**LOCAL MANAGEMENT OF EARLY
STAGE BREAST CANCER
AND
CLINICAL RISK PREDICTION OF
SURVIVAL**

MARISSA VAN MAAREN

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Marissa van Maaren

Local management of early stage breast cancer and clinical risk prediction of survival

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Chapter

1

Chapter 1

General introduction and outline

Introduction

Breast cancer incidence and mortality

With 1.67 million diagnoses in 2012, breast cancer is, after lung cancer, the second most commonly diagnosed cancer in the world.¹ The highest incidence is seen in the western countries and in highly touristic rich tropical islands,² with a third position of the Netherlands, after Belgium and Denmark. The breast cancer incidence is rising, with a peak in diagnoses between 60 and 70 years.³ In 2016, 14,640 Dutch inhabitants were diagnosed with invasive breast cancer, as compared to 13,402 in 2010 and 8,287 in 1990.⁴ This increasing incidence of breast cancer is largely driven by growth and ageing of the population,⁵ but may also partly be attributed to, for example, enhanced detection by the national breast screening programme⁶ and the change in parity-related risk factors.^{7,8} While breast cancer incidence is growing, mortality rates are declining.³ This decline may predominantly be ascribed to earlier diagnosis, improved diagnostics and to the development of more effective treatment strategies.^{9,10} Although the risk of breast cancer mortality has significantly decreased, 1 in 27 women in the Netherlands will ultimately die from breast cancer,³ implying that we still have a significant part to gain.

Local breast surgery: From Halsted to breast conservation

One of the main pillars of breast cancer treatment in early stage breast cancer, defined as stage I-IIIa disease,¹¹ is resection of the primary tumour. It is impressive to witness the development towards the minimally invasive procedures from today as compared to the era in which Halsted's radical operation was the standard procedure.^{12,13} Halsted's radical operation was at first described in 1894 and included resection of the entire breast, the underlying chest muscles (pectoralis major and minor) and all axillary lymph nodes.¹⁴ This procedure remained the standard surgical procedure for nearly seven decades, whereafter it was replaced by a more conservative procedure in which the underlying muscles were not removed: the modified radical mastectomy.¹⁵ In the past, breast cancer was frequently diagnosed in a more advanced stage and minimally invasive preoperative diagnostic procedures were less developed, making it very challenging to perform less extensive procedures.¹⁴ A large clinical study of Fisher *et al.* starting in 1971 revealed equal survival outcomes for modified radical mastectomies and 'simple' mastectomies (without removal of the axillary lymph nodes),¹⁶ thereby further contributing to evidence for less extensive procedures. Veronesi was the first in the world to state that a mastectomy involved unnecessary mutilation in patients with breast tumours smaller than two centimetres and no palpable axillary nodes. He showed that both Halsted's radical mastectomy and the less invasive quadrantectomy followed by whole breast irradiation, both with axillary dissection, led to similar overall and disease-free survival.¹⁷ Concomitantly, increased patient awareness, better education and developments in the field of imaging resulted in earlier diagnoses.¹⁴ Both the increasing evidence for effectiveness of less mutilating surgical procedures and earlier diagnosis led to a gradual replacement of mastectomy by breast conservation. This transition, however, was marked by a wide variation of uptake.

During the past decades, we witnessed the striking developments in the surgical management of breast cancer, ranging from the studies described in the previous paragraph to paradigm-changing clinical trials in the eighties of the last century that put breast-conserving surgery

permanently on the map. Landmark trials by Van Dongen *et al.*, Fisher *et al.* and Veronesi *et al.* showed that breast-conserving surgery with whole breast irradiation led to equal survival rates when compared to mastectomy.¹⁸⁻²⁰

Trends in breast-conserving surgery versus mastectomy

Because of the ‘mutilation’ and asymmetry caused by mastectomy, as stated by Veronesi,¹⁷ breast-conserving surgery was generally considered as a superior treatment, especially in women with larger breasts. The transition to the use of more conservative surgery was principally made by encouraging surgeons to offer women a choice. More and more surgeons responded, resulting in an increasing rate of breast-conserving surgery over the years.^{21,22} However, especially in the United States, mastectomy rates increased again from 2004 onwards.²³⁻²⁵ First, the increasing use of MRI,²⁶ or increased treatment with skin-sparing mastectomies alongside the possibilities of immediate breast reconstruction may have contributed to this shift.²⁷ Second, there is a better understanding of risk factors that can identify women with a higher risk on recurrences, which may, in combination with fear of recurrent cancer, lead to more mastectomies.²⁸ Third, women with breast cancer are increasingly proactive concerning their health. An increasing network of breast cancer survivors helps current patients to gather more information about disease progression and treatment options. However, it has been reported that women largely overestimate their risk on recurrent cancer,²⁹ which may lead to unnecessary fear and consequently to unnecessary mastectomies. Without neglecting that a patient’s wish should play a paramount role in the shared decision-making process, it is of great importance that patients are well informed to be able to make the optimal treatment choice.

Breast-conserving surgery or mastectomy: randomised trials versus observational studies

The landmark studies in which BCS led to comparable clinical results were all randomised clinical trials (RCTs). In a RCT, patients are randomly allocated to study groups receiving one of several clinical interventions. The act of randomising patients ensures that, on average, all potential influencing factors are equally distributed between the treatment groups. Any significant differences in studied outcomes can consequently be attributed to the clinical intervention.³⁰ A RCT is therefore considered to be the golden standard in assessing the efficacy of new therapies. National guidelines consequently base their treatment recommendations preferably on results of these studies. However, RCTs are less appropriate for the assessment of very rare diseases or specific outcomes, or effects that take a very long time to develop. The latter is particularly the case for breast cancer, as this type of disease has, on average, a high survival rate. RCTs are expensive, and do not always reflect the real-world population due to inclusion of a selected population, which may be intentional (in- and exclusion criteria) or by preference of participating doctors and patients.³⁰ Especially the latter causes problems in interpretation of treatment effects in the real-world breast cancer population, where often emotional factors play a role in decision-making. Patients selected for RCTs are shown to be of limited representative value for the entire target population,³¹ as they tend to be younger, more motivated, and more often present without comorbidities.³²⁻³⁴ Since the breast cancer population is ageing, and older patients more often present with comorbidities, results of RCTs may not hold true in this specific population. Observational studies are, for this reason,

increasingly relied on to fill in the gaps in our knowledge about the correct application of the outcomes of RCTs in the daily population. It has been clearly described that when adequately designed and when properly addressing limitations, observational studies provide valid estimates of the outcomes for a cancer population in a lot of circumstances.³²

After the landmark trials of Van Dongen *et al.*,¹⁸ Fisher *et al.*,¹⁹ and Veronesi *et al.*,²⁰ several observational studies have investigated the effect of breast-conserving surgery versus mastectomy on survival rates in the real-world population.³⁵⁻⁴⁰ All of these studies show at least equal or better survival for patients treated with breast-conserving surgery followed by radiation therapy, as compared to patients treated with mastectomy. Although confounding by severity⁴¹ and residual confounding can never be completely avoided in observational studies, results may support clinical decision-making by showing treatment effects in daily practice, also for patient groups that were not eligible for the mentioned randomised clinical trials. Especially as we still have much to gain, such studies may, in combination with results of RCTs, contribute to increased knowledge about treatment effects in daily practice.

Timing of treatments

Breast cancer treatment rarely consists of surgery alone. The combination of surgery with radiation therapy^{42,43} or systemic therapy,⁴⁴ including targeted treatment,⁴⁵ has been shown to improve overall and disease-free survival rates in several specific patient populations. To further improve survival rates, one can hypothesise that the timing of these therapies is of great importance. Importantly, timing of therapy may not only be related to survival, it may also be related to a patient's quality of life. Psychologically, shorter time intervals between surgery and primary or adjuvant (systemic) therapy may be preferred. On the other hand, it is important to take into account the condition of the patient and other factors including the wound healing process. To make a well-considered decision, the primary question is related to the clinical relevance of the time between subsequent therapies. Several studies have shown that timing of radiation therapy⁴⁶⁻⁴⁸ and chemotherapy⁴⁹⁻⁵¹ is unrelated to survival. However, other studies showed a strong relationship between timing of radiation therapy⁵²⁻⁵⁵ or chemotherapy^{56,57} and survival outcomes. As literature is conflicting, it is of crucial relevance to increase our knowledge about the timing of therapies in breast cancer patients. This will ultimately lead to better quality of care.

Clinical risk predictions

To optimise treatment decision-making in the consultation room, it is of great importance to have specific information regarding a patient's prognosis. Adjuvant systemic therapy has been shown to significantly reduce recurrence and consequently mortality rates.^{9,44} Studies on survival outcomes are important to estimate a patient's prognosis and to eventually advise the optimal (adjuvant) treatment for an individual patient. For breast cancer, a lot of prediction models that estimate survival in case of specific patient-, tumour-, and treatment-related characteristics have been developed in the past decades, of which quite a few are currently used in clinical practice to assist in treatment decision-making.⁵⁸ Validation of prediction models is crucial, as data used for prediction models are often derived from a specific population and are partly gathered in retrospect, meaning that applying such a model on a different population with different characteristics may not self-evidently lead to similar

results. Ideally, a prediction model should be validated on the target population before being used in that specific population. However, only a small fraction of existing prediction models are validated in the Dutch population. One example of such a prediction model is Adjuvant! Online,⁵⁹ which was developed using the Surveillance, Epidemiology and End-Results (SEER) registry, which follows approximately 10% of all breast cancer patients in the United States. Women aged 35 to 59 and diagnosed between 1988 and 1992 were included. This model has been validated on populations from Canada, Asia and Europe.⁶⁰⁻⁶⁴ The Dutch national guidelines advised to use this tool in clinical practice from 2008 on.⁶⁵ However, Adjuvant! Online was only validated in the Dutch population from 2009 on, showing that this prediction model overestimated survival outcomes in patients over 65 years⁶⁶ and in patients younger than 40 years.⁶⁷ This knowledge would possibly have resulted in other adjuvant treatment recommendations. This emphasises the importance of validation of prediction models in the target population before using it in clinical practice. In addition, it is of importance to continue validating models on a regular base to ensure that estimates remain representative for the continuously evolving clinical practice. Next to validation of existing models, it is of high relevance to get insight in novel prognostic and predictive factors that may increase the accuracy of risk predictions. As survival rates do not solely depend on conventional patient, tumour- and treatment-related characteristics, clinical risk predictions may still be optimised in order to further individualise prognostic information, treatment recommendations and follow-up.

Currently, most prediction models for mortality or recurrent breast cancer include age, variables related to severity of disease, receptor status and treatment variables. Variables related to severity of disease may include tumour size, number of positive nodes and histological subtype of the tumour (ductal, lobular or else). Despite similarities in these variables, breast cancer remains a very heterogeneous disease, stressing the need for more advanced tumour classifications that could be used in clinical outcome predictions.⁶⁸ The prognostic and predictive value of the following breast cancer subtypes has been demonstrated in a number of studies: luminal A, luminal B, human epidermal growth factor 2 (HER2) positive and triple negative tumours,⁶⁹⁻⁷¹ which are based on oestrogen, progesterone and HER2 receptor status and grade. To further classify patients into risk groups, and further personalise prognostic information and treatment recommendations, it is essential to gain insight in different mortality and recurrence risks (including local and regional recurrences and distant metastases) according to breast cancer subtypes in specific populations.

Another factor that becomes increasingly important to accurately estimate the prognosis of breast cancer patients, is time since diagnosis. As the incidence of breast cancer is rising and mortality rates are declining,^{3,72} a growing number of breast cancer survivors needs to be informed about their prognosis, not just at diagnosis but also during the years after treatment. Therefore, it is of great significance to get more insight in survival rates, taking into account the number of years a patient survived after diagnosis. This type of information does not only give patients enhanced insights in their prognosis, but it can also provide medical experts a more objective basis to estimate the chance of a patient to remain free of disease.⁷³

Outline of this thesis

This thesis has two aims, both related to survival outcomes in daily practice in the Netherlands. The first is related to the fact that breast surgery remains, notwithstanding that there is a clear trend towards less invasive procedures, currently the mainstay in curative treatment of breast cancer. Therefore, the first aim was to get insight in trends in breast surgery over time, and subsequently to determine the effect of different surgical treatments and timing of postoperative radiation therapy on survival outcomes in daily practice.

Furthermore, only a few risk prediction models used in clinical practice are tested for their accuracy on the Dutch population. Moreover, there is an increasing need to improve individual risk predictions, as there are many more factors that contribute to survival outcomes than the conventional patient-, tumour- and treatment-related characteristics. As a result, the second aim of this study was to validate a frequently used prediction model on the Dutch population, and to further increase our insight in survival rates by taking into account breast cancer subtypes and time since diagnosis.

PART I: Trends and survival in breast surgery and timing of postoperative radiation therapy

Chapter 2 starts with the trends and variation in breast-conserving surgery over time in the Netherlands. **Chapter 3** describes survival outcomes following both types of surgery in T1-2N0-1 stage breast cancer. **Chapter 4** describes similar outcomes in T1-2N2 stage breast cancer, and **Chapter 5** further looks into the previously described effects by including results from death certificates to obtain a more reliable outcome, and by looking into specific prognostic patient-, tumour-, and treatment-related characteristics, thereby identifying several subgroups that may possibly benefit from a certain type of surgery. **Chapter 6**, again, describes survival outcomes following breast-conserving surgery and mastectomy. However, this chapter focuses on the reliability and reproducibility of previously presented results by using different methodological approaches that may deal with several biases related to observational studies. This chapter does not aim at definitively solving the discussions around the respective merits of RCTs vs. observational studies, but contributes to the interpretation of the observational type of studies. **Chapter 7** discusses the results from the previous chapters in light of the advantages and disadvantages of observational studies. Since breast-conserving surgery should be followed by radiation therapy, treatment effects can depend on timing, namely the interval between surgery and radiation. **Chapter 8** looks into one of the quality of care indicators for breast cancer in the Netherlands: patients should be treated with radiation therapy within 35 days following breast-conserving surgery. This chapter explores multiple survival outcomes following different time intervals between surgery and the start of radiation therapy and describes the relevance of the indicator as well as the relevance for the patients.

PART II: Clinical risk prediction in breast cancer

Part II focuses on validation and accuracy of clinical risk predictions. **Chapter 9** deals with one of the main problems in clinical prediction modelling, namely the lack of validation in target populations in which the particular model is used. Here, the online prediction tool PREDICT v. 2.0 is validated in the Dutch breast cancer population, as this model is now frequently

used in the Dutch clinical practice following disabling of the Adjuvant! Online prediction tool. **Chapter 10** focuses on the different risks of mortality and recurrences (local and regional recurrences and distant metastases) according to four different breast cancer subtypes: luminal A, luminal B, HER2 positive and triple negative tumours. **Chapter 11** describes the development and validation of a prediction model estimating the conditional extra risk on mortality, meaning the mortality risk of the patient population divided by the mortality risk of the general population, taking into account the number of years a patient survived. This model was primarily developed to give life insurers more accurate information to base their decision on. Lastly, **Chapter 12** describes recurrence risks and survival outcomes for breast cancer patients who survived several years after diagnosis, in order to further individualise risk predictions for the growing number of breast cancer survivors in the Netherlands.

General discussion and future perspectives

Finally, the results of this thesis will be discussed in light of current clinical practice (**Chapter 13**). This thesis ends with some future perspectives and recommendations.

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PART I

Trends and survival in breast surgery and timing of postoperative radiation therapy

Chapter

2

Chapter 2

Nationwide population-based study of trends and regional variation in breast-conserving treatment for breast cancer

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Abstract**Background**

In 2002, landmark trials stated BCS with radiation therapy to be as safe as mastectomy. However, trends in BCS after 2002 have not yet been described in the Netherlands. This historic population-based study aimed to evaluate trends in breast-conserving surgery (BCS) from 1989-2015 in the Netherlands and within nine geographical regions.

Methods

All women diagnosed in 1989-2015 with primary T1-2N0-1 breast cancer, treated with BCS or mastectomy, were selected from the Netherlands Cancer Registry. Crude and casemix-adjusted percentages of BCS were evaluated within and compared between nine Dutch regions for two time periods: 1989-2002 and 2003-2015. With Joinpoint regression analyses the annual percent change of BCS per region over time was assessed. Second, explanatory variables most probably associated with the choice for initial surgery (e.g. age, T and N stage) were evaluated using multivariable logistic regression.

Results

In total, 202,934 patients were included: 80,200 between 1989-2002, and 120,734 between 2003-2015. During 1989-2002, the mean proportion of BCS was 50.6%, varying significantly from 39.1-71.7% between the nine regions. For most regions, a marked rise in BCS use was observed between 2002-2003. During 2003-2015, the mean proportion of BCS increased to 67.4%, varying significantly between regions from 58.5-75.5%. After casemix correction, significant variation remained.

Conclusions

This large nationwide study shows that the use of BCS increased from 1989-2015 in the Netherlands. However, even after adjustment for explanatory variables, large variation existed between the nine regions. This regional variation underlines the urge for implementation of a uniform treatment and decision-making strategy.

Introduction

RCTs published in 2000 and 2002 showed equivalent long-term survival for stage T1–2 N0–1 breast cancer treated by mastectomy or breast-conserving surgery (BCS) combined with adjuvant radiotherapy (RT).^{1–3} Several observational studies^{4–6} have confirmed these results or shown that BCS with RT might even be more beneficial in specific patient groups. Increased quality of life has been shown after BCS with RT compared with mastectomy,^{7,8} and so breast conservation is currently the preferred treatment option for early breast cancer.⁹

Trends in breast surgery over time have been investigated in several populations, including the USA,^{10–13} South America,¹⁴ Europe^{15–17} and Asia.^{18,19} A trend towards increased use of unilateral and bilateral mastectomies has been reported, particularly in the USA.^{12,13,20} In the Netherlands, an earlier study¹⁵ that included patients diagnosed between 1990 and 2002 in two specific regions reported a decreasing trend in BCS in patients aged less than 50 years, but an increasing trend in those aged 70 years or more, with substantial variation between the two regions. A follow-up nationwide study,²¹ including Dutch patients diagnosed between 1990–2001, showed variation between all nine regions.

Since publication of the landmark trials,^{1–3} trends in BCS in the Netherlands have not been described. In the present study, trends in BCS from 1989 to 2015 in women diagnosed with primary stage T1–2 N0–1 breast cancer were evaluated and compared between all nine regions in the Netherlands.

Methods

All women diagnosed with primary invasive T1–2 N0–1 breast cancer, treated with either BCS or mastectomy in a Dutch hospital between 1989 and 2015, were selected from the nationwide Netherlands Cancer Registry. Patients with stage T1–2 N2 disease were excluded to keep the study population as homogeneous as possible. Data on patient-, tumour- and treatment-related characteristics were registered prospectively by trained data managers. Topography, morphology and grade were coded according to the ICD-O second²² or third²³ edition. Tumour stage was classified according to the TNM system of the UICC fifth,²⁴ sixth²⁵ or seventh²⁶ edition, depending on the year of diagnosis. The definition of N1 changed between the fifth and sixth editions (from 2003 onwards). Therefore, for patients diagnosed with N1 disease before 2003, based on the number of positive lymph nodes, nodal status was retained as N1 (1–3 positive nodes), or changed to N2 (4–9 positive nodes) with consequent exclusion from the analysis.

Statistical analysis

Primary outcomes of the study were crude and case mix-adjusted rates of BCS, which were compared between the nine Dutch regions. These regions were based on the former Comprehensive Cancer Centres in the Netherlands, and were anonymized in terms of the security policy of the Netherlands Comprehensive Cancer Organisation. As a secondary outcome, the most probably explanatory variables associated with initial type of surgery were evaluated. Patients were classified as having received BCS or mastectomy based on the first operation. Case mix-adjusted rates were obtained using multivariable logistic regression, corrected for potential confounding variables, which provided odds ratios with 95

percent confidence intervals. Before 2003, several variables were not registered or used in treatment decision-making, so the analyses were performed for two time periods separately: 1989–2002 and 2003–2015. In the first interval, a correction was applied for age, tumour category, nodal status, tumour laterality, sublocalisation within the breast, grade, histological tumour type, axillary lymph node dissection and adjuvant systemic therapy. In the second interval, correction was applied for the same variables, and also for multifocality, hormone and human epidermal growth factor receptor 2 (HER2) receptor status and targeted therapy (trastuzumab). The linear predictor was calculated for all patients and subsequently averaged for each region and year. A non-parametric test for trends was used to determine whether the trend was significant, and variance-weighted least square regression was used to determine whether this trend varied significantly across the nine regions. In addition, for both crude and case mix-adjusted rates, Joinpoint regression analyses were undertaken to evaluate the annual percentage change²⁷ in BCS per region over time (Joinpoint regression program 4.5.0.1; Statistical Methodology and Applications Branch, Surveillance Research Program, National Cancer Institute, Bethesda, Maryland, USA). Detailed information on the methodology can be found elsewhere.²⁷ Tests were two-sided and $p < 0.050$ was considered as statistically significant. All analyses were carried out in Stata® version 14.1 (StataCorp, College Station, Texas, USA).

Results

A total of 202,934 patients were included, of whom 82,200 were diagnosed in 1989–2002 and 120,734 in 2003–2015. None of the patients received neoadjuvant systemic therapy. BCS was more often performed in patients aged 50–69 years, those with T1 tumours, NO tumours, tumours within outer or inner quadrants of the breast (versus central), grade 1, ductal histology (versus lobular), unifocal tumours, hormone receptor- or HER2-positive tumours, and patients who did not have axillary lymph node dissection or adjuvant systemic therapy. Large variation was present between the regions, for both time periods (Table 1).

Table 1. Adjusted odds ratios with 95% confidence intervals of all characteristics according to type of surgery

Period 1: 1989-2002 (n=82,200)					Period 2: 2003-2015 (n=120,734)			
Characteristics	n	BCS (%)	OR _{adjusted} (95% CI)	p-value	n	BCS (%)	OR _{adjusted} (95% CI)	p-value
Age (years)								
<40	5,986	63.9	1		5,482	57.8	1	
40-49	16,362	58.5	0.81 (0.74-0.88)	<0.001	20,227	67.4	1.62 (1.50-1.74)	<0.001
50-59	20,282	59.9	0.80 (0.73-0.87)	<0.001	32,800	74.1	1.87 (1.74-2.01)	<0.001
60-69	19,399	53.2	0.57 (0.52-0.62)	<0.001	33,483	75.2	1.88 (1.75-2.03)	<0.001
70-79	14,578	33.8	0.26 (0.24-0.29)	<0.001	20,542	62.8	1.06 (0.98-1.15)	0.150
≥80	5,593	14.7	0.09 (0.08-0.10)	<0.001	8,200	27.3	0.27 (0.25-0.30)	<0.001
T stage								
T1	48,181	62.8	1		84,165	75.4	1	
T2	34,019	33.4	0.34 (0.33-0.36)	<0.001	36,569	49.0	0.41 (0.40-0.42)	<0.001

Characteristics	Period 1: 1989-2002 (n=82,200)				Period 2: 2003-2015 (n=120,734)			
	n	BCS (%)	OR _{adjusted} (95% CI)	p-value	n	BCS (%)	OR _{adjusted} (95% CI)	p-value
N stage								
NO	50,311	54.7	1		87,116	71.4	1	
N1	31,889	44.1	0.83 (0.78-0.88)	<0.001	33,618	57.2	1.16 (1.11-1.21)	<0.001
Lateralisation								
Left	42,205	50.5	1		61,939	67.4	1	
Right	39,978	50.8	0.97 (0.93-1.01)	0.119	58,787	67.5	0.99 (0.96-1.02)	0.464
Unknown	17	64.7	na	na	8	50.0	na	na
Sublocalisation								
Outer quadrants	40,216	54.3	1		57,400	71.4	1	
Inner quadrants	15,453	55.3	0.97 (0.92-1.03)	0.296	24,703	71.7	0.96 (0.92-1.00)	0.036
Central parts	6,207	35.7	0.47 (0.44-0.52)	<0.001	8,949	56.4	0.51 (0.48-0.54)	<0.001
Overlapping lesions	18,534	43.7	0.64 (0.60-0.67)	<0.001	27,854	59.3	0.66 (0.64-0.69)	<0.001
Unknown	1,790	49.8	na	na	1,828	63.3	na	na
Grade								
1	6,745	60.1	1		30,143	75.0	1	
2	19,640	51.2	0.78 (0.74-0.84)	<0.001	53,107	66.1	0.93 (0.89-0.97)	<0.001
3	19,603	46.4	0.66 (0.62-0.70)	<0.001	32,380	62.9	0.98 (0.93-1.03)	0.507
Unknown	36,212	50.8	na	na	5,104	66.1	na	na
Histological type								
Ductal	64,594	51.1	1		98,820	68.7	1	
Lobular	8,324	45.1	0.80 (0.72-0.88)	<0.001	11,944	58.4	0.69 (0.66-0.73)	<0.001
Mixed	3,494	46.5	0.70 (0.63-0.78)	<0.001	4,147	59.3	0.81 (0.74-0.88)	<0.001
Other	5,788	55.2	1.06 (0.95-1.17)	0.292	5,823	70.3	1.13 (1.05-1.22)	0.001
Multifocality								
			NA	NA				
No					99,789	72.0	1	
Yes					16,479	39.9	0.24 (0.23-0.25)	<0.001
Unknown					4,466	67.1	na	na
HR status								
			NA	NA				
Positive					81,706	68.7	1	
Mixed					18,675	65.8	0.89 (0.86-0.93)	<0.001
Negative					17,130	63.2	0.71 (0.67-0.76)	<0.001
Unknown					3,223	66.5	na	na

Period 1: 1989-2002 (n=82,200)					Period 2: 2003-2015 (n=120,734)			
Characteristics	n	BCS (%)	OR _{adjusted} (95% CI)	p-value	n	BCS (%)	OR _{adjusted} (95% CI)	p-value
HER2 status			NA	NA				
Negative					88,496	68.8	1	
Unclear					7,474	67.1	1.11 (1.04-1.19)	0.002
Positive					11,982	59.6	0.78 (0.72-0.83)	<0.001
Unknown					12,782	65.2	na	na
Axillary lymph node dissection								
Yes	80,774	50.3	1		34,007	51.2	1	
No	1,426	66.7	2.34 (2.01-2.73)	<0.001	86,727	73.8	2.2 (2.11-2.30)	<0.001
Adjuvant systemic therapy								
None	48,121	55.0	1		50,035	74.3	1	
Endocrine therapy	19,654	38.2	0.85 (0.80-0.91)	<0.001	29,944	60.0	0.83 (0.79-0.87)	<0.001
Chemotherapy	10,501	52.5	0.88 (0.81-0.95)	0.001	12,792	65.9	1.10 (1.02-1.18)	0.014
Both	3,924	54.1	0.87 (0.79-0.96)	0.006	27,963	63.8	0.87 (0.82-0.92)	<0.001
Targeted therapy (trastuzumab)			NA	NA				
Yes					7,247	60.5	1	
No					113,487	67.9	1.04 (0.95-1.14)	0.361
Region								
A	11,721	39.0	1		17,021	69.1	1	
B	5,312	57.1	1.78 (1.63-1.94)	<0.001	10,907	64.5	0.80 (0.75-0.85)	<0.001
C	6,319	71.7	3.20 (2.86-3.57)	<0.001	9,697	71.2	1.15 (1.07-1.23)	<0.001
D	15,493	43.0	1.13 (1.05-1.21)	0.001	21,553	71.8	1.04 (0.99-1.10)	0.148
E	9,147	47.2	1.42 (1.31-1.54)	<0.001	11,784	68.4	0.91 (0.85-0.97)	0.002
F	10,804	49.3	1.44 (1.34-1.55)	<0.001	17,093	59.7	0.65 (0.61-0.69)	<0.001
G	11,992	60.9	2.40 (2.20-2.62)	<0.001	16,441	75.5	1.35 (1.27-1.43)	<0.001
H	3,971	70.5	3.70 (3.29-4.15)	<0.001	6,733	58.5	0.49 (0.46-0.53)	<0.001
I	7,441	42.1	1.11 (1.01-1.21)	0.023	9,505	58.9	0.58 (0.55-0.62)	<0.001

Values in parentheses are 95 percent confidence intervals. BCS, breast-conserving surgery. na, not applicable. NA, not available. *Multivariable logistic regression analysis. An odds ratio above 1.00 indicates a higher chance of BCS, whereas a value below 1.00 indicates a higher chance of mastectomy. Missing values were not included in the analyses. In the earlier time period (1989–2002), multifocality, hormone receptor status, human epidermal growth factor receptor 2 (HER2) status and targeted therapy were not registered routinely or determined in clinical practice, and were therefore not included in the analyses of this interval.

Trends in breast-conserving surgery

During the interval 1989–2002, the mean rate of BCS was 50.6 percent, varying from 39.0 to 71.7 percent between the nine regions (Table 1). From 2003 to 2015, the mean rate of BCS increased to 67.4 percent, still with variation from 58.5 to 75.5 percent between the regions. Figure 1 shows the trends in BCS over the entire 1989–2015 period for the nine regions in the Netherlands, with the national average rate of BCS as reference. Most regions showed an increase in BCS over time, with a marked rise between 2002 and 2003. For regions C and H, BCS decreased over time. For all regions together, the trend over time was significant. Joinpoint regression analysis, separating the trends into different segments, showed that the annual rate of BCS varied over time, within and between the regions. For all regions, except E, there was a significant change in the rate of BCS in one or more segments (Table 2; Supplementary Figures 1–9).

Figure 1. Trends in breast-conserving surgery from 1989–2015 in the Netherlands, for the nine different regions separately (A–I). A non-parametric test for trends over time was performed to determine statistical significance for each region, indicated by p-trend in each figure. In each panel the national average is included as a reference and is indicated with a dashed line.

The trend over time across the different regions was significant (Figure 2). In 1989–2002, large variation between the regions was observed. This remained significant even after correction for variables that could have influenced the choice of BCS. Notably, a decrease in BCS was seen in several regions around 2004, followed by an increase thereafter (Figure 3). Joinpoint regression analysis of the case mix-adjusted BCS rates confirmed the large variation in BCS between regions (Table 2; Supplementary Figures 10–18).

Table 2. Annual percentage change of BCS over time using joinpoint regression analysis, for the nine Dutch regions in the Netherlands

Crude BCS percentage				Casemix-adjusted BCS percentage			
Region	Segment	APC (95% CI)	p-value	Region	Segment	APC (95% CI)	p-value
A	1989-2001	2.9 (1.5 to 4.3)*	<0.05	A	1989-2015	2.2 (1.7 to 2.7)*	<0.05
	2001-2004	15.6 (3.0 to 37.8)	0.1				
	2004-2015	-0.3 (-1.1 to 0.6)	0.5				
B	1989-1995	-3.5 (-6.1 to -0.9)*	<0.05	B	1989-2000	-5.0 (-6.2 to -3.8)*	<0.05
	1995-2013	0.9 (0.3-1.5)*	<0.05		2000-2003	12.1 (-8.3 to 37.1)	0.2
	2013-2015	6.1 (-7.4 to 21.5)	0.4		2003-2015	2.1 (1.1 to 3.2)*	<0.05
C	1989-1992	-0.3 (-1.3 to 0.7)	0.5	C	1989-1991	3.2 (-5.6 to 12.9)	0.5
	1992-1995	-16.3 (-23.9 to -8.0)*	<0.05		1991-1994	-10.2 (-18.0 to -1.7)*	<0.05
	1995-2005	2.6 (1.7 to 3.6)*	<0.05		1994-2002	-1.6 (-2.9 to -0.3)*	<0.05
	2005-2015	-0.7 (-1.4 to 0.0)	0.1		2002-2005	8.3 (-1.3 to 18.8)	0.1
D	1989-2000	1.4 (0.4 to 2.4)*	<0.05	D	2005-2015	0.5 (-0.2 to 1.2)	0.2
	2000-2003	14.4 (0.5 to 30.3)*	<0.05		1989-2001	0.1 (-0.4 to 0.7)	0.6
	2003-2015	0.9 (0.4 to 1.4)*	<0.05		2001-2004	9.2 (0.3 to 18.8)*	<0.05
E	1989-2001	0.3 (-0.6 to 1.2)	0.5	E	2004-2015	0.9 (0.4 to 1.4)*	<0.05
	2001-2004	11.6 (-3.0 to 28.3)	0.1		1989-2015	1.8 (1.3 to 2.3)*	<0.05
	2004-2015	0.4 (-0.2 to 1.1)	0.2				
F	1989-1991	-14.5 (-27.6 to 1.0)	0.1	F	1989-2001	-2.6 (-3.5 to -1.8)*	<0.05
	1991-1997	3.9 (-0.5 to 8.3)	0.1		2001-2004	11.6 (-3.7 to 29.3)	0.1
	1997-2015	1.2 (0.7 to 1.7)*	<0.05		2004-2015	1.6 (0.7 to 2.5)*	<0.05
G	1989-1992	-3.1 (-11.3 to 5.8)	0.5	G	1989-2000	-0.5 (-2.3 to 1.3)	0.5
	1992-1998	5.3 (1.6 to 9.1)*	<0.05		2000-2015	3.0 (1.9 to 4.1)*	<0.05
	1998-2015	0.8 (0.4 to 1.2)*	<0.05				
H	1989-1999	-0.1 (-1.2 to 1.0)	0.9	H	1989-1994	-9.1 (-14.3 to -3.5)*	<0.05
	1999-2011	-2.6 (-3.7 to -1.4)*	<0.05		1994-2015	1.2 (0.5 to 1.9)*	<0.05
	2011-2015	4.2 (-2.0 to 10.7)	0.2				
I	1989-2015	1.8 (0.9 to 2.6)*	<0.05	I	1989-2015	0.6 (0.2 to 1.0)*	<0.05

* = indicates that the annual percent change is significantly different from zero. Abbreviations: BCS = breast-conserving surgery, APC = annual percent change, CI = confidence interval.

Explanatory variables

In 1989–2002 (82,200 patients), increasing age was associated with a decreasing rate of BCS (Table 1). Larger tumour size and presence of positive nodes were also related to a lower rate of BCS. Tumours in central or overlapping parts of the breast were associated with a lower rate of BCS than tumours located in the outer quadrants. Tumour grades 2 and 3 were associated with a lower rate of BCS than grade 1. Patients not treated with axillary lymph node dissection had an approximately 2.3 times higher rate of BCS.

Figure 2. Trends in breast-conserving surgery from 1989-2015 in the Netherlands, for the nine different regions combined. Variance-weighted least squares regression was performed to determine whether variation in surgery over time was statistically significant between the regions, indicated by p-trend.

Figure 3. For casemix adjusted trends in breast-conserving surgery from 1989-2015 in the Netherlands, for the nine different regions combined. Variance-weighted least squares regression was performed to determine whether variation in surgery over time, after casemix correction, was statistically significant between the regions, indicated by p-trend.

Adjuvant treatment with endocrine therapy, chemotherapy or both were associated with a lower rate of BCS. Large variation was observed between regions.

In 2003–2015 (120,734 patients), a significant association persisted between age and BCS in all age categories, except for patients aged 70–79 years (Table 1). Age less than 70 years was related to a significantly higher rate of BCS, whereas the reverse was true for age 80 years and above. Notably, all odds ratios for BCS were higher than in the earlier time period, indicating that BCS was performed more often overall. Larger tumour size remained associated with less BCS. However, in contrast to the earlier time period, the presence of positive lymph nodes was associated with an increased BCS rate. Grade 2 was related to a significantly lower rate of BCS than grade 1. Compared with ductal tumours, tumours with lobular and mixed ductal/lobular histology were associated with less BCS, whereas tumours with other histology were associated with a higher rate of breast conservation. Multifocal tumours were less often treated with BCS. Mixed (oestrogen or progesterone receptor-positive) or negative hormone receptor status was also associated with less BCS. Compared with HER2-negative disease, unclear HER2 status was associated with more BCS, whereas HER2-positive disease was associated with a lower rate of BCS. Similar to the earlier time period, absence of axillary lymph node dissection was associated with a 2.2 times higher rate of BCS. Use of endocrine therapy with or without chemotherapy was associated with a lower rate of BCS compared with no systemic therapy, whereas chemotherapy alone was associated with a higher rate. Patients not treated with anti-HER2 therapy (trastuzumab) had a higher rate of BCS. The variation between regions was smaller in the most recent time period than in 1989–2002.

Ductal carcinoma in situ and use of MRI

Certain variables possibly influencing the BCS rate, such as the presence of ductal carcinoma in situ (DCIS) and use of MRI, were available in the Netherlands Cancer Registry from 2011 onwards. The rates of BCS and mastectomy were approximately similar in patients diagnosed with or without a DCIS component, with a significant variation in type of surgery between the nine regions (data not shown). In the cohort diagnosed from 2011 onwards, 52 percent of the patients had some form of associated DCIS, of whom a large proportion would probably have had calcifications alone.

MRI use could also have influenced mastectomy rates. The distribution of initial type of surgery in patients diagnosed in 2011–2015 in whom MRI was performed was compared with that in patients who did not have MRI. Variation in type of surgery was still observed among the nine regions in both groups; however, the proportion of mastectomies was higher among patients who had MRI (data not shown).

Discussion

This large nationwide study showed increasing use of BCS from 1989 to 2015 among patients with T1–2 N0–1 breast cancer in the Netherlands. Large variations were observed between the nine regions that persisted after adjusting for potential explanatory variables.

These results confirm the findings of a previous study¹⁵ that investigated trends in BCS in the Netherlands from 1990 to 2002, showing that regional variation continued to exist after 2003, albeit to a smaller extent. Interestingly, the rate of BCS increased remarkably between

2002 and 2003, after the publication of two important landmark trials^{1,2} showing that BCS had long-term survival outcomes equivalent to those of mastectomy. This impressive increase was probably not only a result of these trials. The first landmark trial, in which several Dutch hospitals participated, was published in 2000.¹ It was therefore expected that the increase in BCS would have started earlier than the present findings indicated. It thus remains unclear which factors actually caused the shift in 2002–2003. Remarkably, after the marked rise in 2002–2003, a sudden decrease was evident for some regions, after which the trend stabilised again. At the international St Gallen consensus meeting on treatment of primary breast cancer in 2001,²⁸ reconstruction following mastectomy was generally considered to be safe. It may be that this acceptance of immediate breast reconstruction partly contributed to the sudden decrease in BCS. Another reason may be the inspection of several quality indicators by the Health Care Inspectorate in the Netherlands in 2004. One of these indicators was the rate of (unplanned) re-excision following non-radical BCS.²⁹ A sensitivity analysis showed that the rates of re-excision (mastectomy following BCS) differed significantly between the nine regions in 2003. Although the differences were small, it may partly explain the sudden decrease in BCS for some regions after 2003.

Multiple variables were associated with type of initial surgery. Age, tumour grade and region were much stronger predictors of initial surgery type in 1989–2002 than in 2003–2015. This may reflect the implementation of BCS over time,^{1–3} combined with developments in adjuvant treatments and interactions with other factors that increasingly played a role in decision-making, such as hormone and HER2 receptor status. Furthermore, presence of positive lymph nodes was associated with less BCS in the earlier time period, but a higher rate of breast conservation in the more recent interval. This may have been a consequence of the increasing awareness that BCS has survival outcomes comparable to those of mastectomy in patients with one to three positive lymph nodes.

The decreasing variation in surgical approach between the regions over time may be explained by the shift from informal regional consensus-based guidelines of the National Breast Cancer Working Group to the introduction of the first national formal evidence-based guidelines³⁰ in the Netherlands in 2001, which stated that 75 percent of patients with primary operable breast cancer were eligible for BCS. These guidelines and the landmark trials may have contributed to the increase in BCS and the reduced variation between regions over time. Variation was, however, still present, indicative of a lack of full consensus about the indications for initial surgery. In clinical practice, clinicians have to deal not only with patient- and tumour-related characteristics, but also with their own experiences and practical and psychological patient aspects, which may explain part of the variation.

Another potential explanation may be related to the quality indicators of care in Netherlands. The most important surgical indicators are related to reduced positive margins.³¹ Breast conservation itself is not measured or encouraged, which can in part be attributed to the associated patient preferences and performance status. Another explanation for the variation may be related to the distance to RT institutes. Patients who live further from a RT facility may have chosen mastectomy to avoid travelling. Distance to an RT institute was previously reported to be associated independently with the use of mastectomy in patients aged 50 years and over.³² A sensitivity analysis in the present cohort showed that most patients were referred to another site for RT, as most hospitals do not have their own RT

facility. The rate of referral ranged from 62 to 92 percent between the regions. However, these rates did not seem to correlate with the rate of BCS or with the distance to RT facilities (data not shown). Furthermore, as the regions may differ regarding socioeconomic status, an additional sensitivity analysis was performed in which correction was made for a derivative of socioeconomic status, based on postal code at diagnosis. This variable was not significant in the multivariable analyses and was therefore considered not to have influenced the results. One of the most important factors influencing the choice of either BCS or mastectomy is patient preference, most often based on the social context of the patient, which could not be accounted for in this study. In a systematic review of both retrospective and prospective studies on patient-reported factors affecting the choice of BCS or mastectomy, Hamelinck and co-workers³³ noted that the majority of patients reported body image as major factor influencing their choice. Other factors were related to survival and recurrence, treatment (including RT following BCS), psychosocial factors and the opinion of their surgeon. In a letter to the editor, Hamelinck *et al.*³⁴ reported that variation in type of surgery could also be explained by age-related preferences, with younger patients (aged 40–64 years) more often preferring BCS than older patients (aged 65 years or older). However, more than half of the patients in both groups preferred BCS (69 and 56 percent respectively). The authors stated that body image was equally important for older patients as for younger patients, but that for several patients the benefit of breast conservation did not outweigh the possible side-effects and inconvenience of adjuvant treatments such as RT.

Another possible factor influencing the type of surgery may have been the presence of DCIS, which was analysed from 2011 onwards in the present cohort. The rates of BCS and mastectomy were approximately similar for patients with and without DCIS, and significant variation in type of surgery remained between the nine regions. Yerushalmi and colleagues³⁵ showed that only the presence of extensive DCIS was associated with use of mastectomy. MRI has been shown to increase mastectomy rates, especially for ductal cancers,³⁶ which can partly be attributed to its improved detection of extensive DCIS components compared with regular mammograms.³⁷ Here, although the proportion of mastectomies was higher for patients who had MRI, there was still variation in type of surgery among the nine regions. The increasing trend in BCS over time in the Netherlands has also been described in other countries.^{17,19,38,39} However, in the USA, trends toward higher rates of patients eligible for BCS who undergo mastectomy have been reported from the beginning of the 21st century,^{12,13,20} which may be related to increasing use of MRI,³⁶ patient preference, fear of recurrence,²⁰ use of skin-sparing mastectomies combined with immediate breast reconstruction,⁴⁰ and/or the increasing availability of autologous reconstructions.⁴¹ Irrespective of the difference in trends between populations, many patients choose mastectomy for these reasons. Patients undergoing BCS have reported better quality of life than patients undergoing mastectomy^{7,8} and patients favour BCS in terms of body image and social and emotional functioning.⁸ However, those undergoing immediate breast reconstruction following mastectomy reported quality of life similar to that in patients having BCS.⁴² In combination with fear of recurrent cancer, this may explain why some patients opt for mastectomy. The fact that the number of mastectomies is rising in the USA, whereas the opposite is seen in the Netherlands, may possibly be explained by differences in patient involvement in decision-making. In the USA, patient involvement was associated with a higher rate of mastectomy,⁴³ which may largely

be ascribed to the patient's risk perception.⁴⁴ In the Netherlands, two recent studies of patient experiences regarding decisions on timing of chemotherapy⁴⁵ and immediate breast reconstruction⁴⁶ showed that not all patients were made aware of the possibilities of primary chemotherapy and immediate breast reconstruction. Although these studies did not address the choice of BCS or mastectomy, the results suggest that there is much to gain in terms of shared decision-making.

A strength of this study is its population-based character, covering the entire Netherlands as well as an extended time period from 1989 to 2015. Trends in BCS before and after publication of the landmark trials that put BCS on the map could thus be investigated. Another strength is the large number of patients and variables, allowing case-mix correction and providing increasing insight into the variation between the nine regions. However, several unmeasured factors could partly explain the remaining variation. Patient preferences were not investigated, which is a limitation of the study. Furthermore, tumour-to-breast volume ratio, contraindications to RT following BCS and BRCA1/2 mutations were not assessed. Moreover, the degree of patient involvement in surgical decision-making, which could not be accounted for in this study, has been shown to affect the type of initial surgery.⁴³

This study has shown an increase in BCS over time in the Netherlands. A steep rise was seen between 2002 and 2003 following publication of landmark trials in 2000¹ and 2002^{2,3} confirming the safety of BCS, and the introduction of the first consensus-based guidelines³⁰ in 2001 stating that approximately 75 percent of primary operable breast cancers are eligible for BCS. Although use of BCS has been and is still increasing in the Netherlands, there is regional variation even after adjustment for explanatory factors. This variation underlines the need for implementation of a uniform treatment and shared decision-making strategy.

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Supplementary material

Supplementary Figure 1. Joinpoint regression of crude trends in BCS over time for region A

Supplementary Figure 2. Joinpoint regression of crude trends in BCS over time for region B

Supplementary Figure 3. Joinpoint regression of crude trends in BCS over time for region C

Supplementary Figure 4. Joinpoint regression of crude trends in BCS over time for region D

Supplementary Figure 5. Joinpoint regression of crude trends in BCS over time for region E

Supplementary Figure 6. Joinpoint regression of crude trends in BCS over time for region F

Supplementary Figure 7. Joinpoint regression of crude trends in BCS over time for region G

Supplementary Figure 8. Joinpoint regression of crude trends in BCS over time for region

Supplementary Figure 9. Joinpoint regression of crude trends in BCS over time for region I

Supplementary Figure 10. Joinpoint regression of adjusted trends in BCS over time for region A

Supplementary Figure 11. Joinpoint regression of adjusted trends in BCS over time for region B

Supplementary Figure 12. Joinpoint regression of adjusted trends in BCS over time for region C

Supplementary Figure 13. Joinpoint regression of adjusted trends in BCS over time for region D

Supplementary Figure 14. Joinpoint regression of adjusted trends in BCS over time for region E

Supplementary Figure 15. Joinpoint regression of adjusted trends in BCS over time for region F

Supplementary Figure 16. Joinpoint regression of adjusted trends in BCS over time for region G

Supplementary Figure 17. Joinpoint regression of adjusted trends in BCS over time for region H

Supplementary Figure 18. Joinpoint regression of adjusted trends in BCS over time for region I

Chapter

3

Chapter 3

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

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Abstract**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 7,552 (20%) patients, of whom 4,647 (62%) received breast-conserving surgery plus radiotherapy and 2,905 (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.

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 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.

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.

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 Oncology¹⁴ using the tumour, node, and metastasis classification system (International Union Against Cancer 5th edition¹⁵ [2000–02] or 6th edition¹⁶ [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 colleagues¹⁷ 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 (i.e., 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.

Results

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, 2,173 (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 (7,783 [21%] patients), data for recurrences were complete for 7,552 (97%) patients. Of this final 2003 cohort, 4,647 (62%) received breast-conserving surgery plus radiotherapy and 2,905 (38%) received mastectomy. To establish the validity of imputed data, we compared observed values of complete cases with imputed values, which showed similar distributions (Supplementary Table 1). 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).

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 Supplementary Table 2.

Figure 1. Flow diagram 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.

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; Supplementary Table 2). Use of adjuvant chemotherapy was higher in the T1N1 group than in the T1N0 group, but was almost equal for T2N0 and T2N1 (Supplementary Table 2). 4,853 (80%) of 6,092 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 1,130 patients with T1N0 stage cancer in the mastectomy group did not receive adjuvant systemic therapy compared with 2,152 (78%) of 2,761 patients in the breast-conserving surgery group. The characteristics of the 2003 subcohort were similar to those of the 2000–04 cohort (Supplementary Table 3), indicating that it could serve as a representative cohort.

Table 1. Baseline characteristics

Characteristics	Mastectomy (n=15,473)	BCT (n=21,734)
Year of diagnosis*		
2000	3,113 (20.1)	3,909 (18.0)
2001	3,171 (20.5)	4,097 (18.9)
2002	3,128 (20.2)	4,248 (19.6)
2003	3,059 (19.8)	4,724 (21.7)
2004	3,002 (19.4)	4,756 (21.9)
Age (years)*		
<40	929 (6.0)	1,232 (5.7)
40-49	2,618 (16.9)	4,264 (19.6)
50-59	3,465 (22.4)	7,222 (33.2)
60-69	2,989 (19.3)	5,479 (25.2)
70-79	3,346 (21.6)	3,098 (14.3)
>79	2,126 (13.7)	439 (2.0)
SES*		
Low	4,686 (30.3)	6,436 (29.6)
Medium	6,319 (40.8)	8,577 (39.5)
High	4,468 (28.9)	6,721 (30.9)
Hospital volume (patients per year)*		
0-49	3,123 (20.2)	4,654 (21.4)
50-99	7,004 (45.3)	9,085 (41.8)
100-149	3,359 (21.7)	4,924 (22.7)
>149	1,987 (12.8)	3,071 (14.1)
Region*		
A	2,087 (13.5)	3,084 (14.2)
B	1,558 (10.1)	1,606 (7.4)
C	1,100 (7.1)	1,772 (8.2)
D	2,346 (15.2)	4,375 (20.1)
E	1,595 (10.3)	2,192 (10.1)
F	3,031 (19.6)	2,484 (11.4)
G	1,848 (11.9)	3,427 (15.8)
H	832 (5.4)	1,335 (6.1)
I	1,076 (7.0)	1,459 (6.7)

Characteristics	Mastectomy (n=15,473)	BCT (n=21,734)
Lateralisation†		
Left	8,131 (52.6)	11,244 (51.7)
Right	7,340 (47.4)	10,489 (48.3)
Unknown	2 (0.0)	1 (0.0)
Sublocalisation*		
Outer quadrants	7,037 (45.5)	11,574 (53.3)
Inner quadrants	2,780 (18.0)	4,711 (21.7)
Central portion	1,378 (8.9)	1,095 (5.0)
Overlapping lesions	3,918 (25.3)	4,036 (18.6)
Unknown	360 (2.3)	318 (1.5)
Histological tumour type*		
Ductal	11,987 (77.5)	17,876 (82.3)
Lobular	1,830 (11.8)	1,730 (8.0)
Mixed	874 (5.7)	798 (3.7)
Other	782 (5.1)	1,330 (6.1)
Differentiation*		
Grade I	2,365 (15.3)	4,821 (22.2)
Grade II	6,275 (40.6)	8,681 (39.9)
Grade III	4,602 (29.7)	5,343 (24.6)
Unknown	2,231 (14.4)	2,889 (13.3)
Tumour size (mm)*		
Median (IQR)	20 (14-27)	15 (11-20)
Unknown	6,013 (38.9)	7,773 (35.8)
Number of positive nodes*		
Median (IQR)	0 (0-1)	0 (0-1)
Unknown	57 (0.4)	37 (0.2)
Multifocality*		
Yes	1,594 (10.3)	434 (2.0)
No	5,721 (37.0)	9,416 (43.3)
Unknown	8,158 (52.7)	11,884 (54.7)
Hormone receptor status*		
ER and PR +	3,946 (25.5)	6,464 (29.7)
ER or PR+	1,029 (6.7)	1,423 (6.6)
ER and PR –	1,127 (7.3)	1,561 (7.2)
Unknown	9,371 (60.6)	12,286 (56.5)
Adjuvant systemic therapy*		
No	7,505 (48.5)	12,145 (55.9)
Hormonal therapy	4,017 (26.0)	3,834 (17.6)
Chemotherapy	1,864 (12.1)	2,778 (12.8)
Both	2,087 (13.5)	2,977 (13.7)

Characteristics	Mastectomy (n=15,473)	BCT (n=21,734)
Axillary lymph node dissection*		
Yes	10,987 (71.0)	9,852 (45.3)
No	4,486 (29.0)	11,882 (54.7)

Data are n (%) or median (IQR). $p < 0.1$ for comparison between treatment groups was considered significant. BCT = breast-conserving surgery plus radiotherapy. 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.

