10 year survival after breast-conserving surgery plus radiotherapy compared with mastectomy in early breast cancer in the Netherlands: a population-based study

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Summary

Background Investigators of registry-based studies report improved survival for breast-conserving surgery plus radiotherapy compared with mastectomy in early breast cancer. As these studies did not present long-term overall and breast cancer-specific survival, the effect of breast-conserving surgery plus radiotherapy might be overestimated. In this study, we aimed to evaluate 10 year overall and breast cancer-specific survival after breast-conserving surgery plus radiotherapy compared with mastectomy in Dutch women with early breast cancer.

Methods In this population-based study, we selected all women from the Netherlands Cancer Registry diagnosed with primary, invasive, stage T1–2, N0–1, M0 breast cancer between Jan 1, 2000, and Dec 31, 2004, given either breast-conserving surgery plus radiotherapy or mastectomy, irrespective of axillary staging or dissection or use of adjuvant systemic therapy. Primary outcomes were 10 year overall survival in the entire cohort and breast cancer-specific survival in a representative subcohort of patients diagnosed in 2003 with characteristics similar to the entire cohort. We estimated breast cancer-specific survival by calculating distant metastasis-free and relative survival for every tumour and nodal category. We did multivariable Cox proportional hazard analysis to estimate hazard ratios (HRs) for overall and distant metastasis-free survival. We estimated relative survival by calculating excess mortality ratios using life tables of the general population. We did multiple imputation to account for missing data.

Findings Of the 37 207 patients included in this study, 21 734 (58%) received breast-conserving surgery plus radiotherapy and 15 473 (42%) received mastectomy. The 2003 representative subcohort consisted of 7552 (20%) patients, of whom 4647 (62%) received breast-conserving surgery plus radiotherapy and 2905 (38%) received mastectomy. For both unadjusted and adjusted analysis accounting for various confounding factors, breast-conserving surgery plus radiotherapy was significantly associated with improved 10 year overall survival in the whole cohort overall compared with mastectomy (HR 0·51 [95% CI 0·49–0·53]; p<0·0001; adjusted HR 0·81 [0·78–0·85]; p<0·0001), and this improvement remained significant for all subgroups of different T and N stages of breast cancer. After adjustment for confounding variables, breast-conserving surgery plus radiotherapy did not significantly improve 10 year distant metastasis-free survival in the 2003 cohort overall compared with mastectomy (adjusted HR 0·88 [0·77–1·01]; p=0·07), but did in the T1N0 subgroup (adjusted 0·74 [0·58–0·94]; p=0·014). Breast-conserving surgery plus radiotherapy did significantly improve 10 year relative survival in the 2003 cohort overall (adjusted 0·76 [0·64–0·91]; p=0·003) and in the T1N0 subgroup (adjusted 0·60 [0·42–0·85]; p=0·004) compared with mastectomy.

Interpretation Adjusting for confounding variables, breast-conserving surgery plus radiotherapy showed improved 10 year overall and relative survival compared with mastectomy in early breast cancer, but 10 year distant metastasis-free survival was improved with breast-conserving surgery plus radiotherapy compared with mastectomy in the T1N0 subgroup only, indicating a possible role of confounding by severity. These results suggest that breast-conserving surgery plus radiotherapy is at least equivalent to mastectomy with respect to overall survival and may influence treatment decision making for patients with early breast cancer.

Funding None.

Lancet Oncol 2016

Published **Online** June 22, 2016 http://dx.doi.org/10.1016/S1470-2045(16)30067-5

See **Online/Comment** http://dx.doi.org/10.1016/S1470-2045(16)30219-4

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Introduction

In the 1980s, findings from randomised controlled trials[1–3] of local treatment of early breast cancer showed that breast-conserving surgery plus radiotherapy resulted in equal survival compared with mastectomy without radiotherapy. Randomised controlled trials are well described to provide high-quality evidence of treatment effects.[4] However, they are often done on highly selected patient populations, excluding, for example, older patients, thereby limiting generalisability of the results.[5] Properly done observational studies, taking confounding variables into account, can produce valid results to assess treatment effects in representative real-world populations.[6] Several subsequent observational studies[7–13] have challenged the equivalence of breast-conserving surgery plus radiotherapy and mastectomy seen in the early randomised controlled trials, showing that breast-conserving surgery plus radiotherapy might be associated with improved survival

Research in context

Evidence before this study

We searched PubMed for scientific literature written in all languages including the terms "breast conserving surgery", "mastectomy", and "survival", from March 30, 1989, until Nov 24, 2015. We included synonyms. We reviewed 94 papers, of which we considered 40 to be relevant. Of these, 23 studied a similar population to ours. Ten were observational studies (eight historic cohort studies and two prospective cohort studies), ten were randomised controlled trials, one was a review, and two were meta-analyses of randomised controlled trials. Randomised controlled trials are considered to be very relevant in understanding of survival after breast-conserving surgery plus radiotherapy and mastectomy. However, observational studies might better reflect the real-world population than do randomised controlled trials. All ten randomised controlled trials showed no differences in survival outcomes when breast-conserving surgery plus radiotherapy was compared with mastectomy. Taking into account the fact that these trials include a selected patient population and were all done in the 1980s and that surgical treatments have been improved in the last few decades, these survival estimates might have changed. The observational studies that we found in our search all show that survival after breast-conserving surgery plus radiotherapy is equal to or improved compared with mastectomy. We found ten observational studies that were done using registry-based data; however, only one was a nationwide population-based study.

Added value of this study

To our knowledge, this study is the first population-based study that combines 10 year overall and breast cancer-specific survival (estimated by distant metastasis-free and relative survival) in early breast cancer, stratified for T and N category. We used a large study population with long follow-up and were able to correct for more confounding variables than were other registry-based studies. Our results suggest that breast-conserving surgery plus radiotherapy is at least equivalent to mastectomy with respect to long-term survival in early breast cancer.

Implications of all the available evidence

Our results agreed with those from previous studies that breast-conserving surgery plus radiotherapy is at least equivalent to mastectomy. Although the choice of mastectomy is increasing, primarily due to fear of recurrent cancer, use of MRI, and access to immediate reconstruction, our study might influence this choice by reducing patients' fears of recurrent cancer after breast-conserving surgery plus radiotherapy.

in early breast cancer compared with mastectomy. However, none of these registry-based studies have reported data for 10 year overall and breast cancer-specific survival. Hence, the influence of confounding by severity and, consequently, non-breast cancer deaths is difficult to identify. Additionally, these studies are limited by correction for a small number of variables and short follow-up.

The aim of this study was to compare long-term survival of breast-conserving surgery plus radiotherapy with mastectomy in women with early breast cancer in a large population-based cohort.

To overcome the possible bias of the absence of information about non-breast cancer death, we estimated 10 year overall and breast cancer-specific survival (distant metastasis-free survival and relative survival) in Dutch women with early breast cancer, treated with either breast-conserving surgery plus radiotherapy or mastectomy. We analysed overall survival in the entire cohort and in subgroups by cancer stage (tumour [T] and node [N] category), as well as breast cancer-specific survival in a subcohort.

