202–2210
15. Corazziari I, Quinn M, Capocaccia R (2004) Standard cancer patient population for age standardising survival ratios. Eur J Cancer 40(15):2307–2316
16. Narod SA (2012) Tumor size predicts long-term survival among women with lymph node-positive breast cancer. Curr Oncol 19(5):249–253
17. Skelly AC, Dettori JR, Brodt ED (2012) Assessing bias: the importance of considering confounding. Evid Based Spine Care J 3(1):9–12
18. Yin W, Di G, Zhou L, Lu J, Liu G, Wu J, Shen K, Han Q, Shen Z, Shao Z (2009) Time-varying pattern of recurrence risk for Chinese breast cancer patients. Breast Cancer Res Treat 114(3):527–535
19. Jatoi I, Tsimelzon A, Weiss H, Clark GM, Hilsenbeck SG (2005) Hazard rates of recurrence following diagnosis of primary breast cancer. Breast Cancer Res Treat 89(2):173–178
20. Dai Kubicky C, Mongoue-Tchokote S (2013) Prognostic significance of the number of positive lymph nodes in women with T1-2N1 breast cancer treated with mastectomy: should patients with 1, 2, and 3 positive lymph nodes be grouped together? Intl J Radiat Oncol Biol Phys 85(5):1200–1205
21. Henson KE, Jagsi R, Cutter D, McGale P, Taylor C, Darby SC (2016) Inferring the effects of cancer treatment: divergent results from early breast cancer trialists' collaborative group meta-analyses of randomized trials and observational data from SEER registries. J Clin Oncol 34(8):803–809
22. Chavez-MacGregor M, Giordano SH (2016) Randomized clinical trials and observational studies: is there a battle? J Clin Oncol 34(8):772–773
23. Lee KJ, Carlin JB (2012) Recovery of information from multiple imputation: a simulation study. Emerg Themes Epidemiol 9(1):3
24. Covelli AM, Baxter NN, Fitch MI, Wright FC (2014) Increasing mastectomy rates-the effect of environmental factors on the choice for mastectomy: a comparative analysis between Canada and the United States. Ann Surg Oncol 21(10):3173–3184
25. Christante D, Pommier SJ, Diggs BS, Samuelson BT, Truong A, Marquez C, Hansen J, Naik AM, Veto JT, Pommier FR (2010) Using complications associated with post-mastectomy radiation and immediate breast reconstruction to improve surgical decision making. Arch Surg 145(9):873–878