In the 2000–04 cohort, 16,686 (77%) of 21,734 patients survived in the breast-conserving surgery plus radiotherapy group compared with 9,229 (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 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, 3,686 (79%) of 4,647 patients survived in the breast-conserving surgery plus radiotherapy group compared with 1,840 (63%) of 2,905 in the mastectomy group (Figure 1). Median follow-up was 11.3 years (IQR 10.3–11.7). Kaplan-Meier curves (Supplementary Figure 1) and HRs (Table 2) were similar to those in the entire 2000–04 cohort. In the 2003 subcohort, 509 (11%) of 4,647 patients in the breast-conserving surgery plus radiotherapy group were diagnosed with distant metastases compared with 427 (15%) of 2,905 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 (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 [95% CI: 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 (Supplementary Table 4).

Table 2. 10-year overall survival

2003 cohort (n=7,552)									
2000-04 cohort (n=37,207)					Crude				
Adjusted					Adjusted				
Crude					Crude				
n	HR	p-value	HR	n	HR	p-value	HR	p-value	p-value
Overall cohort									
Mastectomy	15,473	1	1	2,905	1		1		
BCT	21,734	0.51 [0.49-0.53]	<0.0001	4,647	0.81 [0.78-0.85]*	<0.0001	0.50 [0.45-0.54]	<0.0001	0.81 [0.73-0.89]*
Subgroups									<0.0001
T1N0									
Mastectomy	6,092	1	1	1,130	1		1		
BCT	18,860	0.58 [0.55-0.62]	<0.0001	2,761	0.82 [0.77-0.87]*	<0.0001	0.55 [0.48-0.63]	<0.0001	0.79 [0.68-0.91]§
T1N1									0.002
Mastectomy	2,185	1	1	388	1		1		
BCT	3,741	0.60 [0.54-0.66]	<0.0001	738	0.81 [0.73-0.90]*	<0.0001	0.62 [0.48-0.79]	<0.0001	0.79 [0.60-1.03]
T2N0									0.085
Mastectomy	4,174	1	1	772	1		1		
BCT	3,165	0.52 [0.48-0.56]	<0.0001	704	0.82 [0.75-0.90]**	<0.0001	0.54 [0.45-0.64]	<0.0001	0.85 [0.69-1.04]††
T2N1									0.108
Mastectomy	3,022	1	1	615	1		1		
BCT	2,060	0.56 [0.51-0.61]	<0.0001	444	0.80 [0.72-0.88]††	<0.0001	0.59 [0.48-0.72]	<0.0001	0.85 [0.68-1.08]§§

Data in parentheses are 95% CIs. HR=hazard ratio. Cancer stage is indicated by the T and N status. T=tumour. N=node. BCT=breast-conserving surgery plus radiotherapy. *Corrected for age, socioeconomic status, hospital volume, region, sublocalisation of 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, 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.

Figure 2. Unadjusted 10 year overall survival analysis in the 2000-04 cohort ($n=37,207$). (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.

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

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.

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.

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.

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

Distant metastasis-free survival						Relative survival			
Crude analysis			Adjusted analysis			Crude analysis		Adjusted analysis	
n	HR	p-value	HR	p-value	Excess mortality ratio	Excess mortality ratio	p-value	Excess mortality ratio	p-value
Overall cohort									
Mastectomy	2,905	1	1		1	1		1	
BCT	4,647	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	1,130	1	1		1	1		1	
BCT	2,761	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		1	
BCT	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		1	
BCT	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		1	
BCT	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.

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 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 (distant 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 colleagues²³ showed that absence of comorbidities was independently associated with a 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 category⁹ 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 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 now²⁴ 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 colleagues¹² 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 overview³⁰ – 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 effects. 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.

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Supplementary material

Supplementary Table 1. Distribution of key variables before and after multiple imputation

	Cohort 2000-2004 (n=37,207)		Cohort 2003 (n=7,552)	
Variables	Original	Average imputed	Original	Average imputed
Lateralisation				
Left	52.3	52.1	-	-
Right	47.7	47.9	-	-
Sublocalisation				
Outer quadrants	50.5	50.9	51.0	50.8
Inner quadrants	20.7	20.5	20.8	21.3
Central portion	7.1	6.8	7.2	7.0
Overlapping lesions	21.6	21.8	20.9	20.9
Differentiation grade				
Grade I	23.3	22.9	24.1	25.0
Grade II	45.5	46.8	44.5	44.7
Grade III	31.2	30.2	31.4	30.4
Multifocality				
Yes	10.9	11.5	8.6	8.9
No	89.1	88.5	91.4	91.1
Hormone receptor status				
ER and PR +	66.3	65.2	65.5	65.8
ER or PR +	15.6	16.0	16.3	16.5
ER and PR-	18.1	18.8	18.2	17.7
Tumour size (mm) (median [IQR])	17 [12-23]	17 [12-23]	17 [12-23]	17 [12-23]
Number of positive lymph nodes (median [IQR])	0 [0-1]	0 [0-1]	0 [0-1]	0 [0-1]

Numbers are % unless otherwise specified. The imputation was performed using the mi impute chained equation command in STATA®. Percentages and medians displayed are derived from imputed variables only. Abbreviations: ER = estrogen receptor; PR = progesterone receptor; IQR = interquartile range.

Supplementary Table 2. Baseline characteristics of T1-2N0-1 staged breast cancer patients according to type of surgery in the 2000-2004 cohort (n=37,207)

Characteristics	Mastectomy			Breast-conserving surgery plus radiotherapy						
	Overall (n=15,473)	T1N0 (n=6,092)	T1N1 (n=2,185)	T2N0 (n=4,174)	T2N1 (n=3,022)	Overall (n=21,734)	T1N0 (n=12,768)	T1N1 (n=3,741)	T2N0 (n=3,165)	T2N1 (n=2,060)
Year of diagnosis ¹²⁴										
2000	3,113 (20.1)	1,301 (21.4)	420 (19.2)	842 (20.2)	550 (18.2)	3,909 (18.0)	2,313 (18.1)	685 (18.3)	557 (17.6)	354 (17.2)
2001	3,171 (20.5)	1,255 (20.6)	445 (20.4)	904 (21.7)	567 (18.8)	4,097 (18.9)	2,381 (18.7)	723 (19.3)	589 (18.6)	404 (19.6)
2002	3,128 (20.2)	1,236 (20.3)	471 (21.6)	809 (19.4)	612 (20.3)	4,248 (19.6)	2,448 (19.2)	773 (20.7)	608 (19.2)	419 (20.3)
2003	3,059 (19.8)	1,190 (19.5)	410 (18.8)	805 (19.3)	654 (21.6)	4,724 (21.7)	2,811 (22.0)	753 (20.1)	714 (22.6)	446 (21.7)
2004	3,002 (19.4)	1,110 (18.2)	439 (20.1)	814 (19.5)	639 (21.1)	4,756 (21.9)	2,815 (22.1)	807 (21.6)	697 (22.0)	437 (21.2)
Age ¹²³⁴⁵										
<40	929 (6.0)	296 (4.9)	150 (6.9)	248 (5.9)	235 (7.8)	1,232 (5.7)	554 (4.3)	244 (6.5)	248 (7.8)	186 (9.0)
40-49	2,618 (16.9)	854 (14.0)	457 (20.9)	634 (15.2)	673 (22.3)	4,264 (19.6)	2,085 (16.3)	863 (23.1)	758 (24.0)	558 (27.1)
50-59	3,465 (22.4)	1,463 (24.0)	573 (26.2)	776 (18.6)	653 (21.6)	7,222 (33.2)	4,253 (33.3)	1,307 (34.9)	944 (29.8)	718 (34.9)
60-69	2,989 (19.3)	1,451 (23.8)	404 (18.5)	674 (16.2)	460 (15.2)	5,479 (25.2)	3,544 (27.8)	898 (24.0)	684 (21.6)	353 (17.1)
70-79	3,346 (21.6)	1,449 (23.8)	386 (17.7)	999 (23.9)	512 (16.9)	3,098 (14.3)	2,119 (16.6)	377 (10.1)	409 (12.9)	193 (9.4)
>79	2,126 (13.7)	579 (9.5)	215 (9.8)	843 (20.2)	489 (16.2)	439 (2.0)	213 (1.7)	52 (1.4)	122 (3.9)	52 (2.5)
SES ¹³⁴⁵										
Low	4,686 (30.3)	1,821 (29.9)	634 (29.0)	1,319 (31.6)	912 (30.2)	6,436 (29.6)	3,780 (29.6)	1,056 (28.2)	969 (30.6)	631 (30.6)
Medium	6,319 (40.8)	2,473 (40.6)	928 (42.5)	1,688 (40.4)	1,230 (40.7)	8,577 (39.5)	5,083 (39.8)	1,519 (40.6)	1,205 (38.1)	770 (37.4)
High	4,468 (28.9)	1,798 (29.5)	623 (28.5)	1,167 (28.0)	880 (29.1)	6,721 (30.9)	3,905 (30.6)	1,166 (31.2)	991 (31.3)	659 (32.0)
Hospital volume										
(patients per year) ¹²³⁴⁵										
0-49	3,123 (20.2)	1,253 (20.6)	443 (20.3)	841 (20.2)	586 (16.4)	4,654 (21.4)	2,784 (21.8)	824 (22.0)	619 (19.6)	427 (20.7)
50-99	7,004 (45.3)	2,693 (44.2)	972 (44.5)	1,919 (46.0)	1,420 (47.0)	9,085 (41.8)	5,366 (42.0)	1,530 (40.9)	1,369 (43.3)	820 (39.8)
100-149	3,359 (21.7)	1,316 (21.6)	458 (21.0)	902 (21.6)	683 (22.6)	4,924 (22.7)	2,841 (22.3)	844 (22.6)	747 (23.6)	492 (23.9)
>149	1,987 (12.8)	830 (13.6)	312 (14.3)	512 (12.3)	333 (11.0)	3,071 (14.1)	1,777 (13.9)	543 (14.5)	430 (13.6)	321 (15.6)

Mastectomy		Breast-conserving surgery plus radiotherapy								
Characteristics	Overall (n=15,473)	T1N0 (n=6,092)	T1N1 (n=2,185)	T2N0 (n=4,174)	T2N1 (n=3,022)	Overall (n=21,734)	T1N0 (n=12,768)	T1N1 (n=3,741)	T2N0 (n=3,165)	T2N1 (n=2,060)
Region ¹²³⁴⁵										
A	2,087 (13.5)	799 (13.1)	292 (13.4)	567 (13.6)	429 (14.2)	3,084 (14.2)	1,796 (14.1)	544 (14.5)	439 (13.9)	305 (14.8)
B	1,558 (10.1)	623 (10.2)	237 (10.9)	385 (9.2)	313 (10.4)	1,606 (7.4)	944 (7.4)	295 (7.9)	237 (7.5)	130 (6.3)
C	1,100 (7.1)	429 (7.0)	194 (8.9)	249 (6.0)	228 (7.5)	1,772 (8.2)	1,030 (8.1)	343 (9.2)	239 (7.6)	160 (7.8)
D	2,346 (15.2)	955 (15.7)	353 (16.2)	604 (14.5)	434 (14.4)	4,375 (20.1)	2,512 (19.7)	817 (21.8)	600 (19.0)	446 (21.7)
E	1,595 (10.3)	579 (9.5)	217 (9.9)	458 (11.0)	341 (11.3)	2,192 (10.1)	1,301 (10.2)	352 (9.4)	343 (10.8)	196 (9.5)
F	3,031 (19.6)	1,234 (20.3)	407 (18.6)	803 (19.2)	587 (19.4)	2,484 (11.4)	1,489 (11.7)	364 (9.7)	410 (13.0)	221 (10.7)
G	1,848 (11.9)	706 (11.6)	242 (11.1)	554 (13.3)	346 (11.5)	3,427 (15.8)	2,060 (16.1)	577 (15.4)	463 (14.6)	327 (15.9)
H	832 (5.4)	332 (5.5)	126 (5.8)	204 (4.9)	170 (5.6)	1,335 (16.1)	810 (6.3)	223 (6.0)	183 (5.8)	119 (5.8)
I	1,076 (7.0)	435 (7.1)	117 (5.4)	350 (8.4)	174 (5.8)	1,459 (6.7)	826 (6.5)	226 (6.0)	251 (7.9)	156 (7.6)
Lateralisation ⁴										
Left	8,131 (52.6)	3,218 (52.8)	1,154 (52.8)	2,220 (53.2)	1,539 (51.0)	11,244 (51.7)	6,603 (51.7)	1,946 (52.0)	1,601 (50.6)	1,094 (53.1)
Right	7,340 (47.4)	2,874 (47.2)	1,031 (47.2)	1,954 (46.8)	1,481 (49.0)	10,489 (48.3)	6,164 (48.3)	1,795 (48.0)	1,564 (49.4)	966 (46.9)
Unknown	2 (0.0)				2 (0.1)	1 (0.0)	1 (0.0)			
Sublocalisation ¹²³⁴⁵										
Outer quadrants	7,037 (45.5)	2,715 (44.6)	1,039 (47.6)	1,811 (43.4)	1,472 (48.7)	11,574 (53.3)	6,613 (51.8)	2,080 (55.6)	1,699 (53.7)	1,182 (57.4)
Inner quadrants	2,780 (18.0)	1,223 (20.1)	340 (15.6)	798 (19.1)	419 (13.9)	4,711 (21.7)	3,003 (23.5)	669 (17.9)	680 (21.5)	359 (17.4)
Central portion	1,378 (8.9)	492 (8.1)	202 (9.2)	378 (9.1)	306 (10.1)	1,095 (5.0)	620 (4.9)	227 (6.1)	140 (4.4)	108 (5.2)
Overlapping lesions	3,918 (25.3)	1,490 (24.5)	548 (25.1)	1,105 (26.5)	775 (25.7)	4,036 (18.6)	2,319 (18.2)	723 (19.3)	614 (19.4)	380 (18.5)
Unknown	360 (2.3)	172 (2.8)	56 (2.6)	82 (2.0)	50 (1.7)	318 (1.5)	213 (1.7)	42 (1.1)	32 (1.0)	31 (1.5)
Histological tumour type ¹²³⁴⁵										
Ductal	11,987 (77.5)	4,804 (78.9)	1,777 (81.3)	3,061 (73.3)	2,345 (77.6)	17,876 (82.3)	10,388 (81.4)	3,199 (85.5)	2,533 (80.0)	1,756 (85.2)
Lobular	1,830 (11.8)	605 (9.9)	212 (9.7)	616 (14.8)	397 (13.1)	1,730 (8.0)	1,038 (8.1)	246 (6.6)	293 (9.3)	153 (7.4)
Mixed	874 (5.7)	347 (5.7)	140 (6.4)	195 (4.7)	192 (6.4)	798 (3.7)	423 (3.3)	177 (4.7)	111 (3.5)	87 (4.2)
Other	782 (5.1)	336 (5.5)	56 (2.6)	302 (7.2)	88 (2.9)	1,330 (6.1)	919 (7.2)	119 (3.2)	228 (7.2)	64 (3.1)

Characteristics	Mastectomy		Breast-conserving surgery plus radiotherapy							
	Overall (n=15,473)	T1N0 (n=6,092)	T1N1 (n=2,185)	T2N0 (n=4,174)	T2N1 (n=3,022)	Overall (n=21,734)	T1N0 (n=12,768)	T1N1 (n=3,741)	T2N0 (n=3,165)	T2N1 (n=2,060)
Differentiation ¹²³⁴										
Grade I	2,365 (15.3)	1,270 (20.9)	384 (17.6)	440 (10.5)	271 (9.0)	4,821 (22.2)	3,479 (27.3)	787 (21.0)	337 (10.7)	218 (10.6)
Grade II	6,275 (40.6)	2,526 (41.5)	892 (40.8)	1,643 (39.4)	1,214 (40.2)	8,681 (39.9)	5,067 (39.7)	1,633 (43.7)	1,142 (36.1)	839 (40.7)
Grade III	4,602 (29.7)	1,327 (21.8)	615 (28.2)	1,527 (36.6)	1,133 (37.5)	5,343 (24.6)	2,424 (18.9)	860 (23.0)	1,297 (41.0)	762 (37.0)
Unknown	2,231 (14.4)	969 (15.9)	294 (13.5)	564 (13.5)	404 (13.4)	2,889 (13.3)	1,798 (14.1)	461 (12.3)	389 (12.3)	241 (11.7)
Tumour size (mm) ¹²³⁴⁵										
Median (IQR)	20 (14-27)	14 (10-17)	15 (12-18)	27 (24-32)	28 (25-35)	15 (11-20)	12 (9-15)	15 (12-17)	25 (22-29)	25 (22-29)
Unknown	6,013 (38.9)	2,489 (40.9)	835 (38.2)	1,614 (38.7)	1,075 (35.6)	7,773 (35.8)	4,630 (36.3)	1,310 (35.0)	1,137(35.9)	696 (33.8)
Number of positive nodes ¹³⁵										
Median (IQR)	0 (0-1)	0 (0-0)	1 (1-2)	0 (0-0)	1 (1-2)	0 (0-1)	0 (0-0)	1 (1-2)	0 (0-0)	1 (1-2)
Unknown	57 (0.4)		22 (1.0)		35 (1.2)	37 (0.2)		23 (0.6)		14 (0.7)
Multifocality ¹²³⁴⁵										
Yes	1,594 (10.3)	666 (10.9)	297 (13.6)	332 (8.0)	299 (9.9)	434 (2.0)	250 (2.0)	82 (2.2)	62 (2.0)	40 (1.9)
No	5,721 (37.0)	2,198 (36.1)	711 (32.5)	1,618 (38.8)	1,193 (39.5)	9,416 (43.3)	5,543 (43.4)	1,530 (40.9)	1,446 (45.7)	897 (43.5)
Unknown	8,158 (52.7)	3,228 (53.0)	1,177 (53.9)	2,224 (53.3)	1,529 (50.6)	11,884 (54.7)	6,975 (54.6)	2,129 (56.9)	1,660 (52.4)	1,123 (54.4)
Hormone receptor status ¹²⁴⁵										
ER and PR +	3,946 (25.5)	1,522 (25.0)	627 (28.7)	957 (22.9)	840 (27.8)	6,464 (29.7)	3,855 (30.2)	1,200 (32.1)	768 (24.8)	138 (6.7)
ER or PR+	1,029 (6.7)	410 (6.7)	131 (6.0)	259 (6.2)	229 (7.6)	1,423 (6.6)	840 (6.6)	225 (6.0)	237 (7.5)	674 (32.7)
ER and PR-	1,127 (7.3)	345 (5.7)	124 (5.7)	402 (9.6)	256 (8.5)	1,561 (7.2)	772 (6.1)	199 (5.3)	411 (13.0)	472 (22.9)
Unknown	9,371 (60.6)	3,815 (62.6)	1,303 (59.6)	2,556 (61.2)	1,697 (56.2)	12,286 (56.5)	7,301 (57.2)	2,117 (56.6)	1,731 (54.7)	776 (37.7)

	Mastectomy		Breast-conserving surgery plus radiotherapy							
	Overall	T1N0	T1N1	T2N0	T2N1	Overall	T1N0	T1N1	T2N0	T2N1
Characteristics	(n=15,473)	(n=6,092)	(n=2,185)	(n=4,174)	(n=3,022)	(n=21,734)	(n=12,768)	(n=3,741)	(n=3,165)	(n=2,060)
Adjuvant systemic therapy ¹²³⁴⁵										
No	7,505 (48.5)	4,853 (79.7)	330 (15.1)	1,984 (47.5)	338 (11.2)	12,145 (55.9)	10,128 (79.3)	472 (12.6)	1,407 (44.5)	138 (6.7)
Hormonal therapy	4,017 (26.0)	650 (10.7)	934 (42.8)	1,149 (27.5)	1,284 (42.5)	3,834 (17.6)	1,064 (8.3)	1,475 (39.5)	620 (19.6)	674 (32.7)
Chemotherapy	1,864 (12.1)	357 (5.9)	346 (15.8)	630 (15.1)	531 (17.6)	2,778 (12.8)	962 (7.5)	619 (16.6)	725 (22.9)	472 (22.9)
Both	2,087 (13.5)	232 (3.8)	575 (26.3)	411 (9.9)	869 (28.8)	2,977 (13.7)	614 (4.8)	1,174 (31.4)	413 (13.1)	776 (37.7)
Axillary lymph node dissection ¹²³⁴⁵										
Yes	10,987 (71.0)	3,348 (55.0)	2,082 (95.3)	2,647 (63.4)	2,910 (96.3)	9,852 (45.3)	3,734 (29.2)	3,321 (88.8)	921 (29.1)	1,876 (91.1)
No	4,486 (29.0)	2,744 (45.0)	103 (4.7)	1,527 (36.6)	112 (3.7)	11,882 (54.7)	9,034 (70.8)	420 (11.2)	2,244 (70.9)	184 (8.9)

Numbers are n (%) unless otherwise specified. Abbreviations: SES = social economic status; ER = estrogen receptor; PR = progesterone receptor; IQR = interquartile range. ¹ = significant difference between treatment groups in overall analysis, $p < 0.1$; ² = significant difference between treatment groups in T1N0 analysis, $p < 0.1$; ³ = significant difference between treatment groups in T1N1 analysis, $p < 0.1$; ⁴ = significant difference between treatment groups in T2N0 analysis, $p < 0.1$; ⁵ = significant difference between treatment groups in T2N1 analysis, $p < 0.1$

Supplementary Table 3. Baseline characteristics of T1-2N0-1 staged breast cancer patients according to type of surgery in the 2003 cohort (n=7,552)

Characteristics	Mastectomy		Breast-conserving surgery plus radiotherapy							
	Overall (n=2,905)	T1N0 (n=1,130)	T1N1 (n=388)	T2N0 (n=772)	T2N1 (n=615)	Overall (n=4,647)	T1N0 (n=2,761)	T1N1 (n=738)	T2N0 (n=704)	T2N1 (n=444)
Age ¹²³⁴⁵										
<40	189 (6.5)	59 (5.2)	34 (8.8)	49 (6.4)	47 (7.6)	236 (5.1)	105 (3.8)	39 (5.3)	52 (7.4)	40 (9.0)
40-49	528 (18.2)	170 (15.0)	94 (24.2)	120 (15.5)	144 (23.4)	916 (19.7)	462 (16.7)	167 (22.6)	171 (24.3)	116 (26.1)
50-59	630 (21.7)	267 (23.6)	99 (25.5)	138 (17.9)	126 (20.5)	1,641 (35.3)	971 (35.2)	265 (35.9)	226 (32.1)	179 (40.3)
60-69	559 (19.2)	282 (25.0)	58 (15.0)	128 (16.6)	91 (14.8)	1,144 (24.6)	729 (26.4)	199 (27.0)	155 (22.0)	61 (13.7)
70-79	593 (20.4)	247 (21.9)	68 (17.5)	175 (22.7)	103 (16.8)	621 (13.4)	449 (16.3)	59 (8.0)	74 (10.5)	39 (8.8)
>79	406 (14.0)	105 (9.3)	35 (9.0)	162 (21.0)	104 (16.9)	89 (1.9)	45 (1.6)	9 (1.2)	26 (3.7)	9 (2.0)
SES ¹³⁴⁵										
Low	920 (31.7)	351 (31.1)	116 (29.9)	260 (33.7)	193 (31.4)	1,347 (29.0)	793 (28.7)	202 (27.4)	226 (32.1)	126 (28.4)
Medium	1,165 (40.1)	470 (41.6)	156 (40.2)	277 (35.9)	262 (42.6)	1,849 (39.8)	1,113 (40.3)	302 (40.9)	254 (36.1)	180 (40.5)
High	820 (28.2)	309 (27.4)	116 (29.9)	235 (30.4)	160 (26.0)	1,451 (31.2)	855 (31.0)	234 (31.7)	224 (31.8)	138 (31.1)
Hospital volume										
(patients per year) ¹²³⁴⁵										
0-49	509 (17.5)	215 (19.0)	64 (16.5)	118 (15.3)	112 (18.2)	848 (18.3)	512 (18.5)	132 (17.9)	116 (16.5)	88 (19.8)
50-99	1,424 (49.0)	547 (48.4)	194 (50.0)	388 (50.3)	295 (48.0)	2,114 (45.5)	1,274 (46.1)	339 (45.9)	322 (45.7)	179 (40.3)
100-149	602 (20.7)	209 (18.5)	73 (18.8)	174 (22.5)	146 (23.7)	1,057 (22.8)	606 (22.0)	175 (23.7)	171 (24.3)	105 (23.7)
>149	370 (12.7)	159 (14.1)	57 (14.7)	92 (11.9)	62 (10.1)	628 (13.5)	369 (13.4)	92 (12.5)	95 (13.5)	72 (16.2)

Mastectomy			Breast-conserving surgery plus radiotherapy							
Characteristics	Overall (n=2,905)	T1N0 (n=1,130)	T1N1 (n=388)	T2N0 (n=772)	T2N1 (n=615)	Overall (n=4,647)	T1N0 (n=2,761)	T1N1 (n=738)	T2N0 (n=704)	T2N1 (n=444)
Region ¹²³⁴⁵	363 (12.5)	137 (12.1)	39 (10.1)	111 (14.4)	76 (12.4)	644 (13.9)	392 (14.2)	90 (12.2)	97 (13.8)	65 (14.6)
A	279 (9.6)	117 (10.4)	34 (8.8)	70 (9.1)	58 (9.4)	356 (7.7)	215 (7.8)	49 (6.6)	65 (9.2)	27 (6.1)
B	201 (6.9)	75 (6.6)	26 (6.7)	47 (6.1)	53 (8.6)	389 (8.4)	219 (7.9)	83 (11.3)	51 (7.2)	36 (8.1)
C	489 (16.8)	189 (16.7)	79 (20.4)	118 (15.3)	103 (16.8)	905 (19.5)	522 (18.9)	160 (21.7)	128 (18.2)	95 (21.4)
D	294 (10.1)	112 (9.9)	43 (11.1)	73 (9.5)	66 (10.7)	496 (10.7)	288 (10.4)	80 (10.8)	84 (11.9)	44 (9.9)
E	540 (18.6)	217 (19.2)	74 (19.1)	139 (18.0)	110 (17.9)	525 (11.3)	311 (11.3)	74 (10.0)	92 (13.1)	48 (10.8)
F	379 (13.1)	144 (12.7)	45 (11.6)	112 (14.5)	78 (12.7)	767 (16.5)	473 (17.1)	118 (16.0)	103 (14.6)	73 (16.4)
G	160 (5.5)	66 (5.8)	24 (6.2)	34 (4.4)	36 (5.9)	236 (5.1)	147 (5.3)	39 (5.3)	28 (4.0)	22 (5.0)
H	200 (6.9)	73 (6.5)	24 (6.2)	68 (8.8)	35 (5.7)	329 (7.1)	194 (7.0)	45 (6.1)	56 (8.0)	34 (7.7)
I										
Lateralisation ⁴										
Left	1,561 (53.7)	635 (56.2)	207 (53.4)	406 (52.6)	313 (50.9)	2,423 (52.1)	1,424 (51.6)	389 (52.7)	370 (52.6)	240 (54.1)
Right	1,344 (46.3)	495 (43.8)	181 (46.7)	366 (47.4)	302 (49.1)	2,224 (47.9)	1,337 (48.4)	349 (47.3)	334 (47.4)	204 (46.0)
Sublocalisation ¹²³⁴⁵										
Outer quadrants	1,344 (46.3)	510 (45.1)	201 (51.8)	332 (43.0)	301 (48.9)	2,447 (52.7)	1,422 (51.5)	396 (53.7)	366 (52.0)	263 (59.2)
Inner quadrants	546 (18.8)	254 (22.5)	53 (13.7)	152 (19.7)	87 (14.2)	1,042 (22.4)	672 (24.3)	146 (19.8)	164 (23.3)	60 (13.5)
Central portion	276 (9.5)	94 (8.3)	42 (10.8)	76 (9.8)	64 (10.4)	246 (5.3)	127 (4.6)	56 (7.6)	38 (5.4)	25 (5.6)
Overlapping lesions	697 (24.0)	254 (22.5)	84 (21.7)	200 (25.9)	159 (25.9)	859 (18.5)	507 (18.4)	130 (17.6)	132 (18.8)	90 (20.3)
Unknown	42 (1.5)	18 (1.6)	8 (2.1)	12 (1.6)	4 (0.7)	53 (1.1)	33 (1.2)	10 (1.4)	4 (0.6)	6 (1.4)
Histological tumour type ¹²³⁴⁵										
Ductal	2,267 (78.0)	883 (78.1)	331 (85.3)	553 (71.6)	500 (81.3)	3,809 (82.0)	2,233 (80.9)	633 (85.8)	565 (80.3)	378 (85.1)
Lobular	365 (12.6)	134 (11.8)	27 (7.0)	130 (16.8)	75 (12.2)	384 (8.3)	234 (8.5)	49 (6.6)	68 (9.7)	33 (7.4)
Mixed	123 (4.2)	45 (4.0)	22 (5.7)	28 (3.6)	28 (4.6)	170 (3.7)	88 (3.2)	38 (5.2)	26 (3.7)	18 (4.1)
Other	150 (5.2)	69 (6.1)	8 (2.1)	61 (7.9)	12 (2.0)	284 (6.1)	206 (7.5)	18 (2.4)	45 (6.4)	15 (3.4)

Characteristics	Mastectomy			Breast-conserving surgery plus radiotherapy						
	Overall	T1N0	T1N1	T2N0	T2N1	Overall	T1N0	T1N1	T2N0	T2N1
	(n=2,905)	(n=1,130)	(n=388)	(n=772)	(n=615)	(n=4,647)	(n=2,761)	(n=738)	(n=704)	(n=444)
Differentiation ¹²³⁴										
Grade I	500 (17.2)	264 (23.4)	67 (17.3)	100 (13.0)	69 (11.2)	1,160 (25.0)	848 (30.7)	177 (24.0)	89 (12.6)	46 (10.4)
Grade II	1,230 (42.3)	487 (43.1)	174 (44.9)	321 (41.6)	248 (40.3)	1,839 (39.6)	1,084 (39.3)	319 (43.2)	246 (34.9)	190 (42.8)
Grade III	916 (31.5)	266 (23.5)	119 (30.7)	288 (37.3)	242 (39.5)	1,238 (26.6)	579 (21.0)	181 (24.5)	305 (43.3)	173 (39.0)
Unknown	259 (8.9)	113 (10.0)	28 (7.2)	63 (8.2)	55 (8.9)	410 (8.8)	250 (9.1)	61 (8.3)	64 (9.1)	35 (7.9)
Tumour size (mm) ¹²³⁴⁵										
Median (IQR)	20 (14-26)	14 (10-17)	15 (12-18)	26 (24-32)	28 (25-35)	11 (15-20)	12 (10-16)	15 (12-17)	25 (22-28)	25 (22-30)
Unknown	134 (4.6)	67 (5.9)	18 (4.6)	25 (3.2)	24 (3.9)	194 (4.2)	115 (4.2)	33 (4.5)	26 (3.7)	20 (4.5)
Number of positive nodes ¹³⁵										
Median (IQR)	0 (0-1)	0 (0-0)	1 (1-2)	0 (0-0)	1 (1-2)	0 (0-1)	0 (0-0)	1 (1-2)	0 (0-0)	1 (1-2)
Unknown	19 (0.7)	14 (1.2)	1 (0.3)	3 (0.4)	1 (0.2)	31 (0.7)	21 (0.8)	1 (0.1)	9 (1.3)	
Multifocality ¹²³⁴⁵										
Yes	489 (16.8)	200 (17.7)	91 (23.5)	98 (12.7)	100 (16.3)	129 (2.8)	71 (2.6)	18 (2.4)	32 (4.6)	8 (1.8)
No	2,234 (76.9)	853 (75.5)	271 (69.9)	631 (81.7)	479 (77.9)	4,170 (89.7)	2,474 (89.6)	663 (89.8)	635 (90.2)	398 (89.6)
Unknown	182 (6.3)	77 (6.8)	26 (6.7)	43 (5.6)	36 (5.9)	348 (7.5)	216 (7.8)	57 (7.7)	37 (5.3)	38 (8.6)
Hormone receptor status ¹²⁴⁵										
ER and PR +	1,758 (60.5)	695 (61.5)	263 (67.8)	441 (57.1)	359 (58.4)	3,061 (65.9)	1,856 (67.2)	536 (72.6)	380 (54.0)	289 (65.1)
ER or PR+	509 (17.5)	201 (17.8)	69 (17.8)	128 (16.6)	111 (18.1)	701 (15.1)	411 (14.9)	112 (15.2)	122 (17.3)	56 (12.6)
ER and PR-	542 (18.7)	184 (16.3)	51 (13.1)	178 (23.1)	129 (21.0)	732 (15.8)	377 (13.7)	79 (10.7)	186 (26.4)	90 (20.3)
Unknown	96 (3.3)	50 (4.4)	5 (1.3)	25 (3.2)	16 (2.6)	153 (3.3)	117 (4.2)	11 (1.5)	16 (2.3)	9 (2.0)

	Mastectomy		Breast-conserving surgery plus radiotherapy							
	Overall (n=2,905)	T1N0 (n=1,130)	T1N1 (n=388)	T2N0 (n=772)	T2N1 (n=615)	Overall (n=4,647)	T1N0 (n=2,761)	T1N1 (n=738)	T2N0 (n=704)	T2N1 (n=444)
Adjuvant systemic therapy ¹²³⁴⁵										
No	1,385 (47.7)	891 (78.9)	62 (16.0)	369 (47.8)	63 (10.2)	2,559 (55.1)	2,152 (77.9)	98 (13.3)	287 (40.8)	22 (5.0)
Hormonal therapy	676 (23.3)	112 (9.9)	126 (32.5)	194 (25.1)	244 (39.7)	707 (15.2)	218 (7.9)	250 (33.9)	130 (18.5)	109 (24.6)
Chemotherapy	315 (10.8)	75 (6.6)	41 (10.6)	103 (13.3)	96 (15.6)	507 (10.9)	200 (7.2)	72 (9.8)	150 (21.3)	85 (19.1)
Both	529 (18.2)	52 (4.6)	159 (41.0)	106 (13.7)	212 (34.5)	874 (18.8)	191 (6.9)	318 (43.1)	137 (19.5)	228 (51.4)
Axillary lymph node dissection ¹²³⁴⁵										
Yes	1,864 (64.2)	479 (42.4)	376 (96.9)	416 (53.9)	593 (96.4)	1,716 (36.9)	520 (18.8)	647 (87.7)	136 (19.3)	413 (93.0)
No	1,041 (35.8)	651 (57.6)	12 (3.1)	356 (46.1)	22 (3.6)	2,931 (63.1)	2,241 (81.2)	91 (12.3)	568 (80.7)	31 (7.0)

Numbers are n (%) unless otherwise specified. Abbreviations: SES = social economic status; ER = estrogen receptor; PR = progesterone receptor; IQR = interquartile range. ¹ = significant difference between treatment groups in overall analysis, p<0.1; ² = significant difference between treatment groups in T1N0 analysis, p<0.1; ³ = significant difference between treatment groups in T1N1 analysis, p<0.1; ⁴ = significant difference between treatment groups in T2N0 analysis, p<0.1; ⁵ = significant difference between treatment groups in T2N1 analysis, p<0.1

Supplementary Table 4. Hazard ratios of 10-year distant metastasis-free survival in the 2003 cohort (n=7,552), with different starting points of follow-up.

	Follow-up calculated from last date of surgery		Follow-up calculated from date of diagnosis	
	Adjusted HR [95% CI]	p-value	Adjusted HR [95% CI]	p-value
Overall cohort				
Mastectomy	1		1	
BCT	0.88 [0.77-1.01] ^a	0.070	0.88 [0.77-1.02] ^a	0.081
Subgroups				
T1N0				
Mastectomy	1		1	
BCT	0.74 [0.58-0.94] ^b	0.014	0.75 [0.59-0.96] ^b	0.021
T1N1				
Mastectomy	1		1	
BCT	1.00 [0.71-1.42] ^c	0.994	1.00 [0.71-1.43] ^c	0.965
T2N0				
Mastectomy	1		1	
BCT	0.94 [0.72-1.23] ^d	0.644	0.95 [0.72-1.25] ^d	0.711
T2N1				
Mastectomy	1		1	
BCT	0.95 [0.73-1.224] ^e	0.718	0.95 [0.73-1.23] ^e	0.694

p-values depicted in bold are considered significant ($p < 0.025$). ^a = corrected for region, sublocalisation, histological tumour type, differentiation grade, tumour size (mm), number of positive lymph nodes, hormone receptor status, adjuvant systemic therapy. ^b = corrected for age, sublocalisation, histological tumour type, differentiation grade, tumour size (mm), hormone receptor status, adjuvant systemic therapy. ^c = corrected for region, differentiation grade, tumour size (mm). ^d = corrected for age, sublocalisation, histological tumour type, differentiation grade. ^e = corrected for sublocalisation, tumour size (mm), hormone receptor status. Abbreviations: BCT = breast-conserving surgery plus radiotherapy; HR = hazard ratio; CI = confidence interval.

Supplementary Figure 1. Cumulative 10-year overall survival in T1-2N0-1 staged breast cancer patients in the 2003 cohort, in every T and N subgroup (n=7,552). A = Cumulative 10-year overall survival for breast-conserving surgery plus radiotherapy compared to mastectomy in the whole cohort; B = Cumulative 10-year overall survival for T1N0, T1N1, T2N0, T2N1 subgroups separately, independent of type of surgery; C = Cumulative 10-year overall survival for breast-conserving surgery plus radiotherapy compared to mastectomy in the T1N0 subgroup, in the T1N1 subgroup (D), in the T2N0 subgroup (E), and in the T2N1 subgroup (F). BCT = Breast-conserving surgery plus radiotherapy.

Chapter

3

Chapter 3

Supplementary comment

The mastectomy myth

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The mastectomy myth

Webster's dictionary defines a myth as "a popular belief that has grown up around something or someone; especially one embodying the ideals and institutions of a society or segment of society".

The National Surgical Adjuvant Breast Project (NSABP B-06) and the Milan Cancer Institute first published results of prospective randomised trials^{1,2} comparing mastectomy with breast conservation surgery plus radiotherapy, demonstrating equivalent results in the mid-1980s. 20 year follow-up continued to show no differences in disease-free survival, distant metastasis-free survival, or overall survival.^{3,4} Other similar clinical trials followed these two practice-changing trials and confirmed their results. But a parallel literature also arose, noting that use of mastectomy for early-stage breast cancer was rising, and patients with no apparent contradictions to breast conservation surgery plus radiotherapy continued to choose mastectomy.

What is behind the mastectomy myth? It was clear that senior breast surgeons 30 years ago felt strongly that results from those early studies would not hold up with longer follow-up, and patients opting for breast conservation surgery plus radiotherapy were at higher risk for breast cancer recurrences. Even after the 20 year results were made available, Morrow and colleagues published a study⁵ based on tumour registry data from the American College of Surgeons, documenting that "despite strong evidence supporting the use of breast conservation surgery plus radiotherapy, the majority of women continue to be treated with mastectomy".

Furthermore, a 2016 article⁶ assessing whether an ideal breast conservation rate exists for the treatment of breast cancer was written in response to the increasing rates of mastectomy; the author questions the "perplexing circumstance", given that "recent studies have demonstrated higher survival rates and improved local control associated with breast conservation surgery plus radiotherapy". How much more evidence is needed to convince doctors and patients that breast conservation surgery plus radiotherapy is the better choice for early-stage breast cancer?

A study by Marissa van Maaren and colleagues⁷ published in *The Lancet Oncology* documents strong reasons to debunk the mastectomy myth. The study looks at outcomes for all women in the Netherlands diagnosed with T1–2, N0–1, M0 breast cancer, from 2000 to 2004. Breast conservation surgery plus radiotherapy was compared with mastectomy without radiation in the analysis of a comprehensive national database, which enabled comparable-stage groups to be examined. For patients treated in 2003, the investigators analysed distant metastasis-free survival and specific causes of death, yielding accurate results for breast cancer-specific survival for women treated with both treatment modalities. Relative survival in the Netherlands population was used in the estimates, and patients were matched for age and year. These biostatistics techniques largely overcome a weakness in the study, namely that the two groups had different patient and treatment characteristics.

With 10 years of follow-up, after adjusting for confounding, overall survival of the breast conservation surgery plus radiotherapy group was better for all stages of cancer than that for patients who underwent mastectomy (hazard ratio [HR] 0.81, 95% CI:0.78-0.85; $p<0.0001$). Similar results were seen for patients with all cancer stage subgroups studied (T1N0, T1N1, T2N0, T2N1) in the overall cohort. In the study's 2003 subcohort, patients with T1N0 stage cancer also had better breast cancer-specific survival when treated with breast conservation surgery plus radiotherapy than with mastectomy; differences were not significant in patients with other stages of cancer. The results confirm older randomised trials, and more recent registry-based studies, and the statistical methodology and inclusion of all women should address many of the concerns with both registry studies and applicability of randomised data to the general population.

The mastectomy myth probably started with surgeons several decades ago, and it continues to be a popular belief with patients. Fisher and colleagues⁸ administered a questionnaire to 332 women who opted for mastectomy from 2006 to 2010, aimed at understanding why patients chose the more aggressive surgery; all respondent groups indicated that “lower recurrence risk and improved survival” were the leading reasons that they chose mastectomy.

Will the Netherlands study finally be viewed by all specialties in the medical community as conclusive evidence that breast conservation surgery plus radiotherapy provides women with stage 1 breast cancer a better outcome than mastectomy, provided the patient is not a carrier of mutations in BRCA?

Or will the myth persist? In researching for this Comment, I read the following in a recent magazine story, from a woman with a self-discovered small breast lump. “I have no history in my family and no reason to believe it was breast cancer, but I just knew. Almost as quickly, I made the decision to have a double mastectomy. If I was going to fight, I wanted to face things head on—to be aggressive and get this done”.⁹

A myth supporting an aggressive surgical procedure that is less effective for breast cancer cure than is breast conservation surgery plus radiotherapy should be recognised as an untrue and harmful belief. The evidence is emphatic; those of us responsible for the treatment of women with early-stage breast cancer should communicate this message clearly to our patients.

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Chapter

4

Chapter 4

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

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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 3,071 patients, 1,055 (34.4%) received BCT and 2,016 (65.7%) MAST. BCT and MAST showed equal 10-year OS and RS. After stratification, BCT was significantly associated with improved 10-year OS ($HR_{\text{adjusted}} 0.82$ [95% CI: 0.71-0.96]) and RS ($EMR_{\text{adjusted}} 0.81$ [95% CI: 0.67-0.97]) in T2N2, but not in T1N2. Ten-year DMFS was equal for both treatments ($HR_{\text{adjusted}} 0.87$ [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.

Introduction

Randomised 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 3,078 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 tumour. Patients treated in foreign or unknown hospitals (n=1), with undifferentiated tumours (n=2) or macroscopic residual tumour after surgery (n=4) were excluded, leading to 3,071 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 tumour to date of event. Events that occurred within three months after the date of primary diagnosis were considered as synchronous with the primary tumour and were not counted as events.

Statistical analysis

For both the 2000-2004 cohort and the 2003 cohort, patient-, tumour- and treatment-

related characteristics were summarised 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 (Supplementary Table 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 standardisation 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 observation of scaled Schoenfeld residuals over time. Model fits were tested graphically by 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 as statistically significant. In the 2003 cohort, a p -value < 0.05 was considered as statistically significant. All analyses were performed in STATA® 13.1 (StataCorp LP).

Results

The 2000-2004 cohort included 3,071 patients, of which 1,055 patients (34.4%) received BCT and 2,016 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 (Figure 1).

Patient-, tumour-, and treatment-related characteristics

In general, patients in the BCT group more often had small, ductal, unifocal, well-differentiated and hormone receptor positive tumours localised 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 the 2003 subcohort (Supplementary Table 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, 1,464 deaths were identified. In the BCT group, 414 patients (39.2%) died, compared to 1,041 (51.6%) in the MAST group (Figure 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 (Figure 2a,c,d). T2N2 had worse prognosis compared to T2N1 (Figure 2b). Unadjusted 10-

year RS showed a similar pattern (Figure 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 favour 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 favouring BCT over MAST in T2N2 (Table 2).

Figure 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. Abbreviations: MAST = mastectomy with post-operative radiation therapy; BCT = breast conserving surgery with post-operative radiation therapy; DM+ = distant metastasis; DM- = absence of distant metastasis

Table 1. Baseline characteristics of T1-2N2 staged breast cancer patients according to type of surgery (n=3,071)

Characteristics	MAST			BCT	
	Overall (n=2,016)	T1N2 (n=543)	T2N2 (n=1,473)	Overall (n=1,055)	T1N2 (n=504)
Year of diagnosis ¹²³					
2000	365 (18.1)	89 (16.4)	276 (18.7)	189 (17.9)	99 (19.6)
2001	407 (20.2)	102 (18.8)	305 (20.7)	206 (19.5)	113 (22.4)
2002	439 (21.8)	115 (21.2)	324 (22.0)	191 (18.1)	81 (16.1)
2003	402 (19.9)	126 (23.2)	276 (18.7)	211 (20.0)	94 (18.7)
2004	403 (20.0)	111 (20.4)	292 (19.8)	258 (24.5)	117 (23.2)
Age ¹²³					
<40	204 (10.1)	57 (10.5)	147 (10.0)	93 (8.8)	41 (8.1)
40-49	549 (27.2)	134 (24.7)	415 (28.2)	289 (27.4)	129 (25.6)
50-59	509 (25.3)	143 (26.3)	366 (24.9)	348 (33.0)	181 (35.9)
60-69	329 (16.3)	96 (17.7)	233 (15.8)	184 (17.4)	92 (18.3)
70-79	271 (13.4)	83 (15.3)	188 (12.8)	119 (11.3)	52 (10.3)
>79	154 (7.6)	30 (5.5)	124 (8.4)	22 (2.1)	9 (1.8)
SES					
Low	619 (30.7)	170 (31.3)	449 (30.5)	314 (29.8)	143 (28.4)
Medium	793 (39.3)	209 (38.5)	584 (39.7)	423 (40.1)	205 (40.7)
High	604 (30.0)	164 (30.2)	440 (29.9)	318 (30.1)	156 (31.0)
Hospital volume (patients per year) ¹					
0-49	388 (19.3)	107 (19.7)	281 (19.1)	218 (20.7)	107 (21.2)
50-99	885 (43.9)	253 (46.6)	632 (42.9)	435 (41.2)	206 (40.9)
100-149	461 (22.9)	116 (21.4)	345 (23.4)	223 (21.1)	107 (21.2)
>149	282 (14.0)	67 (12.3)	215 (14.6)	179 (17.0)	84 (16.7)
Region ¹²³					
A	262 (13.0)	66 (12.2)	196 (13.3)	161 (15.3)	78 (15.5)
B	171 (8.5)	45 (8.3)	126 (8.6)	60 (5.7)	23 (4.6)
C	135 (6.7)	35 (6.5)	100 (6.8)	79 (7.5)	41 (8.1)
D	352 (17.5)	104 (19.2)	248 (16.8)	234 (22.2)	116 (23.0)
E	207 (10.3)	41 (7.6)	166 (11.3)	98 (9.3)	48 (9.5)
F	303 (15.0)	83 (15.3)	220 (14.9)	124 (11.8)	59 (11.7)
G	284 (14.1)	73 (13.4)	211 (14.3)	161 (15.3)	83 (16.5)
H	108 (5.4)	36 (6.6)	72 (4.9)	71 (6.7)	35 (6.9)
I	194 (9.6)	60 (11.1)	134 (9.1)	67 (6.4)	21 (4.2)
Lateralisation ¹²					
Left	1,098 (54.5)	313 (57.6)	785 (53.3)	540 (51.2)	255 (50.6)
Right	917 (45.5)	230 (42.4)	687 (46.7)	515 (48.8)	249 (49.4)
Unknown	1 (0.1)		1 (0.1)		

Characteristics	MAST			BCT	
	Overall (n=2,016)	T1N2 (n=543)	T2N2 (n=1,473)	Overall (n=1,055)	T1N2 (n=504)
Sublocalisation ¹²³					
Outer quadrants	1,004 (50.8)	269 (50.6)	735 (50.9)	652 (63.1)	307 (62.7)
Inner quadrants	237 (12.0)	66 (12.4)	171 (11.8)	151 (14.6)	77 (15.7)
Central portion	188 (9.5)	42 (7.9)	146 (10.1)	49 (4.7)	24 (4.9)
Overlapping lesions	547 (27.7)	155 (29.1)	392 (27.2)	182 (17.6)	82 (16.7)
Unknown	40 (2.0)	11 (2.0)	29 (2.0)	21 (2.0)	14 (2.8)
Histological tumour type ¹³					
Ductal	1,619 (80.3)	448 (44.8)	1,171 (79.5)	900 (85.3)	429 (85.1)
Lobular	253 (12.6)	62 (6.2)	191 (13.0)	84 (8.0)	38 (7.5)
Other	144 (7.1)	33 (3.3)	111 (7.5)	71 (6.7)	37 (7.3)
Differentiation ¹²					
Grade I	136 (7.9)	52 (11.2)	84 (6.7)	110 (12.0)	68 (16.0)
Grade II	707 (41.1)	200 (43.0)	507 (40.4)	383 (41.8)	187 (44.0)
Grade III	876 (51.0)	213 (45.8)	663 (52.9)	424 (46.2)	170 (40.0)
Unknown	297 (14.7)	78 (14.4)	219 (14.9)	138 (13.1)	79 (15.7)
Tumour size (mm) ¹²³⁴⁵					
Median (25 – 75%)	25 (20-35)	17 (14-19)	30 (25-38)	21 (16-25)	16 (14-18)
Unknown (%)	798 (39.6)	207 (38.1)	591 (40.1)	379 (35.9)	194 (38.5)
Number of positive nodes ¹³⁵					
Median (25 – 75%)	6 (4-7)	5 (4-7)	6 (4-7)	5 (4-7)	5 (4-6)
Unknown (%)	14 (0.7)	2 (0.4)	12 (0.8)	5 (0.5)	2 (0.4)
Multifocality ¹²³					
Yes	251 (27.8)	85 (33.6)	166 (25.5)	41 (8.5)	22 (9.9)
No	653 (72.2)	168 (66.4)	485 (74.5)	441 (91.5)	201 (90.1)
Unknown	1,112 (55.2)	290 (53.4)	822 (55.8)	573 (54.3)	281 (55.8)
Hormone receptor status ¹²					
ER and PR +	479 (58.4)	137 (58.1)	342 (58.6)	311 (67.6)	150 (70.1)
ER or PR+	148 (18.1)	45 (19.1)	103 (17.6)	70 (15.2)	30 (14.0)
ER and PR-	193 (23.5)	54 (22.9)	139 (23.8)	79 (17.2)	34 (15.9)
Unknown	1,196 (59.3)	307 (56.5)	889 (60.4)	595 (56.4)	290 (57.5)
(Neo-)adjuvant systemic therapy ¹²³					
No	107 (5.3)	24 (4.4)	83 (5.6)	41 (3.9)	19 (3.8)
Hormonal therapy	489 (24.3)	141 (26.0)	348 (23.6)	199 (18.9)	98 (19.4)
Chemotherapy	534 (26.5)	142 (26.2)	392 (26.6)	260 (24.6)	127 (25.2)
Both	886 (44.0)	236 (43.5)	650 (44.1)	555 (52.6)	260 (51.6)

Numbers are n (%) unless otherwise specified. Abbreviations: 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). 1 = significant difference between treatment groups in overall analysis, p<0.1; 2 = significant difference between treatment groups in T1N2 analysis, p<0.1; 3 = significant difference between treatment groups in T2N2 analysis, p<0.1

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 (Figure 1a,b). Median follow-up times to first distant metastasis and death were 8.1 and 11.1 years, respectively.