Methods

Study design and patients

In this population-based study, we selected patients from the Netherlands Cancer Registry. This registry covers the whole Dutch population, recording data for all newly diagnosed malignancies since 1989. We included all female patients diagnosed with primary invasive, pathologically staged T1–2, N0–1, M0 breast cancer (morphology codes 8500–8575, excluding Paget's disease of the nipple) between Jan 1, 2000, and Dec 31, 2004, excluding those with primary carcinoma in situ. We allocated cases to groups according to the most extensive surgery of the primary tumour that the patient had. We excluded patients from the breast-conserving surgery plus radiotherapy group who did not receive radiotherapy after breast-conserving surgery. We excluded patients from the mastectomy group who received radiotherapy after mastectomy. Type of surgery was irrespective of axillary staging or dissection or use of adjuvant systemic therapy. We excluded women who had primary systemic therapy, were treated in foreign or unknown hospitals, or had undifferentiated tumours or macroscopic residual tumour.

Procedures

We obtained patient-related, tumour-related, and treatment-related characteristics from the Netherlands Cancer Registry. The Netherlands Cancer Registry has specialised trained and dedicated registrars who derive these data from hospital records of all patients with a diagnosis of cancer. We coded tumour topography and morphology according to the International Classification of Diseases for Oncology[14] using the tumour, node, and metastasis classification system (International Union Against Cancer 5th edition[15] [2000–02] or 6th edition[16]

[2003–04]). We derived additional data for vital status and date of death from the Municipal Personal Records Database up to Dec 31, 2014.

Primary invasive breast cancer represents patients diagnosed with cancer for the first time. Since the definition of the N1 category in the tumour, node, and metastasis classification system changed between the 5th and 6th editions of the International Classification of Diseases for Oncology, we used the number of positive lymph nodes to classify patients into N categories. We classified patients without involved lymph nodes as N0 and those with one to three positive nodes as N1. We defined axillary dissection as a standardised surgical en-bloc removal of level I and II axillary lymph nodes. Data regarding where patients were treated (by the nine regions in the Netherlands) were also collected and used in the analysis as this may have had an influence on survival. We calculated follow-up from date of diagnosis (overall and relative survival) or last known date of surgery of the primary tumour (distant metastasis-free survival) to date of event. We calculated follow-up for distant metastasis-free survival from date of last surgery of the primary tumour, since this date was the date by which the patient was expected to be tumour free and at risk of recurrent disease. We censored patients at date of event or last date of observation. We defined distant metastases according to Moossdorff and colleagues'[17] consensus-based event definitions for recurrence classification and Definition for the Assessment of Time-to-Event Endpoints in Cancer Trials guidelines.[18] In the distant metastasis-free survival analysis, we did not count deaths as events. To account for the diagnostic period, we considered events that occurred within 3 months of the date of primary diagnosis synchronous with the primary tumour and did not count them as events.

Outcomes

The main outcomes were 10 year overall survival (cumulative probability of being alive 10 years after diagnosis) in the entire 2000–04 cohort, distant metastasis-free survival (free from distant metastases after 10 year follow-up) in the 2003 cohort (all patients diagnosed from Jan 1, 2003, to Dec 31, 2003), and relative survival (ratio of observed survival of patients to the expected survival of the nationwide population) in the 2003 cohort. Distant metastasis-free and relative survival are both indicators for breast cancer-specific survival. For the whole 2000–04 cohort, cause of death was not available in the Netherlands Cancer Registry. To estimate distant metastasis-free survival, data for all recurrences (including distant metastases) within 10 years of diagnosis were gathered directly from patient files. Since this data gathering was only done for the 2003 cohort (because of time and resource constraints), we calculated distant metastasis-free survival only for this 2003 cohort. Because of statistical complexity, we also estimated relative survival for the 2003 cohort only.

Statistical analysis

We summarised patient-related, tumour-related, and treatment-related characteristics, and compared treatment groups using the χ^2 test or Wilcoxon rank sum test, for the entire 2000–04 cohort as well as for the 2003 cohort. As not all items were routinely established or registered for the entire period, we did multiple imputation using the mi impute chained equation command in Stata. As missing values were related to coding rules that changed over time, we considered these values as missing at random. We repeated the imputation 20 times, followed by application of Rubin's rule to combine parameter estimates and standard errors (SEs).[19] To establish the validity of the imputed data, we compared observed values of complete cases with imputed values. We then used the imputed data for analyses.

To estimate crude 10 year overall and distant metastasis-free survival, we applied the Kaplan-Meier method and compared breast-conserving surgery plus radiotherapy and mastectomy groups using the log-rank test, for every T and N category. We did multivariable Cox proportional hazard analysis to correct for confounding and estimate hazard ratios (HRs) with 95% CIs for 10 year overall and distant metastasis-free survival. We estimated 10 year relative survival by calculating excess mortality ratios using general linear models with Poisson distribution, with life tables of the general population as a reference. We established excess mortality ratios with 95% CIs using the Ederer II method.[20] We analysed 10 year relative survival with imputed datasets using a modification of the Stata code described by Nur and colleagues.[21] We based expected survival of the nationwide population on life tables and matched it by age and year of diagnosis. To compare excess mortality ratios with other populations with different age distributions, we did age standardisation as described in the International Cancer Survival Standard.[22]

To adjust all analyses for confounders, we included potential confounding variables (ie, baseline characteristics) that differed between treatment groups and significantly contributed to the outcome in univariable analysis in the multivariable models. We manually removed variables that did not significantly contribute to the multivariable models using backward selection. We tested the proportional hazards assumption by plotting the scaled Schoenfeld residuals of all coefficients over time and inspecting these for consistency. We found no violations. Finally, we tested the goodness of fit of the model graphically by observation of Cox-Snell residuals. Statistical tests were two-sided and we considered a p value of less than 0·05 significant, except for analysis of the 2003 cohort, where we used Bonferroni correction to adjust for multiple testing and used a p value of 0·025. We did all statistical analyses in Stata version 13.1.

Role of the funding source

There was no funding for this study. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

See Online for appendix

40 220 female patients diagnosed with primary invasive breast cancer between 2000 and 2004 from the Netherlands Cancer Registry were eligible. Of these, we excluded 627 (2%) who did not receive radiotherapy after breast-conserving surgery, 2173 (5%) who received radiotherapy after mastectomy, 152 (<1%) who had primary systemic therapy, 28 (<1%) who were treated in foreign or unknown hospitals, ten (<1%) who had undifferentiated tumours, and 23 (<1%) who had macroscopic residual tumour left. The final study population of the 2000–04 cohort therefore consisted of 37 207 (93%) patients with non-metastatic early breast cancer, of whom 21 734 (58%) received breast-conserving surgery plus radiotherapy and 15 473 (42%) received mastectomy (figure 1). For patients diagnosed in 2003 (7783 [21%] patients), data for recurrences were complete for 7552 (97%) patients. Of this final 2003 cohort, 4647 (62%) received breast-conserving surgery plus radiotherapy and 2905 (38%) received mastectomy. To establish the validity of imputed data, we compared observed values of complete cases with imputed values, which showed similar distributions (appendix p1). All analyses based on imputed datasets were similar to complete case analyses, and the estimates were more precise than were complete case analyses (data not shown).

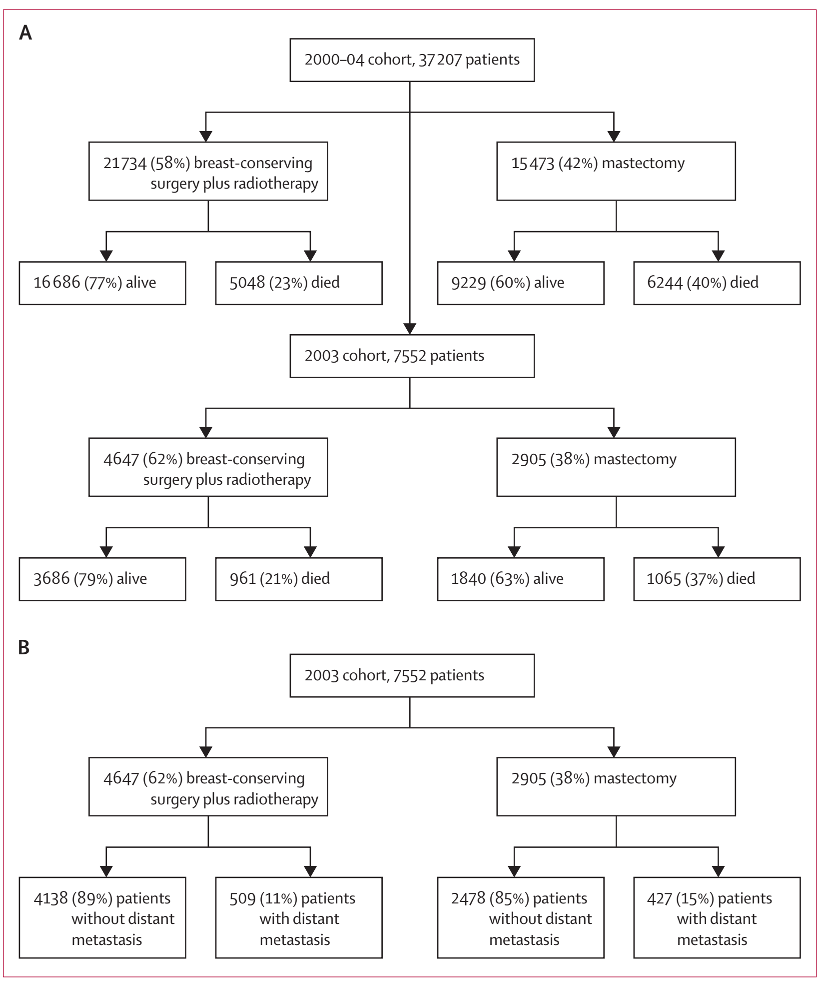

***Figure 1:* Flow diagrams of included patients**

(A) The two cohorts with percentages of patients who are still alive and who died, specified for primary surgery. (B) Presence or absence of distant metastases in the 2003 cohort, specified for primary surgery.

Patient-related, tumour-related, and treatment-related characteristics of the entire 2000–04 cohort according to type of surgery are presented in table 1 and the appendix (pp 2–3). Patients who had mastectomies were generally older and had less favourable tumour characteristics than those who had breast-conserving surgery plus radiotherapy. Additionally, patients who had mastectomy more often received axillary lymph node dissection and adjuvant hormonal therapy than did patients given breast-conserving surgery plus radiotherapy. Stratification for cancer stage (T and N category) showed that node-positive patients (T1N1 and T2N1) received axillary lymph node dissection and adjuvant hormonal therapy more frequently than did node-negative patients (T1N0 and T2N0; appendix pp 2–3). Use of adjuvant chemotherapy was higher in the T1N1 group than in the T1N0 group, but was almost equal for T2N0 and T2N1 (appendix pp 2–3). 4853 (80%) of 6092 patients with T1N0 stage cancer in the mastectomy group had not received adjuvant systemic therapy in the 2000–04 cohort compared with 10 128 (79%) of 12 768 in the breast-conserving surgery plus radiotherapy group. For the 2003 cohort, 891 (79%) of 1130 patients with T1N0 stage cancer in the mastectomy group did not receive adjuvant systemic therapy compared with 2152 (78%) of 2761 patients in the breast-conserving surgery group. The characteristics of the 2003 subcohort were similar to those of the 2000–04 cohort (appendix pp 4–5), indicating that it could serve as a representative cohort.

In the 2000–04 cohort, 16 686 (77%) of 21 734 patients survived in the breast-conserving surgery plus radiotherapy group compared with 9229 (60%) of 15 473 in the mastectomy group (figure 1), after a median follow-up of 11·4 years (IQR 10·0–13·0). Kaplan-Meier analysis and the log-rank test showed that breast-conserving surgery plus radiotherapy was significantly associated with improved overall survival compared with mastectomy in all T and N categories (figure 2, table 2). All subgroups of patients with different cancer stages had different overall survival irrespective of type of surgery, with the T1N0 subgroup being the most favourable and T2N1 being the least (figure 2, table 2). After adjustment for confounders, the adjusted HR for