Figure 2. Cumulative 10-year overall survival in T1-2N2 staged breast cancer patients in the 2000-2004 cohort ($n=3,071$). 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. Abbreviations: MAST = mastectomy with post-operative radiation therapy; BCT = breast conserving surgery with post-operative radiation therapy

Kaplan-Meier analysis showed increased 10-year DMFS for BCT compared to MAST (Figure 4a). Ten-year DFMS was higher for T1N2 than T2N2 (Figure 4b). In T1N2, 10-year DMFS was not significantly different between BCT and MAST (Figure 4c), while BCT showed significantly better 10-year DMFS compared to MAST in T2N2 (Figure 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 two years after diagnosis, followed by two smaller peaks around five and nine years after diagnosis, especially in T2N2 (Supplementary Figure 1).

Figure 3. Cumulative 10-year relative survival in T1-2N2 staged breast cancer patients in the 2000-2004 cohort (n=3,071). 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. Abbreviations: 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.

Table 2. Hazard ratios and excess mortality ratios of breast conserving therapy vs. mastectomy on 10-year overall and relative survival in T1-2N2 staged breast cancer patients in the 2000-2004 cohort (n=3,071)

	Mortality				Relative mortality			
	Crude		Adjusted		Crude		Adjusted	
	n	HR [95% CI]	p-value	HR [95% CI]	EMR [95% CI]	p-value	EMR [95% CI]	p-value
Overall cohort ^a								
MAST	2,016	1		1	1		1	
BCT	1,055	0.69 [0.61-0.77]	<0.001	0.88 [0.77-0.99]	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]	0.77 [0.60-1.00]	0.051	0.81 [0.62-1.05]	0.107
T2N2 ^c								
MAST	1,473	1		1	1		1	
BCT	551	0.73 [0.63-0.84]	<0.001	0.82 [0.71-0.96]	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). ^a = corrected for year of diagnosis, age, social economic status, region, lateralisation, sublocalisation, histological tumour type, differentiation grade, tumour 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 = age, sublocalisation, number of positive lymph nodes, adjuvant systemic therapy. Abbreviations: 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.

Figure 4. Cumulative 10-year distant metastasis-free survival in T1-2N2 staged breast cancer patients in the 2000-2004 cohort ($n=3,071$). 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. Abbreviations: MAST = mastectomy with post-operative radiation therapy; BCT = breast conserving surgery with post-operative radiation therapy; DM = distant metastasis-free survival

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 all causes was larger in the MAST than in the BCT group, indicating that more patients in the 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.

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

	n	Crude		Adjusted	
		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 ($p < 0.05$). ^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. Abbreviations: 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

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 ($HR_{\text{adjusted}} 1.57$ [95% CI: 1.12-2.21]) and breast cancer-specific ($HR_{\text{adjusted}} 1.60$ [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 tumours larger than five centimeters with more than 10 involved lymph nodes. These tumours are often considered as contraindication for BCT¹¹ 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 was 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 two, five and/or nine 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 1mm) tumour size and exact number of positive lymph nodes. Since every centimetre in tumour size is associated with an $\pm 10\%$ increase in 15-year mortality,¹⁶ dichotomization of tumour 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 outcomes²⁰, 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 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 is 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 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 favoured 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 generalisability 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 favoured 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.

Conclusions

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.

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Supplementary material

Supplementary Table 1. Distribution of key variables before and after multiple imputation

Variables	Cohort 2000-2004 (n=3,701)		Cohort 2003 (n=594)	
	Original	Average imputed	Original	Average imputed
Lateralisation (%)				
Left	53.5	53.3	-	-
Right	46.5	46.7	-	-
Sublocalisation (%)				
Outer quadrants	54.4	55.0	56.4	55.6
Inner quadrants	14.0	12.9	15.0	14.1
Central portion	8.1	7.9	8.1	8.6
Overlapping lesions	23.5	24.2	20.5	21.7
Differentiation grade (%)				
Grade I	9.2	9.8	10.1	10.4
Grade II	41.4	41.7	40.4	39.2
Grade III	49.3	48.5	49.5	50.5
Multifocality				
Yes	20.5	22.4	19.1	18.1
No	79.5	77.6	80.9	81.9
Hormone receptor status (%)				
ER and PR+	61.5	59.0	58.8	57.4
ER or PR+	16.2	16.6	17.6	19.1
ER and PR-	22.2	24.4	23.5	23.5
Tumour size (mm)				
(median [IQR])	24 [18-31]	24 [18-32]	25 [19-32]	25 [19-32]
Number of positive lymph nodes				
(median [IQR])	5 [4-7]	5 [4-7]	5 [4-7]	5 [4-7]

The imputation was performed using the `mi impute chained equation` command in STATA®. Percentages and medians displayed are derived from imputed variables only. Abbreviations: ER = estrogen receptor; PR = progesterone receptor; IQR = interquartile range

Supplementary Table 2. Baseline characteristics of T1-2N2 staged breast cancer patients according to type of surgery (n=594). Both groups were treated with axillary lymph node dissection and radiation therapy.

Characteristics	MAST			BCT		
	Overall (n=2,016)	pT1N2 (n=543)	pT2N2 (n=1,473)	Overall (n=1,055)	pT1N2 (n=504)	pT2N2 (n=551)
Age ¹²³						
<40	42 (10.8)	12 (9.9)	30 (11.2)	17 (8.3)	7 (7.6)	10 (8.9)
40-49	98 (25.2)	35 (28.9)	63 (23.5)	53 (25.9)	20 (21.7)	33 (29.2)
50-59	94 (24.2)	30 (24.8)	64 (23.9)	75 (36.6)	35 (38.0)	40 (35.4)
60-69	66 (17.0)	19 (15.7)	47 (17.5)	39 (19.0)	21 (22.8)	18 (15.9)
70-79	50 (12.9)	17 (14.1)	33 (12.3)	16 (7.8)	6 (6.5)	10 (8.9)
>79	39 (10.0)	8 (6.6)	31 (11.6)	5 (2.4)	3 (3.3)	2 (1.8)
SES						
Low	111 (28.5)	34 (28.1)	77 (28.7)	67 (32.7)	30 (32.6)	37 (32.7)
Medium	160 (41.1)	53 (43.8)	107 (39.9)	77 (37.6)	38 (41.3)	39 (34.5)
High	118 (30.3)	34 (28.1)	84 (31.3)	61 (29.8)	24 (26.1)	37 (32.7)
Hospital volume (patients per year)						
0-49	65 (16.7)	21 (17.4)	44 (16.4)	35 (17.1)	13 (14.1)	22 (19.5)
50-99	179 (46.0)	55 (45.5)	124 (46.3)	98 (47.8)	48 (52.2)	50 (44.3)
100-149	91 (23.4)	30 (24.8)	61 (22.8)	45 (22.0)	17 (18.5)	28 (24.8)
>149	54 (13.9)	15 (12.4)	39 (14.6)	27 (13.2)	14 (15.2)	13 (11.5)
Region						
A	55 (14.1)	15 (12.4)	40 (14.9)	25 (12.2)	11 (12.0)	14 (12.4)
B	32 (8.2)	9 (7.4)	23 (8.6)	11 (5.4)	3 (3.3)	8 (7.1)
C	26 (6.7)	9 (7.4)	17 (6.3)	14 (6.8)	8 (8.7)	6 (5.3)
D	67 (17.2)	22 (18.2)	45 (16.8)	46 (22.4)	26 (28.3)	20 (17.7)
E	28 (7.2)	6 (5.0)	22 (8.2)	14 (6.8)	9 (9.8)	5 (4.4)
F	63 (16.2)	17 (14.1)	46 (17.2)	38 (18.5)	14 (15.2)	24 (21.2)
G	52 (13.4)	20 (16.5)	32 (11.9)	27 (13.2)	11 (12.0)	16 (14.2)
H	22 (5.7)	9 (7.4)	13 (4.9)	18 (8.8)	7 (7.6)	11 (9.7)
I	44 (11.3)	14 (11.6)	30 (11.2)	12 (5.9)	3 (3.3)	9 (8.0)
Lateralisation						
Left	211 (54.2)	70 (57.9)	141 (52.6)	101 (49.3)	46 (50.0)	55 (48.7)
Right	178 (45.8)	51 (42.2)	127 (47.4)	104 (50.7)	46 (50.0)	58 (51.3)
Sublocalisation ¹²³						
Outer quadrants	195 (51.1)	62 (51.7)	133 (50.8)	130 (64.4)	57 (62.0)	73 (66.4)
Inner quadrants	47 (12.3)	17 (14.2)	30 (11.5)	35 (17.3)	21 (22.8)	14 (12.7)
Central portion	41 (10.7)	9 (7.5)	32 (12.2)	9 (4.5)	3 (3.3)	6 (5.5)
Overlapping lesions	99 (25.9)	32 (26.7)	67 (25.6)	28 (13.9)	11 (12.0)	17 (15.5)
Unknown	7 (1.8)	1 (0.8)	6 (2.2)	3 (1.5)		3 (2.7)

Characteristics	MAST			BCT		
	Overall (n=2,016)	pT1N2 (n=543)	pT2N2 (n=1,473)	Overall (n=1,055)	pT1N2 (n=504)	pT2N2 (n=551)
Histological tumour type ¹³						
Ductal	319 (82.0)	102 (84.3)	217 (81.0)	183 (89.3)	80 (87.0)	103 (91.2)
Lobular	43 (11.1)	10 (8.3)	33 (12.3)	13 (6.3)	7 (7.6)	6 (5.3)
Other	27 (6.9)	9 (7.4)	18 (6.7)	9 (4.4)	5 (5.4)	4 (3.5)
Differentiation ¹³						
Grade I	25 (7.1)	13 (11.8)	12 (5.0)	31 (16.3)	14 (17.5)	17 (15.5)
Grade II	151 (43.0)	51 (46.4)	100 (41.5)	62 (32.6)	32 (40.0)	30 (27.3)
Grade III	175 (49.9)	46 (41.8)	129 (53.5)	97 (51.1)	34 (42.5)	63 (57.3)
Unknown	38 (9.8)	11 (9.1)	27 (10.1)	15 (7.3)	21 (13.0)	3 (2.7)
Tumour size (mm) ¹³						
Median (25 – 75%)	26.5 (20-35)	17 (15-19)	30 (25-40)	22 (17-27)	17 (15-19)	26 (23-30)
Unknown	25 (6.4)	12 (9.9)	13 (4.9)	7 (3.4)	4 (4.4)	3 (2.7)
Number of positive nodes ¹³						
Median (25 – 75%)	5 (4-7)	5 (4-7)	6 (5-7)	5 (4-7)	5 (4-6)	5 (4-7)
Unknown	7 (1.8)		7 (2.6)	4 (2.0)	2 (2.2)	2 (1.8)
Multifocality ¹²³						
Yes	85 (23.4)	34 (30.4)	51 (20.3)	15 (7.7)	7 (8.1)	8 (7.3)
No	278 (76.6)	78 (69.6)	200 (79.7)	181 (92.4)	80 (92.0)	101 (92.7)
Unknown	26 (6.7)	9 (7.4)	17 (6.3)	9 (4.4)	5 (5.4)	4 (3.5)
Hormone receptor status						
ER and PR+	209 (54.7)	65 (55.1)	144 (54.6)	127 (63.8)	60 (65.9)	67 (62.0)
ER or PR+	79 (20.7)	25 (21.2)	54 (20.5)	33 (16.6)	15 (16.5)	18 (16.7)
ER and PR-	94 (24.6)	28 (23.7)	66 (25.0)	39 (19.6)	16 (17.6)	23 (21.3)
Unknown	7 (1.8)	3 (2.5)	4 (1.5)	6 (2.9)	1 (1.1)	5 (4.4)
(Neo-)adjuvant systemic therapy ¹³						
No	18 (4.6)	5 (4.1)	13 (4.9)	5 (2.4)	3 (3.3)	2 (1.8)
Hormonal therapy	92 (23.7)	27 (22.3)	65 (24.3)	30 (14.6)	14 (15.2)	16 (14.2)
Chemotherapy	82 (21.1)	25 (20.7)	57 (21.3)	44 (21.5)	19 (20.7)	25 (22.1)
Both	197 (50.6)	64 (52.9)	133 (49.6)	126 (61.5)	56 (60.9)	70 (62.0)

Abbreviations: MAST = mastectomy; 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 ($p < 0.1$). 1 = significant difference between treatment groups in overall analysis, $p < 0.1$; 2 = significant difference between treatment groups in T1N2 analysis, $p < 0.1$; 3 = significant difference between treatment groups in T2N2 analysis, $p < 0.1$.

Supplementary Figure. 1. Hazard for distant metastasis in T1-2N2 stage breast cancer within 10 years after diagnosis, overall (left panel) and stratified for T category (right panel).

Chapter

5

Chapter 5

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

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Abstract

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.

Introduction

Large randomised 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 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 generalisable.¹¹ A recent observational population-based study of van Maaren *et al.* showed favourable 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 possibly benefit from BCT, subgroup analyses were performed evaluating these prognostic factors separately in relation to BCSS and OS.

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.

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 tumour 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-, tumour-, 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. Tumour 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 tumour, 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 tumour stage, we used clinical tumour 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 10% nuclear staining of the oestrogen 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, 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 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-, tumour- and treatment-related

characteristics were compared between the treatment groups using the Pearson's X² 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 two-sided and a p-value < 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 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 Supplementary Table 1. 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 (Supplementary Table 2). Information on adjuvant systemic therapy for both cohorts in the T1–2N0–1 stages is shown in Supplementary Tables 3 and 4.

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

Characteristics	1999-2005 (n=60,381)		2006-2012 (n=69,311)	
	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)

	1999-2005 (n=60,381)		2006-2012 (n=69,311)		
	Mastectomy	BCT		Mastectomy	BCT
Characteristics	(n=28,968)	(n=31,413)		(n=27,731)	(n=41,580)
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					
No	NA	NA		19,657 (70.9)	38,265 (92.0)
Yes				7,699 (27.8)	2,836 (6.8)
Unknown				375 (1.4)	479 (1.2)
Tumour localisation					
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)
Tumour 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)

	1999-2005 (n=60,381)		2006-2012 (n=69,311)	
Characteristics	Mastectomy (n=28,968)	BCT (n=31,413)	Mastectomy (n=27,731)	BCT (n=41,580)
Hormonal receptor status				
Negative	NA	NA	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				
Negative	NA	NA	22,280 (80.3)	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)	4,760 (17.2)	41,580 (100)
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 (21.9)
Both	5,070 (17.5)	4,889 (15.6)	8,386 (30.2)	9,753 (23.5)
Contralateral breast cancer				
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)
Not available	21,563 (74.4)	22,205 (70.7)	22,614 (81.5)	21,414 (78.0)

BCT = breast-conserving therapy, FU = follow-up, IQR = interquartile range, NA = not available, na = not applicable

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 (Figure 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 (Figure 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 (Figure 3 and Supplementary Table 5). Further stratification in T1–2N0–1 stage breast cancer for age category, systemic therapy and comorbidity showed similar superior survival for the BCT group (Figure 4 and Supplementary Table 6).

Figure 1. Flowchart of included patients and number of events for all cause and breast cancer-related deaths.

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 (Figure 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 (Figure 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 (Figure 3 and Supplementary Table 5) but not in the T1–2N2 stages (Figure 3 and Supplementary Table 5). 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 (Figure 4 and Supplementary Table 6). This superior outcome was present irrespective of hormonal receptor and HER2 status. No significant difference in BCSS was found between BCT and mastectomy in patients <50 years, patients without comorbidity and patients treated with adjuvant chemotherapy (Figure 4 and Supplementary Table 6). With regard to OS, no significant differences between treatments were found in patients aged <40, and those treated with adjuvant chemotherapy (Figure 4 and Supplementary Table 6).

Figure 2. Kaplan-Meier curves for breast cancer-specific survival 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.

Figure 3. Hazard ratios of breast-conserving therapy compared to mastectomy on breast cancer-specific survival 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, 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.

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 RT.⁵ 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 utilisation rate of RT after mastectomy for N1 disease over time, following the publication of level 1 evidence supporting post-mastectomy radiation therapy (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 lateralisation of the tumour did not affect the survival estimates, we conducted a sensitivity analyses in which we stratified the analyses by lateralisation (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 hypothesise 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 (Supplementary Tables 3 and 4). In the current era of personalised 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. An indirect analysis, stratifying for HER2 status, showed the advantage of BCT over MAST in both HER2 positive and negative patients (Supplementary Table 6). 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 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.^{27–29} 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 generalisability 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 generalisability 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 favourable 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 randomised 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 analysed. 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.

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Supplementary material

Supplementary Table 1. Baseline characteristics (n=129,692) [Extension of Table 1 manuscript]

Characteristics	1999-2005 (n=60,381)		2006-2012 (n=69,311)	
	Mastectomy (n=28,968)	BCT (n=31,413)	Mastectomy (n=27,731)	BCT (n=41,580)
Median FU (years)	11.1 (6.1-13.7)	12.0 (10.3-14.1)	5.9 (4.2-7.7)	6.1 (4.4-8.0)
Median age (IQR) at diagnosis, years	62 (50-74)	57 (50-66)	61 (50-73)	59 (51-67)
Vital status (OS)				
Alive	15,008 (51.8)	22,498 (71.6)	22,227 (80.2)	37,878 (91.1)
Death	13,960 (48.2)	8,915 (28.4)	5,504 (19.8)	3,702 (8.9)
Breast cancer-related death	7,320 (25.3)	4,517 (14.4)	2,666 (9.6)	1,841 (4.4)
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				
No	NA	NA	19,657 (70.9)	38,265 (92.0)
Yes			7,699 (27.8)	2,836 (6.8)
Unknown			375 (1.4)	479 (1.2)
Tumour localisation				
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)
Contralateral breast cancer				
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)

BCT=Breast-conserving therapy, FU = follow-up, IQR=interquartile range, OS = overall survival, NA=not available.

Supplementary Table 2. Baseline characteristics for the subgroup with known comorbidity.

Characteristics	1999-2005 (n=16,613)		2006-2012 (n=14,283)	
	Mastectomy (n=7,405)	BCT (n=9,208)	Mastectomy (n=5,117)	BCT (n=9,166)
Median FU (years- IQR)	11.2 (6.3-14.1)	12.0 (10.3-14.4)	6.9 (4.7-8.5)	7.0 (4.8-8.6)
Median age (IQR) at diagnosis, years	60 (49-73)	58 (49-67)	61 (50-73)	60 (51-68)
Age				
<40	492 (6.6)	465 (5.0)	340 (6.6)	330 (3.6)
40-49	1,449 (19.6)	1,876 (20.3)	924 (18.1)	1,549 (16.9)
50-65	2,534 (34.2)	4,270 (46.4)	1,783 (34.8)	4,453 (48.6)
66-75	1,540 (20.8)	2,104 (22.8)	1,062 (20.8)	2,311 (25.2)
>75	1,390 (18.8)	496 (5.4)	1,008 (19.7)	523 (5.7)
Vital status (OS)				
Alive	3,979 (537)	6,586 (71.5)	3,973 (77.6)	8,196 (89.4)
Death	3,426 (46.3)	2,622 (28.5)	1,144 (22.4)	970 (10.6)
Breast cancer-related death	1,845 (24.9)	1,297 (14.1)	551 (10.8)	488 (5.3)
Year of diagnosis				
1999	1,385 (18.7)	1,346 (14.6)	2006 1,096 (21.4)	1,746 (19.0)
2000	1,218 (16.4)	1,316 (14.3)	2007 1,045 (20.4)	1,674 (18.3)
2001	1,033 (14.0)	1,192 (12.9)	2008 1,001 (19.6)	1,649 (18.0)
2002	894 (12.1)	1,084 (11.8)	2009 661 (12.9)	1,007 (11.0)
2003	811 (11.0)	1,200 (13.0)	2010 518 (10.1)	1,014 (11.1)
2004	993 (13.4)	1,459 (15.8)	2011 406 (7.9)	1,027 (11.2)
2005	1,071 (14.5)	1,611 (17.5)	2012 390 (7.6)	1,049 (11.4)
Multifocality	NA	NA		
No			3,693 (72.2)	8,704 (95.0)
Yes			1,338 (26.1)	394 (4.3)
Unknown			86 (1.7)	68 (0.7)
Tumour localisation				
Outer quadrants	3,251 (43.9)	4,855 (52.7)	2,039 (39.8)	4,448 (48.5)
Inner quadrants	1,145 (15.5)	1,877 (20.4)	769 (15.0)	1,936 (21.1)
Central parts	664 (9.0)	400 (4.3)	482 (9.4)	602 (6.6)
Overlapping parts	2,138 (28.9)	1,930 (21.0)	1,754 (34.3)	2,086 (22.8)
Unknown	207 (2.8)	146 (1.6)	73 (1.4)	94 (1.0)
Tumour stage				
T1a	299 (4.0)	350 (3.8)	228 (4.5)	486 (5.3)
T1b	677 (9.1)	1,878 (20.4)	451 (8.8)	1,910 (20.8)
T1c	2,585 (34.9)	4,763 (51.7)	1,947 (38.0)	4,799 (52.4)
T2	3,844 (51.9)	2,217 (24.1)	2,491 (48.7)	1,971 (21.5)

Characteristics	1999-2005 (n=16,613)		2006-2012 (n=14,283)	
	Mastectomy (n=7,405)	BCT (n=9,208)	Mastectomy (n=5,117)	BCT (n=9,166)
Nodal stage				
N0	4,018 (54.3)	6,534 (71.0)	2,938 (57.4)	6,959 (57.9)
N1	2,527 (34.1)	2,279 (24.8)	1,657 (32.4)	1,932 (21.1)
N2	860 (11.6)	395 (4.3)	522 (10.2)	275 (3.0)
Morphology				
Ductal	5,638 (76.1)	7,457 (81)	3,853 (75.3)	7,705 (84.1)
Lobular	898 (12.1)	764 (8.3)	688 (13.4)	684 (7.5)
Other/unknown	869 (11.7)	987 (10.7)	576 (11.3)	777 (8.5)
Differentiation grade				
Grade I	888 (12.0)	1,880 (20.4)	1,044 (20.4)	2,951 (32.2)
Grade II	2,561 (34.6)	3,332 (36.2)	2,305 (45.0)	3,921 (41.7)
Grade III	2,395 (32.3)	2,196 (23.8)	1,534 (30.0)	2,127 (23.2)
Unknown	1,561 (21.1)	1,800 (19.5)	234 (4.6)	267 (2.9)
Hormonal receptor status	NA	NA		
Negative			1,581 (30.9)	1,227 (13.4)
Positive			3,313 (64.7)	7,811 (85.2)
Unknown			223 (4.4)	128 (1.4)
HER2 status	NA	NA		
Negative			4,081 (79.8)	7,896 (86.1)
Positive			787 (15.4)	901 (9.8)
Unknown			249 (4.9)	369 (4.0)
ALND				
No	1,810 (24.4)	4,777 (51.9)	2,456 (48.0)	6,899 (75.3)
Yes	5,595 (75.6)	4,431 (48.1)	2,661 (52.0)	2,267 (24.7)
Radiation therapy				
No	1,563 (21.1)	na	4,213 (82.3)	na
Yes	5,842 (78.9)	9,208 (100)	904 (17.7)	9,166 (100)
Systemic therapy				
None	2,953 (39.6)	5,052 (54.9)	1,551 (30.3)	4,381 (47.8)
Endocrine therapy	1,969 (26.6)	1,572 (17.1)	1,451 (28.4)	1,895 (20.7)
Chemotherapy	1,218 (16.4)	1,300 (14.1)	591 (11.5)	907 (9.9)
Both	1,283 (17.3)	1,284 (13.9)	1,524 (29.8)	1,983 (21.6)
Contralateral breast cancer				
No	6,853 (92.5)	8,599 (93.4)	4,841 (94.6)	5,687 (62.0)
Yes	552 (7.5)	609 (6.6)	276 (5.4)	3,479 (38.0)

BCT = breast-conserving therapy, FU = follow-up, IQR=interquartile range, OS = overall survival, NA = not available, na = not applicable. ALND = axillary lymph node dissection.

Supplementary Table 3. 1999-2005 cohort: Information on adjuvant systemic therapy for the T1-2N0-1 stages per age category

	No systemic therapy	Endocrine therapy	Chemotherapy	Chemotherapy & endocrine therapy
Age categories				
<40				
Mastectomy	281 (18.8)	30 (2.0)	587 (39.2)	600 (40.1)
BCT	412 (26.2)	40 (2.5)	603 (38.3)	520 (33.0)
40-49				
Mastectomy	1,339 (30.5)	189 (4.3)	1,159 (26.4)	1,703 (38.8)
BCT	2,386 (41.8)	248 (4.3)	1,300 (22.8)	1,776 (31.1)
50-65				
Mastectomy	3,576 (41.6)	2,024 (23.6)	1,429 (16.6)	1,559 (18.2)
BCT	8,338 (57.7)	2,532 (17.5)	1,714 (11.9)	1,862 (12.9)
66-75				
Mastectomy	3,327 (57.9)	2,172 (37.8)	180 (3.1)	65 (1.1)
BCT	4,757 (70.1)	1,832 (27.0)	159 (2.3)	39 (0.6)
>75				
Mastectomy	2,942 (53.0)	2,599 (46.8)	*	*
BCT	941 (62.2)	569 (37.6)	*	*

Numbers are n (%). BCT = breast conserving therapy. T = tumour stage, N= Nodal stage. * <10 patients, not further specified based on discretion regulation of the Statistics Netherlands.

Supplementary Table 4. 2006-2012 cohort: Information on adjuvant systemic therapy for the T1-2N0-1 stages per age category

	No systemic therapy	Endocrine therapy	Chemotherapy	Chemotherapy & endocrine therapy
Age categories				
<40				
Mastectomy	165 (10.1)	43 (2.6)	582 (35.7)	841 (51.6)
BCT	225 (15.9)	46 (3.3)	558 (39.5)	582 (41.2)
40-49				
Mastectomy	866 (19.4)	271 (6.1)	763 (17.1)	2,566 (57.5)
BCT	2,001 (29.9)	487 (7.3)	1,173 (17.5)	3,025 (45.2)
50-65				
Mastectomy	2,639 (29.9)	1,644 (18.6)	1,301 (14.7)	3,242 (36.7)
BCT	9,244 (45.7)	3,776 (18.7)	2,234 (11.1)	4,962 (24.5)
66-75				
Mastectomy	2,095 (40.7)	2,415 (47.0)	278 (5.4)	354 (6.9)
BCT	5,713 (56.7)	3,625 (36.0)	334 (3.3)	405 (4.0)
>75				
Mastectomy	2,094 (41.9)	2,889 (57.8)	*	*
BCT	943 (48.7)	986 (50.9)	*	*

Numbers are n (%). BCT = breast conserving therapy. T = tumour stage, N= Nodal stage. * <10 patients, not further specified based on discretion regulation of the Statistics Netherlands.

Supplementary Table 5. Adjusted hazard ratios for overall and breast cancer-specific survival in the entire cohort and stratified by stage

	1999-2005 (n=60,381)				2006-2012 (n=69,311)			
	BCSS		OS		BCSS		OS	
	n	HR	p-value	HR	n	HR	p-value	HR
Entire cohort								
Mastectomy	28,968	1		1	27,731	1		1
BCT	31,413	0.72 (0.69-0.76) [¥]	<0.0001	0.74 (0.71-0.76) [¥]	41,580	0.75(0.70-0.80) [¥]	<0.0001	0.67 (0.64-0.71) [¥]
								<0.0001
NO-1 stages								
T1abN0								
Mastectomy	2,933	1		1	3,216	1		1
BCT	6,348	0.63 (0.53-0.75) [§]	<0.0001	0.76 (0.69-0.84) [§]	9,978	0.68 (0.51-0.90) [§]	0.007	0.65 (0.55-0.77) [§]
								<0.0001
T1cN0								
Mastectomy	6,379	1		1	6,575	1		1
BCT	11,433	0.77 (0.70-0.84) [§]	<0.0001	0.76 (0.72-0.81) [§]	15,798	0.75 (0.64-0.87) [§]	<0.0001	0.68 (0.62-0.75) [§]
								<0.0001
T1N1								
Mastectomy	3,834	1		1	3,827	1		1
BCT	4,994	0.67 (0.63-0.78) [§]	<0.0001	0.74 (0.68-0.80) [§]	6,084	0.82 (0.67-0.99) [§]	0.043	0.69 (0.6-0.79) [§]
								<0.0001
T2N0								
Mastectomy	6,605	1		1	6,194	1		1
BCT	4,423	0.76 (0.69-0.84) [§]	<0.0001	0.756 (0.71-0.82) [§]	5,523	0.77 (0.67-0.89) [§]	<0.0001	0.67 (0.61-0.75) [§]
								<0.0001
T2N1								
Mastectomy	6,021	1		1	5,255	1		1
BCT	2,832	0.69 (0.63-0.76) [§]	<0.0001	0.69 (0.64-0.74) [§]	2,944	0.67 (0.57-0.78) [§]	<0.0001	0.64 (0.57-0.73) [§]
								<0.0001

1999-2005 (n=60,381)						2006-2012 (n=69,311)					
BCSS			OS			BCSS			OS		
n	HR	p-value	HR	p-value	n	HR	p-value	HR	p-value	HR	p-value
N2-stages											
T1-2N2											
Mastectomy	3,196	1			2,644	1				1	
BCT	1,383	0.75 (0.66-0.84)§	<0.0001	0.73 (0.66-0.81)§	<0.0001	1,273	0.85 (0.71-1.02)∅	0.078	0.75 (0.67-0.92)∅	0.003	

HR = hazard ratio (95% CI). 'T' indicated the tumour stage. 'N' indicated the nodal stage. A p-value indicated in bold is considered as statistically significant (p<0.05). §Corrected for age, year of diagnosis, tumour 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, tumour 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.

Supplementary Table 6. Adjusted hazard ratios for overall and breast cancer-specific survival in T1-2N0-1 breast cancer stratified for age, receptor status, systemic therapy and comorbidity.

2006-2012 (n=65,394)									
1999-2005 (n=55,802)					BCSS				
					OS				
	n	HR	p-value	HR	n	p-value	HR	p-value	p-value
Age									
<40									
Mastectomy	1,498	1		1	1,631		1		1
BCT	1,575	0.83 (0.70-0.99) ^y	0.039	0.86 (0.73-1.01) ^y	1,411	0.063	0.84 (0.62-1.15)*	0.278	0.85 (0.63-1.14)**
40-49									
Mastectomy	4,390	1		1	4,466		1		1
BCT	5,710	0.80 (0.72-0.90) ^y	<0.0001	0.83 (0.75-0.92) ^y	6,686	<0.0001	0.91 (0.74-1.12)\$	0.370	0.78 (0.65-0.94)\$
50-65									
Mastectomy	8,588	1		1	8,826		1		1
BCT	14,446	0.73 (0.68-0.79) ^y	<0.0001	0.77 (0.72-0.81) ^y	20,216	<0.0001	0.78 (0.69-0.89)\$	<0.0001	0.75 (0.68-0.82)\$
66-75									
Mastectomy	5,744	1		1	5,142		1		1
BCT	6,787	0.77 (0.70-0.85) ^y	<0.0001	0.79 (0.74-0.84) ^y	10,077	<0.0001	0.72 (0.62-0.85)\$	<0.0001	0.70 (0.63-0.77)\$
>75									
Mastectomy	5,552	1		1	5,002		1		1
BCT	1,512	0.69 (0.60-0.78) ^y	<0.0001	0.68 (0.63-0.73) ^y	1,937	<0.0001	0.66 (0.55-0.79)\$	<0.0001	0.57 (0.51-0.63)\$

2006-2012 (n=65,394)									
1999-2005 (n=55,802)					2006-2012 (n=65,394)				
BCSS		OS		BCSS		OS			
n	HR	p-value	HR	n	HR	p-value	HR	p-value	p-value
Systemic therapy									
None									
Mastectomy	11,465	1	1	7,859	1		1		
BCT	16,834	0.745 (0.70-0.80)¶	<0.0001	18,126	0.66 (0.57-0.75)±	<0.0001	0.65 (0.60-0.71)±	<0.0001	<0.0001
Chemotherapy									
Mastectomy	3,363	1	1	2,933	1		1		
BCT	3,776	0.72 (0.64-0.80)¶	<0.0001	4,304	0.89 (0.75-1.06)±	0.189	0.87 (0.75-1.0)±		0.069
Endocrine therapy									
Mastectomy	7,014	1	1	7,262	1		1		
BCT	5,221	0.69 (0.62-0.75)¶	<0.0001	8,92	0.76 (0.66-0.88)±	<0.0001	0.68 (0.62-0.75)±	<0.0001	<0.0001
Chemotherapy & endocrine therapy									
Mastectomy	3,930	1	1	7,013	1		1		
BCT	4,199	0.83 (0.74-0.94)¶	0.003	8,977	0.85 (0.71-1.02)±	0.079	0.82 (0.7-0.95)±		0.01
Comorbidity#				n=13,486					
No									
Mastectomy	4,625	1	1	2,653	1		1		
BCT	6,655	0.69 (0.62-0.78)⊕	<0.0001	5,519	0.84 (0.67-1.05)⊖	0.123	0.64 (0.54-0.75)⊖	<0.0001	<0.0001
Yes									
Mastectomy	1,920	1	1	1,942	1		1		
BCT	2,158	0.68 (0.57-0.82)⊕	<0.0001	3,372	0.6 (0.48-0.76)⊖	<0.0001	0.53 (0.46-0.62)⊖	<0.0001	<0.0001

1999-2005 (n=55,802)				2006-2012 (n=65,394)			
BCSS		OS		BCSS		OS	
n	HR	p-value	HR	n	HR	p-value	HR
Hormonal receptor status							
Negative							
Mastectomy				4,316	1		1
BCT		NA		5,661	0.83 (0.73-0.95)»	0.007	0.76 (0.69-0.85)»
Positive							
Mastectomy				20,390	1		1
BCT				34,115	0.70 (0.63-0.76)»	<0.0001	0.65 (0.61-0.69)»
HER2 status							
Negative							
Mastectomy				20,243	1		1
BCT		NA		34,875	0.72 (0.66-.78)©	<0.0001	0.66 (0.63-0.70)©
Positive							
Mastectomy				3,663	1		1
BCT				3,943	0.80 (0.66-0.97)©	0.025	0.69 (0.59-0.80)©

HR = hazard ratio (95%CI). 'T' indicated the tumour stage. 'N' indicated the nodal stage. NA = not available. A p-value indicated in bold is considered as statistically significant (p<0.05).

#only one region in the South of the Netherlands. ‡Corrected for year of diagnosis, tumour stage, nodal stage, morphology, differentiation grade, axillary lymph node dissection, systemic therapy and contralateral breast cancer. ¶Corrected for year of diagnosis, tumour stage, nodal stage, morphology, differentiation grade, axillary lymph node dissection and contralateral breast cancer. ΔCorrected for age, year of diagnosis, tumour stage, nodal stage, morphology, differentiation grade, axillary lymph node dissection, systemic therapy and contralateral breast cancer. *Corrected for year of diagnosis, tumour stage, nodal stage, differentiation grade, systemic therapy, contralateral breast cancer, hormonal receptor status and HER2 status. **Corrected for year of diagnosis, tumour stage, nodal stage, differentiation grade, systemic therapy, contralateral breast cancer, hormonal receptor status and HER2 status. §Corrected for year of diagnosis, tumour 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, tumour stage, nodal stage, morphology, differentiation grade, axillary lymph node dissection, contralateral breast cancer, hormonal receptor status, HER2 status and multifocality. ℓCorrected for age, year of diagnosis, tumour 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, tumour 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, tumour stage, nodal stage, morphology, differentiation grade, axillary lymph node dissection, systemic therapy and contralateral breast cancer, HER2 status and multifocality.

Chapter

6

Chapter 6

A comparison of different statistical techniques dealing with confounding in observational research: measuring the effect of breast-conserving therapy and mastectomy on survival

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Abstract**Background**

Propensity trimming, hierarchical modelling and instrumental variable (IV) analysis are examples of statistical techniques dealing with confounding, cluster-related variation or confounding by severity. This study compared outcomes of these techniques to estimate the relationship of breast-conserving therapy (BCT) and mastectomy with 10-year distant metastasis-free survival (DMFS).

Methods

All women diagnosed in 2005 with primary T1-2N0-1 breast cancer treated with BCT or mastectomy were selected from the Netherlands Cancer Registry. Propensity trimming with inverse probability weighting was used to create a more homogeneous group of patients for which the choice for BCT or mastectomy was not self-evident. Hospital of surgery was used as hierarchical level to handle hospital-related variation, and as IV to reduce the effect of unmeasured confounding. All methods were compared with conventional multivariable Cox regression.

Results

Multivariable Cox regression showed higher 10-years DMFS for BCT than mastectomy [HR 0.70 (95% CI: 0.60-82)]. Propensity trimming on the 10th-90th and the 20th-80th percentile of the propensity score distribution showed similar HRs, as was also the case for hierarchical modelling. IV analysis showed no significant difference between BCT and mastectomy on 10-year DMFS in the entire cohort.

Conclusions

Cox regression, propensity trimming and hierarchical modelling do not eliminate unmeasured confounding. IV analysis can, but finding an IV fulfilling all the assumptions was very difficult. Therefore we cannot conclude that BCT or mastectomy has a causal relationship with 10-year DMFS. We emphasise the importance to critically evaluate all model's assumptions, and to be very careful in drawing firm conclusions based on observational research.

Introduction

In the eighties, randomised controlled trials (RCTs) have shown equal survival for breast-conserving surgery with radiation therapy (BCT) and mastectomy,^{1,2} thereby putting BCT for early breast cancer on the map. RCTs are conducted under very strict conditions, in which randomisation is performed to achieve equality between the studied treatment groups regarding the distribution of factors that may affect outcomes. This procedure ensures that the measured effects are real treatment effects and not a result of residual confounding or confounding by severity, resulting in perfect internal validity.³ However, trial populations are, due to their strictly controlled environment, not always representative for the entire target population.⁴ Older patients are largely underrepresented in RCTs,⁵ trial participants have fewer comorbid conditions than the general population and tend to be more motivated,⁶ thereby affecting the generalisability of the results. Due to limited external validity of RCTs, and taking account of the fact that the above mentioned trials have been conducted more than 30 years ago, comparing BCT with mastectomy may lead to different results in the contemporary real-world population. Consequently, multiple observational studies using more recent data have been performed comparing outcomes of both types of surgery in daily practice.⁷⁻¹⁵ Most of these studies showed that BCT led to increased survival outcomes compared to mastectomy. These studies have been subjected to a lot of criticism because of their observational nature. Although observational studies are more representative for the entire population, the choice for a specific type of surgery is largely related not only to patient and tumour characteristics, such as age and tumour size, but also to patient preferences and surgeon recommendations.¹⁶ Results of observational studies may therefore suffer from residual confounding or confounding by severity.¹⁷ In the past years, several statistical methods have been developed dealing with confounding or confounding by severity, including the use of propensity scores (PS)^{18,19} and instrumental variable (IV) analysis.²⁰ Furthermore, there is a lot of variation in initial type of surgery between hospitals,²¹ which may also partly explain survival differences following BCT and mastectomy, and can be solved by using hierarchical modelling.^{22,23}

Propensity trimming

Propensity trimming is a form of PS analysis.¹⁹ A PS is the conditional probability of assignment to a particular treatment given a patient's characteristics. It is a function of all measured confounding variables such that conditional on the PS, the distribution of confounding variables is equal in both treatment groups.¹⁹ PS analyses do not cover the problem of unmeasured confounding. However, by excluding patients in the nonoverlapping parts of the PS distribution, a more homogeneous group will be created allowing us to study a group that, based on measured confounders, is eligible for both treatment types. Further propensity trimming excludes patients who are present in the tails of the PS distribution.¹⁹ In this manner, patients with the highest likelihood of a certain treatment are excluded, resulting in an even more homogeneous population.

Hierarchical modelling

Hierarchically structured data is frequently present in several research disciplines. For instance, when analysing survival in patients treated with either BCT or mastectomy, all patients are

clustered within hospitals. Hierarchical modelling allows us to take dependency of patients within hospitals into account, and corrects in this manner for cluster-related variation.²³

Instrumental variable analysis

An IV is a variable that influences the probability of receiving a particular treatment, but is unrelated to patient characteristics or prognosis. In this way, an IV behaves similar to randomisation and may overcome the problem of unmeasured confounding in observational studies. Rather than comparing two treatment groups, IV analysis compares groups of patients on the level of the IV. For example, if hospital of surgery largely determines the type of treatment and is unrelated to patient characteristics or prognosis, the analysis compares patients on the level of their hospital.²⁴ To imitate randomisation, the IV should meet the following three assumptions: 1)The IV is associated with treatment. 2)The IV has no effect on the outcome, except through its effect on the treatment itself. 3)The IV is independent of unmeasured confounding. These assumptions require very careful justification, as it is unverifiable whether these assumptions are really met.^{25,26}

Aim of the study

This study aimed to compare outcomes of different statistical techniques dealing with measured confounding, cluster-related variation and confounding by severity to estimate the relationship of BCT and mastectomy with 10-year distant metastasis-free survival (DMFS).

Methods

Patients and study design

For this population-based study, all women diagnosed in 2005 with primary invasive T1-2N0-1 breast cancer, treated with BCT or mastectomy in the Netherlands, were selected from the nationwide Netherlands Cancer Registry (NCR). Patient-, tumour-, and treatment-related characteristics were prospectively registered by trained datamanagers. Tumour topography, morphology and grade were coded according to the International Classification of Diseases for Oncology, seventh edition.²⁷ Stage was coded according to the Tumour, Node and Metastasis (TNM) system of the International Union Against Cancer, sixth edition.²⁸ Data on vital status and date of death were derived from the Municipal Personal Records database, completed until February 2017. Data on distant metastases were retrospectively gathered from patient files, and defined according to existing consensus-based definitions for recurrence classification.²⁹

Statistical analysis

Patient-, tumour-, and treatment-related characteristics were summarised and compared between the treatment groups using the Chi-squared or Wilcoxon rank sum tests. To assess the effect of BCT compared to mastectomy on 10-year DMFS we first used the conventional multivariable Cox proportional hazard regression to estimate hazard ratios (HRs) with 95% confidence intervals (CIs), in which we corrected for potential confounding variables differing significantly between the treatment groups ($p < 0.2$). The variables ultimately corrected for were age (<40, 40-49, 50-59, 60-69, 70-79 and ≥ 80 years), geographical region, sublocalisation of the tumour within the breast, histological subtype, differentiation grade, tumour size,

number of positive lymph nodes, multifocality, HER2 status, use and type of adjuvant systemic therapy and axillary lymph node dissection. Results of the three statistical techniques were compared with the results of the Cox model.

For propensity trimming, we first calculated the PS. This was achieved by performing logistic regression with type of treatment as outcome (0=mastectomy, 1=BCT) and the same characteristics as used in the conventional Cox regression as covariates. To verify its accuracy, we assessed the balance of all measured covariates between the treatment groups among quintiles of patients based on the PS distribution. The PS was considered to be accurate when no significant differences were observed between covariates and the treatment variable in each quintile. Trimming was performed by, first, excluding all patients in the nonoverlapping parts of the PS distribution. Like this, we restricted the analysis to observations within a PS that was common to both patients treated with BCT and mastectomy. Subsequently, we applied further trimming at different cut-off points ($0.1 < PS < 0.9$ and $0.2 < PS < 0.8$) to exclude patients present at the tails of the distribution, meaning that patients with the highest chance to be treated with either BCT or mastectomy were excluded. For the remaining patients, multivariable Cox regression was performed in which we applied inverse probability weighting (IPW),³⁰ which weights are based on each individual's probability of receiving a specific treatment given the PS. For continuous variables, the proportional hazards assumption was tested by plotting the scaled Schoenfeld residuals over time and checking these for consistency. For categorical variables, this assumption was tested by plotting the log of the $-\log$ survival function $\{\log[-\log(S(t))]\}$ against the log of the survival time $[\log(t)]$. When this plot showed linear graphs, the proportional hazards assumption was considered to be met. No deviations were found.

Hierarchical modelling was performed using a multilevel mixed-effects parametric survival model (-mestreg- command in STATA) assuming a Weibull distribution, in which we used hospital of surgery ($n=87$) as hierarchical level. This model uses a likelihood ratio test to determine whether the hierarchical level significantly contributes to the model. As the Weibull distribution assumes a parametric form for the distribution of survival time, we tested this assumption by plotting the log of the $-\log$ survival function $\{\log[-\log(S(t))]\}$ against the log of the survival time $[\log(t)]$. No violations were found. In this model, we corrected for all other potential confounding factors as described above.

For IV analyses, pseudo-observations at 10-years for the survival function were generated using the -stpsurv- command in STATA,³¹ accounting for censored data. Subsequently, these pseudo-observations were used in a linear regression analysis (-ivregress-) using the generalised method of moments (GMM) estimator³¹ and hospital of surgery as IV. This resulted in a coefficient indicating the difference in 10-year DFMS between the two types of surgery. Covariates significantly differing among the hospitals of surgery were added to the model. As there is no statistical test that judges the IV's validity, we evaluated it as follows. First, to get insight in the predictive ability of the chosen IV, we verified whether hospital of surgery was related to type of surgery by comparing the percentage of BCTs among the different hospitals (assumption 1). Assumption 2 and 3 could not be tested, but were carefully thought of. Therefore, we observed the distribution of all measured potential confounders in all hospitals, to get insight in the random assignment of the IV, and we evaluated the effect of hospital of surgery on 10-year DMFS.

For all different methodologies, we performed the analysis in the entire cohort and stratified for T and N stage, as both T and N stage are important prognostic factors for survival. A $p\text{-value} < 0.05$ was considered as statistically significant. All analyses were executed in STATA version 14.1.

Results

A total of 10,327 primary nonmetastatic invasive breast cancer patients diagnosed in 2005 and treated with surgery in the Netherlands were identified. Patients with T3-4N2-3 stage breast cancer ($n=1,950$), patients who received radiation therapy following mastectomy ($n=258$), were treated with BCT without radiation therapy ($n=74$), patients with unknown type of surgery ($n=5$), with macroscopic residual disease ($n=3$) or treated in an unknown hospital ($n=1$) were excluded. The final population consisted of 8,036 patients. Baseline characteristics, specified for type of surgery, are shown in Table 1.

Table 1. Patient-, tumour-, and treatment-related characteristics specified for type of surgery

Characteristics	Mastectomy ($n=2,968$)	Breast-conserving therapy ($n=5,068$)	p-value
Age (years)			
<40	162 (5.5)	264 (5.2)	
40-49	498 (16.8)	994 (19.6)	
50-59	692 (23.3)	1,593 (31.4)	
60-69	574 (19.3)	1,385 (27.3)	
70-79	585 (19.7)	719 (14.2)	
≥ 80	457 (15.4)	113 (2.2)	<0.001
Hospital volume			
0-49	426 (14.4)	705 (13.9)	
50-99	1,747 (58.9)	2,881 (56.9)	
100-149	499 (16.8)	937 (18.5)	
150+	296 (10.0)	545 (10.8)	0.132
Region			
A	366 (12.3)	736 (14.5)	
B	309 (10.4)	453 (8.9)	
C	169 (5.7)	387 (7.6)	
D	497 (16.8)	1,003 (19.8)	
E	308 (10.4)	524 (10.3)	
F	547 (18.4)	586 (11.6)	
G	366 (12.3)	743 (14.7)	
H	187 (6.3)	300 (5.9)	
I	219 (7.4)	336 (6.6)	<0.001

Characteristics	Mastectomy (n=2,968)	Breast-conserving therapy (n=5,068)	p-value
T stage			
T1	1,594 (53.7)	3,840 (75.8)	
T2	1,374 (46.3)	1,228 (24.2)	<0.001
Mean tumour size in mm (IQR)	19 (13-26)	15 (11-20)	<0.001
N stage			
N0	1,936 (65.2)	3,852 (76.0)	
N1	1,032 (34.8)	1,216 (24.0)	<0.001
Mean number of positive lymph nodes (IQR)	0 (0-1)	0 (0-0)	<0.001
Lateralisation			
Left	1,537 (51.8)	2,651 (52.3)	
Right	1,431 (48.2)	2,417 (47.7)	<0.001
Sublocalisation			
Outer quadrants	1,308 (44.1)	2,562 (50.6)	
Inner quadrants	496 (16.7)	1,089 (21.5)	
Central parts	293 (9.9)	288 (5.7)	
Overlapping lesions	803 (27.1)	1,053 (20.8)	<0.001
Unknown	68 (2.3)	76 (1.5)	
Histological tumour type			
Ductal	2,231 (75.2)	4,157 (82.0)	
Lobular	400 (13.5)	407 (8.0)	
Mixed	136 (4.5)	157 (3.1)	
Other	193 (6.5)	333 (6.6)	<0.001
Grade			
1	541 (18.2)	1,370 (27.0)	
2	1,340 (45.2)	2,179 (43.0)	
3	925 (31.2)	1,331 (26.3)	<0.001
Unknown	162 (5.5)	188 (3.7)	
Multifocality			
No	2,122 (71.5)	4,653 (91.8)	
Yes	767 (25.8)	317 (6.3)	<0.001
Unknown	79 (2.7)	98 (1.9)	
Hormonal receptor status			
Positive	1,872 (66.4)	3,442 (67.9)	
Mixed	495 (16.7)	775 (15.3)	
Negative	460 (15.5)	774 (15.3)	0.230
Unknown	41 (1.4)	77 (1.5)	

	Mastectomy (n=2,968)	Breast-conserving therapy (n=5,068)	p-value
HER2 status			
Negative	1,977 (66.6)	3,618 (71.4)	<0.001
Unclear	303 (10.2)	443 (8.7)	
Positive	400 (13.5)	560 (11.1)	
Unknown	288 (9.7)	447 (8.8)	
Adjuvant systemic therapy			
None	1,222 (41.2)	2,780 (54.9)	<0.001
Endocrine therapy	832 (28.0)	801 (15.8)	
Chemotherapy	266 (9.0)	516 (10.2)	
Both	648 (21.8)	969 (19.1)	
Targeted therapy (trastuzumab)			
Yes	142 (4.8)	244 (4.8)	0.951
No	2,826 (95.2)	4,824 (95.2)	
Axillary lymph node dissection			
Yes	1,703 (57.4)	1,503 (29.7)	<0.001
No	1,265 (42.6)	3,565 (70.3)	

Numbers are n (%). p-values indicated in bold are considered as statistically significant ($p < 0.05$). Abbreviations: IQR = interquartile range, HER2 = human epidermal growth factor receptor 2.

Multivariable Cox regression

First, we used multivariable Cox regression to estimate 10-year DMFS. As shown in Table 2, 10-year DMFS was higher for BCT than mastectomy [HR 0.70 (95% CI: 0.60-0.82)]. This result held in T1N0 [HR 0.73 (95% CI: 0.56-0.94)], T2N0 [HR 0.52 (95% CI: 0.37-0.73)] and T2N1 stage [HR 0.71 (95% CI: 0.50-0.99)]. In T1N1 stage, BCT was not statistically different from mastectomy [HR 0.84 (95% CI: 0.53-1.34)].

Propensity trimming

The PS distribution for both types of surgery is shown in Figure 1. The median PS (reflecting the probability of receiving a BCT) was 0.72 (interquartile range: 0.48-0.84). The figure shows the different cut-offs on which propensity trimming was performed. No significant differences between the measured confounders and the treatment variable were found among the quintiles of the PS distribution (data not shown).

When using propensity trimming on the nonoverlapping parts of the PS distribution (>0.009597 and <0.9507796), 10 patients were excluded from the analysis. After IPW weighting, similar results were found as in the multivariable Cox regression [HR 0.70 (95% CI: 0.59-0.83)]. In T2N1 stage, the HR was similar to the HR using multivariable Cox regression, although it was nonsignificant [HR 0.71 (95% CI: 0.49-1.02)]. When trimming on the 10th and 90th percentile, IPW weighting resulted in similar outcomes for each T and N stage as in the conventional Cox regression, except for T1N0 in which no significant difference between BCT and mastectomy was observed anymore [HR 0.86 (95% CI: 0.65-1.13)]. Trimming on the 20th

and 80th percentile gave comparable results (Table 2).

Figure 1. Propensity score distribution per type of surgery. The dark triangle (and solid line) indicates exclusion of patients present in the nonoverlapping parts of the distribution. The open triangle (and dashed/dotted line) indicates trimming on 0.1 and 0.9 of the propensity score distribution. The open diamond (and dashed line) indicates trimming on 0.2 and 0.8 of the propensity score distribution.

Hierarchical modelling

Using hospital of surgery as hierarchical level, BCT was associated with higher 10-year DMFS compared to mastectomy in the entire cohort [HR 0.71 (95% CI:0.61-0.83)]. This result was similar in T1N0 stage. Here, hospital of surgery as hierarchical level did not significantly contribute to the model ($p=0.07$), but was included as the p -value may be sensitive to sample size. In T1N1 stage, BCT was not significantly different from mastectomy (HR 0.88 (95% CI:0.56-1.39)). Of note, hospital of surgery as level did not contribute significantly to the model ($p=1.0$). In T2N0 and T2N1, BCT was significantly related to higher 10-year DMFS than mastectomy. Here, hospital of surgery as hierarchical level significantly contributed to the model (Table 2).

IV analysis

We verified that hospital of surgery ($n=87$) was related to treatment (assumption 1): percentages of BCTs varied from 11.8% to 90.6%. We observed lots of variation in patient-, tumour- and treatment-related characteristics, indicating a non-random assignment of the IV, and we observed significant differences among the hospitals in 10-year DMFS (data not shown). An IV analysis with hospital of surgery as IV and type of surgery as independent variable provided a R^2 of almost zero, implying that hospital of surgery explains very little of the

variability in type of surgery. To correct as good as possible for confounding, we additionally corrected for all measured confounders in subsequent IV analyses. The overall analysis showed no significant difference between BCT and mastectomy on 10-year DMFS [-0.05 (95% CI: -0.13-0.04)]. However, after stratifying for T and N stage, a significant difference in favour of BCT on 10-year DMFS was found in T1N1 stage [-0.13 (95% CI:-0.20 to-0.07)].

Table 2. Hazard ratios for BCT versus mastectomy on 10-year DMFS using different statistical techniques

Statistical technique	Subgroup analyses	Treatment	n	HR (95% CI)	p-value
Multivariable Cox regression	Entire cohort	Mastectomy	2,968	1	
		BCT	5,068	0.70 (0.60-0.82)	<0.001
	T1N0	Mastectomy	1,137	1	
		BCT	3,052	0.73 (0.56-0.94)	0.016
	T1N1	Mastectomy	457	1	
		BCT	788	0.84 (0.53-1.34)	0.464
	T2N0	Mastectomy	799	1	
		BCT	800	0.52 (0.37-0.73)	<0.001
	T2N1	Mastectomy	575	1	
		BCT	428	0.71 (0.50-0.99)	0.046
Propensity trimming nonoverlapping parts excluded	Entire cohort	Mastectomy	2,373	1	
		BCT	4,238	0.70 (0.59-0.83)	<0.001
	T1N0	Mastectomy	872	1	
		BCT	2,508	0.73 (0.56-0.96)	0.023
	T1N1	Mastectomy	375	1	
		BCT	672	0.81 (0.49-1.34)	0.410
	T2N0	Mastectomy	656	1	
		BCT	691	0.58 (0.41-0.81)	0.001
	T2N1	Mastectomy	470	1	
		BCT	367	0.71 (0.49-1.02)	0.066
Propensity trimming 10 th to 90 th percentile	Entire cohort	Mastectomy	1,728	1	
		BCT	3,559	0.75 (0.63-0.89)	0.001
	T1N0	Mastectomy	690	1	
		BCT	1,931	0.86 (0.65-1.13)	0.279
	T1N1	Mastectomy	309	1	
		BCT	627	1.10 (0.66-1.83)	0.726
	T2N0	Mastectomy	428	1	
		BCT	660	0.61 (0.43-0.86)	0.005
	T2N1	Mastectomy	301	1	
		BCT	341	0.61 (0.43-0.88)	0.007

Statistical technique	Subgroup analyses	Treatment	n	HR (95% CI)	p-value
Propensity trimming 20 th to 80 th percentile	Entire cohort	Mastectomy	1,194	1	
		BCT	2,771	0.75 (0.62-0.91)	0.003
	T1N0	Mastectomy	494	1	
		BCT	1,349	0.60 (0.66-1.24)	0.531
	T1N1	Mastectomy	209	1	
		BCT	544	0.92 (0.51-1.64)	0.772
	T2N0	Mastectomy	296	1	
		BCT	586	0.63 (0.43-0.93)	0.021
	T2N1	Mastectomy	195	1	
		BCT	292	0.58 (0.39-0.86)	0.007
Hierarchical modelling using -mestreg-	Entire cohort	Mastectomy	2,968	1	
		BCT	5,068	0.71 (0.61-0.83)	<0.001
	T1N0	Mastectomy	1,137	1	
		BCT	3,052	0.71 (0.55-0.92)*	0.009
	T1N1	Mastectomy	457	1	
		BCT	788	0.88 (0.56-1.39)*	0.587
	T2N0	Mastectomy	799	1	
		BCT	800	0.57 (0.41-0.81)	0.001
	T2N1	Mastectomy	575	1	
		BCT	428	0.71 (0.51-1.00)	0.047
Statistical technique	Subgroup analyses	Treatment	n	Coefficient (95% CI)	p-value
IV analysis	Entire cohort	Mastectomy	2,968	1	
		BCT	5,068	-0.05 (-0.13 to 0.04)	0.293
	T1N0	Mastectomy	1,137	1	
		BCT	3,052	0.03 (-0.07 to 0.13)	0.538
	T1N1	Mastectomy	457	1	
		BCT	788	-0.13 (-0.20 to -0.07)	<0.001
	T2N0	Mastectomy	799	1	
		BCT	800	0.06 (-0.02 to 0.14)	0.154
	T2N1	Mastectomy	575	1	
		BCT	428	0.04 (-0.07 to 0.15)	0.458

A p-value indicated in bold is considered as statistically significant ($p < 0.05$). * = Hospital of surgery ($n=87$) as level did not contribute significantly to the models. Abbreviations: OS = overall survival; DMFS = distant metastasis-free survival; HR = hazard ratio; CI = confidence interval; BCT = breast-conserving surgery.

Discussion

This study evaluated several methods dealing with confounding, cluster-related variation and confounding by severity. We showed that the effect estimates obtained using multivariable Cox regression, propensity trimming and hierarchical modelling were quite similar. The 95% CIs were wider for propensity trimming, as this method excluded a number of patients,

thereby lowering the power. The results of the IV analysis were not directly comparable with those from the other methods. No significant difference between BCT and mastectomy was observed in the entire cohort using this method. Since multivariable Cox regression, propensity trimming and hierarchical modelling do not solve the problem of unmeasured confounding, we cannot conclude that BCT has a causal relationship with 10-year DMFS. IV analysis may deal with unmeasured confounding, but in this study it is questionable whether the IV fulfils assumptions 2 and 3 and therefore no firm conclusions from this method can be drawn either.

Here, we will summarise results of the three statistical techniques. First, we used propensity trimming with IPW weighting, which deals in a different way with confounding when compared to conventional multivariable analysis. PS analysis corrects for all measured (potential) confounders and is a more appropriate method when there are only few events.³² The additional propensity trimming resulted in a more homogeneous group of patients to analyse, by excluding patients who had the highest likelihood of either one or the other treatment,¹⁹ ending up with a group in which both treatments are likely. Our results show that trimming results in slightly different estimates. However, the interpretation of the outcomes remained largely similar. We additionally performed all these analyses using propensity matching¹⁸ instead of IPW, which gave similar results (data not shown). However, both multivariable Cox regression and propensity methods are not able to deal with unmeasured confounding. As we lack data on family history, comorbidities, contraindications for RT or personal circumstances that make one or the other treatment unlikely, residual confounding and confounding by severity is likely to be present, and the treatment effect estimates may still cause biased treatment effects.

When using hierarchical modelling of hospital of surgery to account for cluster-related variation, similar results as conventional multivariable regression were obtained.

The IV analyses were the most challenging. Finding a good IV is very difficult,³³ as was also witnessed in our study. It cannot be verified whether all assumptions of the IV are met,²⁵ However, the best IV we could find in our dataset, hospital of surgery, was evaluated thoroughly. We found that a lot of measured potential confounders in our dataset were significantly different among the hospitals. Only after correcting for all casemix variables, the IV estimate may be valid (no association between unmeasured confounding and the IV). Our IV analyses showed no difference in 10-year DMFS in the entire cohort and in most subgroups, but in T1N1 stage BCT seemed to be related to better DMFS. However, since we cannot verify whether all of the assumptions of the IV are met, we are not able to draw definite conclusions. The surgeon's preference might have been a good alternative as IV. However, as we lacked this information, we could not execute these analyses.

Importantly, all methods used in this study depend on untestable assumptions [no unmeasured confounding in case of PS analysis and multivariable Cox regression, a direct effect of the IV on the outcome (assumption 2) and no association between unmeasured confounding and the IV in IV analysis (assumption 3)]. Therefore, we have to remain careful in making statements in comparing BCT to mastectomy.

Several other studies have compared statistical techniques and its effect on treatment effect estimates.³⁴⁻³⁶ They all showed approximately similar effect estimates using all methods and conclude that results have to be interpreted with care. A strong IV might closely resemble

randomisation, but the unverifiable assumptions need very careful justification. It is of crucial importance to realise that confounding by severity is present in many observational studies and that statistical methods may not be able to account for this. This does, however, not mean that results of observational studies are not informative at all. As RCTs do not provide all answers as well, as they are often carried out in selected populations in a given time frame and in a limited number of patients from selected centres. Moreover, the Hawthorne effect – changes in behaviour by study participants due to the awareness of being observed – may influence outcomes.⁶ For this reason, we continue encouraging the use of observational studies to estimate treatment effects in the real-world population, provided that results are interpreted carefully.

Conclusions

Multivariable Cox regression, propensity trimming and hierarchical modelling do not solve the problem of unmeasured confounding. IV analysis may deal with unmeasured confounding, but in this study it is questionable whether the IV fulfils all assumptions and therefore we cannot conclude that treatment has a causal relationship with 10-year DMFS. We would like to stress that all of these statistical techniques have some very strong untestable assumptions. It is, therefore, of crucial importance to critically evaluate these assumptions and to be very careful in drawing definite conclusions.

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Chapter

7

Chapter 7

Breast-conserving therapy versus mastectomy

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Breast-conserving therapy versus mastectomy

There is an ongoing debate regarding the use of randomised controlled trials (RCTs) versus observational studies when investigating treatment effects in clinical practice.¹ This holds especially true for the comparison of breast-conserving therapy (BCT) and mastectomy (MAST), which gained much attention since the publication of our observational study in *Lancet Oncology*.²

RCTs are highly appreciated as they are close to generate perfectly unbiased treatment comparison estimates. Treatment groups in a RCT are expected to be exchangeable; even when switching the treatment between the compared groups, results will be similar and are solely the effect of the treatment under study. Clinical decisions are largely based on this type of evidence. But is this always the best evidence? Is it always feasible or ethical? In the current era of personalised medicine and 'big data', clinical interpretation of an abundance of data (clinical reasoning) is becoming more and more crucial. It integrates all available and relevant information that may contribute to the best clinical decision-making for individual patients. This generally starts with existing guidelines, completed by evidence extracted from observational studies and clinicians' experiences.³ Importantly, the patient's preference plays an important role in (shared) decision-making.

In general, it is difficult to translate the overall results of a RCT in the response of an individual patient to the investigated treatment. Even for patients with identical characteristics to those in the trial population, the overall treatment effect observed in RCTs would only apply if the probability of treatment benefit and detriment was equally distributed in every individual participant.³ Often, evidence forming the basis of treatment guidelines are based on RCTs conducted a long time ago, while observational studies include a more recently diagnosed population. For BCT and MAST, the trials were all conducted in the eighties. Another important discrepancy between the RCT populations and the real-world population is the increasing share of elderly breast cancer patients in the latter. This is not only due to the ageing population, but also to early detection of breast cancer in the national screening program (which upper age limit is 75 years in the Netherlands), leading to a higher incidence in the elderly. Furthermore, diagnostic and surgical procedures as well as local and systemic therapies improved considerably. Moreover, increasing knowledge about the biological features of breast tumours led to the introduction of more advanced tumour-directed therapies. The combination of these improvements are very likely to affect survival rates. All of these matters cause results from RCTs to be of limited generalisability to the current breast cancer population. As a result, observational studies based on real-life data are increasingly conducted to provide estimates for the daily population.

This is where the battle begins. RCTs and meta-analyses of RCTs are considered to provide the highest quality of evidence, since randomisation leads to almost perfectly unbiased allocation of treatment. These types of studies thereby claim to overrule the evidence obtained by observational studies.⁴ However, high-quality observational studies may provide valid estimates as well, as long as they are properly designed and interpreted with care.⁵

Importantly, these kind of studies can fill the gaps left by RCTs.⁶

Various RCTs confirmed that BCT has equal survival rates as MAST. These trials have been integrated in the current evidence-based guidelines that recommend either BCT or MAST in early breast cancer patients. Various observational studies concluded that BCT led to improved survival rates compared to MAST. Examples are our recently published articles regarding the effect of BCT and MAST in T1-0N0-1 and T1-2N2 breast cancer, using data of the nationwide Netherlands Cancer Registry.^{2,7} We state at least equal survival for both treatments in early breast cancer, thereby confirming results of RCTs. However, for T1N0 stage specifically, we showed that BCT led to significantly higher distant metastasis-free survival compared to MAST.² Of course, we discuss all potential biases and limitations in these studies and are careful with the interpretation. A large strength of these studies is the use of a nationwide population-based cancer registry, covering the entire breast cancer population. In such large populations, we are able to look at several subgroups, such as stage or age, thereby filling the gaps that are generally present in RCTs.

Both RCTs and observational studies are susceptible to particular weaknesses. RCTs contain selected patient populations not representative for the daily population, while in observational studies there is no unbiased allocation of treatment. Thus, neither of those provides flawless information. The essential question we should ask ourselves is: “What sources could have caused bias?” and subsequently, “To what extent could this bias have influenced the results, and is this clinically relevant”? The latter may be explored by sensitivity analyses for specific subgroups. Decision-making should be based on analysing possible consequences we expect to occur to the individual patient in front of us, rather than on guidelines – that are predominantly based on RCTs – only.³ Patients should be informed as good as possible, with all relevant available information, in order to make the right decisions together with their treating physician.

Observational studies cannot replace the largely appreciated RCTs, however, RCTs should not be overrated as well, as they certainly do not make observational studies superfluous. Observational studies do not only reflect the real-life population and give information where RCTs are not possible, they can also function as hypothesis-generating research, providing questions for future RCTs.⁸ Therefore, both types of studies will support clinical decision-making. The one will perfectly complement the other.

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Chapter

8

Chapter 8

The influence of timing of radiation therapy following breast-conserving surgery on 10-year disease-free survival

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Abstract**Background**

The Dutch guidelines advise to start radiation therapy (RT) within 5 weeks following breast-conserving surgery (BCS). However, much controversy exists regarding timing of RT. This study investigated its effect on 10-year disease-free survival (DFS) in a Dutch population-based cohort.

Methods

All women diagnosed with primary invasive stage I-IIIa breast cancer in 2003 treated with BCS + RT were included. Two populations were studied. Population 1 excluded patients receiving chemotherapy before RT. Analyses were stratified for use of adjuvant systemic therapy (AST). Population 2 included patients treated with chemotherapy, and compared chemotherapy before (BCS-chemotherapy-RT) and after RT (BCS-RT-chemotherapy). DFS was estimated using multivariable Cox regression. Locoregional recurrence-free survival (LRRFS), distant metastasis-free survival (DMFS) and overall survival (OS) were secondary outcomes.

Results

Population 1 (n=2,759) showed better DFS and DMFS for a time interval of >55 than a time interval of <42 days. Patients treated with AST showed higher DFS for >55 days (hazards ratio (HR) 0.60 (95% confidence interval (CI): 0.38–0.94)) and 42–55 days (HR 0.64 (95% CI: 0.45–0.91)) than <42 days. Results were similar for DMFS, while timing did not affect LRRFS and OS. For patients without AST, timing was not associated with DFS, DMFS and LRRFS, but 10-year OS was significantly lower for 42–55 and >55 days compared to <42 days. In population 2 (n=1,120), timing did not affect survival in BCS-chemotherapy-RT. In BCS-RT-chemotherapy, DMFS was higher for >55 than <42 days.

Conclusions

Starting RT shortly after BCS seems not to be associated with a better long-term outcome. The common position that RT should start as soon as possible following surgery in order to increase treatment efficacy can be questioned.

Introduction

The relevance of optimal timing of surgery and adjuvant treatment is widely described in the literature, showing that delays in surgery^{1,2} and adjuvant treatments³ are likely to decrease treatment efficacy. In terms of the optimal timing of radiation therapy (RT) following breast-conserving surgery (BCS) much controversy exists. The general perception is that increasing time intervals between BCS and RT are correlated with adverse survival outcomes.⁴⁻⁸ Though, various other studies have shown that time interval between surgery and RT is unrelated to locoregional recurrence-free survival (LRRFS).⁹⁻¹⁴ Others reported that larger time intervals (>53 days) were significantly associated with increased disease-free (DFS) and distant metastasis-free survival (DMFS).^{15,16} However, these study populations are very heterogeneous, making it impossible to draw firm conclusions. Despite this, most indicators aiming to describe quality of care are process indicators regarding timing of therapy. In the Netherlands, the NABON (National Breast cancer Working group) Breast Cancer Audit (NBCA) defined the indicator on timing of RT as within 5 weeks of BCS, for patients not receiving chemotherapy between BCS and RT.¹⁷ In 2013, the annual report of the NBCA demonstrated that this criterion was fulfilled for only 45% of the patients. However, 75% was treated with RT within 6 weeks (42 days) of BCS.¹⁸

No nationwide population-based studies have been performed to investigate the relation between timing of RT following BCS and 10-year DFS, LRRFS, DMFS and overall survival (OS) in early breast cancer in the Netherlands. The aim of this study was to determine the effect of time intervals between BCS and RT on 10-year DFS, LRRFS, DMFS and OS in Dutch breast cancer patients. To achieve this, we investigated two populations: one in which patients receiving chemotherapy before RT were excluded, in order to determine the relevance of the NBCA indicator, and one in which patients receiving chemotherapy before and after RT were compared.

Methods

Design

In this historic cohort study, patient-, tumour- and treatment-related characteristics were obtained from the population-based Netherlands Cancer Registry. Tumour characteristics were coded according to the International Classification of Diseases for Oncology (ICD-O, third edition)¹⁹ and the tumour, node and metastasis (TNM) classification system of the International Union Against Cancer, sixth edition.²⁰ Data on vital status and date of death were derived from the Municipal Personal Records Database. Data on all recurrences that occurred within 10 years after diagnosis were gathered retrospectively from patient files and were complete for all patients included in this study. This study has been approved by the privacy committee of the Netherlands Cancer Registry.

Patients

All women diagnosed with primary invasive stage I-IIIa breast cancer in 2003, treated with BCS with RT, of whom the start date of RT was known and follow-up was complete, were included. Patients who had Paget's disease, macroscopic residual tumour left after the operation, treated in an unknown hospital, had extreme time intervals exceeding 365 days, or were treated with RT before BCS were excluded. First, we investigated our research question

in all early breast cancer patients, where we excluded patients treated with chemotherapy between BCS and RT (Population 1). Since adjuvant systemic therapy (endocrine therapy and/or chemotherapy, AST) has a direct effect on survival,²¹ we stratified these analyses for use of AST. Adjuvant endocrine therapy could have been started before, concurrently with, or following RT. Second, the same research question was studied in patients treated with chemotherapy before RT (BCS-chemotherapy-RT) and we compared the results with patients receiving chemotherapy after RT (BCS-RT-chemotherapy) (Population 2). The patients treated with chemotherapy after RT are consequently part of both populations (Figure 1).

Figure 1. Flowchart of patient selection. Abbreviations: BCS = breast-conserving surgery, RT = radiation therapy. Patients receiving chemotherapy after RT (Population 2) are also part of the adjuvant systemic therapy group of Population 1.

Definitions and outcomes

The time between BCS and RT was defined as the number of days from the date of most recent surgery until the start of RT. Most recent surgery was defined as BCS of the primary tumour, or as the moment of axillary lymph node dissection, if this was performed following BCS. In case of re-excision, the date of last BCS was used. We categorised patients into three interval groups based on the NBICA indicator: <42 days (most patients receive RT within 42 days), 42–55 days and >55 days. For BCS-chemotherapy-RT, the median time interval was larger, and therefore the following interval groups were created, based on the distribution of BCS-RT interval among patients: <112 days, 112–140 days and >140 days. Local and distant recurrences were defined according to existing consensus-based definitions for recurrence

classification.^{22,23} The primary outcome of this study was 10-year DFS (cumulative probability of being free from any recurrence, within 10 years after diagnosis). Secondary outcomes were 10-year LRRFS, 10-year DMFS (cumulative probability of being free from locoregional recurrences or distant metastases, respectively, within 10 years after diagnosis) and 10-year OS (death due to all causes).

Statistical analysis

Potential confounding variables were compared among the interval groups using the Chi-squared, Fisher’s exact or Kruskal–Wallis test. Small amounts of missing data were present for several prognostic variables. Since these missing variables are most likely limited to an earlier year of diagnosis (over recent years the registration of data has become more strict), and were not expected to be related to any unobserved data, we considered the missing data as missing at random. To account for missing data, multiple imputation was performed using the *mi impute chained* equation command in STATA (Release 14, StataCorp LP, College Station, TX, USA). The imputation, based on event indicators and estimated Nelson-Aalen cumulative hazards,²⁴ was performed 20 times and Rubin’s rule was used to combine the estimates and standard errors.²⁵ We used the Kaplan-Meier method and the log-rank test to compare crude 10-year DFS, LRRFS and DMFS among the interval groups. To correct for confounding, we used multivariable Cox regression to estimate hazard ratios (HRs) with 95% confidence intervals (CIs) for 10-year DFS, LRRFS and DMFS. For Population 1, all analyses were stratified for use of AST (chemotherapy and/or endocrine therapy = yes, none = no). For Population 2, analyses were performed separately for BCS-RT-chemotherapy and BCS-chemotherapy-RT. Potential confounding variables (variables that are related to the timing of RT as well as the survival outcomes) varying among interval groups were included in the multivariable models (*p*<0.1). A *p*-value<0.05 was considered to be statistically significant. All analyses were executed in STATA version 14.1.

Results

Population 1 consisted of 2,759 patients (Figure 1). None of the included patients received primary systemic therapy. The median number of days between BCS and RT was 45 (IQR 37–54; Figure 2). The distribution of time interval for patients treated with and without AST is shown in Supplementary Figure 1. Patient, treatment, and tumour-related characteristics per interval group are summarised in Table 1. Longer time intervals were most common in older patients, patients not treated with AST and patients who were referred to a RT department in another hospital. Patients treated with AST showed less favourable tumour characteristics compared to patients not treated with AST (Supplementary Table 1).

Table 1. Population 1, baseline characteristics according to interval category (n=2,759)

Characteristics	<42 days (n=1,079)	42-55 days (n=1,074)	>55 days (n=606)	p-value ^a
Age				
<40	48 (4.5)	35 (3.3)	18 (3.0)	
40-49	178 (16.5)	181 (16.9)	81 (13.4)	
50-64	539 (50.0)	522 (48.6)	292 (48.2)	
≥65	314 (29.1)	336 (31.3)	215 (35.5)	0.068

Characteristics	<42 days (n=1,079)	42-55 days (n=1,074)	>55 days (n=606)	p-value ^a
Social economic status				
Low	301 (27.9)	299 (27.8)	178 (29.4)	0.921
Medium	429 (39.8)	439 (40.9)	237 (39.1)	
High	349 (32.3)	336 (31.3)	191 (31.5)	
Hospital volume				
(patients per year)				
0-49	188 (17.4)	169 (15.8)	89 (14.7)	0.141
50-99	524 (48.6)	497 (46.3)	315 (52.0)	
100-149	240 (22.2)	261 (24.3)	140 (23.1)	
≥150	127 (11.8)	147 (13.7)	62 (10.2)	
Region**				
A	141 (13.1)	110 (10.2)	77 (12.7)	<0.001
B	134 (12.4)	100 (9.3)	49 (8.1)	
C	50 (1.6)	118 (11.0)	66 (10.9)	
D	197 (18.3)	185 (17.2)	124 (20.5)	
E	163 (15.1)	141 (13.1)	66 (10.9)	
F	49 (4.5)	112 (10.4)	111 (18.3)	
G	169 (15.7)	181 (16.9)	74 (12.2)	
H	58 (5.4)	26 (2.4)	14 (2.3)	
I	118 (10.9)	101 (9.4)	25 (4.1)	
Lateralisation				
Left	551 (51.1)	555 (51.7)	315 (52.0)	0.927
Right	528 (48.9)	519 (48.3)	291 (48.0)	
Sublocalisation				
Outer quadrants	587 (54.4)	560 (52.1)	323 (53.3)	0.902
Inner quadrants	221 (20.5)	234 (21.8)	134 (22.1)	
Central portion	65 (6.0)	58 (5.4)	33 (5.5)	
Overlapping lesions	199 (18.4)	210 (19.6)	109 (18.0)	
Unknown	7 (0.7)	12 (1.1)	7 (1.2)	
Histological tumour type				
Ductal	889 (82.4)	845 (78.7)	483 (79.7)	0.087
Lobular	95 (8.8)	97 (9.0)	65 (10.7)	
Mixed	33 (3.1)	55 (5.1)	26 (4.3)	
Other	62 (5.8)	77 (7.2)	32 (5.3)	
Differentiation grade				
Grade I	309 (28.6)	339 (31.6)	184 (30.4)	0.138
Grade II	448 (41.5)	462 (43.0)	263 (43.4)	
Grade III	238 (22.1)	204 (19.0)	104 (17.2)	
Unknown	84 (7.8)	69 (6.4)	55 (9.1)	
Median pathological tumour				
size in mm (IQR)	15 (11-20)	14 (10-19)	14 (10-19)	<0.001
Unknown	17 (1.6)	14 (1.3)	7 (1.2)	

Characteristics	<42 days (n=1,079)	42-55 days (n=1,074)	>55 days (n=606)	p-value ^a
T-stage				
1	824 (76.6)	850 (79.2)	481 (79.5)	0.233
2/3	252 (23.4)	223 (20.8)	124 (20.5)	
Unknown	3 (0.3)	1 (0.1)	1 (0.2)	
Median number of positive nodes (IQR)	0 (0-0)	0 (0-0)	0 (0-1)	0.150
Unknown	11 (1.0)	16 (1.5)	14 (2.3)	
N-stage				
0	848 (79.0)	822 (77.6)	447 (74.6)	0.255
1	213 (19.8)	222 (20.9)	139 (23.2)	
2	13 (1.2)	16 (1.5)	13 (2.2)	
Multifocality				
No	1,008 (93.4)	997 (92.8)	551 (90.9)	0.634
Yes	32 (3.0)	31 (2.9)	22 (3.6)	
Unknown	39 (3.6)	46 (4.3)	33 (5.5)	
Hormone receptor status				
ER and PR positive	750 (69.5)	744 (69.3)	410 (67.7)	0.722
ER or PR positive	165 (15.3)	173 (16.1)	107 (17.7)	
ER and PR negative	135 (12.5)	125 (11.6)	69 (11.4)	
Unknown	29 (2.7)	32 (3.0)	20 (3.3)	
Adjuvant systemic therapy				
No	670 (62.1)	688 (64.1)	403 (66.5)	0.007
Hormonal therapy	208 (19.3)	210 (19.6)	122 (20.1)	
Chemotherapy ^b	79 (7.3)	49 (4.6)	18 (3.0)	
Both	122 (11.3)	127 (11.8)	93 (10.4)	
Axillary lymph node dissection				
No	912 (84.5)	933 (86.9)	520 (85.8)	0.297
Yes	167 (15.5)	141 (13.1)	86 (14.2)	
Residual tumour left				
No	1,007 (93.3)	1,018 (94.8)	556 (91.8)	0.065
Yes (microscopic)	56 (5.2)	41 (3.8)	38 (6.3)	
Unknown	16 (1.5)	15 (1.4)	12 (2.0)	
Referral for RT ^c				
No	202 (18.7)	240 (22.4)	103 (17.0)	0.017
Yes	877 (81.3)	834 (77.7)	503 (83.0)	

Abbreviations: IQR = interquartile range; RT = radiation therapy. Numbers are n (%) unless otherwise indicated. P-values are calculated on known values. ^aA P-value<0.2 is considered significant and indicated in bold. P-values are based on known values only. ^bPatients that received chemotherapy between surgery and radiation therapy were excluded. ^cReferral for RT = patient received RT in another hospital. ^{**}Region indicates the region in the Netherlands where the patient received surgery. Due to confidential aspects these regions are anonymised.

Table 2. Population 2, baseline characteristics according to timing of chemotherapy (n=1,120)

Characteristics	Chemotherapy after RT (n=451)		p-value	Chemotherapy before RT (669)		p-value*
	<42 days	42-55 days	>55 days	<112 days	112-140 days	>140 days
Age						
<40	33 (16.4)	22 (12.5)	6 (8.1)	22 (12.2)	35 (11.6)	23 (12.3)
40-49	65 (32.3)	72 (40.9)	25 (33.8)	64 (35.4)	122 (40.5)	71 (38.0)
50-64	98 (48.8)	75 (42.6)	41 (55.4)	89 (49.2)	133 (44.2)	85 (45.5)
≥65	5 (2.5)	7 (4.0)	2 (2.7)	6 (3.3)	11 (3.7)	8 (4.3)
						0.944
Social economic status						
Low	49 (24.4)	48 (27.3)	15 (20.3)	37 (20.4)	93 (30.9)	62 (33.2)
Medium	71 (35.3)	65 (36.9)	28 (47.8)	85 (47.0)	118 (39.2)	76 (40.6)
High	81 (40.3)	63 (35.8)	31 (41.9)	59 (32.6)	90 (29.9)	49 (26.2)
						0.059
Hospital volume (patients per year)						
0-49	16 (8.0)	22 (12.5)	8 (10.8)	50 (27.6)	42 (14.0)	43 (23.0)
50-99	108 (53.7)	85 (48.3)	37 (50.0)	64 (35.4)	131 (43.5)	103 (55.1)
100-149	46 (22.9)	34 (19.3)	16 (21.6)	39 (21.6)	98 (32.6)	22 (11.8)
≥150	31 (15.4)	35 (19.9)	13 (17.6)	28 (15.5)	30 (10.0)	19 (10.2)
						<0.001
Region**						
1	45 (22.4)	17 (9.7)	5 (6.8)	35 (19.3)	80 (26.6)	29 (15.5)
2	114 (56.7)	117 (66.5)	54 (73.0)	81 (44.8)	165 (54.8)	77 (41.2)
3	42 (20.9)	42 (23.9)	15 (20.3)	65 (35.9)	56 (18.6)	81 (43.3)
						<0.001
Lateralisation						
Left	112 (55.7)	89 (50.6)	41 (55.4)	111 (61.3)	160 (53.2)	99 (52.9)
Right	89 (44.3)	87 (49.4)	33 (44.6)	70 (38.7)	141 (46.8)	88 (47.1)
						0.162
Sublocalisation						
Outer quadrants	130 (64.7)	94 (53.4)	46 (62.2)	113 (62.4)	175 (58.1)	104 (55.6)
Inner quadrants	34 (16.9)	34 (19.3)	10 (13.5)	34 (18.8)	63 (20.9)	48 (25.7)
Central portion	7 (3.5)	12 (6.8)	2 (2.7)	8 (4.4)	13 (4.3)	3 (1.6)
Overlapping lesions	27 (13.4)	34 (19.3)	16 (21.6)	24 (13.3)	43 (14.3)	30 (16.0)
Unknown	3 (1.5)	2 (1.1)	-	2 (1.1)	7 (2.3)	2 (1.1)
						0.385

Characteristics	Chemotherapy after RT (n=451)			p-value	Chemotherapy before RT (669)			p-value*
	<42 days	42-55 days	>55 days		<112 days	112-140 days	>140 days	
Histological tumour type								
Ductal	176 (87.6)	147 (83.5)	65 (87.8)		116 (91.7)	265 (88.0)	166 (88.8)	
Lobular	4 (2.0)	9 (5.1)	2 (2.7)		5 (2.8)	9 (3.0)	8 (4.3)	
Mixed	7 (3.5)	11 (6.3)	5 (6.8)		4 (2.2)	13 (4.3)	7 (3.7)	
Other	14 (7.0)	9 (5.1)	2 (2.7)	0.348	6 (3.3)	14 (4.7)	6 (3.2)	0.782
Differentiation grade								
Grade I	17 (8.5)	19 (10.8)	9 (12.2)		11 (6.1)	28 (9.3)	17 (9.1)	
Grade II	45 (22.4)	61 (34.7)	26 (36.5)		40 (22.1)	78 (25.9)	59 (31.6)	
Grade III/IV***	123 (61.2)	86 (48.9)	31 (46.0)		122 (67.4)	186 (61.8)	104 (55.6)	
Unknown	16 (8.0)	10 (5.7)	4 (5.4)	0.028	8 (4.4)	9 (3.0)	7 (3.7)	0.146
Median pathological tumour size in								
mm (IQR)	19 (15-25)	19 (15-25)	19 (15-23)	0.532	19.5 (15-25)	19 (15-25)	21 (15-26)	0.271
Unknown	1 (0.5)	2 (1.1)	3 (4.1)		3 (1.7)	-	3 (1.6)	
T-stage								
1	112 (55.7)	99 (56.3)	43 (58.1)		100 (55.3)	164 (54.5)	91 (48.7)	
2/3	89 (44.3)	77 (43.8)	30 (40.5)		79 (43.7)	137 (45.5)	96 (51.3)	
Unknown	-	-	1 (1.4)	0.894	2 (1.1)	-	-	0.324
Median number of positive nodes (IQR)	0 (0-1)	1 (0-1)	1 (0-2)	0.073	1 (0-2)	1 (0-2)	1 (0-3)	
Unknown	-	-	-		-	1 (0.3)	-	<0.001
N-stage								
0	102 (50.8)	79 (44.9)	28 (27.8)		89 (49.2)	137 (45.5)	51 (27.3)	
1	92 (45.8)	92 (52.3)	39 (52.7)		77 (42.5)	128 (42.5)	91 (48.7)	
2	7 (3.5)	5 (2.8)	7 (9.5)	0.062	15 (8.3)	36 (12.0)	45 (24.1)	<0.001
Multifocality								
No	188 (93.5)	165 (93.8)	69 (93.2)		169 (93.4)	285 (94.7)	159 (85.0)	
Yes	2 (1.0)	2 (1.1)	1 (1.4)		8 (4.4)	9 (3.0)	8 (4.3)	
Unknown	11 (5.5)	9 (5.1)	4 (5.4)	0.968	4 (2.2)	7 (2.3)	20 (10.7)	0.582

Characteristics	Chemotherapy after RT (n=451)		p-value	Chemotherapy before RT (669)		p-value*
	<42 days	42-55 days	>55 days	<112 days	112-140 days	>140 days
Hormone receptor status						
ER and PR positive	102 (50.8)	101 (57.4)	43 (58.1)	82 (45.3)	160 (53.2)	110 (58.8)
ER or PR positive	22 (11.0)	23 (13.1)	13 (17.6)	24 (13.3)	34 (11.3)	21 (11.2)
ER and PR negative	71 (35.3)	16 (22.9)	16 (21.6)	73 (40.3)	102 (33.9)	52 (27.8)
Unknown	6 (3.0)	2 (2.9)	2 (2.7)	2 (1.1)	5 (1.7)	4 (2.1)
				0.119		0.095
Endocrine therapy						
No	79 (39.3)	49 (27.8)	18 (24.3)	77 (42.5)	104 (34.6)	61 (32.6)
Yes	122 (60.7)	127 (72.2)	56 (75.7)	104 (57.5)	197 (65.5)	126 (67.4)
				0.016		0.103
Axillary lymph node dissection						
No	143 (71.1)	133 (75.6)	54 (73.0)	125 (69.1)	215 (71.4)	129 (69.0)
Yes	58 (28.9)	43 (24.4)	20 (27.0)	56 (30.9)	86 (28.6)	58 (31.0)
				0.626		0.795
Residual tumour left						
No	186 (92.5)	167 (94.9)	70 (95.9)	168 (92.8)	284 (94.4)	177 (94.7)
Yes (microscopic)	9 (4.5)	5 (2.8)	3 (4.1)	8 (4.4)	13 (4.3)	7 (3.7)
Unknown	6 (3.0)	4 (2.3)	1 (1.4)	5 (2.8)	4 (1.3)	3 (1.6)
				0.715		0.933
Referral for RT***						
No	42 (20.9)	49 (27.8)	16 (21.4)	48 (21.6)	62 (20.6)	26 (13.9)
Yes	159 (79.1)	127 (72.2)	58 (78.6)	133 (78.4)	239 (79.4)	161 (86.1)
				0.257		0.011

Numbers are n (%) unless otherwise indicated. P-values were calculated on known values. *A p-value<0.2 is considered significant and indicated in bold. P-values are based on known values only. **Region indicates the region in the Netherlands where the patient received surgery. Due to confidential aspects these regions are anonymised. Region has been reduced to three categories due to low number of events in this cohort. ***Grade III and IV are combined, since only 4 patients presented with grade IV. ****Referral for RT = patient received RT in another hospital

Population 2 consisted of 1,120 patients (Figure 1). The median number of days between BCS and RT was 43 (IQR 35–51) for BCS-RT-chemotherapy, and 124 (IQR 111–144) for BCS-chemotherapy-RT (Supplementary Figure 2). Patient, treatment and tumour-related characteristics per interval group and timing of chemotherapy are summarised in Table 2.

Figure 2. Population 1: Distribution of time intervals between BCS and RT. The left panel shows the distribution without outliers. The right panel shows the distribution including outliers.

Population 1: timing of RT and 10-year survival, stratified for use of AST

In the <42 days group, 178 of 1,079 patients (16.5%) were diagnosed with a recurrence within 10 years of diagnosis. In the 42–55 days group, 141 of 1,074 (13.1%) patients experienced a recurrence, and in the >55 days group, 73 of 606 (12.1%) patients experienced a recurrence. The distribution of distant metastases varied significantly among interval groups, but the distribution of locoregional recurrences did not (Supplementary Figure 3). The distribution of recurrences for patients treated with and without AST is shown in Supplementary Figure 4. Patients treated with adjuvant systemic therapy showed a higher number of distant metastases in the <42 days group, compared to the other groups.

Kaplan–Meier curves of crude 10-year DFS, LRRFS and DMFS for the entire cohort are shown in Supplementary Figure 5. A significant difference among the interval groups was observed for 10-year DFS and DMFS, with the highest DFS and DMFS seen for >55 days, and the lowest for <42 days ($p < 0.05$). Time interval was not significantly associated with 10-year LRRFS. After stratification, 10-year DFS was significantly better for longer time intervals in patients treated with AST (Supplementary Figure 6).

In the multivariable analysis, 10-year DFS was significantly better for the time interval of >55 days (HR 0.71 (95% CI: 0.56–0.90)) compared to <42 days. The HR for 42–55 days was 0.78 (95% CI: 0.64–0.95), compared to <42 days. After stratification, significantly higher DFS was observed for patients treated with AST (HR 0.63 (95% CI: 0.41–0.95) for a time interval of >55 days and 0.71 (95% CI: 0.52–0.98) for 42–55 days compared to <42 days). No differences in DFS among interval groups existed for patients not treated with AST (Table 3).

Ten-year LRRFS was not significantly different among interval groups, which persisted after stratification for use of AST (Table 3).

Table 3. Population 1, 10-year disease-free, locoregional recurrence-free and distant metastasis-free survival for different time intervals between surgery and radiation therapy in breast cancer patients, stratified for use of adjuvant systemic therapy

Time interval	Entire cohort (n=2,759)		No adjuvant treatment (n=1,761)		Adjuvant treatment (n=998)	
	Crude HR [95% CI]	Multivariable [*] HR [95% CI]	Crude HR [95% CI]	Multivariable [†] HR [95% CI]	Crude HR [95% CI]	Multivariable [‡] HR [95% CI]
Primary outcome: 10-year DFS						
<42 days	1	1	1	1	1	1
42-55 days	0.79 [0.63-0.98] p=0.033	0.82 [0.65-1.03] p=0.082	0.89 [0.66-1.19] p=0.423	0.93 [0.69-1.26] p=0.654	0.68 [0.49-0.96] p=0.026	0.64 [0.45-0.91] p=0.013
>55 days	0.73 [0.55-0.95] p=0.004	0.73 [0.55-0.97] p=0.032	0.81 [0.57-1.15] p=0.240	0.84 [0.69-1.26] p=0.340	0.65 [0.42-1.00] p=0.048	0.60 [0.38-0.94] p=0.027
Secondary outcome: 10-year LRRFS						
<42 days	1	1	1	1	1	1
42-55 days	0.69 [0.48-0.97] p=0.035	0.74 [0.51-1.06] p=0.098	0.74 [0.49-1.13] p=0.163	0.79 [0.51-1.21] p=0.271	0.54 [0.27-1.05] p=0.069	0.55 [0.28-1.11] p=0.095
>55 days	0.80 [0.54-1.20] p=0.282	0.90 [0.59-1.36] p=0.611	0.88 [0.55-1.41] p=0.605	0.97 [0.59-1.57] p=0.888	0.63 [0.28-1.40] p=0.255	0.67 [0.29-1.57] p=0.362
Secondary outcome: 10-year DMFS						
<42 days	1	1	1	1	1	1
42-55 days	0.87 [0.67-1.12] p=0.288	0.89 [0.68-1.17] p=0.401	1.05 [0.72-1.52] p=0.817	1.11 [0.75-1.63] p=0.599	0.75 [0.52-1.07] p=0.107	0.68 [0.47-0.99] p=0.044
>55 days	0.66 [0.47-0.92] p=0.015	0.64 [0.45-0.91] p=0.013	0.69 [0.42-1.14] p=0.147	0.71 [0.43-1.19] p=0.191	0.67 [0.42-1.06] p=0.085	0.59 [0.36-0.96] p=0.033

^{*} = corrected for age, hospital volume, region, histological tumour type, differentiation grade, exact tumour size (mm), exact number of positive lymph nodes, residual tumour left after the operation, adjuvant systemic therapy and whether a patient received RT in another hospital. [†] = corrected for hospital volume, region, histological tumour type, exact tumour size (mm), exact number of positive lymph nodes and whether the patient received RT in another hospital. [‡] = corrected for age, region, differentiation grade, exact number of positive lymph nodes, hormone receptor status, type of adjuvant systemic therapy and whether the patient received RT in another hospital. P-values depicted in bold are considered as statistically significant (p<0.05).

Ten-year DMFS was significantly better for a time interval of >55 days (HR 0.64 (95% CI: 0.45–0.92)) compared to <42 days. No significant difference existed between 42–55 and <42 days. After stratification, we revealed that in patients treated with AST, >55 (HR 0.59 (95% CI: 0.36–0.96)) and 42–55 days (HR 0.69 (95% CI: 0.47–1.00)) were significantly related to better 10-year DMFS than <42 days. No significant differences were found for patients not treated with AST (Table 3).

Ten-year OS was not significantly different among interval groups in the entire cohort. However, after stratification, significantly lower OS was observed in patients not treated with AST for >55 days (HR 1.51 (95% CI: 1.17–2.11)) and 42–55 days (HR 1.57 (95% CI: 1.17–1.96)) compared to <42 days between surgery and RT. In patients treated with AST, no significant differences were found (Table 3).

Population 2: timing of RT and 10-year survival, stratified for timing of chemotherapy

For BCS-RT-chemotherapy, 47 of 201 patients (23.4%) in the <42 days group were diagnosed with a recurrence within 10 years of diagnosis. In the 42–55 days group, 30 of 176 (17.1%) patients experienced a recurrence, and in the >55 days group, 8 of 70 (10.8%) patients experienced a recurrence. For BCS-chemotherapy-RT, 31 of 181 patients (17.1%) in the <112 days group were diagnosed with a recurrence within 10 years of diagnosis. In the 112–140 days group, 50 of 301 (16.6%) patients experienced a recurrence, and in the >140 days group, 49 of 187 (26.2%) patients experienced a recurrence. The distribution of any recurrence and distant metastases varied significantly among interval groups – irrespective of timing of chemotherapy – while the distribution of locoregional recurrences did not vary significantly (Supplementary Figure 7).

Kaplan–Meier curves show that for BCS-RT-chemotherapy, time interval is not related to 10-year DFS, LRRFS and DMFS. However, for 10-year DMFS, a clear trend towards significance is observed in favour of longer time intervals ($p=0.052$). For BCS-chemotherapy-RT, shorter time intervals are related to higher 10-year DFS and DMFS ($p=0.05$), while time interval was not significantly associated with 10-year LRRFS (Supplementary Figure 8).

After correction for confounding, time interval was not significantly associated with 10-year DFS, LRRFS and OS for BCS-RT-chemotherapy, while 10-year DMFS was significantly higher for >55 days (HR 0.44 (95% CI: 0.19–0.99)) compared to <42 days. For BCS-chemotherapy-RT, time interval was not significantly associated with any outcome (Table 4).

Discussion

This study shows that in patients not treated with AST after RT, time interval between BCS and RT is not significantly related to 10-year DFS, LRRFS and DMFS, but that increasing time intervals lead to lower 10-year OS. In patients treated with AST after RT, higher 10-year DFS and DMFS at increasing time intervals were seen. In patients treated with chemotherapy (Population 2), we found significantly improved 10-year DMFS for >55 days compared to <42 days in the BCS-RT-chemotherapy group, while time interval is not significantly associated with any outcome in the BCS-chemotherapy-RT group.

This may imply that patients who are treated with adjuvant chemotherapy may possibly benefit from a slightly longer time interval when receiving chemotherapy after RT, while patients not treated with AST may have better OS when start RT <42 days after BCS.

Table 4. Population 2, 10-year disease-free, locoregional recurrence-free and distant metastasis-free survival for different time intervals between surgery and radiation therapy in breast cancer patients, stratified for timing of chemotherapy

Time interval	BCS – RT – chemotherapy (n=451)		BCS – chemotherapy – RT (n=667)	
	Crude	Multivariable*	Crude	Multivariable*
	HR [95% CI]	HR [95% CI]	HR [95% CI]	HR [95% CI]
Primary outcome: 10-year DFS				
<42 days	1	1	1	1
42-55 days	0.70 [0.45-1.11] p=0.133	0.77 [0.48-1.25] p=0.291	0.95 [0.61-1.49] p=0.824	0.91 [0.57-1.44] p=0.679
>55 days	0.45 [0.21-0.95] p=0.036	0.48 [0.22-1.03] p=0.061	1.60 [1.02-2.51] p=0.040	1.24 [0.77-2.01] p=0.374
Secondary outcome: 10-year LRRFS				
<42 days	1	1	1	1
42-55 days	0.74 [0.30-1.80] p=0.505	0.96 [0.38-2.42] p=0.939	1.05 [0.53-2.08] p=0.882	1.11 [0.55-2.25] p=0.770
>55 days	0.88 [0.28-2.72] p=0.820	1.16 [0.36-3.79] p=0.804	1.19 [0.57-2.50] p=0.646	1.99 [0.45-2.21] p=0.987
Secondary outcome: 10-year DMFS				
<42 days	1	1	1	1
42-55 days	0.68 [0.42-1.11] p=0.122	0.72 [0.43-1.20] p=0.212	0.89 [0.54-1.47] p=0.652	0.84 [0.50-1.41] p=0.499
>55 days	0.44 [0.20-0.98] p=0.044	0.44 [0.19-0.99] p=0.048	1.69 [1.03-2.77] p=0.038	1.25 [0.74-2.13] p=0.405

* = corrected for region, grade, sublocalisation within the breast, hormone receptor status, adjuvant endocrine therapy[†] = corrected for social economic status, hospital volume, region, lateralisation, grade, sublocalisation within the breast, number of positive lymph nodes, hormone receptor status, adjuvant endocrine therapy and whether the patient received RT in another hospital. P-values depicted in bold are considered as statistically significant (p<0.05). Abbreviations: BCS = breast-conserving surgery, RT = radiation therapy.

When receiving chemotherapy between BCS and RT (BCS-chemotherapy-RT), timing is not significantly related to all investigated survival outcomes. In general, patients not receiving AST present with a good prognosis, or with a decreased life expectancy due to age or comorbidity. In these patients there is evidence that RT does not affect DMFS.^{26,27} This may explain why RT does not depend on timing in these patients. What may be remarkable for some readers is that the majority of the patients in this population (2003) was not treated with AST. However, this is in line with the Dutch nationwide evidence-based guidelines valid at that time.²⁸ In addition, according to the current Dutch guidelines, these patients would neither be treated with AST nowadays. Importantly, AST in general is recommended when the absolute risk on 10-year mortality is equal to or more than 15%, and for most patients the risk on mortality will be reduced with 4–5%. The guideline states that the survival benefit of chemotherapy is limited in older patients and patients with early, ER positive breast cancer. Since our study population primarily consists of patients with early, ER positive disease, and the share of older patients is substantial, chemotherapy is not expected to be administered to a large proportion of patients. Endocrine therapy is primarily recommended for patients with positive lymph nodes and ER positive breast cancer or patients without positive nodes and unfavourable tumour characteristics. Approximately 20% of our population presented with positive lymph nodes, and around 30% of the patients received endocrine therapy (only or in combination with chemotherapy), which is in line with the abovementioned guidelines.²⁹ Our findings that longer time intervals may lead to better DFS and DMFS in patients treated with AST are more difficult to interpret. Since not all hospitals in The Netherlands have a RT department, BCS-RT time intervals may increase for patients who have to be referred to a RT department of another hospital. However, with the oncological structure as set up in The Netherlands this is not likely to be the case. Moreover, since this factor is not related to the outcome (supporting the before-mentioned), but is directly related to the time interval, it is not a confounding variable and should not explain the observed results. One possible argument may be that patients with worse prognosis receive RT earlier and consequently have a shorter time interval between surgery and RT (so in a way a reversed causal effect). In this study, patients under 40 years were more often treated with RT within 42 days following surgery. In addition, patients in the <42 days group had slightly larger tumours compared to the other groups, and more often had a higher grade. Another suggested mechanism deals with the release of various humoral factors after surgery leading (amongst others) to angiogenesis which contributes to the process of wound healing. This is hypothesised to contribute to growth of previously dormant metastatic cells.³¹ It should be stressed also that normally RT deteriorates the ability of cancer cells to create angiogenesis and, hereby, deteriorates the ability to metastasise. Starting RT too early after surgery may, due to the release of various humoral factors, lead to repair of this type of radiation-induced damage and may therefore not lead to deterioration of angiogenesis. The latter may also explain why we find an effect of timing on DMFS, but not on LRRFS. However, this hypothesis should be confirmed in further studies. Since the chance of metastases is related to several prognostic characteristics of the tumour – that are presumably worse in patients treated with chemotherapy – the effect of timing of RT following surgery may be more pronounced in patients receiving chemotherapy after RT. However, this outcome definitely needs further research, also given the complexity

of the interplay between RT and AST.³² Our study agrees with other studies that timing of RT is not significantly related to DFS in patients not treated with AST.^{14,33} However, two other studies showed the opposite.^{15,16} Possible explanations for this discrepancy are the use of different intervals between treatments, different study designs (population-based vs single-centre-based), and different study populations. Our results confirm previous studies showing no relationship between timing of RT and LRRFS.^{9,14-16} Furthermore, another study found that a time interval over seven months between BCS and RT did not affect DFS and DMFS in patients receiving chemotherapy before RT, thereby confirming our results.³⁴ Finally, we found lower OS for patients not treated with AST with increasing time intervals. This may be explained by the larger share of older patients in the larger interval groups.