	Mastectomy (n=15 473)	Breast-conserving surgery plus radiotherapy (n=21 734)
Year of diagnosis*		
2000	3113 (20%)	3909 (18%)
2001	3171 (20%)	4097 (19%)
2002	3128 (20%)	4248 (20%)
2003	3059 (20%)	4724 (22%)
2004	3002 (19%)	4756 (22%)
Age (years)*		
<40	929 (6%)	1232 (6%)
40–49	2618 (17%)	4264 (20%)
50–59	3465 (22%)	7222 (33%)
60–69	2989 (19%)	5479 (25%)
70–79	3346 (22%)	3098 (14%)
>79	2126 (14%)	439 (2%)
SES*		
Low	4686 (30%)	6436 (30%)
Medium	6319 (41%)	8577 (39%)
High	4468 (29%)	6721 (31%)
Hospital volume (patients per year)*		
0–49	3123 (20%)	4654 (21%)
50–99	7004 (45%)	9085 (42%)
100–149	3359 (22%)	4924 (23%)
>149	1987 (13%)	3071 (14%)
Region*		
A	2087 (13%)	3084 (14%)
B	1558 (10%)	1606 (7%)
C	1100 (7%)	1772 (8%)
D	2346 (15%)	4375 (20%)
E	1595 (10%)	2192 (10%)
F	3031 (20%)	2484 (11%)
G	1848 (12%)	3427 (16%)
H	832 (5%)	1335 (6%)
I	1076 (7%)	1459 (7%)
Lateralisation†		
Left	8131 (53%)	11 244 (52%)
Right	7340 (47%)	10 489 (48%)
Unknown	2 (<0·1%)	1 (0%)
Sublocalisation*		
Outer quadrants	7037 (45%)	11 574 (53%)
Inner quadrants	2780 (18%)	4711 (22%)
Central portion	1378 (9%)	1095 (5%)
Overlapping lesions	3918 (25%)	4036 (19%)
Unknown	360 (2%)	318 (1%)
(Continued from previous column)		
Histological tumour type*		
Ductal	11 987 (77%)	17 876 (82%)
Lobular	1830 (12%)	1730 (8%)
Mixed	874 (6%)	798 (4%)
Other	782 (5%)	1330 (6%)
Differentiation*		
Grade I	2365 (15%)	4821 (22%)
Grade II	6275 (41%)	8681 (40%)
Grade III	4602 (30%)	5343 (25%)
Unknown	2231 (14%)	2889 (13%)
Tumour size (mm)*		
Median	20 (14–27)	15 (11–20)
Unknown	6013 (39%)	7773 (36%)
Number of positive nodes*		
Median	0 (0–1)	0 (0–1)
Unknown	57 (<0·1%)	37 (<0·1%)
Multifocality*		
Yes	1594 (10%)	434 (2%)
No	5721 (37%)	9416 (43%)
Unknown	8158 (53%)	11 884 (55%)
Hormone receptor status*		
ER and PR positive	3946 (26%)	6464 (30%)
ER or PR positive	1029 (7%)	1423 (7%)
ER and PR negative	1127 (7%)	1561 (7%)
Unknown	9371 (61%)	12 286 (57%)
Adjuvant systemic therapy*		
No	7505 (49%)	12 145 (56%)
Hormonal therapy	4017 (26%)	3834 (18%)
Chemotherapy	1864 (12%)	2778 (13%)
Both	2087 (13%)	2977 (14%)
Axillary lymph node dissection*		
Yes	10 987 (71%)	9852 (45%)
No	4486 (29%)	11 882 (55%)

(Table 1 continues in next column)

Data are n (%) or median (IQR). p<0·1 for comparison between treatment groups was considered significant. SES=socioeconomic status. ER=oestrogen receptor. PR=progesterone receptor. *p<0·0001 for comparison between treatment groups. †p=0·119 for comparison between treatment groups.

Table 1: **Baseline characteristics**

10 year overall survival was 0·81 (95% CI 0·78–0·85) in the overall cohort, favouring breast-conserving surgery plus radiotherapy over mastectomy; the HRs were similar in all T and N categories in this cohort (table 2). In the 2003 subcohort, 3686 (79%) of 4647 patients survived in the breast-conserving surgery plus radiotherapy group compared with 1840 (63%) of 2905 in the mastectomy group (figure 1). Median follow-up was 11·3 years (IQR 10·3–11·7). Kaplan-Meier curves (appendix p 6) and HRs (table 2) were similar to those of the entire 2000–04 cohort.

In the 2003 subcohort, 509 (11%) of 4647 patients in the breast-conserving surgery plus radiotherapy group were diagnosed with distant metastases compared with 427 (15%) of 2905 in the mastectomy group (figure 1). Median follow-up was 9·8 years (IQR 5·6–10·0). Kaplan-Meier analysis and the log-rank test showed that, overall, breast-conserving surgery plus radiotherapy was significantly associated with better 10 year distant metastasis-free survival than that for mastectomy

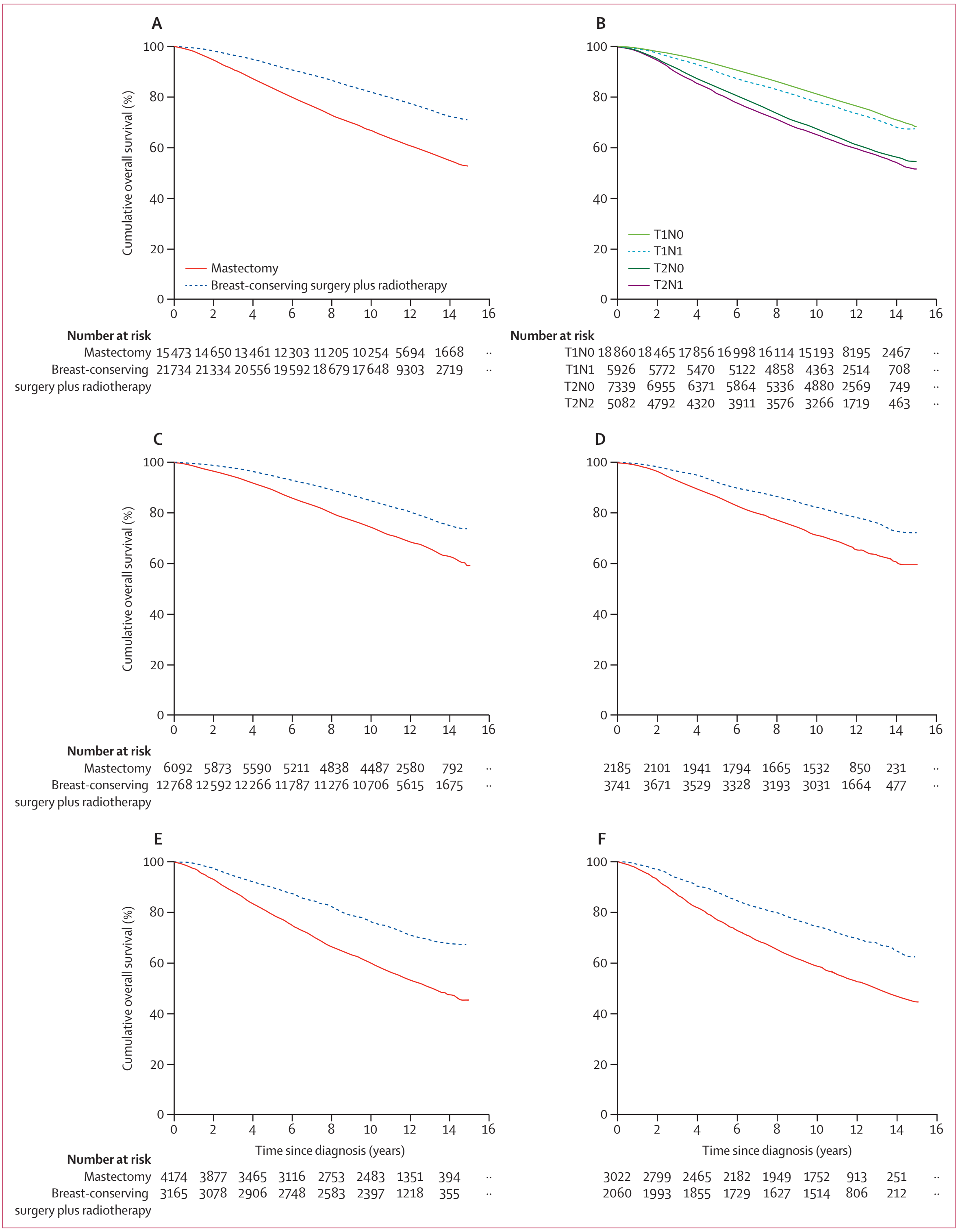

***Figure 2:* Unadjusted 10 year overall survival analysis in the 2000–04 cohort**

(A) Breast-conserving surgery plus radiotherapy compared with mastectomy in the whole cohort. (B) Patients with T1N0, T1N1, T2N0, and T2N1 stage cancer, irrespective of type of surgery. Breast-conserving surgery plus radiotherapy compared with mastectomy in patients with (C) T1N0, (D) T1N1, (E) T2N0, and (F) T2N1 stage cancer.