Strengths and limitations of the study

To our knowledge, this is the first study that investigated the relevance of the NBCA indicator in the Netherlands, and moreover, the overall effect of timing of RT on survival. Besides, we compared the effect of timing in patients receiving chemotherapy before and after RT. These results give a more complete picture of the effect of time interval between BCS and RT. The study's population-based setting increases the generalisability of the results.

A limitation of this study is lacking data on postoperative complications, delaying RT, lymphovascular invasion, mitotic activity index and HER2 receptor status. Any differences in these factors or other unmeasured confounders among interval groups may have introduced confounding by severity. For the HER2 status, it must be noted that it was not routinely determined in 2003, with anti-HER2 therapies being introduced in Dutch clinical practice only in 2005. For patients receiving chemotherapy before RT (BCS-chemotherapy-RT), we lacked data on start of the last cycle of chemotherapy. Therefore, we could not take the time between last cycle of chemotherapy and start of RT into account. Since endocrine therapy is quite often started concurrently with RT, we do not expect that the use of endocrine therapy caused a delay in starting RT. Another limitation is that we could not include 1,482 patients (35% of total) due to an unknown start date of RT. As this number is substantial, we thoroughly investigated this population. Fortunately, these patients had similar baseline characteristics and survival outcomes as the population under study. In addition, since start dates of RT are cumbersome to retrieve retrospectively from RT reports, we do not expect that patients with a missing start date are a selective group. Therefore, we do not expect this to have influenced our results other than a lower number of included patients. Finally, as this study is observational, we cannot exclude additional confounding by severity and residual confounding.

Implications for clinical practice

Our most important message is that it is not necessary to start RT as soon as possible after BCS, as it does not increase survival rates. Patients should be informed about this, preventing them from worrying about tumour growth and worse outcomes in case of a longer time interval between BCS and RT. In addition, the relevance of the NBCA indicator may be questioned. These results may not only be useful for the Dutch clinical practice, but it may also be of importance for other countries. There is a lot of controversy regarding timing of RT. Population-based studies, such as this study, may contribute to a better understanding

of the effect of timing on survival outcomes and may refute the common understanding that RT should start as soon as possible after RT. Clearly, we cannot conclude that delays can be extended infinitely: other studies suggested that delays exceeding 20 weeks^{4,35} lead to reduced survival rates. In addition, from a psychological point of view a short time interval can be more convenient.

The question raises whether it would be beneficial to start chemotherapy before RT (BCS-chemotherapy-RT). Additional analyses on our data revealed that the sequence of chemotherapy and RT does not affect 10-year survival outcomes (data not shown). This is confirmed by a recently published randomised trial.³⁶ However, since the optimum timing of RT may largely be related to several prognostic factors,¹⁰ further research needs to define a precise range in delay that has the most favourable effect on survival in predefined subgroups. The fact that the majority of our population was not treated with AST (which is according to our guidelines), may limit the generalisability of the results to other countries, where the indication for administering AST may differ.

Importantly, developments in the treatment of breast cancer include the increasing use of primary systemic therapy. It should be further investigated whether these results hold true when systemic therapy is not given after, but before surgery of the primary tumour. It would also be of interest to investigate if the results hold true in subgroups based on molecular subtype.

Conclusions

For patients not treated with AST, timing of RT is not significantly associated with 10-year DFS, LRRFS and DMFS, but larger time intervals are associated with lower OS. The latter may be explained by the increased proportion of elderly patients in the larger time interval groups. However, patients treated with AST may benefit from a slightly longer time interval between BCS and RT when receiving chemotherapy after RT (BCS-RT-chemotherapy). For patients receiving chemotherapy before RT, time interval does not influence survival rates. However, the possible interplay between timing of chemotherapy and timing of RT needs further elucidation. In addition, the results should be evaluated further in different subgroups. All in all, we conclude that starting RT as soon as possible after BCS may not be necessary. This suggests that the relevance of the NBCA indicator in the Netherlands, as well as the common position that RT should start as soon as possible after RT can be questioned.

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Supplementary material

Supplementary Table 1. Population 1, baseline characteristics according to use of adjuvant systemic therapy (n=2,759)

Characteristics	No adjuvant treatment (n=1,761)			p-value ^a	Adjuvant treatment (998)			p-value ^a
	<42 days	42-55 days	>55 days		<42 days	42-55 days	>55 days	
Age								
<40	13 (1.9)	10 (1.5)	6 (1.5)		35 (8.6)	25 (6.5)	12 (5.9)	
40-49	105 (15.7)	99 (14.4)	46 (11.4)		73 (17.9)	82 (21.2)	35 (17.2)	
50-64	337 (50.3)	354 (51.5)	208 (51.6)		202 (49.4)	168 (43.5)	84 (41.4)	
≥65	215 (32.1)	225 (32.7)	143 (35.5)	0.562	99 (24.2)	111 (28.8)	72 (35.5)	0.062
Social economic status								
Low	183 (27.3)	188 (27.3)	119 (29.5)		118 (28.9)	111 (28.8)	59 (29.1)	
Medium	287 (42.8)	290 (42.2)	158 (39.2)		142 (34.7)	149 (38.6)	79 (38.9)	
High	200 (29.9)	210 (30.5)	126 (31.3)	0.817	149 (36.4)	126 (32.6)	65 (32.0)	0.700
Hospital volume (patients per year)								
0-49	133 (19.9)	112 (16.3)	60 (14.9)		55 (13.5)	57 (14.8)	29 (14.3)	
50-99	312 (46.6)	298 (43.3)	211 (52.4)		212 (51.8)	199 (51.6)	104 (51.2)	
100-149	147 (21.9)	184 (26.7)	93 (23.1)		93 (22.7)	77 (20.0)	47 (23.2)	
≥150	78 (11.6)	94 (13.7)	39 (9.7)	0.016	49 (22.7)	53 (13.7)	23 (11.3)	0.922
Region								
A	116 (17.3)	93 (13.5)	58 (14.4)		25 (6.1)	17 (4.4)	19 (9.4)	
B	76 (11.3)	47 (6.8)	26 (6.5)		58 (14.2)	53 (13.7)	23 (11.3)	
C	23 (3.4)	57 (8.3)	33 (8.2)		27 (6.6)	61 (15.8)	33 (16.3)	
D	102 (15.2)	107 (15.6)	78 (19.4)		95 (23.2)	78 (20.2)	46 (22.7)	
E	91 (13.6)	93 (13.5)	47 (11.7)		72 (17.6)	48 (12.4)	19 (9.4)	
F	38 (5.7)	86 (12.5)	85 (21.1)		11 (2.7)	26 (6.7)	26 (12.8)	
G	119 (17.7)	122 (17.7)	53 (13.2)		50 (12.2)	59 (15.3)	21 (10.3)	
H	50 (7.5)	22 (3.2)	11 (2.7)		8 (2.0)	4 (1.0)	3 (1.5)	
I	55 (8.2)	61 (8.8)	12 (3.0)	<0.001	63 (15.4)	40 (10.4)	13 (6.4)	<0.001

Characteristics	No adjuvant treatment (n=1,761)			Adjuvant treatment (998)			p-value ^a	p-value ^a
	<42 days	42-55 days	>55 days	<42 days	42-55 days	>55 days		
Lateralisation								
Left	334 (49.9)	354 (51.5)	208 (51.6)	217 (53.1)	201 (52.1)	107 (52.7)		
Right	336 (50.2)	334 (48.5)	195 (48.4)	192 (46.9)	185 (47.9)	96 (47.3)	0.794	0.962
Sublocalisation								
Outer quadrants	353 (52.7)	358 (52.0)	212 (52.6)	234 (57.6)	202 (52.3)	111 (54.7)		
Inner quadrants	144 (21.5)	173 (25.2)	98 (24.3)	77 (19.0)	61 (15.8)	36 (17.7)		
Central portion	39 (5.8)	25 (3.6)	21 (5.2)	26 (6.4)	33 (8.6)	12 (5.9)		
Overlapping lesions	130 (19.4)	126 (18.3)	67 (16.6)	69 (17.0)	84 (21.8)	42 (20.7)		
Unknown	4 (0.6)	6 (0.9)	5 (1.2)	3 (0.8)	6 (1.6)	2 (1.0)	0.355	0.383
Histological tumour type								
Ductal	533 (79.6)	526 (76.5)	311 (77.2)	356 (87.0)	319 (82.6)	172 (84.7)		
Lobular	75 (11.2)	70 (10.2)	53 (13.2)	20 (4.9)	27 (7.0)	12 (5.9)		
Mixed	20 (3.0)	31 (4.5)	14 (3.5)	13 (3.2)	24 (6.2)	12 (5.9)		
Other	42 (6.3)	61 (8.9)	25 (6.2)	20 (4.5)	16 (4.2)	7 (3.5)	0.197	0.331
Differentiation grade								
Grade I	252 (37.6)	284 (41.3)	147 (36.5)	57 (13.9)	55 (14.3)	37 (18.2)		
Grade II	317 (47.3)	176 (43.7)	176 (43.7)	131 (32.0)	151 (39.1)	87 (42.9)		
Grade III	48 (7.2)	37 (9.2)	37 (9.2)	190 (46.5)	159 (41.2)	67 (33.0)		
Unknown	53 (7.9)	43 (10.7)	43 (10.7)	31 (7.6)	21 (5.4)	12 (5.9)	0.308	0.012
Pathological tumour size in mm (IQR)	13 (10-17)	12 (9-16)	12 (9-16)	18 (14-24)	18 (13-23)	18 (12-24)		
Unknown	11 (1.6)	10 (1.5)	2 (0.5)	6 (1.5)	4 (1.0)	5 (2.5)	0.001	0.517
Number of positive nodes (IQR)	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-1)	1 (0-1)	1 (0-2)	0.165	
Unknown				7 (1.7)	1 (0.3)	4 (2.0)		0.002

Characteristics	No adjuvant treatment (n=1,761)			p-value ^a	Adjuvant treatment (998)			p-value ^a
	<42 days	42-55 days	>55 days		<42 days	42-55 days	>55 days	
Multifocality								
No	629 (93.9)	639 (92.9)	370 (92.9)		379 (92.7)	358 (92.8)	181 (89.2)	
Yes	21 (3.1)	20 (2.9)	20 (2.9)		11 (2.7)	11 (2.9)	6 (3.0)	
Unknown	20 (3.0)	29 (4.2)	29 (4.2)	0.613	19 (4.7)	17 (4.4)	16 (7.9)	0.967
Hormone receptor status								
ER and PR positive	490 (73.1)	477 (69.3)	263 (65.3)		260 (63.57)	267 (69.2)	147 (72.4)	
ER or PR positive	97 (14.5)	108 (15.7)	69 (17.1)		68 (16.6)	65 (16.8)	38 (18.7)	
ER and PR negative	62 (9.3)	78 (11.3)	53 (13.2)		73 (17.9)	47 (12.2)	16 (7.9)	
Unknown	21 (3.1)	25 (3.6)	18 (4.5)	0.135	8 (2.0)	7 (1.8)	2 (1.0)	0.011
Adjuvant systemic therapy								
No					-	-		
Hormonal therapy	NA	NA	NA		208 (50.9)	210 (54.4)	122 (60.1)	
Chemotherapy ^b					79 (19.3)	49 (12.7)	18 (8.9)	
Both					122 (29.8)	127 (32.9)	63 (31.0)	0.006
Axillary lymph node dissection								
No	610 (91.0)	647 (94.0)	373 (92.6)		302 (73.8)	286 (74.1)	147 (72.4)	
Yes	60 (9.0)	41 (6.0)	30 (7.4)	0.109	107 (26.2)	100 (25.9)	56 (27.6)	0.902
Residual tumour left								
No	635 (94.8)	658 (95.6)	369 (91.6)		372 (93.7)	360 (96.0)	187 (94.9)	
Yes (microscopic)	31 (4.6)	26 (3.8)	28 (7.0)		25 (6.3)	15 (4.0)	10 (5.1)	
Unknown	4 (0.6)	4 (0.6)	6 (1.5)	0.054	12 (2.9)	11 (2.9)	6 (3.0)	0.353
Referral for RT								
No	119 (17.8)	156 (22.7)	74 (18.4)		83 (20.3)	84 (21.8)	29 (14.3)	
Yes	551 (82.2)	532 (77.3)	329 (81.6)	0.054	326 (79.7)	302 (78.2)	174 (85.7)	0.086

Numbers are n (%) unless otherwise indicated. P-values were calculated on known values. ^a A p-value<0.2 is considered significant and indicated in bold. ^b Patients who received chemotherapy between surgery and radiation therapy were excluded. NA = not applicable.

Supplementary Figure 1. Population 1: Distribution of time intervals between BCS and RT, stratified for use of adjuvant systemic therapy. A = patients not treated with adjuvant systemic therapy, B = patients treated with adjuvant systemic therapy. The left panels show the distribution without outliers. The right panels show the distribution including outliers.

Supplementary Figure 2. Population 2: Distribution of time intervals between BCS and RT, stratified for timing of chemotherapy. A = patients treated with chemotherapy before RT, B = patients treated with chemotherapy after RT. The left panels show the distribution without outliers. The right panels show the distribution including outliers.

Supplementary Figure 3. Population 1: Distribution of recurrences within 10-years after diagnosis among interval groups. ** = significant difference between interval groups ($p < 0.05$)

Supplementary Figure 4. Population 1: Distribution of recurrences among interval groups, stratified for use of adjuvant systemic therapy.

Supplementary Figure 5. Population 1: 10-year disease-free, locoregional recurrence-free ant distant metastasis-free survival for the entire cohort.

Supplementary Figure 6. Population 1: 10-year disease-free, locoregional recurrence-free and distant metastasis-free survival. The left panel shows patients not treated with adjuvant systemic therapy. The right panel shows patients treated with adjuvant systemic therapy.

Supplementary Figure 7. Population 2: Distribution of recurrences within 10 years of diagnosis among interval groups, stratified for timing of chemotherapy. ** = significant difference between interval groups (p<0.05)

Supplementary Figure 8. 10-year disease-free, locoregional recurrence-free and distant metastasis-free survival, stratified for timing of chemotherapy. The left panel shows patients treated with chemotherapy before RT. The right panel shows patients treated with chemotherapy after RT.

PART II

Clinical risk prediction in breast cancer

Chapter

9

Chapter 9

Validation of the online prediction tool PREDICT v. 2.0 in the Dutch breast cancer population

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Abstract**Background**

PREDICT version 2.0 is increasingly used to estimate prognosis in breast cancer. This study aimed to validate this tool in specific prognostic subgroups in the Netherlands.

Methods

All operated women with non-metastatic primary invasive breast cancer, diagnosed in 2005, were selected from the nationwide Netherlands Cancer Registry (NCR). Predicted and observed 5- and 10-year overall survival (OS) were compared for the overall cohort, separated by oestrogen receptor (ER) status, and predefined subgroups. A >5% difference was considered as clinically relevant. Discriminatory accuracy and goodness-of-fit were determined using the area under the receiver operating characteristic curve (AUC) and the Chi-squared test.

Results

We included 8,834 patients. Discriminatory accuracy for 5-year OS was good (AUC 0.80). For ER positive and ER negative patients, AUCs were 0.79 and 0.75, respectively. Predicted 5-year OS differed from observed by 1.4% in the entire cohort, 0.7% in ER positive and 4.9% in ER negative patients. Five-year OS was accurately predicted in all subgroups. Discriminatory accuracy for 10-year OS was good (AUC 0.78). For ER positive and ER negative patients AUCs were 0.78 and 0.76, respectively. Predicted 10-year OS differed from observed by 1.0% in the entire cohort, 0.1% in ER positive and 5.3% in ER negative patients. Ten-year OS was overestimated (6.3%) in patients ≥ 75 years and underestimated (13.%) in T3 tumours and patients treated with both endocrine therapy and chemotherapy (6.6%).

Conclusions

PREDICT predicts OS reliably in most Dutch breast cancer patients, although results for both 5-year and 10-year OS should be interpreted carefully in ER negative patients. Furthermore, 10-year OS should be interpreted cautiously in patients ≥ 75 years, T3 tumours and in patients considering endocrine therapy and chemotherapy.

Introduction

Adjuvant systemic therapy is shown to reduce recurrence rates in breast cancer patients.^{1,2} In the current era of personalised cancer medicine, limiting under- and overtreatment is increasingly important to optimise the therapeutic benefit while minimising short- and long-term side effects of treatment.³ To personalise breast cancer treatment, several prediction tools have been developed including the online tools Adjuvant! Online⁴ and PREDICT.⁵ Adjuvant! Online is developed using the Surveillance, Epidemiology and End-Results (SEER) registry and predicts 10-year risks for recurrence, breast cancer specific-mortality and mortality due to other causes, including the expected benefit of adjuvant systemic treatments based on patient- and tumour-related factors. In the Netherlands, the online prediction tool Adjuvant! Online⁴ has widely been used in clinical practice.⁶ However, Adjuvant! Online has been described to overestimate survival outcomes in several breast cancer population.⁷⁻¹¹ PREDICT was developed using cancer registry data from the United Kingdom (UK) and predicts 5-year and 10-year overall survival (OS) for individual breast cancer patients, based on several patient- and tumour-related characteristics.⁵ It also provides the expected benefits of chemotherapy, endocrine therapy and trastuzumab. PREDICT version 1 was released in 2011, and the use of the tool increased steadily until 2016, whereafter its use increased substantially following disabling of Adjuvant! Online.¹² PREDICT version 1 has been validated on multiple independent case-cohorts from several countries including the UK, Canada, Malaysia and the Netherlands.¹³⁻¹⁸ Yet PREDICT has not been validated on the entire Dutch breast cancer population. Moreover, a new version of PREDICT, version 2.0, has become available recently.¹⁹ In version 2.0, the model was improved with the addition of the options of using the exact tumour size in millimetres, the exact number of positive lymph nodes, and the presence of micrometastases. In addition, follow-up was extended.

This study aimed to validate the online prediction tool PREDICT version 2.0 in a large population-based cohort in the Netherlands. Separate analyses were performed to study its validity in specific prognostic subgroups.

Methods

Design

In this large historic population-based cohort study, data on patient-, tumour- and treatment-related characteristics were obtained from the Netherlands Cancer Registry (NCR). The NCR is hosted by the Netherlands Comprehensive Cancer Organisation (IKNL), employing trained registrars to derive data of all patients newly diagnosed with cancer directly from patient records. Tumour topography and morphology were coded according to the International Classification of Diseases for Oncology (ICD-O), 3rd edition.²⁰ Staging was coded according to the tumour, node and metastasis (TNM) classification system, 6th edition.²¹ Additional data on vital status and date of death were derived from the Municipal Personal Records database, which was complete until February 2016.

Patients

All women diagnosed with non-metastatic primary invasive breast cancer in 2005 in the Netherlands, who received surgery as part of their treatment, were included. Patients who received primary systemic therapy or had no pathologically established tumour were

excluded. In addition, patients with unknown tumour size, number of positive lymph nodes, differentiation grade or oestrogen receptor (ER) status were excluded, since PREDICT does not allow missing values for these variables.

Statistical analysis

The outcomes of interest were 5-year and 10-year OS. The original script of PREDICT was used to calculate the expected OS and this was compared with observed OS obtained from the NCR. Comparisons were performed for the overall cohort, separated by ER status, and for subgroups based on age, stage, presence of micrometastases, grade, human epidermal growth factor receptor 2 (HER2) status, type of surgery, use and type of adjuvant systemic therapy and generation chemotherapy. A 95% confidence interval (CI) was calculated for the observed numbers. The predicted proportions are no real proportions, but reflect the sum of all predictions for each individual. As uncertainties around these predictions were not built into PREDICT, confidence intervals around the prediction estimates and differences could not be calculated. To assess goodness-of-fit of the model in each subgroup, observed and average predicted events were compared using a Chi squared-test. Mode of detection and Ki67 status were set to unknown for each patient as these variables were not registered in the NCR. Consequently, PREDICT uses the weighted mean coefficient of the unknown variable for these patients. For 2,278 patients who received chemotherapy, it was unknown which generation chemotherapy was administered. For this reason, every analysis was performed four times. Patients were classified as second generation, third generation, a combination of second and third generation (meaning that for these patients the mean coefficient of second generation and third generation was used in the predictions) or they were excluded. The analyses were compared, and no significant differences in calibration and discrimination between the four methods were observed, both for 5-year and 10-year OS (Supplementary Figure 1 to 4). Based on these results, it was decided to include all patients with an unknown chemotherapy generation and classify them as a combination of second and third generation for all further analyses.

As PREDICT has been generated on ER positive and ER negative patients separately, overall results were stratified by ER status, and graphical discrimination and calibration were determined. Discrimination was graphically shown in a receiver operating characteristic (ROC) curve. Here, the sensitivity (the proportion of patients who survived and were predicted correctly) was plotted against the 1-specificity (the proportion of patients who did not survive but were predicted as they would have survived). The discriminatory accuracy was quantified by the area under the ROC curve (AUC). An AUC of 0.5 indicates that the model performs as good as flipping a coin, whereas an AUC of 1 indicates perfect discrimination. In addition, model calibration was determined by plotting the averages of the observed against the predicted outcomes [with 95% confidence interval (CI)], grouped by quintiles based on the predicted estimates. The estimates were subsequently compared with the perfect prediction line ($y=x$). An a priori assumption was that PREDICT accurately predicted OS whenever the differences between predicted and observed outcomes were within a range of 5%, since differences outside of this range were considered as clinically relevant. A p-value <0.05 was considered as statistically significant. All statistical analyses were performed in STATA version 14.1.

Figure 1. Discriminatory accuracy of 5-year overall survival for the entire cohort, ER+ patients and ER- patients. Abbreviations: ROC = receiver operating characteristic curve, ER = oestrogen receptor

Figure 1. Discriminatory accuracy of 5-year overall survival for the entire cohort, ER+ patients and ER- patients. Abbreviations: ROC = receiver operating characteristic curve, ER = oestrogen receptor

Figure 3. Discriminatory accuracy of 10-year overall survival for the entire cohort, ER+ patients and ER- patients. Abbreviations: ROC = receiver operating characteristic curve, ER = oestrogen receptor

Figure 4. Discriminatory accuracy of 10-year overall survival for the entire cohort, ER+ patients and ER- patients. Abbreviations: ROC = receiver operating characteristic curve, ER = oestrogen receptor

Results

In total, 10,338 patients with operated, non-metastatic primary invasive breast cancer, diagnosed in 2005 were identified. Patients receiving primary systemic therapy (n=529), patients without a pathologically established tumour stage (n=2) or unknown tumour size in millimetres (n=332), missing number of positive lymph nodes (n=118), unknown differentiation grade (n=418) or ER status (n=105) were excluded, leading to a final study population of 8,834 patients (85% of the total population). Most patients presented with T1 (60.4%), N0 stage (62.2%), grade II (45.1%), ER positive (82.2%) and HER2-negative disease (69.8%). The majority of the patients did not receive adjuvant systemic therapy (61.7%) (Table 1). The median age was 58 years (interquartile range: 49-69 years). Median follow-up of this population was 10.4 years (interquartile range 9.2-10.7).

Discriminatory accuracy and calibration for 5-year OS

In the entire Dutch validation population, discriminatory accuracy for 5-year OS was good with an AUC of 0.80. Within ER positive and ER negative patients separately, the AUCs were 0.79 and 0.75, respectively (Figure 1). The predicted number of survivors after 5 years in the entire cohort was 7,595.2 (86.0%) compared to 7,723 (87.4%) observed survivors (Table 1). The difference was 1.4%, which was not significant ($p=0.14$). In ER positive patients, the difference between predicted and observed survivors was 0.7% ($p=0.53$). In ER negative patients, the difference between predicted and observed survivors was 4.9%, which was statistically significant ($p=0.02$), but just within the range of 5% (Table 1). Figure 2 shows the predicted and observed 5-year OS by quintiles of the predicted survival. For the entire cohort and for ER positive patients, the predicted and observed 5-year OS do not differ significantly. However, for ER negative patients, the predicted 5-year OS was significantly lower than the observed 5-year OS, with the largest deviations seen in the lowest and highest quintiles (Figure 2). For patients treated with breast-conserving surgery, 5-year OS was slightly underestimated with 2.9% ($p=0.03$), but this was within the range of 5%. For all other predefined subgroups no statistically significant differences between predicted and observed events were observed (Table 1).

Discriminatory accuracy and calibration for 10-year OS

In the entire Dutch validation population, discriminatory accuracy for 10-year OS was good with an AUC of 0.78. Within ER positive and ER negative patients separately, the AUCs were 0.78 and 0.76, respectively (Figure 3). The predicted number of survivors after 10 years in the entire cohort was 6,404 (72.5%) compared to 6,493 (73.5%) observed events. The difference was 1.0%, which was not significant ($p=0.27$). In ER positive patients, the difference between predicted and observed survivors was 0.1% ($p=0.92$). In ER negative patients, the difference between predicted and observed events was 5.3%, which was statistically significant ($p=0.01$) (Table 1). Figure 3 shows the predicted and observed 10-year OS by quintiles of the predicted survival. For the entire cohort and for ER positive patients, the predicted 5-year OS did not differ from the observed 5-year OS. However, for ER negative patients a significant underestimation was seen ($p=0.01$), with the most pronounced deviations in the two highest quintiles. In the predefined subgroups, a significant overestimation (6.3%, $p<0.01$) of 10-year OS was observed in patients ≥ 75 years.

Table 1. Observed and predicted 5- and 10-year overall survival by patient-, tumour- and treatment-related characteristics

	5-year OS					10-year OS				
	N (%)	Predicted (%)	Observed (%, 95% CI)	Difference (%)	p-value*	Predicted (%)	Observed (%, 95% CI)	Difference (%)	p-value*	
Entire cohort	8,834 (100)	7,595.2 (86.0)	7,723 (87.4) (86.7 – 88.1)	-127.8 (-1.4)	0.14	6,404.2 (72.5)	6,493 (73.5) (72.6 – 74.4)	-88.8 (-1.0)	0.27	
ER status										
Positive	7,263 (82.2)	6,466.9 (89.0)	6,517 (89.7) (89.0 – 90.4)	-50.1 (-0.7)	0.53	5,454.2 (75.1)	5,460 (75.2) (74.2 – 76.2)	-5.8 (-0.1)	0.92	
Negative	1,571 (17.8)	1,128.3 (71.8)	1,206 (76.8) (74.6 – 78.8)	-77.5 (-4.9)	0.02	950.0 (60.5)	1,033 (65.8) (63.3 – 68.1)	-83.0 (-5.3)	0.01	
Age										
<40	495 (5.6)	437.5 (88.4)	451 (91.1) (88.3 – 93.5)	-13.5 (-2.7)	0.52	393.3 (79.5)	404 (81.6) (77.9 – 84.9)	-10.7 (-2.2)	0.59	
40-49	1,735 (19.6)	1,562.7 (90.1)	1,602 (92.3) (91.0 – 93.5)	-39.3 (-2.2)	0.32	1,413.7 (81.5)	1,485 (84.0) (83.8 – 87.2)	-71.3 (-2.6)	0.06	
50-64	3,529 (40.0)	3,173.0 (90.0)	3,247 (92.0) (91.1 – 92.9)	-74.0 (-2.1)	0.19	2,826.8 (80.1)	2,918 (82.7) (81.4 – 83.9)	-91.2 (-2.6)	0.09	
65-74	1,869 (21.2)	1,606.5 (6.0)	1,644 (88.0) (86.4 – 89.4)	-37.5 (-2.0)	0.35	1,302.1 (69.7)	1321 (70.7) (68.6 – 71.7)	-18.9 (-1.0)	0.60	
≥75	1,206 (13.7)	815.5 (67.6)	779 (64.6) (61.8 – 67.3)	36.5 (3.0)	0.20	468.2 (38.8)	392 (32.5) (29.9 – 35.2)	76.2 (6.3)	<0.001	

5-year OS						10-year OS			
Observed						Observed			
N (%)		Predicted (%)	(%, 95% CI)	Difference (%)	p-value*	Predicted (%)		(%, 95% CI)	Difference (%)
T stage									p-value*
1	5,331 (60.4)	4,822.1 (90.5)	4,912 (92.1) (91.4 – 92.8)	-89.9 (-1.7)	0.19	4,233.0 (79.4)	4,280 (80.3) (79.2 – 81.4)	-47.0 (-0.9)	0.47
2	3,176 (36.0)	2,563.9 (80.7)	2,592 (81.6) (80.3 – 83.0)	-28.1 (-0.9)	0.58	2,035.7 (64.1)	2,058 (64.8) (63.1 – 66.5)	-22.3 (-0.7)	0.62
3	230 (2.6)	145.8 (63.4)	164 (71.3) (65.5 – 77.2)	-18.2 (-7.9)	0.13	95.2 (41.4)	125 (54.3) (47.7 – 60.9)	-29.8 (-13.0)	<0.001
4	97 (1.1)	63.4 (65.4)	55 (56.7) (46.3 – 66.7)	8.4 (8.7)	0.29	40.2 (41.5)	30 (30.9) (21.7 – 40.1)	10.2 (10.6)	0.11
N stage									
0	5,496 (62.2)	4,908.9 (89.3)	4,994 (90.9) (90.1 – 91.6)	-85.1 (-1.5)	0.23	4,257.0 (77.5)	4,290 (78.1) (77.0 – 79.2)	-33.0 (-0.6)	0.61
1	2,408 (27.3)	2,057.5 (85.4)	2,078 (86.3) (84.9 – 87.7)	-20.5 (-0.8)	0.65	1,715.6 (71.2)	1,723 (71.6) (69.8 – 73.4)	-7.4 (-0.3)	0.86
2	604 (6.8)	439.2 (72.7)	455 (75.3) (71.9 – 78.8)	-15.8 (-2.6)	0.45	320.1 (53.0)	349 (57.8) (53.9 – 61.7)	-28.9 (-4.8)	0.11
3	326 (3.7)	189.6 (58.1)	196 (60.1) (54.8 – 65.4)	-6.4 (-2.0)	0.64	111.4 (34.2)	131 (40.2) (34.9 – 45.5)	-19.6 (-6.0)	0.06
Presence of micrometastases									
No	8,321 (94.2)	7,130.6 (85.7)	7,251 (87.1) (86.4 – 87.9)	-120.4 (-1.4)	0.15	5,995.5 (72.1)	6,090 (73.2) (72.2 – 74.1)	-94.5 (-1.1)	0.22
Yes	513 (5.8)	464.5 (90.6)	472 (92.0) (89.7 – 94.4)	-7.5 (-1.5)	0.73	408.7 (79.7)	403 (78.6) (75.0 – 82.1)	5.7 (1.1)	0.78

10-year OS									
5-year OS									
Grade									
	N (%)	Predicted (%)	Observed (%, 95% CI)	Difference (%)	p-value*	Predicted (%)	Observed (%, 95% CI)	Difference (%)	p-value*
I	1,992 (22.6)	1,841.2 (92.4)	1,856 (93.2) (92.1 – 94.3)	-14.8 (-0.7)	0.73	1,632.5 (82.0)	1,620 (81.3) (79.6 – 83.0)	12.5 (0.6)	0.75
II	3,983 (45.1)	3,507.5 (88.1)	3,546 (89.0) (88.1 – 90.0)	51.5 (-1.0)	0.38	2,968.3 (74.5)	2,979 (74.8) (73.4 – 76.1)	-10.7 (-0.3)	0.84
III	2,859 (32.4)	2,246.5 (78.6)	2,321 (81.2) (79.7 – 82.6)	-74.5 (-2.6)	0.12	1,803.3 (63.1)	1,894 (66.2) (64.5 – 68.0)	-90.7 (-3.2)	0.03
HER2 status									
Negative	6,169 (69.8)	5,350.0 (86.7)	5,433 (88.1) (87.3 – 88.9)	-83.0 (-1.3)	0.26	4,524.0 (73.3)	4,580 (74.2) (73.2 – 75.3)	-56.0 (-0.9)	0.41
Positive	1,149 (13.0)	950.3 (82.7)	1,001 (87.1) (85.2 – 89.1)	-50.7 (-4.4)	0.10	804.5 (70.0)	853 (74.2) (71.7 – 76.8)	-48.5 (-4.2)	0.09
Unknown	1,516 (17.2)	1,294.8 (85.4)	1,289 (85.0) (83.2 – 86.8)	5.8 (0.4)	0.86	1,075.6 (71.0)	1,060 (69.9) (67.6 – 72.2)	15.6 (1.0)	0.63
Type of surgery									
Breast-conserving surgery	5,070 (57.4)	4,563.0 (90.0)	4,709 (92.9) (92.2 – 93.6)	-146.0 (-2.9)	0.03	4,008.5 (79.1)	4,162 (82.1) (81.0 – 83.1)	-153.5 (-3.0)	0.02
Mastectomy	3,764 (42.6)	3,032.2 (80.1)	3,014 (80.1) (78.8 – 81.4)	18.2 (0.5)	0.74	2,395.7 (63.6)	2,331 (61.9) (60.4 – 63.5)	64.7 (1.7)	0.19

5-year OS						10-year OS			
Observed			Observed			Observed			
N (%)	Predicted (%)	(%, 95% CI)	Difference (%)	p-value*	Predicted (%)	(%, 95% CI)	Difference (%)	p-value*	
Adjuvant systemic therapy									
No	5,454 (61.7)	4,730.9 (86.7)	4,748 (87.1)	-17.2 (-0.3)	0.81	3,952.2 (72.5)	3,888 (71.3)	64.2 (1.1)	0.31
			(86.2 – 87.9)				(70.1 – 72.5)		
Endocrine therapy	214 (2.4)	172.4 (80.6)	165 (77.1)	7.4 (3.5)	0.57	126.6 (59.2)	112 (52.3)	14.6 (6.8)	0.19
			(71.5 – 82.7)				(45.6 – 59.0)		
Chemotherapy	2,306 (26.1)	1,904.4 (82.6)	1,985 (86.1)	-80.6 (-3.5)	0.06	1,632.3 (70.8)	1,743 (75.6)	-110.7 (-4.8)	0.01
			(84.7 – 87.5)				(73.8 – 77.3)		
Both	860 (9.7)	787.5 (91.6)	825 (95.9)	-37.5 (-4.4)	0.18	693.1 (80.6)	750 (87.2)	-56.9 (-6.6)	0.03
			(94.6 – 97.3)				(85.0 – 89.4)		
Generation chemo-therapy									
No chemotherapy	5,668 (64.2)	4,903.3 (86.5)	4,913 (86.7)	-9.7 (-0.2)	0.89	4,078.8 (72.0)	4,000 (70.6)	78.8 (1.4)	0.22
			(85.8 – 87.6)				(69.4 – 71.8)		
Generation 2	615 (7.0)	555.1 (90.3)	585 (95.1)	-29.9 (-4.9)	0.20	491.3 (79.9)	532 (86.5)	-40.7 (-6.6)	0.07
			(93.4 – 96.8)				(83.8 – 89.2)		
Generation 3	416 (4.7)	355.7 (85.5)	378 (90.9)	-22.3 (-5.3)	0.24	311.0 (74.8)	344 (82.7)	-33.0 (-7.9)	0.06
			(88.1 – 93.6)				(79.1 – 86.3)		
Generation un-known	2,135 (24.2)	1,781.0 (83.4)	1,847 (86.5)	-66.0 (-3.1)	0.12	1523.1 (71.3)	1,617 (75.7)	-93.9 (-4.4)	0.02
			(85.1 – 88.0)				(73.9 – 77.6)		

Abbreviations: OS = overall survival, N = total number, SE = standard error, CI = confidence interval, ER = oestrogen receptor, HER2 = human epidermal growth factor receptor. *The p-value was calculated by using a Chi²-test. P-values indicated in bold are considered as statistically significant (p<0.05)

Ten-year OS was significantly underestimated by PREDICT in T3 tumours (13.0%, $p < 0.01$), grade III (3.2%, $p = 0.03$), patients treated with breast-conserving surgery (3.0%, $p = 0.02$), patients treated with chemotherapy only (4.8%, $p = 0.01$, patients treated with both endocrine therapy and chemotherapy (6.6%), $p = 0.03$) and in patients with an unknown generation of chemotherapy (4.4%, $p = 0.02$). However, the only differences outside the range of 5%, were in patients ≥ 75 years (overestimation), T3 tumours and patients treated with both endocrine therapy and chemotherapy (underestimation) (Figure 4).

Discussion

PREDICT version 2.0 accurately predicts 5-year OS in the entire Dutch validation population and in all pre-defined subgroups. Ten-year survival was predicted quite well, although underestimation was observed in ER negative patients, T3 tumours and patients treated with both endocrine therapy and chemotherapy. In addition, 10-year OS was overestimated in patients ≥ 75 years. Of note, 5-year OS for ER negative patients was underestimated (4.9%). Although this difference was within the range of 5%, it was statistically significant and became larger when estimating 10-year OS.

The finding that 10-year OS was underestimated in ER negative patients, but was accurately predicted in ER positive patients is in contrast to a previous validation study of PREDICT version 2.0 where slightly better predictions were reported for ER negative patients than for ER positive patients.¹⁹ A possible explanation for this discrepancy may be the inclusion of different populations (UK versus Dutch population). Two previous studies in the Netherlands have validated PREDICT version 1.2. The first, only including patients ≥ 65 years, showed that PREDICT version 1.2 largely overestimated 5-year OS in patients ≥ 85 years, and that 10-year OS was highly overestimated in patients ≥ 75 years.¹⁷ The second, only including patients < 50 years, showed that PREDICT version 1.2 accurately predicted 10-year OS in patients < 50 years, but that it was underestimated for patients < 40 years.¹⁸ Another validation study of the 1.2 version in the UK in patients < 40 years showed that 10-year OS was accurately predicted, but that 5-year OS was highly overestimated with 25%.¹⁵ The updated version 2.0 is described to provide more accurate predictions in all age groups in three independent validation cohorts, in contrast to version 1.2,¹⁴ suggesting that the newest version may perform better in all subgroups based on age.¹⁹ Our study confirms this for 5-year OS, which was accurately predicted in all subgroups based on age. However, for patients ≥ 75 years, we still found an overestimation for 10-year OS. Of note, this was to a much lesser extent than the previous validation study in the Netherlands.¹⁷ The still existing overestimation of 10-year OS in patients ≥ 75 years may partially be explained by the prevalence of comorbidities in older patients. PREDICT gives survival estimates for individual patients based on the average comorbidity for women with breast cancer of a similar age.¹² However, any increased prevalence of comorbidities or an overrepresentation of older patients in our cohort may have led to a lower OS.

Our findings that PREDICT version 2.0 underestimates 10-year OS in T3 tumours and patients treated with both endocrine therapy and chemotherapy may partly be explained by the fact that the PREDICT model has been generated on a population diagnosed from 1999 to 2003 in the UK. Our validation population consisted of patients diagnosed in 2005, in which differences in OS may partly reflect increased survival over time. Another explanation may be

the differences in health care provided in the Netherlands and the UK.

The large underestimations in patients with T3 stage is most likely to be explained by an underrepresentation of this group in the UK development population,⁵ but it may also be caused by differences in treatment strategies or other prognostic characteristics differing between our validation population and the development population. Of course, patients with T3 stage have a poorer prognosis compared to patients with T1 or T2 stage and have a higher likelihood of being treated with adjuvant systemic therapy. Since PREDICT is designed to assist in taking treatment decisions, the underestimation of 10-year OS may be therefore of less relevance in this specific patient group as far as decision-making is concerned. It remains of course a shortcoming for the prediction of outcome to inform the patients. Similarly, for the underestimation of 10-year OS in patients treated with both endocrine therapy and chemotherapy, it should be noted that treatment effects cannot be extracted from predictions of the model, as the patients included in the validation had already received their treatment, independent of the predictions in the model.

The accuracy of a prediction model can be interpreted in different ways. Several studies consider a difference between predicted and observed outcomes of less than 2% as accurate,^{8,22} while other studies base their interpretation on the 95% CI and corresponding p-value.^{16,18} According to the Dutch national guidelines, adjuvant systemic therapy is recommended in case of an absolute risk of 10-year breast cancer-related mortality of 15% or more. With the 15-year relative mortality reductions described by the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) ranging between 20 and 57%,¹ the absolute mortality reduction for most patients will be at least 4-5%.²³ A significant difference between predicted and observed survival of 5% may therefore systematically be accepted as the threshold to alter treatment decisions and was selected as a measure for whether or not differences between predicted and observed outcomes are of clinical relevance.

Importantly, we should be aware that any inaccurate prediction for a specific subgroup as a whole does not mean that this is applicable to every single patient in this subgroup.

Strengths and limitations

To our knowledge, this is the first population-based study in the Netherlands covering the entire PREDICT target population that validates PREDICT version 2.0 in specific prognostic subgroups. The population-based setting and the large number of included patients increase the generalisability and reliability of the results.

A limitation of this study is the absence of knowledge on cause-specific mortality, preventing us from determining whether discrepancies are due to breast cancer-specific mortality or other causes of death. Another limitation of this study is the lack of data on mode of detection and Ki67, which were set to unknown for all patients accordingly. Symptomatic cancers are more likely to present with unfavourable tumour characteristics compared to screen-detected cancers.²⁴ Thereby, this limitation may partly be neutralised by inclusion of the most important prognostic tumour characteristics in the PREDICT model. However, even after correction for these characteristics, mode of detection remains associated with survival outcomes²⁴ and may therefore have affected our results. Furthermore, Ki67 has been described to play an important role in breast cancer prognosis,²⁵ and not taking Ki67 status into account may have affected the results. However, substantial heterogeneity is observed in

the methods of Ki67 assessment,²⁶ which may limit its usefulness in determining a patient's prognosis and may explain why it is not routinely used in the Netherlands.

Conclusions

PREDICT accurately predicts 5-year OS in the overall Dutch validation population, and in all predefined sub-groups. Although within the range of 5%, 5-year OS for ER negative patients should be interpreted with care. Furthermore, 10-year OS was overestimated for patients ≥ 75 years, and underestimated for ER negative disease, T3 tumours and for patients receiving both endocrine therapy and chemotherapy. Given PREDICT's intentions to guide treatment decision-making, PREDICT may serve as a reliable prediction tool for the Dutch breast cancer population. However, 5-year OS should be interpreted cautiously in ER negative disease, and 10-year OS should be interpreted with care in patients ≥ 75 years, ER negative disease, T3 tumours and in patients considering endocrine therapy and chemotherapy.

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Supplementary material

Supplementary Figure 1. Observed and predicted 5-year overall survival for the entire cohort, with different classifications of patients with unknown generation chemotherapy

Supplementary Figure 2. Observed and predicted 10-year overall survival for the entire cohort, with different classifications of patients with unknown generation chemotherapy

Supplementary Figure 3. Discriminatory accuracy of 5-year overall survival for the entire cohort, with different classifications of patients with unknown generation chemotherapy

Supplementary Figure 4. Discriminatory accuracy of 10-year overall survival for the entire cohort, with different classifications of patients with unknown generation chemotherapy

Chapter

10

Chapter 10

10-year recurrence rates for breast cancer subtypes in the Netherlands: a large population-based study

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Abstract**Background**

Here we report for the first time the relation between breast cancer subtypes and 10-year recurrence rates and mortality in the Netherlands.

Methods

All operated women diagnosed with invasive non-metastatic breast cancer in 2005 in the Netherlands were included. Patients were classified into breast cancer subtypes according to ER, PR, HER2 status and grade: luminal A, luminal B, HER2 positive and triple negative. Percentages and hazards of recurrence were compared among subtypes. Adjusted 10-year overall (OS) and recurrence-free survival (RFS) were calculated using multivariable Cox regression.

Results

Of 8,062 patients, 4,482 (56%) were luminal A, 2,090 (26%) luminal B, 504 (6%) HER2 positive and 986 (12%) triple negative. Local recurrences (7.5%) and distant metastases (25.6%) occurred most often in HER2 positive disease and the least often in luminal A (3.7% and 9.5%, respectively). Regional recurrences were most often diagnosed in triple negative disease (5.2%), and the least often in luminal A (1.7%).

HER2 positive and triple negative subtypes had the highest recurrence rates in the second year, while luminal A and B showed a more continuous pattern over time, with lobular tumours recurring more often. After adjustment for differences in baseline characteristics, triple negative disease showed worse 10-year OS and triple negative and HER2 positive disease had the lowest 10-year RFS.

Conclusions

In the Netherlands, breast cancer subtypes are important predictors for 10-year recurrence rates. Knowledge on recurrence and survival rates according to these different subtypes, in combination with other prognostic factors, can support patient-tailored treatment and individualised follow-up.

Introduction

Regardless of similarities in standard clinicopathological characteristics, breast cancer remains a very heterogeneous disease, comprising widely varying morphologic and biological features, clinical behaviour and treatment responses.¹ This heterogeneity makes patient-tailored treatment strategies challenging, and highlights the need for more differentiated tumour classifications, useful to predict clinical outcomes.² Numerous studies have already shown that oestrogen (ER) and progesterone receptor (PR) status play an important role in breast cancer prognosis and treatment response,³⁻⁵ and that joint expression of ER and PR status (hormonal receptor status) identifies breast cancer variants better than either ER or PR expression levels alone.⁶ Besides, human epidermal growth factor receptor 2 (HER2) status has frequently been shown to be an important prognostic and predictive factor in breast cancer.^{7,8} The prognostic and predictive value of ER, PR and HER2 status increases when the three are combined.⁹ Studies have shown that the combined expression levels of ER, PR and HER2 into so-called intrinsic molecular subtypes increases its prognostic and predictive value.¹⁰⁻¹² The classification of tumours into luminal A, luminal B, HER2 positive and triple negative disease has been accepted by international panels that emphasise the importance to base therapeutic decisions on intrinsic molecular subtypes of breast cancer.^{13,14} Due to lacking data on gene expression levels, many studies use information on ER, PR and HER2 status which is based on immunohistochemistry to classify patients according to breast cancer subtypes. Both subtypes based on gene expression and on immunohistochemistry are shown to be independent predictors of survival and recurrence risk, reflected in a myriad of publications.¹⁵⁻²²

However, long-term (≥ 10 -year) recurrence rates in daily practice are rarely described in the literature, as many studies lack follow-up beyond five years from diagnosis. In order to optimise patient-tailored breast cancer treatment, it is crucial to gain insight in long-term recurrence and mortality rates according to the different breast cancer subtypes. The aim of this study was to analyse the relation between breast cancer subtypes and 10-year rates of recurrence and mortality in women diagnosed with non-metastatic breast cancer in the Netherlands, using a nationwide population-based registry.

Methods

Patients

All women diagnosed with invasive non-metastatic breast cancer in 2005 treated with local surgery in the Netherlands were included. Patients with unknown ER, PR, or HER2 status were excluded. Patient-, tumour-, and treatment-related characteristics were obtained from the nationwide Netherlands Cancer Registry. Tumour topography, morphology and grade were coded according to the International Classification of Diseases for Oncology, 3rd edition.²³ Staging was coded according to the tumour, node and metastasis (TNM) classification system, 6th edition.²⁴ Data on vital status and date of death were derived from the Municipal Personal Records database, which was complete until February 2017. Data on recurrences (including locoregional recurrence and distant metastases) were retrospectively gathered from patient files. Recurrences were defined according to existing consensus-based definitions for recurrence classification.²⁵ Patients who emigrated out of the Netherlands or were treated in a foreign hospital were excluded from this follow-up.

Definitions

Patients were classified into four breast cancer subtypes (adapted from the St Gallen International Expert Consensus)¹³ according to ER, PR, HER2 status (based on immunohistochemistry) and tumour grade: luminal A (ER or PR positive, HER2 negative and grade 1 or 2), luminal B (ER or PR positive, HER2 positive, or HER2 negative with grade 3), HER2 positive (ER and PR negative and HER2 positive) and triple negative (ER, PR and HER2 negative). Originally, Ki-67 was used to classify patients in either luminal A or B.¹³ However, due to lacking data on Ki-67 we used grade to classify high risk luminal A tumours into the luminal B group. A tumour was considered to be ER or PR positive when at least 10% positive nuclei were present. Less than 10% was regarded as negative. HER2 positivity was defined as a positive immunohistochemistry (3 positive, at least 10% of cells with membrane staining of strong intensity). It was negative when less than 10% of the cells showed membrane staining. In case of a 2 positive immunohistochemistry score (at least 10% of cells stained with moderate intensity), an amplification test was performed that overruled the results of the immunohistochemistry. To calculate the risk on a specific recurrence, the first local, regional or distant recurrence was used, irrespective of another recurrence that occurred earlier, if applicable. A sensitivity analysis was performed to determine whether results would be different when taking the first event only, and ignoring subsequent events. Ten-year recurrence-free (RFS) and overall (OS) survival were defined as the cumulative probability of being free from locoregional or distant recurrences or being alive within 10 years after diagnosis, respectively. Contralateral breast cancer was not regarded as a recurrence, so for 10-year RFS patients remained at risk when experiencing a contralateral event. Patients who died during follow-up and did not experience a recurrence were censored.

Statistical analysis

For each breast cancer subtype separately, descriptive statistics were performed to characterise the study population with regard to patient-, tumour-, and treatment-related characteristics. Ten-year recurrence rates were specified for breast cancer subtype. Hazards on recurrences over time were graphically designed using the `-sts graph-` function in the statistical software program STATA. Ten-year OS and RFS were calculated using the Kaplan-Meier method, and outcomes per breast cancer subtype were compared using the log-rank test. As lobular carcinoma of the breast is known to have different molecular features and a different behaviour than for example ductal tumours,²⁶ we additionally analysed 10-year recurrence rates, hazards, OS and RFS for ductal versus lobular tumours. Due to the small number of patients and events in HER2 positive and triple negative tumours, we restricted this analysis to luminal A and luminal B subtypes. Lastly, for confounding adjusted 10-year OS and RFS were determined using multivariable Cox proportional hazard analyses, in which a correction was applied for potential confounding variables based on clinical foreknowledge and availability. Variables included were: age, tumour stage, nodal stage, lateralisation and sublocalisation of the tumour within the breast, differentiation grade, histological tumour type, multifocality, type of surgery, adjuvant systemic treatment, targeted therapy and axillary lymph node dissection. Manual backward selection ($p < 0.1$) was performed to remove variables that did not significantly contribute to the model. The proportional hazards assumption was tested by plotting the log of the $-\log$ survival function $\{\log[-\log(S(t))]\}$ against

the log of the survival time [log(t)]. When this plot showed linear graphs, the proportional hazards assumption was considered to be met. No deviations were found. A p -value <0.05 was considered to be statistically significant. All statistical analyses were performed in STATA version 14.1 (StataCorp LP).

Results

Follow-up was completed for 10,325 of in total 10,426 patients eligible for inclusion (99%). Of the 10,325 patients, 2,263 patients were excluded due to missing ER, PR, HER2 status or tumour grade, preventing them from being classified as one of the breast cancer subtypes. Finally, 8,062 patients were included in this study of whom 4,482 (55.6%) had a luminal A tumour, 2,090 (25.9%) had luminal B, 504 (6.3%) had HER2 positive and 986 (12.2%) had triple negative. Patient-, tumour-, and treatment-related characteristics separated by breast cancer subtype are shown in Table 1. In general, patients with the triple negative subtype were the youngest, and patients with luminal A were the oldest. Patients with luminal A breast cancer presented with the most favourable characteristics in terms of grade, T stage and N stage. Lobular histology was present in 14.9% of the luminal A patients, compared to 4.9%, 3.0% and 0.8% in luminal B, triple negative and HER2 positive disease (Table 1).

Table 1. Patient-, tumour- and treatment-related characteristics of the entire cohort, separated by molecular subtype (n=8,062)

	Luminal A	Luminal B	HER2 positive	Triple negative	p-value*
	4,482 (55.6%)	2,090 (25.9%)	504 (6.3%)	986 (12.2%)	
Age					
<40	170 (3.8)	189 (9.1)	42 (8.3)	127 (12.9)	<0.001
40-49	828 (18.5)	543 (26.0)	104 (20.6)	233 (23.6)	
50-59	1,264 (28.2)	537 (25.7)	163 (32.4)	266 (27.0)	
60-69	1,079 (24.1)	392 (18.8)	114 (22.6)	183 (18.6)	
70-79	757 (16.9)	279 (13.3)	49 (9.7)	125 (12.7)	
>79	384 (8.6)	150 (7.2)	32 (6.4)	52 (5.3)	
Lateralisation					
Left	2,282 (50.9)	1,088 (52.1)	256 (50.8)	538 (54.6)	0.203
Right	2,200 (49.1)	1,002 (47.9)	248 (49.2)	448 (45.4)	
Sublocalisation					
Outer quadrants	2,102 (46.9)	965 (46.2)	245 (48.6)	510 (51.7)	0.003
Inner quadrants	840 (18.7)	363 (17.4)	90 (17.9)	185 (18.8)	
Central parts	386 (8.6)	166 (7.9)	36 (7.1)	48 (4.9)	
Overlapping lesions	1,076 (24.0)	552 (26.4)	126 (25.0)	233 (23.6)	
Unknown	78 (1.7)	44 (2.1)	7 (1.4)	10 (1.0)	

	Luminal A 4,482 (55.6%)	Luminal B 2,090 (25.9%)	HER2 positive 504 (6.3%)	Triple negative 986 (12.2%)	p-value*
Histological tumour type					
Ductal	3,282 (75.5)	1,875 (89.7)	473 (93.9)	850 (86.2)	<0.001
Lobular	669 (14.9)	102 (4.9)	4 (0.8)	30 (3.0)	
Mixed	248 (5.5)	79 (3.8)	6 (1.2)	11 (1.1)	
Other	183 (4.1)	34 (1.6)	21 (4.2)	95 (9.6)	
Grade					
I	1,643 (36.7)	74 (3.5)	10 (1.8)	33 (3.3)	NA
II	2,839 (63.3)	330 (15.8)	105 (20.8)	161 (16.3)	
III	-	1,613 (77.2)	340 (67.5)	713 (72.3)	
Unknown	-	73 (3.5)	49 (9.7)	79 (8.0)	
Multifocality					
No	3,746 (83.6)	1,641 (78.5)	387 (76.8)	847 (85.9)	<0.001
Yes	630 (14.1)	384 (18.4)	95 (18.9)	105 (10.7)	
Unknown	106 (2.4)	65 (3.1)	22 (4.4)	34 (3.5)	
T stage					
1	2,956 (65.9)	951 (45.5)	209 (41.5)	425 (43.1)	<0.001
2	1,277 (28.5)	863 (41.3)	203 (40.3)	430 (43.6)	
3	90 (2.0)	69 (3.3)	19 (3.8)	31 (3.1)	
4	33 (0.7)	29 (1.4)	6 (1.2)	12 (1.2)	
Unknown	126 (2.8)	178 (8.5)	67 (13.3)	88 (8.9)	
N stage					
0	2,767 (61.7)	996 (47.7)	225 (44.6)	574 (58.2)	<0.001
1	1,224 (27.3)	612 (29.3)	118 (23.4)	199 (20.2)	
2	228 (5.1)	179 (8.6)	58 (11.5)	71 (7.2)	
3	108 (2.4)	118 (5.6)	38 (7.5)	45 (4.6)	
Unknown	155 (3.5)	185 (8.9)	65 (12.9)	97 (9.8)	
Type of surgery					
BCS with RT	3,218 (56.6)	454 (51.4)	203 (40.3)	552 (56.0)	<0.001
BCS without RT	68 (1.2)	6 (0.7)	5 (1.0)	6 (0.6)	
Mastectomy with RT	615 (10.8)	150 (17.0)	128 (25.4)	167 (16.9)	
Mastectomy without RT	1,787 (31.4)	274 (31.0)	168 (33.3)	261 (26.5)	
Axillary lymph node dissection					
No	2,398 (53.5)	877 (42.0)	202 (40.1)	507 (51.4)	<0.001
Yes	2,084 (46.5)	1,213 (58.0)	302 (59.9)	479 (48.6)	
Primary systemic therapy					
No	4,372 (97.6)	1,923 (92.0)	441 (87.5)	901 (91.4)	<0.001
Yes	110 (2.5)	167 (8.0)	63 (12.5)	85 (8.6)	

	Luminal A	Luminal B	HER2 positive	Triple negative	p-value*
	4,482 (55.6%)	2,090 (25.9%)	504 (6.3%)	986 (12.2%)	
Adjuvant systemic therapy					
None	2,362 (52.7)	334 (16.0)	180 (35.7)	380 (38.5)	
Endocrine therapy	1,036 (23.1)	708 (33.9)	12 (2.4)	12 (1.2)	
Chemotherapy	38 (0.9)	52 (2.5)	301 (59.7)	582 (59.0)	
Both	1,046 (23.3)	996 (47.7)	11 (2.2)	12 (1.2)	<0.001
Targeted therapy (trastuzumab)					
No	4,475 (99.8)	1,720 (82.3)	248 (49.2)	982 (99.6)	
Yes	7 (0.2)	370 (17.7)	256 (50.8)	4 (0.4)	<0.001

*The p-value is calculated on known values only. A p-value indicated in bold is considered as statistically significant ($p < 0.05$). Abbreviations: NA = not applicable, due to empty cells (luminal A); BCS = breast-conserving surgery; RT = radiation therapy.

10-year recurrence rates per breast cancer subtype

In the entire population, 4.7% of the patients experienced a local recurrence within 10 years, 3.0% was diagnosed with a regional recurrence and in 15.0% of the patients a distant metastasis occurred. A sensitivity analysis on our data, examining only the first event to calculate the risk on a recurrence, showed slightly lower percentages (4.4%, 2.6%, 13.5%), but similar results for breast cancer subtypes (data not shown).

Figure 1. 10-year percentages of recurrent breast cancer, per breast cancer subtype. All percentages differed significantly ($p < 0.05$) between the subtypes. Abbreviations: HER2 = human epidermal growth factor receptor 2.

Local recurrences were most often diagnosed in patients with HER2 positive disease (7.5%), compared to 7.1% in triple negative, 5.0% in luminal B and 3.7% in luminal A, respectively. Regional recurrences within 10 years were most often diagnosed in the triple negative subtype (5.2%), compared to 4.5%, 4.0% and 1.7% in luminal B, HER2 positive and luminal A, respectively. Distant metastases within 10-years were experienced by 25.6% of patients

with HER2 positive disease, by 23.2% of patients with triple negative disease, by 20.0% of patients with luminal B disease and 9.5% in patients with luminal A disease. All differences among the subtypes were statistically significant. For all types of recurrences, luminal A showed the lowest incidence (Figure 1). Results were further specified according to the use of trastuzumab in HER2 positive patients (all patients in the HER2 positive subtype, and part of the patients in the luminal B subtype). When no trastuzumab was given to HER2 positive patients, the percentages of recurrences increased (Supplementary Figure 1).

The hazards of recurrences are shown in Figure 2. For the HER2 positive and triple negative subtypes, a clear peak was observed at two years after diagnosis for all types of recurrences, especially for distant metastases. Notably, the hazard of distant metastasis for luminal A and B showed a more constant pattern, and after four years the hazard of HER2 positive and triple negative subtypes became much lower than that of the luminal subtypes (Figure 2). Results were specified for the use of trastuzumab. In both the luminal B and HER2 positive subtypes, recurrence rates were higher for patients who did not receive trastuzumab (Supplementary Figure 2 and 3). For patients not treated with trastuzumab within the luminal B subtype, the hazard of distant metastases appeared to be higher in the first three years after diagnosis compared to patients who did receive trastuzumab, whereafter this hazard declined again (Supplementary Figure 2).

10-year crude overall and recurrence-free survival according to breast cancer subtype

Median follow-up to last observation or death of all patients was 11.3 years (interquartile range 9.3-11.7 years); this was similar for all subtypes. In total, 70.0% of all patients was alive at the end of follow-up. The percentages of survivors per breast cancer subtype were 74.0%, 67.0%, 64.3% and 61.4% within luminal A, luminal B, HER2 positive and triple negative disease, respectively.

Median follow-up to first recurrence or last observation is 9.5 years (interquartile range 5.4-10 years). For luminal A, median follow-up was 9.6 years (interquartile range 6.3-10 years), for luminal B 9.5 years (interquartile range 5.0-10 years), for HER2 positive 9.2 years (interquartile range 2.8-10 years) and for triple negative 9.2 (interquartile range 2.9-10 years). In total, 81.9% of all patients was free of disease 10 years after diagnosis. The percentages of patients free of recurrences per breast cancer subtype were 87.5%, 76.6%, 70.0% and 73.4% for luminal A, luminal B, HER2 positive and triple negative disease, respectively.

A graphical representation of both 10-year OS and RFS is shown in Figure 3. The results were further specified according to the use of trastuzumab in a subset of luminal B and in HER2 positive patients, showing that patients treated with trastuzumab had better OS and RFS (Supplementary Figure 4).

Ductal versus lobular: 10-year crude overall and recurrence-free survival according to breast cancer subtype

In total, 6,580 patients had a ductal tumour, of which 3,382 (51.4%) were luminal A and 1,875 (28.5%) were luminal B. Lobular tumours were present in 805 patients of which 669 (83.1%) were luminal A, and 102 (12.7%) were luminal B.

Within the luminal A subtype, no significant difference in local and regional recurrences was found between ductal and lobular tumours. However, distant metastases occurred

Figure 2. Hazards on recurrences in 10 years following diagnosis, specified for breast cancer subtype. Abbreviations: LR = local recurrence, RR = regional recurrence, DM = distant metastasis, HER2 = human epidermal growth factor receptor 2.

Within the luminal B subtype, no significant difference in regional recurrences and distant metastases was seen between ductal and lobular tumours. However, the percentage of local recurrences in lobular tumours was significantly higher than in ductal tumours (9.8 vs. 4.6%, $p=0.019$) (Figure 4). These differences are also clearly visible in the hazards of recurrences over time (Supplementary Figure 5). With regard to 10-year OS, a significant higher OS for ductal tumours compared to lobular tumours within the luminal A subtype was found ($p=0.014$), but not within the luminal B subtype. Regarding 10-year RFS, no significant differences between ductal and lobular tumours in both luminal A and B subtypes were found. However, both OS and RFS rates for lobular tumours were lower than for ductal tumours (Supplementary Figure 6).

Figure 3. 10-year overall and recurrence-free survival, specified for breast cancer subtype. Abbreviations: HER2 = human epidermal growth factor receptor 2.

10-year confounding-adjusted overall and recurrence-free survival according to breast cancer subtype

After correction for confounding variables, triple negative disease was associated with a significantly lower 10-year OS, compared to luminal A [HR 1.25 (95% CI: 1.05-1.48)]. Luminal B [HR 1.10 (95% CI: 0.93-1.29)] and HER2 positive disease [HR 1.03 (95% CI: 0.83-1.29)] showed equal 10-year OS as luminal A (Table 2).

Regarding for confounding adjusted 10-year RFS, luminal B showed lower RFS compared to luminal A [HR 1.22 (95% CI: 0.99-1.50)], although not statistically significant. However, HER2 positive [HR 1.45 (95% CI: 1.09-1.93)], and triple negative [HR 1.36 (95% CI: 1.07-1.73)] showed significantly worse 10-year RFS compared to luminal A (Table 2).

Discussion

This study described the 10-year recurrence rates and for confounding adjusted 10-year OS and RFS according to breast cancer subtype in the Dutch breast cancer population, diagnosed in 2005. We showed that luminal A breast cancer was associated with the lowest recurrence rates, while HER2 positive and triple negative breast cancers were associated with the highest recurrence rates. Especially for HER2 positive and triple negative breast cancers,

the recurrence rates were highest around two years after diagnosis, while luminal A and B showed a more continuous pattern with recurrences also later on during follow-up. We additionally showed that the distribution of breast cancer subtypes is different for lobular and ductal tumours, and that lobular tumours show a different 10-year recurrence pattern than ductal tumours. When adjusting for confounding, triple negative disease was associated with the lowest 10-year OS, and HER2 positive and triple negative disease were related to the lowest 10-year RFS.

Figure 4. 10-year percentages of recurrent breast cancer for luminal A and luminal B, specified for ductal and lobular tumours. Chi2 tests ($p < 0.05$ is considered as statistically significant): Within the luminal A subtype, the percentage of distant metastases differed significantly between ductal and lobular tumours (9.1 vs. 12.0%, $p = 0.021$). Within the luminal B subtype, the percentage of local recurrences differed significantly between ductal and lobular tumours (4.6 vs. 9.8%, $p = 0.019$). Other differences between ductal and lobular tumours were not significant.

Table 2. Adjusted hazard ratios for 10-year overall and recurrence-free survival in breast cancer patients according to breast cancer subtype

Subtype	n	10-year OS		10-year RFS	
		HR (95% CI) ^a	p-value	HR (95% CI) ^b	p-value
Luminal A	4,482	1		1	
Luminal B	2,090	1.10 (0.93-1.29)	0.271	1.22 (0.99-1.50)	0.063
HER2 positive	504	1.03 (0.83-1.29)	0.766	1.45 (1.09-1.93)	0.012
Triple negative	986	1.25 (1.05-1.48)	0.013	1.36 (1.07-1.73)	0.011

A p-value indicated in bold is considered as statistically significant ($p < 0.05$). ^a Variables included in the final multivariable model were: age, tumour stage, nodal stage, sublocalisation of the tumour within the breast, differentiation grade, type of surgery, adjuvant systemic treatment, targeted therapy and axillary lymph node dissection. ^b Variables included in the final multivariable model were: age, tumour stage, nodal stage, sublocalisation of the tumour within the breast, differentiation grade, histological tumour type, multifocality, type of surgery, adjuvant systemic treatment and targeted therapy. Abbreviations: OS = overall survival, RFS = recurrence-free survival, HR = hazard ratio, CI = confidence interval, HER2 = human epidermal growth factor receptor 2.

The distribution of breast cancer subtypes in the Dutch breast cancer population (55.6% luminal A, 25.9% luminal B, 6.3% HER2 positive and 12.2% triple negative) was similar to that found in a Korean²⁷ and a Norwegian population,²⁸ but different from the distribution

found in a Canadian¹⁷ and Chinese population,²⁰ in which luminal B disease was less common (16.0% and 7.5%, respectively) and HER2 positive breast cancer was more common (12% and 12.6%, respectively). On the other hand, in a German population, luminal A was less common (44.7%) and luminal B was more common (38.0%).²¹ Differences in these distributions may be explained by different definitions of breast cancer subtypes. For example, in the German population grade was not taken into account, but Ki-67 was, probably explaining the differences between luminal A and B. However, it has been described that especially grade plays an important role in the prognosis and classification of breast cancer subtypes,²⁸ and that grade is associated with Ki-67 in luminal A tumours.^{29,30} Indeed, in our study we show that more patients can be classified as low risk (luminal A) by using grade in the definition of breast cancer subtype. In grade 2 breast cancers, it has been shown that Ki-67 assessment suffers from a lot of inter- and intraobserver variability,³¹ possibly explaining part of the differences. However, it should be noted that this variability may also be present to some extent in grade assessment.³² In the Netherlands, we define ER and PR positivity as $\geq 10\%$ positive nuclei, while in the United States a cut-off of 1% is used, which may also lead to differences in the classification of patients into breast cancer subtypes.

The lowest recurrence rates we found in luminal A breast cancers confirms results from previously published studies.^{17,20,22} In addition, triple negative and HER2 positive disease were shown to have a worse prognosis compared to the other subtypes, as was also shown before.^{16,17,23} A Canadian study showed that, after a median follow-up of 6.9 years, 2% of luminal A breast cancers had a local recurrence, compared to 4% in luminal B, 8% in HER2 positive, and 12% in triple negative.¹⁷ Our study showed 10-year local recurrence rates of 3.7%, 5.0%, 7.5% and 7.1% for the four subtypes, respectively. Interestingly, taking into account that our study had a longer follow-up, the local recurrence rates in luminal A and B were lower in the Canadian study, while the rates in HER2 positive and triple negative were higher as compared to our study. This suggests not only that for the latter two subtypes rates are lower in the Netherlands, but also that luminal A and B may have a greater tendency to recur later on in the follow-up. This highlights the importance of at least 10 years of follow-up when studying recurrences, as demonstrated in several studies.^{34,35} The same Canadian study showed that distant metastases occurred in 6.4% of luminal A, 12.1% of luminal B, 19.2% of HER2 positive and 27.4% of triple negative breast cancers,¹⁷ while in our study these percentages were 9.5%, 20.0%, 25.6% and 23.2%. In our study, percentages of distant metastases were higher than in the Canadian study, which may partly be attributed to the fact that not all patients were treated with trastuzumab in our study. For the other subtypes, the same pattern is seen as for local recurrences, increasing the evidence for the luminal subtypes to recur later on in the follow-up. Another Chinese study with a median follow-up of 5.7 years demonstrated local recurrences rates of 12.7%, 15.7%, 19.1% and 20.9% in luminal A, luminal B, HER2 positive and triple negative subtypes, respectively,²⁰ which is very high compared to our results. Interestingly, a preceding Dutch study showed that the hazard of recurrences was highest around two years after diagnosis, and that a second (smaller) peak was observed around nine years after diagnosis.³⁵ In our study, the peak at nine years was less pronounced, but mostly visible for distant metastasis in the luminal A and luminal B subtype, which may possibly be related to an extinguished effect of endocrine therapy.³⁶ The highest incidence of recurrences around two years after diagnosis, as described before,³⁷ was

observed as well in our study. Importantly, we showed that this peak was most prominent in HER2 positive and triple negative disease.

In this study, we showed that lobular tumours recur more often than ductal tumours, with a significantly higher rate of distant metastases in luminal A disease, and significantly more local recurrences in luminal B disease. The importance of analysing survival and recurrence rates for ductal and lobular tumours separately is underlined by a review of McCart Reed *et al.*,²⁶ in which is shown that lobular tumours present with a distinctive mutation pattern and that intra-abdominal metastases are more common compared to tumours of another histology. Several other studies showed the distinctive pattern of metastases in lobular breast tumours^{38,39} and the importance of using the lobular histology as prognostic factor.⁴⁰ In our study, metastases during follow-up were more likely to present in the intra-abdominal area, and less likely to present in the liver or lungs in lobular tumours than in ductal tumours (data not shown), thereby confirming previous literature.^{38,39} This emphasises the need for future research to focus on breast cancer subtypes within a histological tumour type such as lobular or ductal breast cancer.

An important strength of this study is its population-based character, thereby increasing the generalisability of the results. Furthermore, an active follow-up, which was complete for 99% of all included patients, was conducted in which all recurrent events were registered that occurred within 10 years after diagnosis, thereby ensuring collection of recurrences with high accuracy. To the best of our knowledge, this is the first study in the Netherlands that evaluated 10-year recurrence rates according to breast cancer subtype. In addition, we adjusted for confounding adjusted OS and RFS, providing reliable outcomes by correcting for other prognostic variables that may have had an influence on the results and confirming the independent prognostic effect of breast cancer subtype. A possible limitation of this study is the inclusion of patients diagnosed in 2005. First, treatment strategies and survival rates have been improved, leading to lower recurrence rates of time, as was also shown by a preceding Dutch study looking at 5-year recurrence rates over time.⁴¹ Second, HER2 status determination and administration of trastuzumab was introduced in 2005 and was therefore not performed for all patients in this cohort. Patients with an unknown HER2 status were excluded, but in patients with a known HER2 status there were still differences in use of trastuzumab. For this reason, we additionally assessed all outcomes for luminal B and HER2 positive according to the use of trastuzumab, showing that patients treated with trastuzumab had better outcomes. Our results that HER2 positive breast cancers, together with triple negative breast cancers, were associated with the lowest RFS should therefore be interpreted with care. Furthermore, lacking data on Ki-67 prevented us from including this marker in the classification of breast cancer subtypes. However, as there is substantial heterogeneity and there are variable levels of validity in methods of Ki-67 assessment, it may be questioned whether inclusion of this marker may improve breast cancer subtype classification.⁴² Unfortunately, data on comorbidities was lacking, preventing us from making any statements about this variable, nor to eliminate it as a confounder.

Together, our results show clear differences in 10-year recurrence rates among the four breast cancer subtypes. Even after adjustment for confounding, significantly lower 10-year OS and RFS were found for triple negative and HER2 positive breast cancer. The latter should, however, be interpreted with care, as not all patients with HER2 positive disease were treated

with trastuzumab in this study. It is expected that current recurrence rates are much lower for this subgroup. However, these results emphasise the importance of classifying patients according to breast cancer subtype, which may help individualise the follow-up. With respect to the latter, it is important to realise that other factors such as histological tumour type (ductal, lobular, etcetera) may play an important role in personalised risk stratification as well.

Conclusions

This study confirms that, although local and regional recurrence rates are low overall, breast cancer subtypes are important predictors for 10-year recurrence rates in the Netherlands. Luminal A showed the lowest recurrence rates, but together with luminal B these subtypes are more likely to recur later on in the follow-up, while HER2 positive and triple negative subtypes had the greatest tendency to recur in the second year. Knowledge on (patterns of) recurrences and survival rates according to these different breast cancer subtypes can support patient-tailored treatment and individualised follow-up.

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Supplementary Figure 1. Percentages of recurrences within 10 years from diagnosis, specified use of trastuzumab in patients with a positive HER2 status in luminal B and HER2 breast cancer. All percentages of recurrences differed significantly ($p<0.05$) between the subtypes. Abbreviations: LB = luminal B, HER2 = human epidermal growth factor receptor 2, HER2+ = HER2 positive subtype. No means no trastuzumab, yes means that trastuzumab was administered.

Supplementary Figure 2. Hazards on recurrences in 10 years following diagnosis, specified for use of trastuzumab in luminal B disease. Abbreviations: LR = local recurrence, RR = regional recurrence, DM = distant metastasi

Supplementary Figure 3. Hazards on recurrences in 10 years following diagnosis, specified for use of trastuzumab in HER2 positive disease. Abbreviations: LR = local recurrence, RR = regional recurrence, DM = distant metastasi

Supplementary Figure 4. 10-year overall and recurrence-free survival, specified for use of trastuzumab in patients with a positive HER2 status in luminal B (A) and HER2 breast cancer (B).

Supplementary Figure 5. Hazards on recurrences in 10 years following diagnosis for luminal A and luminal B, specified for ductal and lobular tumours. Abbreviations: LR = local recurrence, RR = regional recurrence, DM = distant metastasis.

Supplementary Figure 6. 10-year overall and recurrence-free survival in luminal A and luminal B, specified for ductal and lobular tumours. Log-rank tests ($p < 0.05$ is considered as statistically significant): Within the luminal A subtype, a significant difference ($p = 0.014$) between ductal and lobular tumours was observed. Other differences between ductal and lobular tumours were not significant.

Chapter

11

Chapter 11

A conditional model predicting the 10-year annual extra risk of mortality compared to the general population: a large population-based study in Dutch breast cancer patients

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Abstract**Background**

Many cancer survivors are facing difficulties in getting a life insurance; raised premiums and declinatures are common. We generated a prediction model estimating the conditional extra mortality risk of breast cancer patients in the Netherlands. This model can be used by life insurers to accurately estimate the additional risk of an individual patient, conditional on the years survived.

Methods

All women diagnosed with stage I-III breast cancer in 2005-2006, treated with surgery, were selected from the Netherlands Cancer Registry. For all stages separately, multivariable logistic regression was used to estimate annual mortality risks, conditional on the years survived, until 10 years after diagnosis, resulting in 30 models. The conditional extra mortality risk was calculated by subtracting mortality rates of the general Dutch population from the patient mortality rates, matched by age, gender and year. The final model was internally and externally validated, and tested by life insurers.

Results

We included 23,234 patients: 10,101 stage I, 9,868 stage II and 3,265 stage III. The final models included age, tumour stage, nodal stage, lateralisation, location within the breast, grade, multifocality, hormonal receptor status, HER2 status, type of surgery, axillary lymph node dissection, radiotherapy, (neo)adjuvant systemic therapy and targeted therapy. All models showed good calibration and discrimination. Testing of the model by life insurers showed that insurability using the newly-developed model increased with 13%, ranging from 0%-24% among subgroups.

Conclusions

The final model provides accurate conditional extra mortality risks of breast cancer patients, which can be used by life insurers to make more reliable calculations. The model is expected to increase breast cancer patients' insurability and transparency among life insurers.

Introduction

Cancer incidence is rising, while mortality rates are decreasing.^{1,2} The growing number of cancer survivors aims to reintegrate into society, but encounters several problems. While several studies focus on return to work,³⁻⁶ another major problem is the difficulty of getting a life insurance, often needed for a mortgage, which is getting far less attention. A study on socio-economic implications of cancer survivorship, published in 2012, showed that 60% of the applications for a life insurance by cancer survivors was declined.⁷ In the Netherlands, life insurers work with internationally available data on cancer survival to estimate a patient's mortality risk. These data can be different between insurance companies and are not transparent due to life insurers' competition policy. Providing life insurers identical data to base their decision on may enhance transparency. Besides, Dutch life insurers may make better informed decisions by using data specifically addressing mortality risks for cancer patients and survivors in the Netherlands.

Usually, survival is estimated from diagnosis, which is of limited value for cancer patients who survived several years, since these estimates will be heavily influenced by patients who died during the first years following diagnosis. It is more appropriate to have survival estimates of patients who already survived the years that are relevant for the particular cancer patient.^{8,9} By estimating this so-called conditional survival, survival estimates are modified by only including patients still alive at a relevant time point. As breast cancer is one of the most commonly diagnosed cancers in the world,¹⁰ this cancer type was selected to study conditional survival in the Netherlands aiming to provide accurate data for life insurers. Conditional survival has been reported for many cancers, among others in breast cancer.^{8,11-16} However, prediction models estimating the conditional extra mortality risk, compared to the general population, have not been generated yet. These types of models would not only provide life insurers a better basis for their decision, it also provides medical experts a more objective basis to deem a patient cured of disease.¹⁷

This study aimed to generate a prediction model for breast cancer patients estimating the annual extra mortality risk compared to the general population, conditional on zero to nine years survived.

Methods

Study population

We included all female operated patients diagnosed with stage I-III breast cancer in 2005-2006 from the Netherlands Cancer Registry (NCR). This population-based registry contains prospectively registered data on all patients newly diagnosed with cancer from 1989 onwards. This study was approved by the privacy committee of the NCR.

Data collection

Data on patient-, tumour-, and treatment-related characteristics were obtained from the NCR. Tumour topography and morphology were coded according to the International Classification of Diseases for Oncology.¹⁸ Staging was coded using the tumour, node, and metastasis classification system of the International Union Against Cancer, 6th edition.¹⁹ Additional data on vital status and date of death were derived from the Municipal Personal Records database and were complete until February 2017.

Outcomes

The annual extra risks on mortality until 10 years after diagnosis, using conditional survival points from zero to nine years. The extra risk was defined as the additional risk of a breast cancer patient at a specific time point after diagnosis, compared to the general population, calculated for stage I, II and III separately.

Statistical analysis

Patient-, tumour-, and treatment-related characteristics were summarised, separated by stage of disease. Annual mortality risks, for every stage of disease, were calculated using conditional logistic regression. Conditional risks were estimated by excluding patients who had died at start of every analysis (x years after diagnosis). Extra risks were calculated by subtracting the risk of the general population by the risk of the patient population, where matching took place on age, gender and calendar year. To match the patient population to the general population, we calculated yearly risks (so they could be matched on calendar year). Accordingly, for each stage of disease 10 models were generated calculating the 1-year mortality risk at diagnosis, and one to nine years after diagnosis. Altogether, 30 models were generated. For each stage separately, prognostic variables were included in the model when they significantly contributed to one of the models ($p < 0.1$). Prognostic variables could differ per stage of disease. Furthermore, as occasionally the number of events was limited, some variables were reduced to less categories. Variables included for analyses were: age, tumour stage, nodal stage, lateralization, location within the breast, tumour differentiation grade, histological tumour type, multifocality, hormonal receptor status (ER/PR status), HER2 status, type of surgery, axillary lymph node dissection, use of adjuvant systemic therapy, primary systemic therapy, targeted therapy and radiotherapy. For all patients the pathological tumour and nodal stages were used, except for patients treated with primary systemic therapy, for who the clinical tumour and nodal stages were used. In case of a re-excision, we used the most extensive operation as type of surgery. No stepwise, backward or forward selection was performed, since these methods are shown to result in unstable and unreproducible models and the selected variables are sensitive to random fluctuations in the data.²⁰ Variance-covariance matrices were used to calculate 95% confidence intervals (CI).

Validation

Goodness-of-fit of each underlying model was determined by the Hosmer-Lemeshow test in deciles based on the predicted risk. A non-significant test implied that the observed mortality did not differ significantly from the predicted mortality risk.²¹ Discriminatory accuracy was determined by the Area Under the Receiver Operating Characteristic (ROC) curve (AUC). An AUC of 0.5 indicates that the model is as good as flipping a coin, while an AUC of 1.0 represents perfect discriminatory accuracy.

For every underlying model, internal validation was performed by manual bootstrapping with 1000 replicates. The model was applied to every bootstrap sample, whereafter the AUC was calculated. The difference between the original and the mean AUC of the 1000 replicates was used as correction factor and subtracted from the original AUC. This bias-corrected AUC was used as a measure for internal validation.

External validation was performed on patients diagnosed in 2007-2008, with the same

inclusion criteria as the development population. Only the first eight models of every stage were externally validated, as follow-up for these patients was only completed until eight years from diagnosis.

Before the final model was made available for life insurers, the model was tested for its effect on daily practice. This included the analysis of 50 patients per life insurer with specific characteristics and number of years survived, based on randomly selected records from the NCR (anonymised). In the Netherlands, there are 10 insurance companies specialised in life insurances, which were all invited. Life insurers were asked to provide the mortality risks of the patients based on the currently used guidelines (which differed among life insurers and were confidential). These mortality risks were consequently translated into acceptance (with or without premium raise) or rejection. All results were collected by the Centre for Insurance Statistics in the Netherlands, to comply with the Antitrust legislation, and subsequently anonymously provided to the Netherlands Comprehensive Cancer Organisation (IKNL). For every stage of disease and age category, results of the newly-developed model were compared with results of the currently used guidelines. Specification of the exact levels of premium raise was not possible according to the Antitrust legislation.

All statistical analyses were performed in Stata/SE version 14.1 (StataCorp LP) and Microsoft Excel 2016.

Results

Study population

The study population comprised 23,234 patients. Patient-, tumour-, and treatment-related characteristics per stage were summarised in Table 1. The mean age was 59 years (interquartile range 49-69 years). Most patients were diagnosed with stage I disease (43.5%) (Table 1). Median follow-up from date of diagnosis to date of last observation was 10.6 years (interquartile range 8.7 to 11.3 years).

Table 1. Patient-, tumour-, and treatment-related characteristics

Characteristics	Stage I (n=10,101)	Stage II (n=9,868)	Stage III (n=3,265)
Age (years)			
<40	405 (4.0)	657 (6.7)	261 (8.0)
40-64	5,978 (59.2)	5,804 (58.8)	1,959 (60.0)
≥65	3,718 (36.8)	3,407 (34.5)	1,045 (32.0)
Pathological tumour stage			
T1	10,051 (99.5)	3,037 (30.8)	666 (20.4)
T2	-	6,516 (66.0)	1,351 (41.4)
T3	-	273 (2.8)	646 (19.8)
T4	-	-	569 (17.4)
Unknown	50 (0.5)	42 (0.4)	33 (1.0)

Characteristics	Stage I (n=10,101)	Stage II (n=9,868)	Stage III (n=3,265)
Pathological nodal stage			
N0	9,835 (97.4)	3,960 (40.1)	154 (4.7)
N1	-	5,761 (58.4)	613 (18.8)
N2	-	-	1,571 (48.1)
N3	-	-	886 (27.1)
Unknown	266 (2.6)	147 (1.5)	41 (1.3)
Location			
Outer quadrants	4,740 (46.9)	4,702 (47.7)	1,420 (43.5)
Inner quadrants	2,221 (22.0)	1,724 (17.5)	379 (11.6)
Central parts	623 (6.2)	751 (7.6)	313 (9.6)
Overlapping lesions	2,296 (22.7)	2,517 (25.5)	1,068 (2.6)
Unknown	221 (2.2)	174 (1.8)	85 (2.6)
Differentiation grade			
Well	2,979 (29.5)	1,558 (15.8)	289 (8.9)
Moderate	4,424 (43.8)	4,206 (42.6)	1,132 (34.7)
Poor	2,109 (20.9)	3,431 (34.8)	1,399 (42.9)
Unknown	589 (5.8)	673 (6.8)	445 (13.6)
Histological tumour type			
Ductal	8,231 (81.5)	7,857 (79.6)	2,523 (77.3)
Lobular	896 (8.9)	1,214 (12.3)	516 (15.8)
Mixed	408 (4.0)	393 (4.0)	163 (5.0)
Other	566 (5.6)	404 (4.1)	63 (1.9)
Multifocality			
No	8,528 (84.4)	8,069 (81.8)	2,370 (72.6)
Yes	1,255 (12.4)	1,554 (15.8)	756 (23.2)
Unknown	318 (3.2)	245 (2.5)	139 (4.3)
Hormonal receptor status			
ER and PR positive	6,887 (68.2)	6,331 (64.2)	1,811 (55.5)
ER or PR positive	1,631 (16.2)	1,581 (16.0)	605 (18.5)
ER negative	1,286 (12.7)	1,888 (19.1)	837 (25.6)
Unknown	297 (2.9)	68 (0.7)	12 (0.4)
HER2 status			
Negative	7,464 (73.9)	7,444 (75.4)	2,281 (69.9)
Unclear	938 (9.3)	354 (3.6)	85 (2.6)
Positive	950 (9.4)	1,457 (14.8)	682 (20.9)
Unknown	749 (7.4)	613 (6.2)	217 (6.7)

Characteristics	Stage I (n=10,101)	Stage II (n=9,868)	Stage III (n=3,265)
Type of surgery			
Breast-conserving surgery	6,956 (68.9)	4,670 (47.3)	731 (22.4)
Mastectomy	3,137 (31.1)	5,194 (52.6)	2,533 (77.6)
Unknown	8 (0.1)	4 (0.0)	1 (0.0)
Axillary lymph node dissection			
No	8,544 (84.6)	3,364 (34.1)	116 (3.6)
Yes	1,557 (15.4)	6,504 (65.9)	3,149 (96.5)
Radiation therapy			
No	3,208 (31.8)	4,501 (45.6)	436 (13.4)
Yes	6,893 (68.2)	5,367 (54.4)	2,829 (86.7)
Adjuvant systemic therapy			
No	8,012 (79.3)	1,808 (18.3)	532 (16.3)
Endocrine therapy	883 (8.7)	3,440 (34.9)	851 (26.1)
Chemotherapy	564 (5.6)	1,416 (14.4)	562 (17.2)
Both	642 (6.4)	3,204 (32.5)	1,320 (40.4)
Primary systemic therapy			
No	10,055 (99.5)	9,322 (94.5)	2,659 (81.4)
Yes	46 (0.5)	546 (5.5)	606 (18.6)
Targeted therapy			
No	9,853 (97.5)	8,936 (90.6)	2,756 (84.4)
Yes	248 (2.5)	932 (9.4)	509 (15.6)

Numbers are n (%). Abbreviations: ER = oestrogen receptor, PR = progesterone receptor, HER2 = human epidermal growth factor receptor.

Prediction models

For all underlying models estimating the mortality risk for stage I, we selected the following predictive variables: age, location within the breast, tumour differentiation grade, histological tumour type, multifocality, hormonal receptor status (ER/PR status), HER2 status, type of surgery, axillary lymph node dissection, use of adjuvant systemic therapy, primary systemic therapy, targeted therapy and radiotherapy. For the underlying models estimating the mortality risk for stage II, we selected the same predictive variables as for stage I, but added the variables tumour stage and nodal stage. For the underlying models predicting the mortality risk for stage III, the same predictive variables as for stage II were used. All 30 underlying models, including the 95% CIs, were embedded in a prediction model which is available on <https://predictiemodel.verzekeraars.nl>. A screenshot of the prediction model, currently available in Dutch, is shown in Supplementary Figure 1.

Validation

All goodness-of-fit tests for all underlying models were non-significant, indicating no significant difference between observed and predicted mortality (Table 2). Discriminatory

accuracy was moderate to good for all models with AUCs ranging from 0.69-0.90 (Table 2). After bootstrapping, the bias-corrected AUCs ranged from 0.67-0.88 (Table 2), indicating moderate to good discriminatory accuracy for all underlying models as a measure for internal validation.

Table 2. Overview of the Hosmer-Lemeshow test, the AUC and the bias-corrected AUC as measures for goodness-of-fit, discriminatory accuracy and internal validation of the models

Model	Stage I (n=10,101)			Stage II (n=9,868)			Stage III (n=3,265)		
	HL test p-value	AUC	Bias- corrected AUC	HL test p-value	AUC	Bias- corrected AUC	HL test p-value	AUC	Bias- corrected AUC
Year 0-1	0.499	0.81	0.79	0.087	0.86	0.83	0.351	0.90	0.88
Year 1-2	0.896	0.76	0.75	0.190	0.80	0.79	0.539	0.83	0.81
Year 2-3	0.883	0.75	0.73	0.577	0.75	0.74	0.089	0.77	0.75
Year 3-4	0.251	0.72	0.69	0.601	0.75	0.74	0.385	0.74	0.72
Year 4-5	0.679	0.71	0.70	0.291	0.71	0.70	0.190	0.74	0.71
Year 5-6	0.229	0.70	0.68	0.944	0.73	0.72	0.713	0.73	0.69
Year 6-7	0.579	0.72	0.70	0.644	0.73	0.72	0.286	0.71	0.67
Year 7-8	0.746	0.69	0.67	0.513	0.71	0.70	0.203	0.74	0.71
Year 8-9	0.291	0.74	0.73	0.595	0.74	0.73	0.231	0.73	0.69
Year 9-10	0.632	0.71	0.70	0.572	0.77	0.76	0.178	0.72	0.68

Abbreviations: HL = Hosmer-Lemeshow; AUC = Area under the receiver operating characteristic curve.

For external validation on patients diagnosed in 2007-2008, 24,761 patients were included of who 11,227 (45.3%) had stage I, 10,410 (42.0%) stage II and 3,124 (12.6%) stage III. Baseline characteristics of this validation population are shown in Supplementary Table 1. The external validation showed good calibration for all models. Calibration was expressed as the expected percentage of mortality using the newly-developed model minus the observed percentage of mortality in the validation population. Although several models showed a statistically significant difference between expected and observed mortality, the percentages were very small (<3% for 1 model, <1% for all other models). Discriminatory accuracy was moderate to good for all models with AUCs ranging from 0.61-0.87 (Table 3).

Table 3. Calibration and discrimination of the model on the external validation population (2007-2008, n=24,761)

Model	Stage I (n=11,227)		Stage II (n=10,410)		Stage III (n=3,124)	
	Expected – observed	AUC	Expected – observed	AUC	Expected – observed	AUC
Year 0-1	2.72	0.71	-0.10	0.87	-0.80	0.86
Year 1-2	-0.66	0.68	0.31	0.76	-0.26	0.81
Year 2-3	-0.11	0.66	0.28	0.72	-0.21	0.74
Year 3-4	0.44	0.65	-0.28	0.69	-0.40	0.69

Model	Stage I (n=11,227)		Stage II (n=10,410)		Stage III (n=3,124)	
	Expected – observed	AUC	Expected – observed	AUC	Expected – observed	AUC
Year 4-5	-0.73	0.63	-0.17	0.70	0.19	0.61
Year 5-6	-0.02	0.67	0.53	0.70	-0.06	0.66
Year 6-7	0.14	0.69	0.07	0.69	1.51	0.68
Year 7-8	-0.11	0.66	0.46	0.70	0.94	0.64
Year 8-9	-	-	-	-	-	-
Year 9- 10	-	-	-	-	-	-

Calibration is expressed as the expected mortality of the newly-developed model minus the observed mortality in the validation population. Validation of the last two models per stage was not possible due to lack of follow-up after eight years. Abbreviations: AUC = area under the receiver operating characteristic curve.

Model testing

Altogether, eight of the 10 life insurers responded. Figure 1 summarises the insurability of the 50 cases for every stage and age category. Overall, the insurability increased from 43%-56%. However, the lower number of declined applications resulted in a higher number of accepted applications with temporary or permanent premium raises. The number of applications accepted at standard rates decreased from 8%-4%. Patients aged 40-64 and patients with stage III breast cancer benefited the most of the newly-developed model compared to the currently used guidelines: insurability (with or without premium raise) increased from 44%-62% and from 21%-45%, respectively.

Results were further specified for the age groups <40 and 40-64 years (for the group ≥65 years numbers were too small) (Figure 1). For all (ex-)patients <40 years, the percentage of rejections decreased by using the newly-developed model. As more patients were accepted, temporary or permanent premium increases were more common. For patients <40 years with stage II disease, the number of acceptations at standard rates decreased from 5%-0%. (Ex-)patients aged <40 with stage III breast cancer benefited the most from the new model, with acceptance rates increasing from 13% using the current guidelines to 34% with the newly-developed model. (Ex-)patients aged 40-64 with stage I disease showed the least benefit of the newly-developed model. The number of rejections remained identical, but the number of acceptations at standard rates declined from 34%-11% using the new model. However, acceptance rates were for this group the highest, namely 86%. For patients aged 40-64 with stage II and III disease, the newly-developed model showed less rejections, and the number of acceptations at standard rates remained similar.

Discussion

A conditional prediction model for the annual extra mortality risk of breast cancer patients compared to the general population was generated. This prediction model provides life insurers with more reliable information to base their decision on, which is shown to result in increased insurability of breast cancer patients in a test using 50 random patients.

The benefit of the newly-developed model in terms of insurability was greatest for patients with stage III breast cancer. Especially for (ex-)patients <40 years with stage III disease,

insurability was almost tripled. This is of great importance as this group mostly applies for a life insurance, as part of a mortgage. For patients with stage I disease, the newly-developed model did not add much benefit in terms of insurability. This may be explained by the fact that higher staged breast cancers, when recurring, most often recur in the first few years following diagnosis.²² Being alive an increasing number of years following diagnosis considerably lowers the remaining risk on locoregional recurrences and distant metastases and consequently the risk of death.

As this model is specifically designed for the number of years survived, it provides life insurers enhanced insight in increasing survival probabilities over time, resulting in a higher chance to get accepted. The higher acceptance rates were mainly acceptances with premium increases, as patients whose applications were first rejected are now mostly accepted against a raised premium. The exact premium raise could not be specified due to life insurers' competition policy, the Antitrust legislation, and the relatively low number of tested cases. However, these premium raises varied widely between life insurers. Some patients were first accepted at standard rates, but had to pay a premium raise using the newly-developed model. Fortunately, these raises were low and may not outweigh the increased number of acceptations. Furthermore, an application of a specific patient which is rejected by one life insurer may be accepted by another. Although our model provides a more objective basis for life insurers to base their decision on, it does not change the large differences in the consequences for the premium. We showed that for patients aged 40-64 with stage I disease, the number of acceptations at standard rates decreased from 34%-11% using the new model. Notably, every life insurer tested the model on the same 50 cases, so results are presented at the level of the life insurers, and not on individual level. A sensitivity analysis of the data showed that, when individual patients would apply at multiple life insurers, every patient in this test was insurable (either at standard rates or with premium raises). This information should, however, be cautiously interpreted, as premiums are sometimes very high (data not shown due to the Antitrust legislation). Therefore, breast cancer patients and survivors – especially patients aged 40-64 with stage I disease – are advised to apply for a life insurance at different life insurers, and to compare the outcomes.

Multiple prediction models for breast cancer have been developed, of which many predict the overall mortality risk.²³⁻²⁷ One of these models, the Breast Cancer Conditional Outcome Calculator (CancerMath.net),²⁶ estimates conditional survival, thereby increasing its usability for patients who survived several years. Accuracy of this model was considered to be modest in Southeast Asian women with breast cancer.²⁸ This model, however, does not provide the annual mortality risks and does not show uncertainty around the estimates. Especially the latter is important, since communication of risk prediction models to patients is shown to be very difficult.²⁹

Our study has several strengths. First, we corrected patients' mortality rates for the mortality rates of the general Dutch population. Herewith, more information on a patient's individual extra risk is provided. Second, we used the NCR to cover the entire Dutch breast cancer population, thereby enhancing the generalisability of the model. Third, a large number of patients (n=23,234) was included, allowing us to include a large number of predictive factors. A limitation is the lack of knowledge on performance status or comorbidities. Irrespective of a previous cancer diagnosis, comorbidity may lead to a lower chance to be insured.

Figure 1. Comparison of insurability of (ex-)breast cancer patients between currently used guidelines (A) and the newly-developed model (B).

Figure 2. Further specification of the comparison of insurability of (ex-)breast cancer patients between current guidelines (A) and the newly-developed model (B).

Furthermore, cancer patients with comorbidities are less likely to receive the standard cancer treatments, and their risk of postoperative complications is higher compared to patients without comorbidities, resulting in lower overall survival rates.³⁰⁻³² However, by adjusting the observed mortality for the expected mortality risks of the general population, matched by age, gender and calendar year, we partly solved this problem by correction for age- and gender-related comorbidities. Furthermore, we lacked data on recurrences during follow-up. This might lead to an overestimated mortality risk for patients who are free of disease during follow-up and an underestimated mortality risk for patients diagnosed with a recurrence during follow-up. Another limitation is the use of the general Dutch population as a reference. Baseline mortality risks of other countries may differ from those in the Netherlands, which may have consequences for the applicability of this model in other countries. Therefore, before using this model on a specific target population, the model should be validated on that population. Lastly, predictive modelling in general has limitations. The risk produced by a certain model is based on an underlying model population with certain characteristics that are most often collected retrospectively. These patients have been treated according to clinical guidelines that were valid at time of diagnosis, which is in this case over 10 years ago. One can imagine that results of this specific underlying population may be different in future patients. Besides, since two patients with exactly similar characteristics may respond completely different on a certain treatment, it should be communicated to patients that the risk produced by the model does not have to count for them per se. Therefore, it is vital to take any other prognostic information into account, such as development of new therapies and outcomes of randomised controlled trials.

Conclusions

In this study, a conditional prediction model for the annual extra mortality risk of breast cancer patients compared to the general population was generated. This model was internally and externally validated and was tested in practice with satisfying results. The model is publicly available and ready to be used by life insurers in the Netherlands. By providing all life insurers the same base for their decision, we hope to increase transparency to patients. For a year, all applications by breast cancer patients and survivors will be processed by life insurers using both the current guidelines and the newly-developed model. Thereafter, the results will be analysed and included in further discussions on insurability of breast cancer patients and survivors between the Dutch Federation of Cancer Patient Organisations and the Dutch Association of Insurers. Furthermore, the model will be updated regularly, to ensure that life insurers work with the most recent and reliable data. In future, prediction models for other types of cancers will be developed.

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Supplementary material

Supplementary Figure 1. Screenshot of prediction model using data of a fictive patient, in Dutch.

Supplementary Table 1. Patient-, tumour-, and treatment-related characteristics of the validation population (2007-2008)

Characteristics	Stage I (n=11,227)	Stage II (n=10,410)	Stage III (n=3,124)
Age (years)			
<40	443 (4.0)	648 (6.2)	251 (8.0)
40-64	6,476 (57.7)	6,093 (58.5)	1,884 (60.3)
≥65	4,308 (38.4)	3,669 (35.2)	989 (31.7)
Pathological tumour stage			
T1	11,186 (99.6)	3,147 (30.2)	650 (20.8)
T2	-	6,936 (66.6)	1,326 (42.5)
T3	-	281 (2.7)	646 (20.7)
T4	-	-	470 (15.0)
Unknown	41 (0.4)	46 (0.4)	32 (1.0)
Pathological nodal stage			
N0	10,967 (97.7)	4,201 (40.4)	122 (3.9)
N1	-	6,058 (58.2)	630 (20.2)
N2	-	-	1,468 (47.0)
N3	-	-	872 (27.9)
Unknown	260 (2.3)	151 (1.5)	32 (1.0)
Lateralisation			
Left	5,749 (51.2)	5,326 (51.2)	1,649 (52.8)
Right	5,477 (48.8)	5,083 (48.8)	1,475 (47.2)
Unknown	1 (0.0)	1 (0.0)	-

Characteristics	Stage I (n=11,227)	Stage II (n=10,410)	Stage III (n=3,124)
Sublocation			
Outer quadrants	5,150 (45.9)	4,908 (47.2)	1,385 (44.3)
Inner quadrants	2,564 (22.8)	1,783 (17.1)	340 (10.9)
Central parts	709 (6.3)	868 (8.3)	273 (8.7)
Overlapping lesions	2,582 (23.0)	2,675 (25.7)	1,050 (33.6)
Unknown	222 (2.0)	176 (1.7)	76 (2.4)
Differentiation grade			
1	3,577 (31.9)	1,651 (15.9)	260 (8.3)
2	4,775 (42.5)	4,287 (41.2)	1,097 (35.1)
3	2,325 (20.7)	3,611 (34.7)	1,260 (40.3)
Unknown	550 (4.9)	861 (8.3)	507 (16.2)
Histological tumour type			
Ductal	9,248 (82.4)	8,211 (78.9)	2,427 (77.7)
Lobular	991 (8.8)	1,257 (12.1)	489 (15.7)
Mixed	421 (3.8)	474 (4.6)	143 (4.6)
Other	567 (5.1)	468 (4.5)	65 (2.1)
Multifocality			
No	9,638 (85.9)	8,459 (81.3)	2,214 (70.9)
Yes	1,512 (13.5)	1,836 (17.6)	829 (26.5)
Unknown	77 (0.7)	115 (1.1)	81 (2.6)
Hormonal receptor status			
ER and PR positive	7,648 (68.1)	6,625 (63.6)	1,761 (56.4)
ER or PR positive	1,914 (17.1)	1,737 (16.7)	595 (19.1)
ER negative	1,481 (13.2)	1,988 (19.1)	758 (24.3)
Unknown	184 (1.6)	60 (0.6)	10 (0.3)
HER2 status			
Negative	9,428 (84.0)	8,647 (83.1)	2,317 (74.2)
Unclear	339 (3.0)	87 (0.8)	18 (0.6)
Positive	1,113 (9.9)	1,413 (13.6)	723 (23.1)
Unknown	347 (3.1)	263 (2.5)	66 (2.1)
Type of surgery			
Breast-conserving surgery	7,695 (68.5)	4,854 (46.6)	713 (22.8)
Mastectomy	3,521 (31.4)	5,554 (53.4)	2,411 (77.2)
Unknown	11 (0.1)	2 (0.0)	-
Axillary lymph node dissection			
No	10,126 (90.2)	3,959 (38.0)	109 (3.5)
Yes	1,101 (9.8)	6,451 (62.0)	3,015 (96.5)

Characteristics	Stage I (n=11,227)	Stage II (n=10,410)	Stage III (n=3,124)
Radiation therapy			
No	3,611 (32.2)	4,627 (44.5)	423 (13.5)
Yes	7,616 (67.8)	5,783 (55.6)	2,701 (86.5)
Adjuvant systemic therapy			
No	8,202 (73.1)	1,766 (17.0)	513 (16.4)
Endocrine therapy	1,432 (12.8)	3,773 (36.2)	819 (26.2)
Chemotherapy	750 (6.7)	1,545 (14.8)	524 (16.8)
Both	843 (7.5)	3,326 (32.0)	1,268 (40.6)
Primary systemic therapy			
No	11,133 (99.2)	9,469 (90.7)	2,471 (79.1)
Yes	94 (0.8)	941 (9.0)	653 (20.9)
Targeted therapy			
No	10,873 (96.9)	9,379 (90.1)	2,519 (80.6)
Yes	354 (3.2)	1,031 (9.9)	605 (19.4)

Numbers are n (%). Abbreviations: ER = oestrogen receptor, PR = progesterone receptor, HER2 = human epidermal growth factor receptor.