	2000–04 cohort (n=37 207)					2003 cohort (n=7552)				
	n	Crude analysis		Adjusted analysis		n	Crude analysis		Adjusted analysis	
		HR	p value	HR	p value		HR	p value	HR	p value
Overall cohort										
Mastectomy	15 473	1	..	1	..	2905	1	..	1	..
Breast-conserving surgery plus radiotherapy	21 734	0·51 (0·49–0·53)	<0·0001	0·81 (0·78–0·85)*	<0·0001	4647	0·50 (0·45–0·54)	<0·0001	0·81 (0·73–0·89)†	<0·0001
Subgroups										
T1N0										
Mastectomy	6092	1	..	1	..	1130	1	..	1	..
Breast-conserving surgery plus radiotherapy	12 768	0·58 (0·55–0·62)	<0·0001	0·82 (0·77–0·87)‡	<0·0001	2761	0·55 (0·48–0·63)	<0·0001	0·79 (0·68–0·91)§	0·002
T1N1										
Mastectomy	2185	1	..	1	..	388	1	..	1	..
Breast-conserving surgery plus radiotherapy	3741	0·60 (0·54–0·66)	<0·0001	0·81 (0·73–0·90)¶	<0·0001	738	0·62 (0·48–0·79)	<0·0001	0·79 (0·60–1·03)||	0·085
T2N0										
Mastectomy	4174	1	..	1	..	772	1	..	1	..
Breast-conserving surgery plus radiotherapy	3165	0·52 (0·48–0·56)	<0·0001	0·82 (0·75–0·90)**	<0·0001	704	0·54 (0·45–0·64)	<0·0001	0·85 (0·69–1·04)††	0·108
T2N1										
Mastectomy	3022	1	..	1	..	615	1	..	1	..
Breast-conserving surgery plus radiotherapy	2060	0·56 (0·51–0·61)	<0·0001	0·80 (0·72–0·88)‡‡	<0·0001	444	0·59 (0·48–0·72)	<0·0001	0·85 (0·68–1·08)§§	0·181

Data in parentheses are 95% CIs. HR=hazard ratio. Cancer stage is indicated by the T and N status. T=tumour. N=node. *Corrected for age, socioeconomic status, hospital volume, region, sublocalisation of tumour, histological tumour type, differentiation grade, tumour size, number of positive lymph nodes, hormone receptor status, and adjuvant systemic therapy. †Corrected for age, socioeconomic status, hospital volume, sublocalisation of tumour, histological tumour type, differentiation grade, tumour size, number of positive lymph nodes, hormone receptor status, and adjuvant systemic therapy. ‡Corrected for age, hospital volume, region, sublocalisation of tumour, differentiation grade, tumour size, and hormone receptor status. §Corrected for age, socioeconomic status, region, histological tumour type, differentiation grade, tumour size, hormone receptor status, and adjuvant systemic therapy. ¶Corrected for age, socioeconomic status, region, sublocalisation of tumour, differentiation grade, tumour size, number of positive lymph nodes, adjuvant systemic therapy, and axillary lymph node dissection. ||Corrected for age, region, sublocalisation of tumour, and tumour size. **Corrected for age, socioeconomic status, region, sublocalisation of tumour, differentiation grade, hormone receptor status, tumour size, and adjuvant systemic therapy. ††Corrected for age, differentiation grade, tumour size, adjuvant systemic therapy, and axillary lymph node dissection. ‡‡Corrected for age, socioeconomic status, region, sublocalisation of tumour, histological tumour type, tumour size, number of positive lymph nodes, hormone receptor status, adjuvant systemic therapy, and axillary lymph node dissection. §§Corrected for age, region, sublocalisation of tumour, tumour size, hormone receptor status, and axillary lymph node dissection.

Table 2: **10 year overall survival**

(HR 0·66 [95% CI 0·58–0·75]; p<0·0001; figure 3, table 3). In patients with T1N0 stage cancer, breast-conserving surgery plus radiotherapy was associated with improved 10 year distant metastasis-free survival compared with mastectomy (p<0·0001; figure 3, table 3). In patients with other stages of cancer (T1N1, T2N0, T2N1), we found no significant differences between treatments (figure 3). After adjustment for confounders, the adjusted HR was 0·88 (95% CI 0·77–1·01), indicating no significant difference between breast-conserving surgery plus radiotherapy and mastectomy (table 3). However, after stratification by cancer stage, breast-conserving surgery plus radiotherapy was associated with improved 10 year distant metastasis-free survival in the T1N0 subgroup (adjusted HR 0·74 [0·58–0·94]). In patients with T1N1, T2N0, or T2N1 stage cancer, we noted no significant difference between treatments (table 3). We repeated the analyses with follow-up calculated from date of diagnosis, which resulted in similar estimates (appendix p 7).

Overall, crude 10 year relative survival in the 2003 cohort was significantly better for breast-conserving surgery plus radiotherapy than for mastectomy (p<0·0001; figure 4, table 3). After stratification for cancer stage, we observed significantly different proportions of crude relative survival for all cancer stage subtypes, irrespective of the type of surgery given (figure 4, table 3). Breast-conserving surgery plus radiotherapy was only significantly related to improved 10 year relative survival in patients with T1N0 stage cancer (figure 4, table 3). After adjustment for confounding, the adjusted excess mortality ratio for 10 year relative survival was 0·76 (95% CI 0·64–0·91; table 3). After stratification for cancer stage, the favourable outcome of breast-conserving surgery plus radiotherapy compared with mastectomy remained in patients with T1N0 stage cancer only.