Chapter

12

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10-year conditional recurrence risks, overall and relative survival for breast cancer patients in the Netherlands: taking account of event-free years

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Abstract**Background**

Survival estimates from diagnosis are of limited importance for (ex-)breast cancer patients who survived several years, as it includes information on already deceased patients. This study analysed the 10-year conditional risk of recurrent breast cancer in specific prognostic subgroups. Secondly, we investigated 10-year conditional overall (OS) and relative survival (RS), adjusted for confounding.

Methods

All women diagnosed in 2005 with operated T1-2N0-1 breast cancer were selected from the Netherlands Cancer Registry. Patients were classified into T1N0, T1N1, T2N0 and T2N1 stage. Ten-year conditional recurrence rates were calculated from diagnosis, and for patients without an event (local (LR), regional recurrence (RR), distant metastasis (DM) or death) every year following diagnosis. Ten-year conditional OS was calculated using multivariable Cox regression. RS was estimated by dividing patient survival rates by those of the general Dutch population.

Results

We included 7,969 patients: 52.3% had T1N0, 15.3% T1N1, 19.9% T2N0 and 12.5% T2N1 stage. For T1N0, 10-year LR rates changed from 4.6% at diagnosis to 0.5% in year 10. RR rates changed from 2.3%-0.2% and DM rates changed from 7.8%-0.6%. For T2N1 stage, the LR, RR and DM rates changed from 6.2%-0.8%, 5.2%-0.4% and 19.6%-1.5%, respectively. For the luminal A subtype, LR, RR and DM rates changed from 3.9%-0.4%, 1.7%-0.5% and 7.3%-1.1%, while for triple negative these rates changed from 5.6%-0.7%, 4.9%-0.2% and 16.7%-0%, respectively. Differences between subgroups attenuated over time and all recurrence rates became $\leq 1.5\%$ in year 10. Ten-year OS and RS, adjusted for confounding, showed declining risk differences between subgroups over time.

Conclusion

Differences in recurrence rates, OS and RS between prognostic subgroups declined as years passed by. These results highlight the importance of taking into account disease-free years to more accurately predict (ex-)breast cancer patients' prognosis over time.

Introduction

The incidence of breast cancer is rising.¹ Meanwhile, due to improved treatment and diagnostic procedures, mortality rates are declining.² This results in an increasing number of breast cancer survivors. In 2017, the 10-year prevalence of women with breast cancer in the Netherlands was 131,383.¹ A patient's prognosis is often communicated by physicians based on available survival and recurrence rates, usually calculated from diagnosis. However, survival estimates from diagnosis are of limited importance for (ex-)breast cancer patients who survived several years, as these analyses only include patients who are still alive or disease-free at a certain time point after diagnosis.^{3,4} Conditional survival analyses are more relevant, as they calculate the probability of surviving an additional number of years, given that someone has already survived x years.³ Taking into account that survival and recurrence rates vary over time, conditional survival analyses will result in more accurate prognostic information for breast cancer patients and survivors. Several studies have reported conditional survival rates for breast cancer in different populations,^{3,5-8} showing that these survival rates ameliorate with increasing time from diagnosis. Importantly, it has been shown that conditional survival is especially of relevance for patients with an initial poor prognosis, as for most of these patients the chance to survive a number of years is lower than for patients with an initial better prognosis. Patients who do survive x years have to be provided with updated information regarding their prognosis.³ In general, female breast cancer survivors in the Netherlands have a good prognosis, which improves as years pass by. However, a small, but significant excess mortality during the whole 20 years of follow-up has been observed compared to the general population, which may among others be due to (late) recurrences.⁹ As fear of recurrent cancer is very common in breast cancer survivors,¹⁰ most likely caused by substantial overestimation of recurrence risks,¹¹ it is relevant to get insight in time-dependent recurrence risks. Long-term follow-up is rarely available in population-based research. As a consequence, no studies have been performed yet that investigate the 10-year conditional risk of local recurrence (LR), regional recurrence (RR) and distant metastasis (DM) in breast cancer patients. This study aimed to analyse the breast cancer recurrence risk over time in specific prognostic subgroups according to T and N stage and breast cancer subtype, conditional on the number of years survived, in T1-2N0-1 stage breast cancer patients in the Netherlands. As a second objective, we investigated 10-year conditional overall (OS) and relative survival (RS) for all subgroups, adjusted for confounding.

Methods

Study population

For this population-based cohort study, patients were selected from the Netherlands Cancer Registry (NCR). This registry contains prospectively recorded patient-, tumour-, and treatment-related characteristics of all newly diagnosed malignancies from 1989 on. We included all women diagnosed in 2005 with pathologically staged T1-2N0-1 breast cancer treated with either breast-conserving therapy or mastectomy. Patients were classified into T1N0, T1N1, T2N0 and T2N1 stage, and according to breast cancer subtype.

Data collection

Data on patient-, tumour-, and treatment-related characteristics were retrieved from the NCR.

Tumour topography and morphology were coded according to the International Classification of Diseases for Oncology.¹² Staging was coded using the tumour, node, and metastasis classification system of the International Union Against Cancer, 6th edition.¹³ Additional data on vital status and date of death were derived from the Municipal Personal Records database, completed up to February 2017. Data on recurrences (including LR, RR and DM) were retrospectively gathered from patient files.

Outcomes and definitions

The primary outcomes of interest were conditional 10-year LR, RR and DM rates. This was defined by the probability of being diagnosed with a LR, RR or DM within 10-years following diagnosis, taking into account the number of event-free years that passed. An event was defined as death, LR, RR or DM. By calculating the remaining risk on a recurrence within 10 years after diagnosis at a certain time point, more insight in the distribution of recurrences over the years could be obtained. As secondary outcomes, 10-year conditional OS and RS were investigated, adjusted for confounding. Crude 10-year OS was defined as the probability of being alive within 10-years from diagnosis, taking into account the number of years survived. RS was used as a measure for disease-specific survival, and was calculated by dividing the observed survival of the patient population by the expected survival of the general Dutch population. All outcomes were calculated per T and N subgroup and breast cancer subtype as both are very important prognostic factors. Breast cancer subtypes were defined as luminal A (ER or PR positive, HER2 negative and grade 1 or 2), luminal B (ER or PR positive, HER2 positive, or HER2 negative with grade 3), HER2 positive (ER and PR negative and HER2 positive) and triple negative (ER, PR and HER2 negative). ER or PR positivity was defined as at least 10% positive nuclei. Less than 10% was regarded as negative. HER2 positivity was defined as a positive immunohistochemistry (3 positive, at least 10% of cells with strong intensity membrane staining). It was negative when less than 10% showed membrane staining. In case of an immunohistochemistry score of 2 (at least 10% of cells stained with moderate intensity), an amplification test was performed that overruled the results of the immunohistochemistry. Recurrences were defined according to existing consensus-based definitions for recurrence classification.¹⁴ Contralateral breast cancer was not counted as event; any subsequent recurrence was included in the analysis.

Statistical analysis

Patient-, tumour-, and treatment-related characteristics were summarised and compared between subgroups using the Chi-squared or Fisher's exact test. For each T and N subgroup and breast cancer subtype, 10-year conditional recurrence risks from diagnosis were determined. The 10-year conditional risks were calculated for all patients from diagnosis, and on patients who were event-free after one to nine years following diagnosis. This risk was calculated as percentage of patients that was diagnosed with a LR, RR, or DM within 10-years from diagnosis at the specific time point following diagnosis. Crude 10-year conditional OS was calculated as the proportion of patients that was still alive at 10 years following diagnosis as part of the entire study population. To calculate 10-year RS, this OS proportion was divided by the average survival rate of the general Dutch population, where patients were matched to the general population on age, sex and calendar year. This procedure was performed by

making use of the `strs-` command in Stata, developed by Dickman and Coviello.¹⁵ Multivariable Cox proportional hazard analyses were performed to obtain hazard ratios (HRs) with 95% confidence intervals (CIs) of 10-year OS from diagnosis, and conditional on one to nine years survived. For confounding adjusted 10-year RS was estimated by calculating excess mortality ratios (EMRs) using general linear models with Poisson distribution, with life tables of the general population as a reference. EMRs with 95% CIs were determined using the Ederer II method.¹⁶ The probability of being alive 10 years following diagnosis was calculated at zero to nine years from diagnosis. The conditional analyses at one to nine years from diagnosis were calculated exclusively on patients alive at start of every analysis. Potential confounding variables were first tested in univariable analysis, whereafter all significantly contributing variables ($p < 0.1$) were included in the multivariable model. Subsequently, variables that did not significantly contribute to the multivariable model were eliminated using manual backward selection. Potential confounding variables tested for all T and N subgroups were: age, social economic status, region of diagnosis, lateralisation and sublocalisation of the tumour, histological subtype, grade, multifocality, hormonal receptor status, HER2 status, type of surgery, axillary lymph node dissection, use and type of adjuvant systemic therapy and targeted therapy. For Cox regression, the proportional hazards assumption was tested by plotting the log of the $-\log$ survival function $\{\log[-\log(S(t))]\}$ against the log of the survival time $[\log(t)]$. When producing linear graphs, the proportional hazards assumption was considered to be met. No deviations were found. A p -value < 0.05 was considered as statistically significant. All statistical analyses were performed in Stata/SE version 14.1 (StataCorp LP).

Results

Study population and characteristics

In 2005, 13,023 women in the Netherlands were diagnosed with invasive breast cancer. For this study, we excluded patients with a history of breast cancer ($n=902$), unknown stage disease ($n=106$), metastatic breast cancer ($n=622$), no pathologically established tumour ($n=162$), synchronous breast cancer (defined as second breast cancer within 90 days, $n=276$), no surgery ($n=602$) or incomplete 10-year follow-up ($n=24$). In total, 10,329 patients were identified of who 10-year follow-up was available. We additionally excluded patients with pT3-4pN2-3 stage disease ($n=2,035$) and patients treated with breast conservation without radiation therapy or mastectomy with radiation therapy ($n=329$), to obtain a homogeneous population. The final study population consisted of 7,969 patients, of whom 4,166 (52.3%) had T1N0, 1,223 (15.3%) T1N1, 1,583 (19.9%) T2N0 and 997 (12.5%) T2N1 stage breast cancer (Figure 1). Patients in the T1N0 and T1N1 subgroup more often had a low grade tumour as compared to patients in the T2N0 and T2N1 subgroup. Patients with a T1N0 tumour were the least often treated with adjuvant systemic therapy (Table 1). Of all patients, 1,702 patients (21.4%) had an unknown breast cancer subtype due to lacking data on receptor status or grade. These patients were consequently excluded from the analyses according to breast cancer subtype. Of the remaining 6,267 patients, 3,774 (60.2%) had luminal A, 1,465 (23.4%) had luminal B, 314 (5.0%) had HER2 positive and 714 (11.4%) had triple negative disease (Figure 1). Patient-, tumour-, and treatment-related characteristics per breast cancer subtype are shown in Table 2. The median follow-up from date of diagnosis to date of death or censoring was 11.4 years (interquartile range 10.9 to 11.7 years).

Ten-year conditional recurrence risks per T and N subgroup

At diagnosis, the lowest risks on LR and RR within 10-years were found in T1N1 stage (2.4% and 2.2%, respectively), while the lowest risk on DM (7.8%) within 10 years was found in T1N0 stage. T2N1 stage showed the highest risks on 10-year LR, RR and DM (6.2%, 5.2% and 19.6%, respectively) at time of diagnosis. The total 10-year conditional risks on any recurrence declined as time passed, even as the differences between the prognostic subgroups. For T1N0 stage, the percentage of 10-year LR declined from 4.6% at diagnosis to 0.5% in the last year. For 10-year RR, the risk declined from 2.3% at diagnosis to 0.2% in the last year. For 10-year DM it ranged from 7.8% at diagnosis to 0.6% in the last year. For T2N1 stage, the group with the highest risk from diagnosis, these percentages declined as follows: from 6.2% to 0.8%, from 5.2% to 0.4% and from 19.6% to 1.5% for LR, RR and DM, respectively. Conditional on nine years survived, the risks on recurrences for the 10th year ranged between 0.5 and 0.8% for LR, between 0.2 and 0.4% for RR and between 0.6 and 1.5% for DM among the different T and N subgroups (Figure 2).

Figure 1. Consort diagram of included patients.

10-year conditional recurrence risks per breast cancer subtypes

The 10-year risks from diagnosis on LR, RR and DM were lowest for the luminal A subgroup (3.9%, 1.7% and 7.3%, respectively). Patients with triple negative disease showed the highest 10-year risk on LR, RR and DM at diagnosis (5.6%, 4.9% and 16.7%, respectively). The total risk on recurrences declined over time, and became as low as 0% for HER2 positive, 0.9% for triple negative, 1.8% for luminal A and 2.2% for luminal B disease in the 10th year. Interestingly, from the fifth year from diagnosis on, HER2 positive tumours displayed a 10-year RR risk of zero, and in the last year all 10-year recurrence risks were 0% (Figure 2).

Table 1. Baseline characteristics of the entire study population according to T and N subgroup (n=7,969)

Characteristics	T1N0 (n=4,166)	T1N1 (n=1,223)	T2N0 (n=1,583)	T2N1 (n=997)	p-value*
Age (years)					
<40	188 (4.5)	95 (7.8)	88 (5.6)	46 (4.6)	<0.001
40-49	633 (15.2)	265 (21.7)	316 (20.0)	257 (35.8)	
50-59	1,268 (30.4)	371 (30.3)	356 (22.5)	270 (27.1)	
60-69	1,164 (27.9)	278 (22.7)	316 (20.0)	187 (18.8)	
70-79	752 (18.1)	155 (12.7)	274 (17.3)	120 (12.0)	
≥80	161 (3.9)	59 (4.8)	233 (14.7)	117 (11.7)	
Social economic status					
Low	1,241 (29.8)	366 (29.9)	508 (32.1)	294 (29.5)	0.158
Medium	1,676 (40.2)	498 (40.7)	577 (36.5)	412 (41.3)	
High	1,249 (30.0)	359 (29.4)	498 (31.5)	291 (29.2)	
Region of diagnosis					
A	552 (13.3)	186 (15.2)	223 (14.1)	138 (13.8)	0.017
B	429 (10.3)	106 (8.7)	125 (7.9)	105 (10.5)	
C	275 (6.6)	104 (8.5)	105 (6.6)	78 (16.3)	
D	791 (19.0)	226 (18.5)	286 (18.1)	162 (16.3)	
E	410 (9.8)	108 (8.8)	157 (9.9)	100 (10.0)	
F	557 (13.4)	149 (12.2)	253 (16.0)	134 (13.4)	
G	612 (14.7)	168 (13.7)	207 (13.1)	138 (13.8)	
H	245 (5.9)	90 (7.4)	92 (5.8)	62 (6.2)	
I	295 (7.1)	86 (7.0)	135 (8.5)	80 (8.0)	
Lateralisation					
Left	2,169 (52.1)	616 (50.4)	834 (52.7)	531 (53.3)	0.527
Right	1,997 (47.9)	607 (49.6)	749 (47.3)	466 (46.7)	
Sublocalisation					
Outer quadrants	2,013 (48.3)	595 (48.7)	738 (46.6)	493 (49.5)	<0.001
Inner quadrants	889 (21.3)	209 (17.1)	328 (20.7)	153 (15.4)	
Central parts	261 (6.3)	105 (8.6)	126 (8.0)	84 (8.4)	
Overlapping lesions	922 (22.1)	291 (23.8)	367 (23.2)	251 (25.2)	
Unknown	81 (1.9)	23 (1.9)	24 (1.5)	16 (1.6)	

Characteristics	T1N0 (n=4,166)	T1N1 (n=1,223)	T2N0 (n=1,583)	T2N1 (n=997)	p-value*
Grade					
1	1,241 (29.8)	315 (25.8)	223 (14.1)	129 (12.9)	<0.001
2	1,871 (44.9)	569 (46.5)	628 (39.7)	437 (43.8)	
3	841 (20.2)	283 (23.1)	681 (43.0)	402 (40.3)	
Unknown	213 (5.1)	56 (4.6)	51 (3.2)	29 (2.9)	
Histological tumour type					
Ductal	3,421 (82.1)	1,048 (85.7)	1,212 (76.6)	803 (80.5)	<0.001
Lobular	357 (8.6)	103 (8.4)	210 (13.3)	133 (13.3)	
Mixed	176 (4.2)	47 (3.8)	52 (3.3)	39 (3.9)	
Other	212 (5.1)	25 (2.0)	109 (6.9)	22 (2.2)	
Multifocality					
No	3,552 (85.3)	987 (80.7)	1,367 (86.4)	814 (81.6)	<0.001
Yes	515 (12.4)	214 (17.5)	188 (11.9)	155 (15.6)	
Unknown	98 (2.4)	22 (1.8)	28 (1.8)	28 (2.8)	
Hormonal receptor status					
Positive	2,881 (69.2)	907 (74.2)	934 (59.0)	650 (65.2)	<0.001
Mixed	658 (15.8)	180 (14.7)	250 (15.8)	170 (17.1)	
Negative	526 (12.6)	129 (10.6)	393 (24.8)	173 (17.4)	
Unknown	101 (2.4)	7 (0.6)	6 (0.4)	4 (0.4)	
HER2 status					
Negative	2,821 (67.7)	914 (74.7)	1,096 (69.2)	722 (72.4)	<0.001
Unclear	522 (12.5)	53 (4.3)	125 (7.9)	45 (4.5)	
Positive	428 (10.3)	161 (13.2)	223 (14.1)	144 (14.4)	
Unknown	395 (9.5)	95 (7.8)	139 (8.8)	86 (8.6)	
Type of surgery					
Mastectomy	1,133 (27.2)	451 (36.9)	797 (50.4)	572 (57.4)	<0.001
Breast-conserving therapy	3,033 (72.8)	772 (63.1)	786 (49.7)	425 (42.6)	
Axillary lymph node dissection					
No	3,481 (83.6)	88 (7.2)	1,168 (73.8)	55 (5.5)	<0.001
Yes	685 (16.4)	1,135 (92.8)	415 (26.2)	942 (94.5)	
Adjuvant systemic therapy					
None	3,342 (80.2)	176 (14.4)	407 (25.7)	79 (7.9)	<0.001
Endocrine therapy	333 (8.0)	423 (34.6)	519 (32.8)	338 (33.9)	
Chemotherapy	218 (5.2)	114 (9.3)	292 (18.5)	141 (14.1)	
Both	273 (6.6)	510 (41.7)	365 (23.1)	439 (44.0)	

Characteristics	T1N0 (n=4,166)	T1N1 (n=1,223)	T2N0 (n=1,583)	T2N1 (n=997)	p-value*
Targeted therapy					
No	4,076 (97.8)	1,120 (91.6)	1,481 (93.6)	916 (91.9)	
Yes	90 (2.2)	103 (8.4)	102 (6.4)	81 (8.1)	<0.001

Numbers are n(%). Abbreviations: HER2 = human epidermal growth factor receptor 2. * = p-values are calculated on known values only. p-values depicted in bold are considered as statistically significant.

Figure 2. 10-year conditional risk on recurrences, from the first until the tenth year, stratified for T and N subgroup (left figures) and breast cancer subtype (right figures). Percentages are shown below the graphs. Abbreviations: DM = distant metastasis, RR = regional recurrence, LR = local recurrence.

Ten-year conditional overall and relative survival per T and N subgroup

At 10 years from diagnosis, 78.9% of patients with T1N0 stage were still alive, compared to 77.3%, 65.7% and 63.3% in T1N1, T2N0 and T2N1, respectively. Conditional on nine years

survived, these rates became 97.1%, 97.3%, 96.6% and 95.6% for the 10th year, respectively (Figure 3). Compared to T1N0 stage, T1N1, T2N0 and T2N1 stage were related to lower 10-year OS, when corrected for confounding. Similar effects were seen conditional on one to seven years survived, although the difference between T and N subgroup became smaller. From year eight on, there was no significant difference in OS for the 9th and 10th year between T and N subgroups anymore (Figure 4).

Table 2. Baseline characteristics according to molecular subtype (n=7,969)

	Luminal A (n=3,774)	Luminal B (n=1,465)	HER2 positive (n=314)	Triple negative (n=714)	Unknown (n=1,702)	p-value*
Age (years)						
<40	142 (3.8)	112 (7.7)	24 (7.6)	87 (12.2)	52 (3.1)	<0.001
40-49	650 (17.2)	368 (25.1)	45 (14.3)	159 (22.3)	249 (14.6)	
50-59	1,085 (28.8)	405 (27.7)	107 (34.1)	194 (27.2)	474 (27.9)	
60-69	959 (25.4)	301 (20.6)	86 (27.4)	147 (20.6)	452 (26.6)	
70-79	665 (17.6)	186 (12.7)	32 (10.2)	97 (13.6)	321 (18.9)	
≥80	273 (7.2)	93 (6.4)	20 (6.4)	30 (4.2)	154 (9.1)	
Social economic status						
Low	1,160 (30.7)	445 (30.4)	86 (27.4)	213 (29.8)	505 (29.7)	0.149
Medium	1,518 (40.2)	560 (38.2)	114 (36.3)	280 (39.2)	691 (40.6)	
High	1,096 (29.0)	460 (31.4)	1144 (36.3)	221 (31.0)	506 (29.7)	
Region of diagnosis						
A	585 (15.5)	182 (12.4)	32 (10.2)	102 (14.3)	198 (11.6)	<0.001
B	284 (7.5)	175 (12.0)	37 (11.8)	63 (8.8)	206 (12.1)	
C	277 (7.3)	87 (5.9)	17 (5.4)	49 (6.9)	132 (7.8)	
D	761 (20.2)	304 (20.8)	70 (22.3)	137 (19.2)	193 (11.3)	
E	376 (10.0)	158 (10.8)	29 (9.2)	68 (9.5)	144 (8.5)	
F	444 (11.8)	167 (11.4)	48 (9.2)	97 (13.6)	337 (19.8)	
G	535 (14.2)	185 (12.6)	35 (11.2)	97 (13.6)	273 (16.0)	
H	240 (6.4)	88 (6.0)	23 (7.3)	50 (7.0)	88 (5.2)	
I	272 (7.2)	119 (8.1)	23 (7.2)	51 (7.1)	131 (7.7)	
Lateralisation						
Left	1,920 (50.9)	770 (52.6)	162 (51.6)	386 (54.1)	912 (53.4)	0.383
Right	1,854 (49.1)	695 (47.4)	152 (48.4)	328 (45.9)	790 (46.4)	
Sublocalisation						
Outer quadrants	1,806 (47.9)	678 (46.3)	150 (47.8)	372 (52.1)	833 (48.9)	0.082
Inner quadrants	740 (19.6)	287 (19.6)	67 (21.3)	151 (21.2)	334 (19.6)	
Central parts	297 (7.9)	104 (7.1)	23 (7.3)	35 (4.9)	117 (6.9)	
Overlapping lesions	865 (22.9)	367 (25.1)	71 (22.6)	151 (21.2)	377 (22.2)	
Unknown	66 (1.8)	29 (2.0)	3 (1.0)	5 (0.7)	41 (2.4)	

Characteristics	Luminal A (n=3,774)	Luminal B (n=1,465)	HER2 positive (n=314)	Triple negative (n=714)	Unknown (n=1,702)	p-value*
T stage						
1	2,771 (73.4)	834 (56.9)	177 (56.4)	371 (52.0)	1,236 (72.6)	
2	1,003 (26.6)	631 (43.1)	137 (43.6)	343 (48.0)	466 (27.4)	<0.001
N stage						
0	2,679 (71.0)	947 (64.6)	219 (69.8)	547 (76.6)	1,357 (79.7)	
1	1,095 (29.0)	518 (35.4)	95 (30.3)	167 (23.4)	345 (20.30)	<0.001
Grade						
1	1,438 (38.1)	65 (4.4)	7 (2.2)	28 (3.9)	370 (21.7)	
2	2,336 (61.9)	255 (17.4)	82 (26.1)	133 (18.6)	699 (41.1)	
3	-	1,125 (76.8)	216 (68.8)	525 (73.5)	341 (20.0)	NA
Unknown	-	20 (1.4)	9 (2.9)	28 (3.9)	292 (17.2)	
Histological tumour type						
Ductal	2,909 (77.1)	1,325 (90.4)	293 (93.3)	617 (86.4)	1,340 (78.7)	
Lobular	508 (13.5)	63 (4.3)	1 (0.3)	17 (2.4)	214 (12.6)	
Mixed	193 (5.1)	50 (3.4)	3 (1.0)	7 (1.0)	61 (3.6)	
Other	164 (4.4)	27 (1.8)	17 (5.4)	73 (10.2)	87 (5.1)	<0.001
Multifocality						
No	3,222 (85.4)	1,195 (81.6)	255 (81.2)	643 (90.1)	1,406 (82.6)	
Yes	476 (12.6)	228 (15.6)	47 (15.0)	52 (7.3)	269 (15.8)	<0.001
Unknown	76 (2.0)	42 (2.9)	12 (3.8)	19 (2.7)	27 (1.6)	
Type of surgery						
Mastectomy	1,280 (33.9)	610 (41.6)	145 (46.2)	226 (31.7)	692 (40.7)	
Breast-conserving therapy	2,494 (66.1)	855 (58.4)	169 (53.8)	488 (68.4)	1,010 (59.3)	<0.001
Axillary lymph node dissection						
No	2,262 (59.9)	787 (53.7)	185 (58.9)	461 (64.6)	1,097 (64.5)	
Yes	1,512 (40.1)	678 (46.3)	129 (41.1)	253 (35.4)	605 (35.6)	<0.001
Adjuvant systemic therapy						
None	2,252 (59.7)	290 (19.8)	116 (36.9)	262 (36.7)	1,084 (63.7)	
Endocrine therapy	800 (21.2)	465 (31.7)	8 (2.6)	9 (1.3)	331 (19.5)	
Chemotherapy	25 (0.7)	33 (2.3)	181 (57.6)	436 (61.1)	90 (5.3)	
Both	697 (18.5)	677 (46.2)	9 (2.9)	7 (1.0)	197 (11.6)	<0.001
Targeted therapy						
No	3,771 (99.9)	1,255 (85.7)	174 (55.4)	713 (99.9)	1,680 (98.7)	
Yes	3 (0.1)	210 (14.3)	140 (44.6)	1 (0.1)	22 (1.3)	<0.001

Numbers are n(%). Abbreviations: HER2 = human epidermal growth factor receptor 2, NA = not applicable. * = p-value was calculated on known values only, patients with unknown molecular subtype were excluded from these analyses. P-values depicted in bold are considered as statistically significant (p<0.05).

When correcting for mortality in the general population, 10-year RS rates were 96.5%, 92.1%, 91.4% and 79.3% for T1N0, T1N1, T2N0 and T2N1 stage, respectively. Conditional on nine years survived, these rates became 98.0%, 98.0%, 97.7% and 96.5%, in the 10th year, respectively (Figure 3). For confounding-adjusted RS showed similar results as was found for OS (median follow-up was 11.4 years). In the first three years, T1N0, T2N0 and T2N1 stage showed a significantly higher excess mortality as compared to T1N0 stage. However, in the subsequent years until 10 years from diagnosis, no significant differences were observed anymore for T1N1 and T2N0 compared to T1N0 stage. The higher excess mortality ratios of T2N1, compared to T1N0, were visible from diagnosis until conditional on seven years survived. However, the interrelationship between the four T and N subgroups declined drastically over time (Figure 5).

Figure 3. 10-year conditional overall and relative survival, from the first until the tenth year, stratified for T and N subgroup and breast cancer subtype.

Ten-year conditional overall and relative survival per breast cancer subtype

Of the entire population, 1,702 patients (21.4%) had an unknown breast cancer subtype due to missing data on receptor statuses or grade. These patients were excluded, leaving 6,267 patients for analysis. At 10-years from diagnosis, 81.4% of the patients with luminal A disease were still alive, compared to 77.3%, 76.4% and 70.0% in luminal B, HER2 positive and triple negative, respectively. Conditional on nine years survived, these rates became 97.2%, 96.6%,

98.3% and 96.5%, respectively (Figure 3). After adjustment for confounders, lower 10-year OS at time of diagnosis was observed for luminal B and triple negative, compared to luminal A. HER2 negative disease was not significantly different from luminal A regarding OS. Similar effects were seen conditional on one to six years survived. Conditional on seven and eight years survived, no significant differences among the subtypes were observed. However, in the last year (conditional on nine years survived), luminal B was associated with lower OS compared to luminal A (Figure 4).

Figure 4. Hazard ratios on 10-year conditional overall survival stratified for T and N subgroup and breast cancer subtype. In this figure, the differences between T and N subgroups in relation to 10-year OS are shown, when correcting for all relevant confounding variables. T1N0 stage was used as a reference for all analyses. Over time, the differences between T and N subgroups in relation to OS waned. Abbreviations: CI = confidence interval.

When correcting for mortality in the general population, 10-year RS rates were 95.0%, 93.2%, 89.0% and 79.6% for luminal A, luminal B, HER2 positive and triple negative disease, respectively. Conditional on nine years survived, these rates became 99.6%, 98.5%, 100.6% and 98.3%, in the 10th year, respectively (Figure 3). For confounding adjusted RS (median follow-up was 11.4 years) also showed waning differences between the subtypes over time. Conditional on zero to three years survived, clear differences between the subtypes were observed with triple negative disease showing the lowest RS and luminal A showing the

highest RS. From four years after diagnosis on, no difference in RS between HER2 positive and luminal A were present anymore. For luminal B, compared to luminal A, no differences in 10-year RS were observed at seven to nine years from diagnosis. The difference between triple negative and luminal A disease declined over time, however, conditional on eight years survived, triple negative disease was associated with lower 10-year RS compared to luminal A (Figure 5).

Figure 5. Excess mortality ratios on 10-year conditional relative survival stratified for T and N subgroup and breast cancer subtype. T1N0 stage was used as a reference for all analyses. In this figure, the differences between T and N subgroups in relation to 10-year RS (as a measure for disease-specific survival) are shown, when correcting for all relevant confounding variables. T1N0 stage was used as a reference for all analyses. Abbreviations: CI = confidence interval.

Discussion

This study showed that 10-year recurrence risks from diagnosis, conditional on the number of event-free years, declined over time for all prognostic subgroups. Remarkably, at diagnosis clear differences between subgroups were observed regarding recurrences, which attenuated as more years passed. This finding is likely to be explained by the initial prognosis of the patients. Wangchinda *et al.* showed that larger and node positive tumours were more

likely to recur in the first few years following diagnosis.¹⁷ Our study supports these results by showing that the divergent recurrence rates between T and N subgroups attenuated as year passed. Being free of disease at one to nine years following diagnosis increases the chance of being free of disease at 10 years following diagnosis.

The importance of stratifying patients according to T and N stage has been shown in a recent publication of Pan *et al.* showing that the risk of DM is strongly correlated with T and N stage.¹⁸ The lowest 10-year LR and RR risks from diagnosis were found in T1N1 stage, while this was expected in T1N0 stage (lowest risk group). The difference in RRs between these two subgroups was negligible (2.3 vs. 2.2%), but the percentage of LRs in T1N0 was almost doubled as compared to the percentage of LRs in T1N1 stage (4.6 vs. 2.4%). A likely explanation is that patients with T1N1 stage breast cancer were treated more intensively than patients with T1N0 stage breast cancer. Indeed, in the studied era, only 20% of T1N0 breast cancer patients received adjuvant systemic therapy, compared to 86% in T1N1. A recent study showed that a larger proportion of T1N0 breast cancers benefited from adjuvant systemic therapy, regardless of molecular subtype, tumour size, age and presence of comorbidities,¹⁹ which may explain our results. However, one should realise that the 10-year LR risk is still very low for both T1N0 and T1N1 stage. In addition, the Dutch national guidelines advised adjuvant systemic therapy in case of an absolute risk of 10-year breast cancer-related mortality of 15% or more. As patients with T1N0 stage breast cancer generally have a lower risk of 10-year breast cancer-related mortality, these patients were only advised adjuvant systemic therapy in case of other risk factors. An additional analysis on our data on patients with a known subtype shows that almost 10% of all T1N0 breast cancers was triple negative, compared to 6.5% in the T1N1 group. Triple negative breast cancers are previously shown to be more often classified as N0²⁰ and are associated with increased LR risks²¹ compared to other subtypes. We showed that patients with triple negative disease had the highest 10-year risk on LR, RR and DM at diagnosis. Over time, differences between breast cancer subtypes became smaller. Of note, luminal B breast cancers showed the highest risk of recurrences, conditional on two to nine years survived. This means that in luminal B disease recurrences more often occur after some years from diagnosis, while they occur most often in the first few years for the other subtypes (especially for HER2 positive and triple negative). Our result that the highest recurrence risks from diagnosis were found in triple negative disease confirms a previously performed systematic review, in which results of seven studies investigating LR and RR according to molecular subtypes were combined.²² The finding that in HER2 positive disease no RRs were found from the fifth year from diagnosis on may partly be attributed to the effectiveness of trastuzumab, which is shown to increase the 5-year disease-free survival significantly,²³ or the low number of events. Ten-year OS and RS were significantly different between the prognostic subgroups. However, these differences attenuated over time, as shown before.²⁴ Similar to the waning differences in recurrence risks over time, this can be explained by the initial prognosis of the patients: patients with an initial poorer prognosis are more likely to decrease in the first few years. Janssen-Heijnen and colleagues⁹ showed that conditional RS of stage I-III breast cancer patients in the Netherlands remained similar or improved over time. Furthermore, they showed that although long-term prognosis was very good, there was still significant excess mortality in the patient population compared to the general Dutch population, up to 20 years from diagnosis. The authors suggested that

this may be due to late recurrences, second tumours or late side-effects of breast cancer treatment. Our study has shown that the conditional risk of recurrences declines over the years, becoming as low as only a few percent in the last years. Whether this small risk may contribute to the described excess mortality rates beyond 10 years, is unclear. In our study, we showed that RS rates in the 10th year following diagnosis ranged between 96.5% and 98.0% for the different T and N subgroups, confirming a small but persistent excess mortality compared to the general Dutch population.

A strength of this study is the use of a nationwide population-based cancer registry, which increases the generalisability of the results. In addition, follow-up information on recurrences was extracted from patient records in retrospect, thereby ensuring that recurrence data was collected with high accuracy. Furthermore, very little population-based studies have been conducted that investigated the 10-year recurrence risk in breast cancer patients. Baade *et al.*³ recommended that knowledge on conditional survival estimates should be incorporated in routine statistical reporting, as these estimates provide more accurate information for patients who survived several years after their diagnosis. Uncertainty has multiple times been reported as a very important factor that negatively affects quality of life in breast cancer survivors.²⁵⁻²⁷ Therefore, we would like to emphasise that conditional estimates better reflect the risk of recurrence at a certain time point following diagnosis, and that it may help patients dealing with uncertainty about their future. In addition, information on conditional recurrence risks and survival is important to assess the relevance of prolonged endocrine therapy and/or adjuvant chemotherapy.

A limitation of this study is that HER2 status evaluation and use of trastuzumab was introduced in 2005. As a result, not all patients with HER2 positive disease may have been treated with trastuzumab, which may have led to higher recurrence rates for these patients as compared to patients diagnosed in more recent years. Another limitation is lacking data on Ki-67, which was originally used to classify patients in luminal A or luminal B. However, in this study we used grade to classify high risk luminal A tumours into the luminal B group. Furthermore, it is expected that contemporary recurrence risks are lower than the risks observed in our study, due to improvements in diagnostics,²⁸ surgical procedures²⁹ and adjuvant systemic treatment.³⁰ Especially regarding the latter, our results should be interpreted in light of the increasingly personalised use of adjuvant systemic therapy as a result of the MINDACT³¹ and TAILORx³² trials, both showing specific patient groups in which less or no use of adjuvant systemic treatment is noninferior to the standard recommendation. Lastly, it should be noted that beyond 10 years from diagnosis, recurrences are described to occur at a steady rate in oestrogen receptor positive disease,^{18,24} which may be related to the concept of tumour dormancy, which is thought to be a possible cause of late recurrences.³³ Longer follow-up beyond 10 years should give further information on late recurrences and its relationship with prognostic subgroups.

Conclusions

To our knowledge, this is the first study showing conditional 10-year recurrence risks in each subsequent year after diagnosis. Besides, we demonstrated that the difference in recurrence risks and survival between the prognostic subgroups wanes with more disease-free years from diagnosis. This is very important information to be communicated to patients, especially

to those remaining free of disease over time. Fear of recurrent cancer has been shown to be related to a high feeling of unmet needs in breast cancer patients,¹⁰ even years after their primary treatment.³⁴ The results of this study may contribute to increased awareness of lower recurrence risks over time, especially for patients with an initial high risk of recurrence. In addition, information on conditional risks may help personalise follow-up, as for some patients less frequent follow-up visits may be sufficient.^{35,36}

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Chapter

13

Chapter 13

General discussion and future perspectives

General discussion

In this thesis, several aspects of quality of breast cancer care are discussed. Breast-conserving surgery and mastectomy as surgical treatment for breast cancer have the largest share in this thesis, as breast surgery remains for now the most important component of the curative treatment of breast cancer, albeit often in a less extensive form. For this reason, the primary aim of this thesis was to get insight in the trends in breast surgery over time, and subsequently to determine the effect of these surgical treatments and timing of postoperative radiation therapy on survival outcomes in the real-world population.

In daily practice, prediction models are frequently used to estimate a patient's prognosis and consequently to aid clinical decision-making regarding individualised (adjuvant) treatments. Therefore, it is of crucial importance to validate such models. In addition, insight in any other informative prognostic and predictive factors for breast cancer will improve the accuracy of prediction models. Therefore, the second aim of this thesis was to increase our insight both in the accuracy of an existing prediction model and in important factors that may further increase accurate prediction of survival outcomes. This was achieved by validation of a frequently used prediction model on the Dutch population, by evaluating recurrence risks and survival according to different breast cancer subtypes, by creating a model that predicts the extra mortality risk compared to the general population, and by determining recurrence rates and survival conditional on the number of years survived.

The conclusions of this thesis are as follows:

- 1) The use of breast-conserving surgery increased over the years in the Netherlands, with significant variations between geographical regions.
- 2) Breast-conserving therapy is at least equal to mastectomy in terms of 10-year overall and distant metastasis-free survival in T1-2N0-1 staged breast cancer patients.
- 3) Breast-conserving therapy is at least equal to mastectomy with radiation therapy in terms of 10-year overall, relative and distant metastasis-free survival in T1-2N2 staged breast cancer patients.
- 4) Breast-conserving therapy is at least equal to mastectomy in terms of 10-year overall and breast cancer-specific survival in T1-2N0-2 staged breast cancer patients, even after stratification for important prognostic variables such as age, receptor status, use and type of systemic therapy and presence of comorbidities.
- 5) Multivariable Cox regression, propensity trimming, hierarchical modelling and instrumental variable analysis all require a very careful justification of the underlying assumptions and results should be carefully interpreted.
- 6) Observational studies are a valuable complement to existing randomised controlled trials.
- 7) Starting radiation therapy as soon as possible after surgery does not improve survival outcomes.
- 8) The online tool PREDICT reliably predicts 5- and 10-year overall survival in most Dutch breast cancer patients, although results should be interpreted cautiously in several subgroups.
- 9) Breast cancer subtypes are associated with 10-year risks of recurrences and

mortality.

- 10) A conditional prediction model for the annual extra mortality risk of (ex-)breast cancer patients compared to the general population was generated and it performed well in an external population.
- 11) Differences in recurrence risks and survival between prognostic T and N subgroups decline with an increasing number of disease-free years after diagnosis.

PART I: Trends and survival in breast surgery and timing of postoperative radiation therapy

Breast-conserving treatment on the rise, or not?

In 1971, The National Surgical Adjuvant Breast and Bowel Project of Fisher *et al.* initiated a randomised controlled trial (B-04) to determine whether simple mastectomy led to similar survival outcomes as Halsted's radical mastectomy. Ten-year results of this trial demonstrated that the less extensive surgical procedure led to similar survival outcomes as Halsted's procedure.¹ In 1990, the National Institutes of Health Consensus Development Conference recommended breast-conserving surgery with radiation therapy (breast-conserving therapy) for most women with stage I or II breast cancer.² However, evaluations of trends in breast-conserving therapy before and after publication of this recommendation revealed that although most early breast cancer patients were treated with breast-conserving therapy, the majority of stage II breast cancer patients still underwent a mastectomy during the nineties.³ In addition, considerable variation in use of breast-conserving therapy was present between regions in the United States,⁴ and predictors for breast-conserving therapy use did not correspond to those suggested in guidelines.⁵ The rather slow overall adoption of breast-conserving therapy alongside the regional variation suggested that patients possibly were not informed enough, i.e. shared decision-making left a lot to be desired.⁶ In the Netherlands, only a limited increase in use of breast-conserving therapy was observed from 1990 to 2002.^{7,8} This minimal increase, together with the reported regional variation⁸ emphasised the need for optimisation of the shared decision-making process in the Netherlands as well.

The European Organisation for Research and Treatment of Cancer (EORTC) 10801 trial of Van Dongen *et al.* was the first in publishing long-term results on survival following breast-conserving therapy and mastectomy in both stage I and stage II breast cancer (median follow-up 13.4 years).⁹ They showed similar survival rates for both treatment types. In 2002, this was followed by results of the NSABP B-06 of Fisher *et al.*¹⁰ and the Milan¹¹ trial of Veronesi *et al.* showing that even the 20-year overall, disease-free and distant metastasis-free survival rates were similar for both treatment groups. These trials were expected to have had an influence on the Dutch clinical practice, especially since the EORTC 10801 trial included Dutch hospitals. In **Chapter 2**, we showed that the overall trend in the use of breast-conserving therapy after 2002 (following the publication the landmark trials described above) further increased, although considerable variation remained present between regions, even after adjustment for several variables potentially influencing the choice for type of surgery. Although several studies already demonstrated equivalent survival rates for breast-conserving therapy and mastectomy,¹²⁻²³ and quality of life and social well-being are reported to be equal or higher following breast-conserving therapy,²⁴⁻²⁷ it is striking to notice

that there are even increasing trends in mastectomies observed.²⁸⁻³⁰ Moreover, these trends are not only witnessed in the United States, but also in some regions in the Netherlands. The main reason for this may be explained by a lack of incentives to strive for more breast conservation. In the Netherlands, there are several indicators for quality of care³¹, but, in contrast to for example the European Society of Breast Cancer Specialists (EUSOMA) guidelines and quality indicators,³² none of them encourages or measures the use of breast-conserving surgery. This can partly be explained by the fact that type of breast surgery is largely related to age, tumour characteristics, the patients' preference,³³ family history,³⁴ use of magnetic resonance imaging (MRI),³⁵ differences in the use of immediate²⁶ or autologous³⁶ breast reconstructions following a mastectomy or any (personal) condition that makes either one or the other treatment more preferable.³⁷ However, there is also evidence for type of surgery to be related to the surgeon's recommendation, which is associated with lower patient involvement³⁸ and a higher mastectomy rate.³⁹ Together with the most important surgical indicators in the Netherlands, which are related to reduction of positive margins and re-excisions following primary surgery³¹, this may contribute to higher mastectomy rates in some regions in the Netherlands. Identification of regions with the lowest number of breast-conserving surgeries may form a basis for further research in which patient preferences and other important factors contributing to the choice for type of surgery can be analysed. In this way, more insight can be obtained in the role of the patient in the shared decision-making process. Increased patient education and participation is suggested to reduce mastectomy rates and consequently variation, although other factors playing a role in treatment decision-making should be kept in mind.⁶ Getting more insight in the reasons behind variation in surgical treatment may improve treatment decision-making: well-informed patients make better choices.

The changing role of surgery in the management of breast cancer: an apparent contradiction

In the introduction of this thesis the shift from Halsted's radical operation to less invasive breast-conserving techniques was expounded. The introduction of less invasive surgical procedures has not only affected surgery of the breast, but also management of the axilla. The NSABP trial B-32 was the largest trial showing that sentinel lymph node biopsy alone without additional axillary lymph node dissection was safe in terms of overall and disease-free survival in patients with clinically negative lymph nodes.⁴⁰ In addition, the less invasive sentinel lymph node biopsy, compared to axillary lymph node dissection, is by multiple studies reported to significantly reduce postoperative morbidity and to increase quality of life.⁴¹ Besides, results of the American College of Surgeons Oncology Group (ACOSOG) Z0011 showed that even for patients with one or two positive sentinel lymph nodes, a sentinel lymph node dissection alone was non-inferior to patients treated with axillary lymph node dissection in terms over overall and disease-free survival.⁴² Consequently, the number of axillary lymph node dissections decreased drastically over the past years. In addition, several ongoing trials are currently evaluating the safety and efficacy of completely omitting axillary surgery in patients with a low risk of axillary metastases.⁴³ Moreover, less invasive axillary surgery has been shown to improve patients' quality of life.⁴⁴ Similarly, conservative surgery of the breast has been associated with less complications⁴⁵ and equal or improved quality of life and cosmetic satisfaction^{26,27} in breast cancer patients and survivors than mastectomy.

As described in several publications: less is more.^{46,47} In light of the trend towards minimally invasive axillary surgery, it seems highly contradictory that – while we have increasing information on the efficacy of breast conservation – mastectomy rates are still rising in some regions and some countries.^{28-30,48} In addition, it seems that the trend towards minimally invasive surgery of the axilla has evolved much faster than it does for less extensive breast surgery. A large part of this apparently inconsistent phenomenon may be explained by elusiveness of the reasons behind survival differences following breast-conserving therapy and mastectomy. There is a lot of disbelief that less invasive breast surgery may lead to better survival outcomes. However, considering the fact that breast cancer treatment may consist of surgery, systemic therapy and/or radiation therapy, the mechanism behind these differences may be very complex. Perhaps we should focus less on the mechanisms behind survival differences following breast-conserving therapy and mastectomy, and focus more on the results (both survival outcomes and quality of life) we observe in the daily population.

The ongoing debate: observational studies vs. randomised controlled trials in estimating the effect of breast-conserving therapy and mastectomy

As described before, several randomised controlled trials have shown equivalent survival rates for both breast-conserving therapy and mastectomy.⁹⁻¹¹ Various observational cohort studies investigating these treatment effects in real-world populations reported equal or sometimes improved survival rates for breast-conserving therapy as compared to mastectomy.¹²⁻²³ In **Chapter 3**, **Chapter 4**, and **Chapter 5** of this thesis, it was shown that this also counted for the Dutch breast cancer population, and that some subgroups may even benefit from breast-conserving therapy. Several publications criticised these types of studies regarding their observational nature, as randomised controlled trials are considered to be the golden standard in comparative effectiveness research due to their random treatment allocation.^{49,50} Despite a good correlation between outcomes of randomised and non-randomised studies, treatment effects are most often found to be larger in non-randomised studies.⁵¹ Other studies reported that results of well-designed non-randomised studies do not systematically overestimate treatment effects^{49,52} suggesting that these results may perfectly complement results from existing randomised trials, provided that they are interpreted carefully. In case of surgical treatment effects in breast cancer, many studies fairly refer to the well-designed and widely cited trial results of Van Dongen *et al.*,⁹ Fisher *et al.*,¹⁰ and Veronesi *et al.*¹¹ However, the fact that all patients included in these trials were diagnosed in the seventies and early eighties is never elaborated on. Taking into account the drastically improved survival rates over the years⁵³ – which is also evident in the Netherlands⁵⁴ – the improved local and regional control,⁵⁵ better diagnostics,⁵⁶ developments in adjuvant systemic therapy⁵⁷ and more individualised treatment strategies,⁵⁸ it is highly expected that outcomes of those randomised trials are different in the contemporary breast cancer population. Results may also have changed in view of the fact that much more patients are eligible for breast-conserving therapy now than in the seventies and early eighties, which is a result of earlier diagnosis, increasing knowledge on the safety of breast conservation⁵⁹ and the shift from adjuvant systemic therapy to primary systemic therapy.⁶⁰ In addition, it should be noted that the strict selection of trial participants does not reflect the patients as we see them in daily practice. Trial participants are shown to be younger, more motivated and tend to have less comorbidities than the real-world patient

population.^{61,62} Particularly in case of breast cancer, which is increasingly diagnosed in older women, trial results are not directly applicable to daily practice. All of these developments should be kept in mind when comparing results from more recent observational studies with those of older randomised controlled trials. Of course, in observational studies one can never completely eliminate residual confounding or confounding by severity as a result of different baseline characteristics in treatment comparison groups. Many challenges and limitations related to observational research can be minimised or even eliminated by using appropriate statistical techniques, but as presented in **Chapter 6**, all of these methods rely on very strict and often untestable assumptions making it very difficult to draw firm conclusions based on observational research. Nonetheless, the power of observational research should not be underestimated. Especially not when taking into account the fact that the studies presented in this thesis are based on the Netherlands Cancer Registry, which is a nationwide registry covering the entire Dutch population from 1989 onwards.⁶³ The Netherlands Cancer Registry receives regular notifications of the nationwide Pathology Archive (PALGA) of all newly diagnosed malignancies. Subsequently, dedicated and trained data managers register patient-tumour- and treatment-related characteristics of these patients. Every year, the Netherlands Cancer Registry is linked with the Dutch Hospital Data and National Medical Registry to include any missed cancer diagnoses. Data on vital status and date of death (if applicable) are obtained through linkage with the Municipal Personal Records database. Completeness of the Netherlands Cancer Registry was in 1995 estimated to be over 96%⁶⁴ and is expected to have further increased over the years. The strengths of such a complete database is the accurate reflection of patients as seen in daily practice. Randomised controlled trials, as is explained in **Chapter 7**, often reflect a very selected – most often younger and healthier – population which limits their external validity. Besides, randomised trials are conducted under very strict conditions with sometimes different follow-up visits as compared to daily clinical practice.⁶⁵ Even if patients in the target population have identical characteristics to those in the trial population, overall treatment effects observed in randomised controlled trials would only apply to the target population if the likelihood of treatment benefit and detriment is equally likely in every trial individual.⁶⁶ Considering the ageing population, which involves an increasing incidence of comorbidities, a growing number of breast cancer patients takes medication. The interaction between breast cancer and other diseases, and the interplay of adjuvant systemic therapy with some form of other medication is not well understood. In colorectal cancer patients, for example, it has been reported that neuropathic symptoms following chemotherapy treatment were more pronounced in patients with co-occurring diabetes,⁶⁷ indicating that treatment effects are different in the real-world population when compared to a trial population. It is of crucial importance to take a patient's personal situation into account.

Another research example in which observational studies are indispensable, is to investigate whether timing of adjuvant treatment may affect survival rates in several subpopulations. Not only the treatment itself is crucial for survival, but timing of therapies is important as well. It is unethical and probably unfeasible to randomise patients between short and long time intervals between, for example, breast-conserving surgery and postoperative radiation therapy. In addition, randomised trials often lack power to investigate treatment effects in specific prognostic subpopulations.⁶⁵ One can imagine that almost every patient

prefers postoperative radiation therapy as quick as possible following surgery. The fact that sometimes a slightly longer time interval between surgery and postoperative radiation therapy occurs may frighten patients, as they might think that a quick start of radiation therapy increases their chance of completely getting rid of all cancer cells. Population-based studies can be a solution to study the effect of different time intervals between therapies, in which confounding factors have to be taken into account adequately. Although residual confounding can never be excluded, results of such studies can give insight in survival outcomes following different time intervals between surgery and postoperative radiation therapy. As described in **Chapter 8**, time intervals of 42-55 days and over 55 days between breast-conserving surgery and postoperative radiation therapy did not negatively affect survival rates as compared to a time interval of less than 42 days. In the Netherlands, a time interval of ≤ 35 days is defined by the National Breast cancer Working group (NABON) Breast Cancer Audit (NBCA)³¹ and used as indicator for quality of care. Although a fast initiation of radiation therapy following surgery may be preferred by some, it should be communicated to patients that a slightly longer time interval does not seem to negatively affect survival rates. Interestingly, the EUSOMA working group included timing of the start of initial treatment in their set of quality of care indicators, but not timing of postoperative radiation therapy.³²

To sum up, randomised controlled trials provide real treatment effects due to its very strict setting and random allocation. However, observational studies may provide complementary information on treatment effects in the real-world population. Especially the relatively low number of patients in a trial prevents researchers from investigating the effect of a certain treatment in specific subpopulations. Only trial results may therefore not always be sufficient. For this reason, information of both observational and randomised studies should be considered when investigating treatment effects in daily practice.

Breast-conserving therapy should be the preferred treatment in early breast cancer, when this is appropriate and medically feasible

In the early eighties of the last century, professor Veronesi already considered a mastectomy to be an unnecessary mutilation in patients with a small breast tumour (<2 centimetres, no palpable axillary nodes).⁶⁸ Later on, following long-term results of the same trial, Veronesi concluded that in small breast cancers, mastectomies should have no role.⁶⁹ Apparently, this statement is not shared by many others as it is obvious from literature that still lots of patients with small tumours are treated with a mastectomy. Before elaborating on the important share of the patient in this decision-making process, it is of crucial importance to realise that offering patients a choice of treatments indicates that outcomes of both treatments are equal. In terms of survival, it is difficult to draw firm conclusions as all studies that showed a survival difference in favour of breast-conserving therapy were not randomised. However, as a lot of studies evaluated survival and quality of life following breast-conserving therapy and mastectomy and none of them showed a possible advantage in favour of mastectomy, we should question ourselves whether we should not offer breast-conserving therapy as the preferred treatment for most patients.⁷⁰ Breast conservation leads to less morbidity⁷¹ and surgical complications^{45,72} than mastectomy, all of which affect quality of life. Furthermore, opting for mastectomy to avoid radiation therapy is not always a sound basis for a decision, as postmastectomy radiation therapy is indicated in most patients with positive lymph nodes

and may complicate breast reconstruction planning.⁷³ Of course, the above-mentioned reasoning may not be relevant for BRCA mutation carriers, patients with a contraindication for radiation therapy, presence of extensive ductal carcinoma in situ, very young age or more than focally positive margins. However, in most other situations, breast-conserving therapy is safe and should be considered as the preferred treatment for most early stage breast cancer patients.⁷⁴ Developments in use of intraoperative radiation therapy,⁷⁵ the shift from adjuvant systemic therapy to primary systemic therapy⁷⁶ and the renewed attention for preoperative radiation therapy⁷⁷ are expected to further increase the possibilities for breast-conserving therapy.

Only well-informed patients are able to make a well-educated choice with regard to their treatment

A patient's preference for a mastectomy is, of course, absolutely justified, provided that the patient is well informed about both surgical procedures, its associated outcomes, the impact on quality of life and the consequences for possible adjuvant systemic therapy. Many patients substantially overestimate their recurrence risk.^{78,79}

Patients who reported the communication with a clinician to have influenced their risk perception on recurrent breast cancer were most likely to have a reasonably accurate comprehension of their actual recurrence risk.⁸⁰ However, women who ascribed their risk perception the most to uncertainty and/or family and personal history were more likely to overestimate their recurrence risk.^{79,80} Given the fact that even patients with ductal carcinoma in situ, which is actually a precursor of invasive breast cancer, substantially overestimate their risk of recurrence,^{79,81,82} there is an urgent need to better inform breast cancer patients, so they are able to make a well-educated choice. Especially fear of recurrent cancer and improved survival has been reported to be the main reasons for women choosing for mastectomy,^{83,84} even though evidence on better survival following a mastectomy is absent. The trend towards an increasing number of contralateral prophylactic mastectomies⁸⁵⁻⁸⁷ cannot be neglected as well, particularly when taking into account the fact that many patients do not know that bilateral mastectomy does not improve survival.⁸⁸ The use of MRI is multiple times reported to be associated with increased (contralateral prophylactic) mastectomy rates.^{89,90} However, other studies reported that MRI use did not significantly affect mastectomy rates^{91,92} or that a significant relationship was present for ductal tumours, but not for lobular tumours³⁵ and patients treated with primary systemic therapy.⁹³ This suggests that the relationship between MRI and mastectomy rates may largely depend on other patient-, tumour-, and treatment-related characteristics, suggesting that a better characterisation of patients undergoing breast-conserving therapy or mastectomy is necessary. This strengthens the importance of shared decision-making regarding surgical treatment even more.⁹⁴

Only well-informed patients are able to make the right choice concerning their treatment. However, the decision-making process is shown to be complex and problematic for many patients.⁹⁵ One can imagine that women feel distressed at time of their breast cancer diagnosis, and that they are overwhelmed with information, which they are not able to process in a short period of time. In addition, Mitchell *et al.*⁹⁶ showed that many patients do not feel completely informed about the surgical possibilities. For this reason, it is of crucial importance to further optimise the shared decision-making process, in which particular attention will be

given to a patient's uncertainty. When uncertainty or anxiety is due to a lack of information, this may be reduced by simplifying, breaking down and organising the information to make it clear.⁹⁷ However, not all uncertainty may be diminished. For example, influences of family and community are often neglected.⁶ Clinicians can help patients in accepting their uncertainty without compromising the patient's risk perception by discussing all the information in the context of the patient's specific situation.⁹⁸ In addition, treatment decision tools may help patients in making the right choice about their treatment, and should therefore be integrated in clinical practice.⁹⁹ A well-informed patient is a patient who understands the benefits and risks of both surgical procedures and its combination with possible (adjuvant) systemic treatment. She has to have an accurate perception of survival and recurrence risk, and has to understand the potential consequences of her treatment with respect to quality of life and psychological well-being. Especially for patients for whom breast-conserving therapy is achievable and appropriate, breast-conserving therapy should be offered as the preferred treatment. If a well-informed patient, eligible for breast-conserving therapy, still opts for a mastectomy based on persisting uncertainty, this is a perfectly justified choice.

PART II: Clinical risk prediction in breast cancer

The role of clinical risk prediction models in shared decision-making

Shared decision-making is nowadays widely considered as a crucial part in good quality health care, as the important role of patient preferences is becoming increasingly recognised.^{100,101} To make a solid decision regarding a certain treatment, a patient has to be provided with all the relevant information, tailored to the patient's personal needs. With respect to adjuvant systemic treatment, it is important for patients to understand the possible benefits and harms to make the right decision. It is widely known that adjuvant systemic treatment reduces mortality and recurrence rates.^{102,103} However, the extent to which adjuvant systemic treatment provides a benefit is for every patient different and depends on several patient- and tumour-related characteristics. Both under- and overtreatment should be limited by increasing the personalisation of treatment and prescribing medication only to patients who benefit most of it, to avoid unnecessary complications.¹⁰⁴ Nationwide guidelines already provide an overview of appropriate treatments for certain risk groups and are a first filter in a range of treatment possibilities. Additional use of online prediction tools can further personalise a patient's risk profile. It has been described that the use of prediction models in the consultation room often increases patients' understanding of their prognosis.¹⁰⁵ The first step in making the decision process easier is the use of accurate risk predictions, which can be achieved by validation of already existing clinical risk prediction models.

Validation of prediction models

There are a lot of prediction models that predict the benefit of adjuvant systemic treatment on survival rates. However, only few of those models are validated on the actual target population. External validation of a model on a different population than it was developed on is regarded as more important than internal validation (which uses a random subsample of the development population) as it evaluates generalisability rather than reproducibility.^{106,107} Differences in population characteristics, health care systems, methods of measurement

and definitions of variables and outcomes between populations may cause a poor model performance. Another important aspect is the presence of a wide variety in quality and methodology of prediction models, which may complicate interpretation of the model's outcomes in other populations.¹⁰⁸ This makes it of crucial importance to externally validate prediction models before using it in clinical practice.¹⁰⁶

In the introduction of this thesis, Adjuvant! Online¹⁰⁹ was mentioned as an example of a frequently used model in the Dutch clinical practice and was also recommended in the Dutch national guidelines from 2008 on. Interestingly, at that time, Adjuvant! Online was not validated yet on the Dutch population. A study on breast cancer specialists' view on and use of clinical prediction models revealed that 37% of the participating oncologists assumed that Adjuvant! Online's estimates were sufficiently accurate as the national guidelines were partly based on results of this prediction model.¹¹⁰ It is remarkable that clinicians attach so much value to a model of which its performance on the target population is unknown. Especially when taking into account the fact that Adjuvant Online! has been developed on women from the United States, aged 35 to 59 and diagnosed between 1988 and 1992. As the risk of being diagnosed with breast cancer in the Netherlands is the highest between 60 and 70 years,¹¹¹ one can imagine that predictions developed on younger patients from a different country may not be applicable to the Dutch population. It is, therefore, remarkable that such a prediction model was recommended in the national guidelines while no one knew whether the model's performance was adequate. Without validation, one is unsure whether a model predicts accurate, possibly resulting in suboptimal treatment recommendations. As Adjuvant! Online is currently unavailable, most clinicians switched to the online prediction tool PREDICT.¹¹² This tool was developed on non-metastatic breast cancer patients diagnosed between 1999 and 2003, surgically treated in East Anglia, England. The model provides expected benefits of chemotherapy, endocrine therapy and trastuzumab in terms of 5-year and 10-year overall survival. In **Chapter 9** of this thesis, PREDICT was validated on the Dutch breast cancer population. PREDICT turned out to accurately estimate 5-year and 10-year overall survival in the entire population. However, subgroup analyses showed that 5-year overall survival was underestimated in ER negative tumours, and that 10-year overall survival was underestimated in ER negative tumours, T3 staged tumours and patients treated with both endocrine therapy and chemotherapy. In addition, in patients of 75 years and older, 10-year overall survival was overestimated by PREDICT. As described above, it is very important to accurately judge the performance of a prediction model on the target population. However, it is shown to be difficult to determine the clinical utility of a model, especially when a prediction model would change decision-making.¹¹³ Therefore, results should be interpreted in light of the characteristics of the tumour, the treatment possibilities and the social context of the patient. For example, for T3 staged tumours the validation study in this thesis showed that 5-year overall survival was predicted accurately, but that 10-year overall survival was underestimated with 13 percent. This result means that for a patient with a T3 staged breast tumour, when using this model, her long-term survival is on average 13 percent higher than the model predicts. In general, a lower predicted survival rate may potentially lead to overtreatment with adjuvant systemic therapy. However, for patients with a T3 staged tumour the Dutch national guidelines already recommend chemotherapy, so in this case overtreatment will be less of an issue since it would not change clinical practice. However,

for a patient's risk perception the results of this validation study are still of great importance: an underestimated predicted survival may lead to unrealistic uncertainty about a patient's future. Taking into account the fact that communication of survival probabilities using risk prediction models is already very complex,¹⁰⁵ it has at least to be clear whether these survival probabilities are accurate. In the Netherlands, results of PREDICT should be discussed with the patient in light of its performance in the Dutch clinical practice.

Breast cancer subtype as important prognostic factor for survival and recurrence risk

To make sure a model predicts as accurate as possible, it is of great importance to get insight in patient-, tumour- and treatment-related characteristics that may influence survival rates. Next to the traditional clinical prognostic variables, the underlying biology of the tumour becomes increasingly important.¹¹⁴ Molecular subtypes have been shown to act as independent prognostic factors for survival and treatment response,¹¹⁵ and were initially derived from gene expression profiles.^{114,116} At the St Gallen international expert consensus meeting, it was advised to integrate molecular subtypes in primary treatment decisions¹¹⁷. Since many registry-based studies lack information on gene expression profiles, these molecular subtypes are often defined using immunohistochemically determined receptor statuses. These adapted breast cancer subtypes (luminal A, luminal B, HER2 positive and triple negative subtypes) are widely used and have been shown to independently predict recurrence and survival rates.¹¹⁸⁻¹²⁰ **Chapter 10** describes 10-year recurrence and survival rates according to these adapted breast cancer subtypes in the Netherlands, which was the first registry-based study that had information on 10-year follow-up according to these subtypes. This study confirmed that breast cancer subtypes were independent prognostic factors for 10-year recurrence and survival rates. In addition, it was shown that HER2 positive and triple negative subtypes tended to recur most often in the second year, while luminal A and luminal B showed a more continuous pattern with recurrences also occurring later on in the follow-up. The latter finding confirms earlier studies showing that ER positivity is related to recurrences beyond five years from diagnosis.^{121,122} In general, patients diagnosed with HER2 positive and triple negative disease have a worse prognosis as compared to patients with luminal A or luminal B disease.¹¹⁸⁻¹²⁰ An important message from this study is that patients with HER2 positive or triple negative disease who survived some years, should be made aware that their risk on a recurrence is considerably lower than it was at diagnosis.

Conditional survival

Survival rates do not only depend on clinical and molecular characteristics, but are also likely to increase as years pass by. For patients who survived several years following their diagnosis, risk estimates calculated at time of diagnosis may not be appropriate anymore. This issue becomes more important since improvements in diagnostics and treatment strategies lead to a growing number of breast cancer survivors with long-term survival.¹²³ Many of them experience problems in their return to work¹²⁴ or in applying for a life insurance,¹²⁵ which is often required to obtain a mortgage. Especially the latter problem is considerable: in a study published in 2012, 60% of the applications for a life insurance by cancer survivors in the Netherlands was declined.¹²⁵ Decisions of life insurers were based on estimation of mortality risks from time of diagnosis. They used internationally available survival rates, which were

believed not to be representative for the Dutch breast cancer population. Moreover, most patients only apply for a life insurance some years after their diagnosis, and breast cancer survival rates are shown to increase as time passes.¹²⁶

In 2015, the Dutch Federation of Cancer Patient organisations (NFK) activated the Dutch Association of Insurers to find a solution for the problem as stated above. As the Dutch Association of Insurers was willing to improve the insurance underwriting process, the Netherlands Comprehensive Cancer Organisation (IKNL) was asked to play a role in this project by creating a prediction model based on data from the nationwide Netherlands Cancer Registry.

In **Chapter 11**, a conditional model was developed that specifically addressed mortality risks of breast cancer patients in the Netherlands, as compared to the general Dutch population, taking into account the years a patient already had survived. Such conditional models are described to provide more reliable estimates of patients in the years after their diagnosis.¹²⁷ The final model was built in such a way that mortality rates were calculated only on patients who were alive at a certain time point following diagnosis. Next to a satisfying internal and external validation, the model was tested in practice on a random selection of 50 breast cancer patients based on data from the Netherlands Cancer Registry. Eight of the 10 Dutch insurance companies specialised in life insurances participated in this test, in which they were asked for their decisions when these 50 patients would apply for a life insurance, at diagnosis or some years after their diagnosis. This information was collected by the Centre for Insurance Statistics in the Netherlands, anonymised, and consequently analysed for agreements and discrepancies between the currently used data and the newly-developed model. This analysis showed that insurability of breast cancer patients increased by using the newly-developed model, which may be explained by the introduction of conditional survival,¹²⁷ the use of more recent data specifically based on the Dutch breast cancer population, and the detailed information on patient-, tumour- and treatment-related characteristics which allows a more accurate prediction. The latter, however, raises an important ethical issue. For patients it may not be desirable to provide more information on their disease to life insurers. However, in consultation with the NFK, it was decided that provision of more detailed information did not outweigh the benefits of the newly-developed model in terms of insurability. Providing all life insurers a similar underlying model to base their calculation on will not solve the large differences in premium raises between insurers, but it may increase transparency to patients by informing them on the used data.

In estimating breast cancer prognosis, not only overall survival is a relevant outcome measure. As many breast cancer patients and survivors experience fear of recurrent cancer, even years after their diagnosis,¹²⁸ it is relevant to get insight in (conditional) recurrence risks. In **Chapter 12**, these conditional recurrence risks were evaluated in the Dutch population, taking into account the disease-free years following diagnosis. The distributions of local recurrences, regional recurrences and distant metastases were specified according to tumour and nodal stage and breast cancer subtype, as important prognostic factors. Over time, the differences in recurrence risks between the different tumour and nodal stages and breast cancer subtypes declined. It has been described earlier that larger and node positive tumours are at highest risk of recurrence in the first few years following diagnosis.¹²¹ For patients who are still alive several years after their diagnosis it is relevant to know that their recurrence risk

declines over time. In contrast, for patients with an initial good prognosis (for example T1N0 stage, which is the largest group of breast cancer patients, or luminal A disease), it should be communicated that average recurrence risks described in literature may not always be representative for their personal risk.

Future perspectives and recommendations

In the current era of personalised medicine, under- and overtreatment can be limited due to increasing knowledge on tumour characteristics and long-term treatment effects. The patient's role in personalised medicine is becoming increasingly recognised. To further optimise the role of the patient in the shared decision-making process, two key elements have to be addressed. First, more focus should be laid on validation and improvement of existing prediction models to increase insight in prognosis, late side effects of treatments and quality of life. Second, information provision to patients has to be optimised.

This thesis elaborates on the fact that prediction models used in the shared decision-making process are not routinely validated on the target population, which may lead to suboptimal treatment recommendations and unrealistic risk perceptions. As the online tool PREDICT¹¹² is now validated in the Dutch population, clinicians in the Netherlands are recommended to use this model in clinical practice in adjuvant treatment decision-making, taking into account the limitations described in this thesis. Validation procedures in general can be facilitated by using the semi-automated validation tool of the Evidencio platform: <https://www.evidencio.com>, which enables routine validation of prediction models.

Future research should focus on the optimisation of existing clinical prediction models instead of developing new ones on the same issue. Prediction models currently used in breast cancer care are often based on traditional clinicopathological characteristics. However, as the intrinsic biology of the tumour is becoming increasingly recognised, risk predictions may become more accurate when traditional prognostic factors are combined with information on the biological subtype of the tumour. Furthermore, more attention should be paid to the social context of the patient. Any existing comorbidities, presence of a BRCA mutation and performance status of the patient may all influence prognosis and treatment choices and should therefore be integrated in clinical risk prediction. Moreover, as breast cancer has in general a good survival,¹²⁶ late treatment effects should play an important role in the decision-making process. Ideally, prediction models should predict not only overall survival, but also the risk on late side effects of adjuvant treatment¹²⁹ and quality of life. These aspects are not only of importance for treatment decision-making, they are also relevant for management of uncertainties. Especially when taking into account the growing number of breast cancer survivors,¹¹¹ the question 'what happens after curative treatment of breast cancer?' is becoming increasingly important. Adequate survival and recurrence rates, taking into account the number of years survived or disease-free following diagnosis should increase a patient's risk perception. In addition, such information may contribute to personalisation of follow-up. For example, the risk prediction model INFLUENCE,¹³⁰ available on <https://www.utwente.nl/en/techmed/influence/nomogram/> provides the conditional annual risk on local and regional recurrences. Identification of patients with a low or high risk on a recurrence

not only increases insight in prognosis, but may also form a basis for shared decision-making regarding the follow-up plan.

A challenge in optimising the shared decision-making process is the provision of adequate and complete information to patients. With respect to primary treatment, there is no evidence – nor from observational studies, neither from randomised trials – that breast-conserving therapy (when appropriate and medically feasible) may possibly lead to worse survival outcomes than mastectomy. In addition, patients who underwent breast-conserving therapy reported equal or higher quality of life and social well-being than patients who underwent mastectomy.²⁴⁻²⁷ Therefore, this thesis states that breast-conserving therapy should be considered as the preferred treatment option in T1-2N0-2 stage breast cancer, when it is achievable. The main concern is now that many patients report to experience fear of recurrent cancer and feel that they should opt for mastectomy to minimise the chance on a recurrence.^{83,84} Next to the importance of better use of available (cancer registry) data and cautious interpretation of the results, these studies underline the necessity of better communication to patients, which should be a key focus for further research. An example of better information provision to patients may be the use of a decision aid. In the Netherlands, the PATIENT+ decision aid has been developed to provide patients individualised information on both surgical treatment options: breast-conserving therapy and mastectomy.¹³¹ This decision aid is available on <https://www.keuzehulp.info/pp/borstkanker/intro>. It includes information on breast cancer in general, it describes the benefits and advantages of both types of surgery and provides clear information on survival, recurrence rates and cosmetic satisfaction. Such decision aids may decrease the inaccurate risk perceptions of higher recurrence rates following a mastectomy. In addition, patients are able to fill in their ideas and preferences (for example, if they think that they would have a larger risk on a recurrence following breast-conserving therapy than following mastectomy, or that they are reluctant to undergo radiation therapy). In this manner, it helps patients considering all the benefits and harms to choose the right treatment for their specific situation. Using results of such decision aids in the consultation room may increase the role of the patient in the shared decision-making process.

In observational research in general, survival rates and predictions have the limitation of being based on data obtained from records from patients diagnosed a long time ago. It is of crucial importance to interpret these results in light of the evolving clinical practice. To keep up with the developments in diagnostics and treatments and the increasing knowledge on the biology of the tumour, it is vital to regularly update the analyses to ensure that patients are provided with the most recent information. Researchers should think of proper methodologies to answer specific research questions, taking into account possible confounding by severity and unmeasured confounding that may bias the results. Despite its limitations, population-based research provides us with the unique opportunity to study a variety of research questions in large populations, and to concentrate on specific prognostic subgroups.

Ultimately, we strive for the most suitable treatment and the most appropriate risk information for every individual, in which the patients' preference and social context play a central role.

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SUMMARY

NEDERLANDSE SAMENVATTING

DANKWOORD

CURRICULUM VITAE

LIST OF PUBLICATIONS

PHD PORTFOLIO

SUMMARY

Summary

Breast cancer is the second most commonly diagnosed cancer worldwide. In the Netherlands, breast cancer incidence is rising, while mortality rates are declining. Still, 1 in 27 women diagnosed with breast cancer will eventually die due to the disease. Taking into account the fact that over 14,000 women in the Netherlands are diagnosed with breast cancer each year, breast cancer remains an important health problem.

As local surgery is currently the most important component of curative breast cancer treatment, a large part of this thesis focused on trends in breast surgery and survival following breast-conserving therapy and mastectomy. Since breast-conserving therapy includes the use of postoperative radiation therapy, this thesis additionally addressed the effect of timing of radiation therapy on survival outcomes. Furthermore, attention was paid to the use of proper methodologies and the value of observational research on comparative treatment effects as a complement to randomised controlled trials.

The second part of this thesis concentrated on clinical risk prediction of survival in breast cancer. Here, the focus was laid on the validation of an existing prediction model that is frequently used in clinical practice, on the impact of breast cancer subtypes on recurrence rates, and on the use of conditional survival, i.e. taking into account the number of years a patient survived.

PART I: Trends and survival in breast surgery and timing of postoperative radiation therapy

Chapter 2 describes the trends in the use of breast-conserving surgery in the Netherlands before and after publication of landmark trials that put this type of surgery on the map. It was shown that the incidence of breast-conserving surgery has increased over time, but that large variation existed between the nine Dutch regions. Throughout the period 1989 to 2002, the mean percentage of breast-conserving surgery in the Netherlands was 50.6%, varying from 39.1% to 71.7% among the nine regions. From 2003 to 2015, the average percentage of breast-conserving surgeries increased to 67.4%, fluctuating from 58.5% to 75.5% among the nine Dutch regions. The variation was larger before publication of the landmark trials, and attenuated after the publication of these trials, even though the variation was still considerable. Explanatory variables for the variation, besides geographical region, were age, T and N stage, sublocalisation of the tumour within the breast, tumour grade, histological tumour type, multifocality, hormonal receptor status, HER2 status, axillary lymph node dissection, adjuvant systemic therapy, and targeted therapy. Remaining variation can potentially be explained by unmeasured factors such as patient' and doctors' preferences and the degree of shared decision-making, and are subject of further research.

Subsequently, **Chapter 3** showed that breast-conserving therapy led to at least equal 10-year overall, distant metastasis-free and relative survival rates in T1-2N0-1 stage breast cancer in the Netherlands, when adjusting for a large number of potential confounding variables, compared to mastectomy. After stratifying these results for tumour and nodal stage, the significant benefit of breast-conserving therapy as compared to mastectomy was only present in T1N0 stage breast cancer.

Chapter 4 showed similar outcomes in T1-2N2 stage breast cancer. As N2 staged patients generally have the indication for radiation therapy, breast-conserving therapy was compared

with mastectomy with postoperative radiation therapy in this population. Both types of local treatment were shown to be equal in terms of 10-year overall, distant metastasis-free and relative survival.

To further explore treatment effects in the Dutch breast cancer population, in **Chapter 5**, a linkage with the Statistics Netherlands was performed to obtain information on cause of death. In addition, treatment effects were estimated in the following subgroups: 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). This study showed that breast-conserving therapy led to equal or better overall and breast cancer-specific survival rates as compared to mastectomy in all prognostic subgroups, after adjustment for confounding.

In **Chapter 3**, **Chapter 4** and **Chapter 5**, treatment effects were studied in the Dutch population using data from the Netherlands Cancer Registry. These observational types of researches may suffer from residual, unmeasured confounding, confounding by severity – meaning that the severity of disease is associated with the administered treatment – and hospital-related variation. All these types of biases may affect the estimated outcomes and consequently lead to incorrect interpretations of treatment effects. This emphasises the importance of adequately designed studies using proper methods. There are many statistical methods developed that may deal with these types of biases. In **Chapter 6**, four different methods – multivariable Cox regression, propensity trimming, hierarchical modelling and instrumental variable analysis – were applied on the research question: “what is the effect of breast-conserving therapy and mastectomy on 10-year distant metastasis-free survival?” This study aimed to show the difficulties in selecting the right method and to inform others to carefully handle results from observational research. Results of propensity trimming (excluding patients with the highest probability of being treated with either one or the other treatment) and hierarchical modelling (using hospital of surgery as hierarchical level, thereby correcting for hospital-related variation) did not differ from those of conventional multivariable Cox regression: they all showed a similar significant benefit of breast-conserving therapy as compared to mastectomy on 10-year distant metastasis-free survival. Results of instrumental variable analyses, using hospital of surgery as instrumental variable, showed no significant difference between the two types of treatment. However, the assumptions of this statistical method were not considered to be met. This study concluded that, although assumptions of all methods need to be very carefully thought of, results from observational studies may be a valuable complement to randomised controlled trials, as long as they are interpreted cautiously.

Chapter 7 further emphasised the importance of observational research as compared to randomised controlled trials. Here, the strengths and weaknesses of both study types were discussed. In general, randomised controlled trials are close to provide perfectly unbiased treatment comparison estimates, due to the random allocation of patients to treatment groups. Nevertheless, translating overall treatment effects of a trial to an individual patient’s response is very difficult. Especially when taking into account the fact that randomised controlled trials are restricted to predefined limits in inclusion. Using population-based registries, several specific prognostic subgroups – such as older patients – can be studied

which are not covered in the trial population. Observational studies can certainly not replace randomised controlled trials, but they give complementary information on the unselected real-life population where randomised controlled trials are not performed.

As breast-conserving surgery is typically followed by postoperative radiation therapy, one can imagine that the timing of radiation therapy following surgery may be important for survival outcomes. For this reason, the effect of different time intervals between breast-conserving surgery and postoperative radiation therapy on 10-year disease-free survival was investigated in **Chapter 8**. Here, two populations were studied. In population 1, patients receiving chemotherapy before radiation therapy were excluded, as the use of chemotherapy in between is largely related to the time interval. The following time intervals between surgery and radiation therapy were compared: <42 days, 42-55 days and >55 days. In population 2, patients receiving chemotherapy before and after radiation therapy were studied. For patients treated with chemotherapy after radiation therapy, 42-55 days and >55 days were compared with <42 days. For patients treated with chemotherapy before radiation therapy, 112-140 days and >140 days were compared with <112 days. For all of these analyses it was shown that shorter time intervals did not improve recurrence and survival rates. Therefore, the quality indicator in the Netherlands that states that patients have to be treated with radiation therapy within 35 days following surgery can be questioned, and patients should be informed that a slightly longer time interval does not negatively affect their risk of recurrence and survival.

PART II: Clinical risk prediction in breast cancer

Prediction models used in the shared (treatment) decision-making process are not routinely validated, which may result in suboptimal treatment recommendations and unrealistic risk perceptions. As the target population may be different from the development population with respect to patient-, tumour- and treatment-related characteristics, validation of currently available prediction models is crucial. The online prediction tool PREDICT estimates 5-year and 10-year overall survival, and the expected benefit of adjuvant systemic therapy in patients with primary operated stage I-III breast cancer. After inactivation of Adjuvant! Online, PREDICT became the most frequently used prediction tool in Dutch clinical practice. To assess its validity on the Dutch population, this model was validated in **Chapter 9**. This validation study showed that PREDICT accurately predicts overall survival in most Dutch breast cancer patients, but that results for both 5-year and 10-year overall survival should be interpreted cautiously in ER negative tumours, as PREDICT slightly underestimated survival outcomes for this group. In addition, 10-year overall survival was shown to be overestimated in patients 75 years and older, in T3 tumours and patients treated with both endocrine therapy and chemotherapy.

The relevance of breast cancer subtypes in clinical risk prediction is becoming increasingly recognised, as the underlying biology of the tumour is shown to greatly affect recurrence and survival rates. In **Chapter 10**, the effect of breast cancer subtypes on 10-year recurrence and survival rates in the Dutch population was described. It was shown that breast cancer subtypes were independently associated with these survival outcomes: luminal A disease was related to the lowest percentages of recurrences, while triple negative disease showed the highest percentages of recurrences. This knowledge further paves the way to increased

patient-tailored treatment and individualised follow-up.

Accurate risk prediction is not only important for treatment decision-making and a patient's risk perception. It is also of at least equal relevance for cancer survivors who are finding their way back into the society. In the Netherlands, a study showed that approximately 60% of cancer survivors are facing difficulties in the application for a life insurance. The data used by life insurers for these decisions were based on internationally available survival rates, which were considered to be outdated and not representative for the Dutch population. As most cancer survivors only apply for a life insurance a couple of years after their diagnosis, and it is known that survival rates increase as time passes by, it is of great importance to take into account the number of years survived in estimating a patient's prognosis. **Chapter 11** described the development of a model predicting the conditional annual extra risk on mortality compared to the general Dutch population. By accounting for the number of years survived, this model provides more accurate estimates for patients who apply for a life insurance several years after their diagnosis. The model was both internally and externally validated with satisfying results. The model was additionally tested on a random selection of patients from the Netherlands Cancer Registry, and compared to insurer's guidelines that were valid before the introduction of this model. Test results showed that the newly developed model, in general, increased insurability of breast cancer patients. Further monitoring of the use of this model is necessary to identify any remaining problems in the application for a life insurance needing further research.

In **Chapter 12**, conditional 10-year recurrence and survival rates were assessed for patients with early stage breast cancer, according to T and N stage and breast cancer subtype as important prognostic factors. It was revealed that differences in outcomes between these prognostic subgroups attenuated as time passed by. For this reason, the most important message from this study is that conditional survival estimates specific for a risk profile should be used in patient communication. This should lead to a more accurate risk perception of patients.

In conclusion, this thesis showed that breast-conserving therapy is at least equal to mastectomy in T1-2N0-2 stage breast cancer in terms of 10-year overall and breast cancer-specific survival. Combined with results of randomised controlled trials, this thesis contributes to increased awareness that a mastectomy does not reduce the risk of recurrence and mortality, as compared to breast-conserving therapy. Besides, this thesis revealed the importance of specific risk profiles and use of conditional survival in clinical risk prediction. Overall, communication to patients, based on relevant data, plays a central role and should form the basis of the shared decision-making process. Ultimately, this will lead to better treatment decisions and more realistic risk perceptions.

NEDERLANDSE SAMENVATTING

(Dutch summary)

Nederlandse samenvatting

Borstkanker is wereldwijd de op één na meest voorkomende vorm van kanker. In Nederland stijgt de incidentie van borstkanker, terwijl de kans om hieraan te overlijden juist daalt. Echter overlijdt nog steeds 1 op de 27 vrouwen gediagnosticeerd met borstkanker aan deze ziekte. In gedachte houdend dat ieder jaar meer dan 14.000 vrouwen in Nederland borstkanker krijgen, blijft dit een belangrijk gezondheidsprobleem.

Omdat een operatie nog altijd het meest belangrijke onderdeel is van de behandeling van borstkanker, beschrijven we in het eerste deel van dit proefschrift de trends in en overleving na een borstsparende operatie of een amputatie. Omdat een borstsparende operatie in principe altijd gevolgd wordt door bestraling, wordt hier ook aandacht aan besteed, specifiek aan het effect van het tijdsinterval tussen de operatie en de bestraling op de overleving. Verder gaat dit proefschrift in op het gebruik van goede methodologie en de waarde van observationeel onderzoek als aanvulling op bestaande gerandomiseerde klinische trials.

Het tweede deel van dit proefschrift gaat over het voorspellen van de kans op terugkeer van borstkanker en overlijden na een borstkankerdiagnose. In dit deel wordt een validatie van een bestaand predictiemodel besproken, wordt de impact van onderliggende biologische subtypes beschreven en wordt ingegaan op het effect van het aantal jaar dat iemand heeft overleefd na de diagnose (conditionele overleving).

Deel I: Trends in en overleving na borstoperaties en timing van postoperatieve bestraling

In **Hoofdstuk 2** worden de trends beschreven in het gebruik van een borstsparende operatie in Nederland voor en na de publicatie van belangrijke gerandomiseerde trials die de borstsparende operatie op de kaart hebben gezet. Dit hoofdstuk laat zien dat het percentage borstsparende behandelingen over de tijd toeneemt, maar dat er veel variatie bestaat tussen de regio's in Nederland. Over de gehele periode van 1989 tot en met 2002 bedroeg het gemiddelde percentage borstsparende behandelingen 50,6%. Dit percentage varieerde van 39,1% tot 71,7% tussen de verschillende regio's. Van 2003 tot en met 2015 steeg het gemiddelde percentage tot 67,4%, waarbij de variatie tussen regio's tussen de 58,5% en de 75,5% lag. De variatie was groter in de periode van 1989 tot en met 2002 – vóór de publicatie van de hiervoor genoemde trials – en nam vervolgens af, hoewel de variatie nog steeds aanzienlijk was. Verklarende factoren voor de variatie, los van de verschillende regio's, waren: leeftijd, tumor- en klierstadium, locatie van de tumor in de borst, graad van de tumor, histologisch subtype, multifocaliteit, hormoonreceptorstatus, HER2 status, het verrichten van een okselklierdissectie, postoperatieve systemische therapie en doelgerichte therapie. Overige variatie kan mogelijk worden verklaard door ongemeten factoren, zoals de voorkeur van de arts of patiënt en de mate van gedeelde besluitvorming, en zijn belangrijk voor toekomstig onderzoek.

Hoofdstuk 3 laat zien dat een borstsparende operatie gevolgd door bestraling een minstens gelijke 10-jaars algehele, metastasevrije en relatieve (vergeleken met de algemene Nederlandse populatie) overleving geeft als een amputatie in patiënten met T1-2N0-1 stadium borstkanker (een tumor tot vijf centimeter met niet meer dan drie aangedane lymfeklieren). Na specificatie voor het tumor- en klierstadium bleek er een voordeel te zijn van de borstsparende behandeling ten opzichte van de amputatie in patiënten met een

tumor tot twee centimeter, zonder aangedane klieren, T1N0.

In **Hoofdstuk 4** werden vergelijkbare uitkomsten gevonden in patiënten met T1-2N2 stadium borstkanker (een tumor tot vijf centimeter met vier tot negen aangedane lymfeklieren). Echter, omdat voor patiënten met vier tot negen aangedane klieren bestraling wordt geadviseerd, werd hier de borstsparende behandeling (inclusief bestraling) vergeleken met een amputatie gevolgd door bestraling. Beide behandelingen waren vergelijkbaar op het gebied van 10-jaars algehele, metastasevrije en relatieve overleving.

De behandel effecten werden verder onderzocht in **Hoofdstuk 5**, waarbij de Nederlandse Kankerregistratie werd gekoppeld met het doodsoorzakenregister van het Centraal Bureau voor de Statistiek. Vervolgens werden de behandel effecten apart geanalyseerd in de volgende subgroepen: leeftijd (<40, 40–49, 50–65, 66–75, >75 jaar), hormoonreceptorstatus (negatief of positief), HER2 status (negatief of positief), postoperatieve systemische therapie (geen, chemotherapie, hormoontherapie of beide) en comorbiditeit ten tijde van de diagnose (aan- of afwezig). Deze studie liet zien dat, vergeleken met een amputatie, een borstsparende operatie gevolgd door bestraling gelijke of soms betere algehele en borstkankerspecifieke overleving gaf in alle subgroepen, ook na correctie voor mogelijk versturende variabelen.

In **Hoofdstuk 3**, **Hoofdstuk 4** en **Hoofdstuk 5** werden behandel effecten geschat in de Nederlandse populatie met behulp van data uit de Nederlandse Kankerregistratie. Dit soort observationele onderzoeken naar behandel effecten gaan gepaard met mogelijke aanwezigheid van ongemeten versturende variabelen, verschillen in ernst van de ziekte tussen de behandelgroepen en variatie tussen ziekenhuizen. Deze zogeheten ‘bias’ kan het echte effect van de behandeling op de uitkomst vertekenen. Dit fenomeen maakt dat het belangrijk is dat observationele studies adequaat zijn opgezet en dat de juiste methoden zijn gebruikt. Er zijn verschillende statistische methoden ontwikkeld die kunnen omgaan met de aanwezigheid van versturende factoren. In **Hoofdstuk 6** werden vier verschillende methoden – multivariabele Cox regressie, propensity trimming, hiërarchisch modelleren en instrumentele variabele analyse – toegepast op de onderzoeksvraag: “wat is het effect van een borstsparende operatie gevolgd door bestraling en een amputatie op de 10-jaars metastasevrije overleving?” Deze studie had als doel om de lezers te informeren over de moeilijkheden rondom het selecteren van de juiste statistische methode, en om te laten zien dat er goed moet worden nagedacht over de assumpties, behorende bij deze methoden. Resultaten van de propensity trimming methode (waarbij vrouwen met de hoogste kans op de één of andere behandeling werden geëxcludeerd) en het hiërarchisch modelleren (waarbij ziekenhuis van operatie werd gebruikt als level en er dus gecorrigeerd werd voor variatie tussen ziekenhuizen) weken niet af van de veelgebruikte multivariabele Cox regressieanalyse. Alle methoden lieten een voordeel zien voor de borstsparende behandeling ten opzichte van de amputatie. Daarentegen liet de instrumentele variabele analyse geen verschil zien in 10-jaars metastasevrije overleving tussen de twee groepen. Echter, volgens deze studie werd niet voldaan aan alle assumpties van deze methode. Deze studie concludeerde dat, ondanks dat er goed nagedacht moet worden over de assumpties van alle methoden, observationele studies een waardevolle toevoeging kunnen zijn op bestaande gerandomiseerde trials, zolang de resultaten maar voorzichtig worden geïnterpreteerd.

In **Hoofdstuk 7** werd er verder ingegaan op de relevantie van observationeel onderzoek in vergelijking tot gerandomiseerde klinische trials. In dit hoofdstuk werden de voor- en nadelen

van beide soorten onderzoek bediscussieerd. Over het algemeen geven gerandomiseerde trials bijna perfecte behandelvergelijkingen, omdat patiënten hier random worden toegewezen aan de één of andere behandeling en er dus geen sprake kan zijn van versturende factoren. Echter is het ontzettend lastig om behandel-effecten van een trial te vertalen naar een individuele patiënt in de dagelijkse praktijk. Dit komt vooral doordat gerandomiseerde trials zeer strenge inclusiecriteria hanteren en dus niet representatief zijn voor de dagelijkse borstkankerpopulatie. Met behulp van kankerregistraties die de gehele populatie omvatten kunnen specifieke subgroepen – zoals oudere patiënten – worden bestudeerd, die vaak geen onderdeel uitmaken van de trialpopulatie. Dit hoofdstuk concludeerde dat observationele studies absoluut geen vervanging kunnen zijn van gerandomiseerde trials, maar dat zij informatie kunnen geven over de dagelijkse populatie waar gerandomiseerde trials dit niet kunnen wegens inherente selectie.

Omdat een borstsparende operatie normaal gesproken wordt gevolgd door bestraling kan men zich voorstellen dat het tijdsinterval tussen de operatie en de start van de bestraling van belang kan zijn voor overlevingsuitkomsten. Om deze reden werd in **Hoofdstuk 8** het effect van verschillende tijdsintervallen op de 10-jaars ziektevrije overleving bestudeerd. Er werden twee populaties onderzocht. In populatie 1 werden patiënten die chemotherapie ontvingen voor de bestraling geëxcludeerd, omdat dit gerelateerd is aan een langer tijdsinterval. De volgende tijdsintervallen tussen de operatie en de bestraling werden bestudeerd: <42 dagen, 42-55 dagen en >55 dagen. In populatie 2 werden patiënten die chemotherapie ná de bestraling kregen apart bestudeerd van patiënten die chemotherapie vóór de bestraling ontvingen. Voor de eerste groep werden tijdsintervallen van 42-55 dagen en >55 dagen vergeleken met het tijdsinterval van <42 dagen. Voor de tweede groep werden tijdsintervallen van 112-140 dagen en >140 dagen vergeleken met <112 dagen. Alle analyses lieten zien dat kortere tijdsintervallen niet leidden tot een betere (ziektevrije) overleving. Om deze reden kan de kwaliteitsindicator in Nederland dat aangeeft dat patiënten binnen 35 dagen na hun operatie moeten starten met bestraling in twijfel getrokken worden. Ook is het belangrijk patiënten te informeren dat een iets langer tijdsinterval tussen de operatie en de bestraling geen effect heeft op hun overleving.

Deel II: Het voorspellen van de prognose bij borstkanker

Predictiemodellen worden veel gebruikt in het proces van gedeelde besluitvorming. Echter worden dit soort modellen niet routinematig gevalideerd, wat kan leiden tot suboptimale behandeladviezen en onrealistische risicoschattingen. De doelpopulatie waar het model op wordt gebruikt kan anders zijn dan de populatie waarop een model is gebaseerd, bijvoorbeeld door verschillen in patiënt-, tumor- en behandelgerelateerde factoren. Om deze reden is het van groot belang om modellen te valideren op de doelpopulatie voordat deze daadwerkelijk worden gebruikt. Het online predictiemodel PREDICT voorspelt de 5-jaars en 10-jaars algehele overleving en het verwachte voordeel van postoperatieve systemische therapie (hormoon- en/of chemotherapie) in patiënten met primair geopereerde stadium I-III borstkanker. Na de inactivatie van het model Adjuvant! Online werd PREDICT het meest gebruikte predictiemodel bij borstkankerpatiënten in Nederland. Om de betrouwbaarheid van dit model te testen in de Nederlandse populatie werd het model gevalideerd in **Hoofdstuk 9**. Deze validatiestudie liet zien dat PREDICT de algehele overleving nauwkeurig voorspelt voor de meeste vrouwen met

borstkanker in Nederland, maar dat resultaten van zowel de 5-jaars als de 10-jaars algehele overleving van patiënten met ER negatieve tumoren voorzichtig geïnterpreteerd moeten worden omdat PREDICT deze uitkomsten iets onderschatte. Daarnaast werd de 10-jaars overleving overschat in patiënten van 75 jaar en ouder, in tumoren groter dan vijf centimeter en in patiënten die zowel hormoon- als chemotherapie kregen.

De relevantie van onderliggende biologische subtypen wordt in toenemende mate erkend, omdat het aangetoond is dat deze subtypen sterk gerelateerd zijn aan de kans op terugkeer van de ziekte en overleving. In **Hoofdstuk 10** wordt het effect van deze subtypes op de 10-jaars kans op terugkeer van de ziekte en overleving beschreven in de Nederlandse populatie. Dit hoofdstuk liet zien dat ook in Nederland deze subtypen geassocieerd zijn met de kans op recidieven en overleving: het luminal A type presenteerde de minste recidieven, terwijl het triple negatieve type de meeste recidieven liet zien. Deze kennis is belangrijk voor het geven van beter geïndividualiseerde behandeling en follow-up.

Nauwkeurige voorspelling van de prognose is niet alleen belangrijk voor besluitvorming rondom de behandeling of de risicoschatting van een patiënt. Het is ook minstens zo belangrijk voor patiënten en kankeroverlevers die hun weg terug in de maatschappij proberen te vinden. In Nederland liet een studie zien dat ongeveer 60% van de kankeroverlevers problemen ondervond bij het afsluiten van een levensverzekering. De data die levensverzekeraars gebruikten voor zo'n besluit waren gebaseerd op internationaal beschikbare informatie over overleving, die beschouwd werd als gedateerd en niet representatief voor de Nederlandse populatie. Omdat de meeste patiënten die kanker hebben of hebben gehad pas een aantal jaar na hun diagnose een levensverzekering afsluiten, en het bekend is dat de overleving stijgt naarmate de tijd verstrijkt, is het van groot belang om deze jaren na de diagnose mee te nemen in de voorspelling van de prognose van een patiënt. **Hoofdstuk 11** beschrijft de ontwikkeling van een predictiemodel dat de jaarlijkse extra kans op overlijden voorspelt vergeleken met de algemene Nederlandse populatie, gegeven dat iemand x aantal jaren heeft overleefd. Door hiermee rekening te houden geeft het model nauwkeurigere schattingen van de prognose voor patiënten die een aantal jaar na hun diagnose een levensverzekering aanvragen. Het ontwikkelde model werd zowel intern (op een random selectie van dezelfde populatie) als extern (op een andere populatie) gevalideerd met bevredigende resultaten. Het model werd ook getest op een random selectie van patiënten uit de Nederlandse Kankerregistratie, en vergeleken met de richtlijnen van levensverzekeraars die geldig waren voordat het nieuwe model werd geïntroduceerd. De resultaten lieten zien dat, over het algemeen, het nieuwe model tot verbeterde verzekeraarbaarheid leidt. Het verder monitoren van het gebruik van dit model is noodzakelijk om eventuele resterende problemen bij het afsluiten van een levensverzekering in kaart te brengen en hier verder onderzoek naar te doen.

In **Hoofdstuk 12** werden de 10-jaars kansen op recidieven en overleving vastgesteld voor patiënten met een vroeg stadium van borstkanker, rekening houdend met het aantal jaren overleefd en gespecificeerd voor het tumor- en klierstadium en het onderliggend subtype. In dit hoofdstuk wordt beschreven dat verschillen in uitkomsten tussen prognostische subgroepen kleiner werden naarmate de tijd verstreek. De belangrijkste boodschap van deze studie is daarom ook dat het voor patiënten belangrijk is dat hun prognose wordt gecommuniceerd op basis van het aantal ziektevrije jaren en het specifieke risicoprofiel. Dit zal uiteindelijk leiden tot betere risicoschattingen voor patiënten.

Concluderend: dit proefschrift laat zien dat een borstsparende behandeling gevolgd door bestraling een minstens zo goede overleving geeft als een amputatie bij patiënten met T1-2N0-2 stadium borstkanker (een tumor tot vijf centimeter met niet meer dan negen positieve klieren). Samen met resultaten van gerandomiseerde trials draagt dit proefschrift bij aan een vergroot bewustzijn dat, vergeleken met een borstsparende behandeling, een amputatie de kans op terugkeer van ziekte of overlijden niet verkleint. Daarnaast laat dit proefschrift de relevantie van specifieke risicoprofielen en het gebruik van het aantal (ziektevrije) jaren na de diagnose zien in de voorspelling van de prognose. Communicatie van deze data naar de patiënt speelt een centrale rol en zou de basis moeten vormen van het proces rondom de gedeelde besluitvorming. Uiteindelijk zal dit leiden tot betere behandelbesluiten en realistischere risicoschattingen.

DANKWOORD

(Acknowledgements)

Dankwoord

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Kort na deze overleggen volgde altijd de “Brain Boost Lunch”, waar naast veel gezelligheid ook de meest uiteenlopende onderwerpen aan bod kwamen: statistiek, resultaten van onderzoek, literatuurbesprekingen, noem het maar op. De laagdrempeligheid van deze bijeenkomsten maakte dat ik altijd alles in de groep durfde te gooien. Alle tips die ik kreeg hebben me altijd enorm geholpen om net wat meer uit mijn onderzoek te halen.

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Naast mijn werkdagen bij het IKNL, werkte ik op maandag altijd op de Universiteit Twente. De tweewekelijkse vakgroepoverleggen van de afdeling Health Technology and Services Research waren altijd erg leerzaam en gezellig. Ook heb ik genoten van al die keren dat de ‘bakkokaal’ rondging, of dat er weer iets gevierd moest worden aan de koffietafel. Alle collega's van HTSR, graag wil ik jullie danken voor de afgelopen drie jaar!

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Marissa, juli 2018

CURRICULUM VITAE

Curriculum Vitae

Marissa Corine van Maaren was born on August 21st, 1989 in Apeldoorn, the Netherlands. She completed secondary school at Christelijk Lyceum in Apeldoorn in 2008, and obtained her bachelor's degree in Chemistry, study route Crime Science in 2012. In the last year of this study, she did two internships. During the first, she investigated the relationship between genes involved in iron metabolism and the occurrence of tuberculosis at the Stellenbosch University in South Africa. The second internship focused on the function and regulation of several proteins involved in cancer development. Subsequently, she did a premaster in Biomedical Sciences at the Radboud University in Nijmegen, which she completed in 2013. This premaster was followed by a master's degree in Biomedical Sciences, specialised in both pathobiology and epidemiology, which she obtained in 2015 with distinction "Bene Meritum". During her master's, she did an internship at the Laboratory of Pediatric Oncology of the Radboud University Medical Centre where she studied the role of several proteins in B-cell precursor acute lymphoblastic leukaemia. Her second internship was at the Netherlands Comprehensive Cancer Organisation (IKNL), which she finished with the 'best student award 2014-2015' for her thesis on "Survival after lumpectomy and radiotherapy versus mastectomy in early-stage breast cancer patients". Directly after completing this trajectory, she started working at the IKNL as a junior researcher, and as an external PhD student at the University of Twente. During her PhD, she visited several congresses and took several courses. In addition, she co-organised several symposia and courses at the IKNL, and supervised several students. From September 1st on, she will continue to work at the IKNL as a postdoctoral researcher on rare cancers.

LIST OF PUBLICATIONS

List of publications

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