Discussion

In this study, patients with early, non-metastatic breast cancer treated with breast-conserving surgery plus radiotherapy had improved 10 year overall survival compared with that in patients treated with mastectomy. In a subset of patients with T1N0 stage disease, unadjusted analysis showed that 10 year breast cancer-specific survival, including distant metastasis-free survival and relative

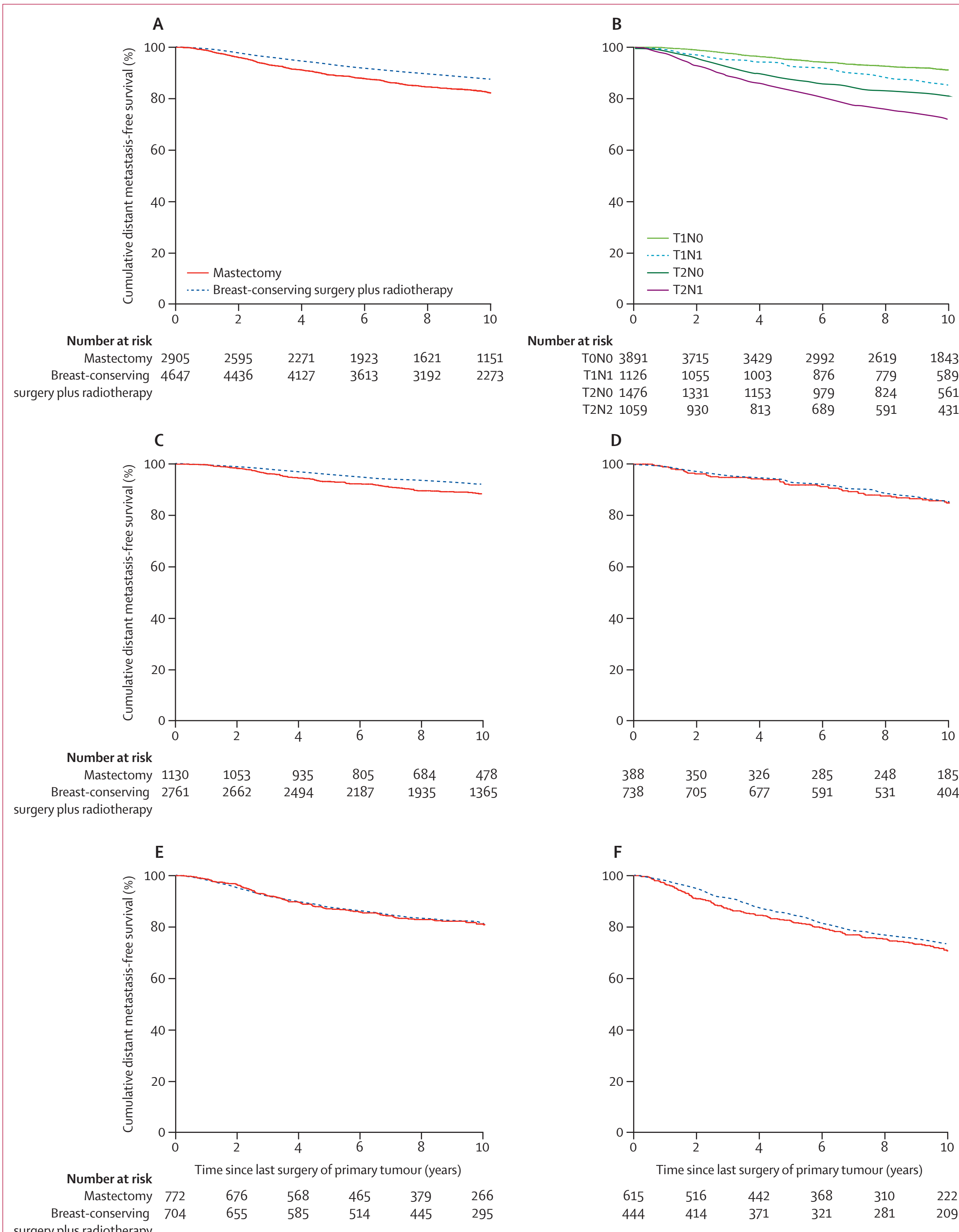

Figure 3: **Unadjusted 10 year distant metastasis-free survival in the 2003 cohort**
(A) Breast-conserving surgery plus radiotherapy compared with mastectomy in the whole cohort. (B) Patients with T1N0, T1N1, T2N0, and T2N1 stage cancer, irrespective of type of surgery. Breast-conserving surgery plus radiotherapy compared with mastectomy in patients with (C) T1N0, (D) T1N1, (E) T2N0, and (F) T2N1 stage cancer.

	n	Distant metastasis-free survival				Relative survival			
		Crude analysis		Adjusted analysis		Crude analysis		Adjusted analysis	
		HR	p value	HR	p value	Excess mortality ratio	p value	Excess mortality ratio	p value
Overall 2003 subcohort									
Mastectomy	2905	1		1		1		1	
Breast-conserving surgery plus radiotherapy	4647	0·66 (0·58–0·75)	<0·0001	0·88 (0·77–1·01)*	0·070	0·58 (0·49–0·69)	<0·0001	0·76 (0·64–0·91)†	0·003
Subgroups									
T1N0									
Mastectomy	1130	1	..	1	..	1	..	1	..
Breast-conserving surgery plus radiotherapy	2761	0·64 (0·51–0·82)	<0·0001	0·74 (0·58–0·94)‡	0·014	0·51 (0·36–0·73)	<0·0001	0·60 (0·42–0·85)§	0·004
T1N1									
Mastectomy	388	1	..	1	..	1	..	1	..
Breast-conserving surgery plus radiotherapy	738	0·94 (0·67–1·33)	0·741	1·00 (0·71–1·42)¶	0·994	0·75 (0·48–1·18)	0·214	0·71 (0·45–1·13)||	0·148
T2N0									
Mastectomy	772	1	..	1	..	1	..	1	..
Breast-conserving surgery plus radiotherapy	704	0·98 (0·76–1·26)	0·855	0·94 (0·72–1·23)**	0·644	0·90 (0·65–1·25)	0·539	0·94 (0·66–1·33)††	0·720
T2N1									
Mastectomy	615	1	..	1	..	1	..	1	..
Breast-conserving surgery plus radiotherapy	444	0·86 (0·67–1·10)	0·234	0·95 (0·73–1·24)‡‡	0·718	0·79 (0·59–1·05)	0·121	0·81 (0·58–1·12)§§	0·202

Data in parentheses are 95% CIs. We used life tables of the general Dutch population, matched by age and year of diagnosis, as a reference. HR=hazard ratio. T=tumour. N=node. *Corrected for region, sublocalisation of tumour, histological tumour type, differentiation grade, tumour size, number of positive lymph nodes, hormone receptor status, and adjuvant systemic therapy. †Corrected for age, socioeconomic status, hospital volume, sublocalisation of tumour, histological tumour type, differentiation grade, tumour size, number of positive lymph nodes, hormone receptor status, and adjuvant systemic therapy. ‡Corrected for age, sublocalisation of tumour, histological tumour type, differentiation grade, tumour size, hormone receptor status, and adjuvant systemic therapy. §Corrected for age, socioeconomic status, region, histological tumour type, differentiation grade, tumour size, hormone receptor status, and adjuvant systemic therapy. ¶Corrected for region, differentiation grade, and tumour size. ||Corrected for age, region, sublocalisation of tumour, and tumour size. **Corrected for age, sublocalisation of tumour, histological tumour type, and differentiation grade. ††Corrected for age, differentiation grade, tumour size, adjuvant systemic therapy, and axillary lymph node dissection. ‡‡Corrected for sublocalisation of tumour, tumour size, and hormone receptor status. §§Corrected for age, region, sublocalisation of tumour, tumour size, hormone receptor status, and axillary lymph node dissection.

Table 3: **10 year distant metastasis-free and relative survival in the 2003 cohort**

survival, was improved in patients treated with breast-conserving surgery plus radiotherapy compared with patients treated with mastectomy; this difference was not observed between treatment groups in patients with other stages of disease. After adjusting for confounders, the difference in breast cancer-specific survival (metastasis-free and relative survival) remained significant in patients with T1N0 stage disease.

The difference in outcomes between 10 year overall and breast cancer-specific survival might need further clarification. Older patients with larger, more aggressive lobular or multifocal tumours are thought to more often receive mastectomy than breast-conserving surgery plus radiotherapy, which is also seen in our data. These patients have lower survival because of worse tumour characteristics, and age and confounding by severity are issues. For this reason, observational studies only reporting overall survival outcomes[12,13] might not adequately compare treatment effects. Breast cancer-specific survival might estimate real treatment effects more reliably than might overall survival by eliminating the large influence of age and comorbidities (leading to non-breast cancer deaths), which are expected to have a larger influence on overall survival in the mastectomy group than in the breast-conserving surgery group. However, Adkisson and colleagues[23] showed that absence of comorbidities was independently associated with patient's choice of mastectomy over breast-conserving surgery plus radiotherapy, and primary tumour characteristics were not associated with treatment choice, indicating that the above-mentioned argument does not always hold.

Our result that breast-conserving surgery plus radiotherapy was associated with improved overall survival in early breast cancer is substantiated by conclusions from other observational studies.[7–13] The only one of these studies that stratified the analysis for T and N cancer stage category[9] described 5 year overall and breast cancer-specific survival after breast-conserving surgery plus radiotherapy equal to or better than mastectomy, but did not report exact estimates by cancer stage. In our study, the breast-conserving surgery results are mainly determined by the T1N0 category, as this group accounts for more than 50% of the entire cohort. Thus, studies

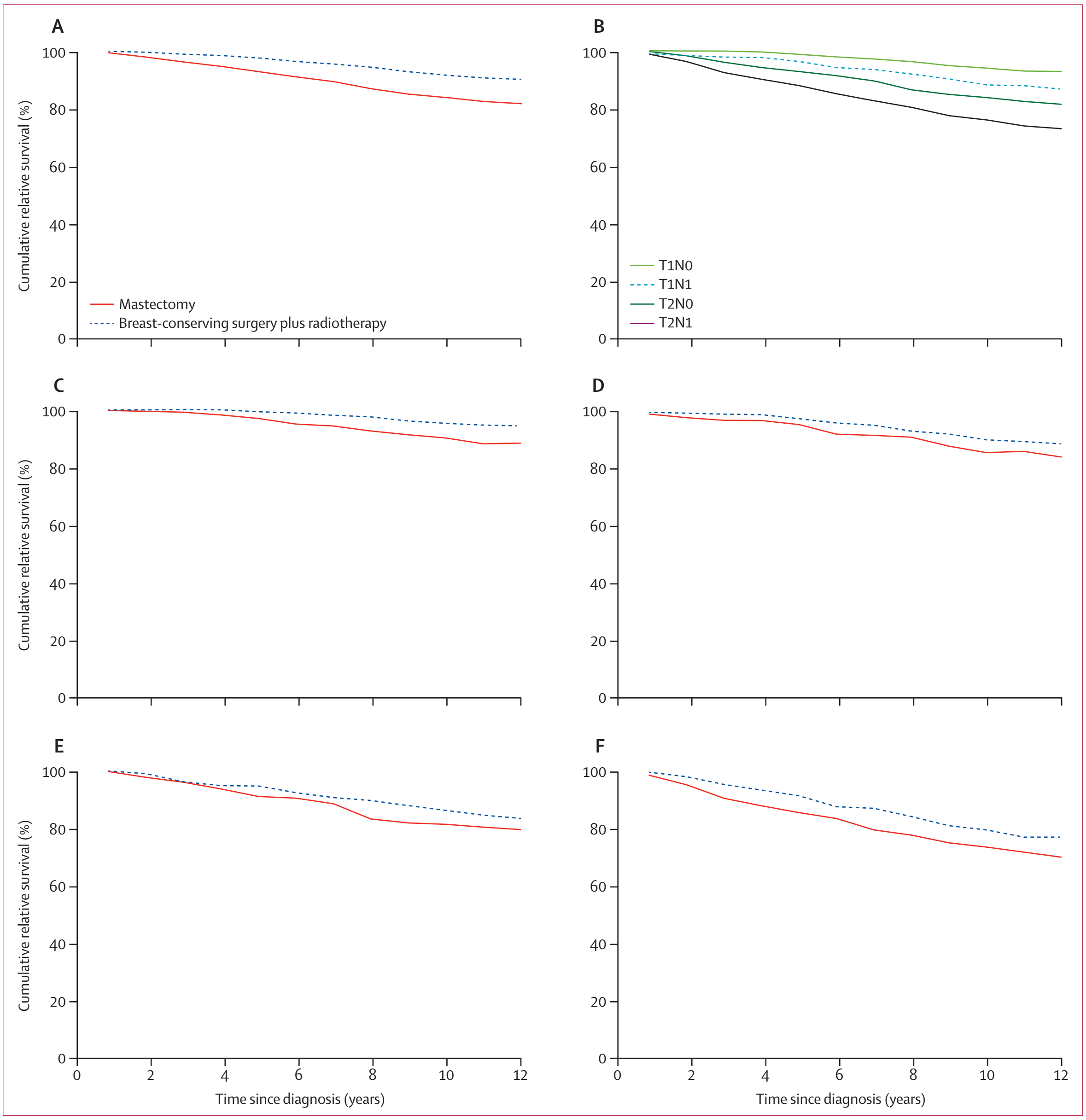

Figure 4: Unadjusted 10 year relative survival in the 2003 cohort

(A) Breast-conserving surgery plus radiotherapy compared with mastectomy in the whole cohort. (B) Patients with T1N0, T1N1, T2N0, and T2N1 stage cancer, independent of type of surgery. Breast-conserving surgery plus radiotherapy compared with mastectomy in patients with (C) T1N0, (D) T1N1, (E) T2N0, and (F) T2N1 stage cancer. We used life tables of the general Dutch population, matched by age and year of diagnosis, as a reference.

that only report one outcome measure for the whole group should be interpreted with caution.

Our results are not consistent with outcomes of previous randomised controlled trials,[1–3] which showed overall and distant metastasis-free survival to be equal for breast-conserving surgery plus radiotherapy and mastectomy in early breast cancer. This inconsistency can be explained by the different study designs (randomised controlled trials versus historic cohort design) and patient populations,[5] and the fact that these randomised controlled trials were all done in the 1980s, when local recurrence was much higher after breast-conserving surgery plus radiotherapy than it is now[24] and when population-based screening programmes were non-existent. To establish if the starting point of follow-up in our study (last date of primary surgery) could partly explain the difference, we repeated the analyses with date of diagnosis as the starting point of follow-up and found similar results, indicating that this factor did not influence our results. Furthermore, diagnostic, surgical, and radiotherapy procedures have improved over the last 30 years, which might explain why we observed an improvement in patients treated with breast-conserving surgery plus radiotherapy compared with patients treated with mastectomy.

Onitilo and colleagues[12] investigated overall survival after breast-conserving surgery with and without radiotherapy compared with mastectomy and showed that overall survival for breast-conserving surgery without radiotherapy was equal to that for mastectomy, but overall survival was longer for breast-conserving surgery plus radiotherapy than for mastectomy. The authors suggest that the finding that breast-conserving surgery plus radiotherapy is better than mastectomy is more likely to be related to the addition of radiotherapy than to the surgery itself. The Early Breast Cancer Trialists' Collaborative Group showed that addition of radiotherapy after breast-conserving surgery for early-stage breast cancer avoided about one breast cancer death by year 15 for every four breast cancer recurrences avoided by year 10.[25] As adjuvant systemic therapy is expected to have a similar effect to postoperative radiotherapy on recurrence risk,[26] the effect of postoperative radiotherapy alone can only be studied in patients who did not receive adjuvant systemic therapy. In our study, a significant difference in 10 year distant metastasis-free survival in favour of breast-conserving surgery plus radiotherapy was only found in patients with T1N0 stage cancer. More than 75% of patients in this subgroup had not received adjuvant systemic therapy (compared with 7–48% of patients with other stages of cancer). Part of this effect could therefore be attributed to postoperative radiotherapy in the breast-conserving surgery plus radiotherapy group. The interplay between risk factors and efficacy of systemic treatment and the influence of locoregional treatments on survival is complex.[27] The intuitive notion that the influence of radiotherapy might be most evident in patients with positive lymph nodes therefore might not hold in this study.

To our knowledge, this study is the first population-based study investigating overall and breast cancer-specific survival in subgroups of patients with T1N0, T1N1, T2N0, and T2N1 stage breast cancer, with 10 years of follow-up. An important strength of the study is use of data from the Netherlands Cancer Registry that includes all Dutch women diagnosed with breast cancer, which enhances the validity of the results and provides a good reflection of daily practice. Furthermore, the Netherlands Cancer Registry has detailed and thorough records, which allowed us to account for more confounding variables than other registry-based studies,[7–13] and to provide valid adjusted survival estimates. In addition, besides stratification for breast cancer T and N stage, we used exact (up to 1 mm) tumour size and number of positive lymph nodes in the multivariable analyses. Importantly, a decline of 1 cm in tumour size has been associated with a reduction in 15 year mortality of about 10%.[28] Since the range in tumour size in every T category is up to a few cm and patients who have mastectomy more often have larger tumours than do those who have breast-conserving surgery plus radiotherapy, we accounted for exact size to eliminate this possibly large effect on the outcome. Additionally, an increasing number of positive lymph nodes is associated with worse overall survival.[29]

As in all observational studies, our results could have been influenced by confounding by severity and residual unknown confounding, despite our extensive corrections. Since overall survival is not breast cancer specific, this outcome might be influenced by non-breast cancer deaths. This influence is largely overcome by use of distant metastasis-free and relative survival, which are an approximation for breast cancer-specific survival. Findings from the Early Breast Cancer Trialists' Collaborative Group overview[30]—looking at breast cancer-specific survival after mastectomy compared with mastectomy plus radiotherapy—showed that survival curves of patients who had mastectomy with and without radiotherapy do not separate until at least 5 years after treatment. In our study, survival curves separate earlier, which might reflect differences in baseline characteristics between treatment groups.

Some additional limitations of this study should be mentioned. After developments in diagnostic and therapeutic strategies, treatment guidelines for women with early breast cancer have changed and our study population may not reflect outcomes for women currently being treated. For example, our study population might have an underuse of adjuvant systemic therapy compared with current treatment standards. However, according to the Dutch guidelines,[31] low-risk early stage breast cancer patients still do not receive adjuvant systemic therapy. As this factor applies for both breast-conserving surgery plus radiotherapy and mastectomy, it is not expected to have biased the results. Unfortunately, in the period studied, information about HER2 status was very scarce, was not established or registered on a large scale, and was not part of decision making regarding targeted therapy. Since HER2 status has been shown to be a strong prognostic factor for relapse,[32] any difference in HER2 status between treatment groups might have influenced survival outcomes. The absence of data for comorbidities and relevant contraindications to radiotherapy could also have influenced the results. The presence of missing data can be considered a weakness of this study. We did multiple imputation to achieve better and more reliable estimates of the differences than if imputation was not done when data were missing. Even with substantial amounts of missing data, this technique provides effect estimates similar to those obtained with complete case analysis. Additionally, a gain in precision has been achieved.[33] In this study, all analyses based on imputed datasets were similar to complete case analyses, and the estimates were more precise than were complete case analyses (data not shown).

Our results, along with previous studies, provide convincing evidence that breast-conserving surgery plus radiotherapy is at least equivalent to mastectomy with respect to long-term survival in early breast cancer. Although the choice of mastectomy is increasing, primarily due to fear of recurrent cancer, use of MRI, and access to immediate reconstruction,[34] our study might influence this choice by reducing patients' fears of recurrent cancer after breast-conserving surgery plus radiotherapy. Shared decision making in treatment choices between physicians and patients is advisable, taking into account the associated psychological effect. In case both treatments are suitable, patients should be adequately informed regarding both treatments, discussing not only better cosmetic aspects of breast-conserving surgery plus radiotherapy compared with mastectomy, but also long-term overall and breast cancer-specific survival probabilities. Additionally, mastectomy can remain the first choice of treatment for specific groups of patients such as women with a known genetic alteration associated with a high risk of second primary breast cancer, those with contraindications for radiotherapy, such as patients with Li-Fraumeni syndrome, and for women with a large tumour-to-breast ratio.[35,36] Whether these results hold true for operative choices after primary systemic therapy is unclear. Since too few patients were given primary systemic therapy to draw meaningful conclusions, we excluded those receiving primary systemic therapy from our study. Although 10 year breast cancer-specific survival was improved for breast-conserving surgery plus radiotherapy compared with mastectomy in T1N0 disease only, suggesting a possible role for confounding by severity (including presence of comorbidities) in overall survival, our study results emphasise that breast-conserving surgery plus radiotherapy is at least equivalent to mastectomy concerning survival and these results might form a basis for further analytical and predictive modelling in view of individual (stratified) prognosis and outcome of treatment in early breast cancer.

Contributors

MCvM, PP, and LJAS did the literature search, designed the study, interpreted data, and discussed and wrote the manuscript. MCvM was also responsible for the statistical methods, data analysis, and figures and tables. LdM designed the study, interpreted data, reviewed the statistical methods, and discussed and wrote the manuscript. GHdB, JJJ, TvD, and SCL interpreted data and discussed and wrote the manuscript. SS designed the study, interpreted data, and discussed and wrote the manuscript.

Declaration of interests

We declare no competing interests.

Acknowledgments

We 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.

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