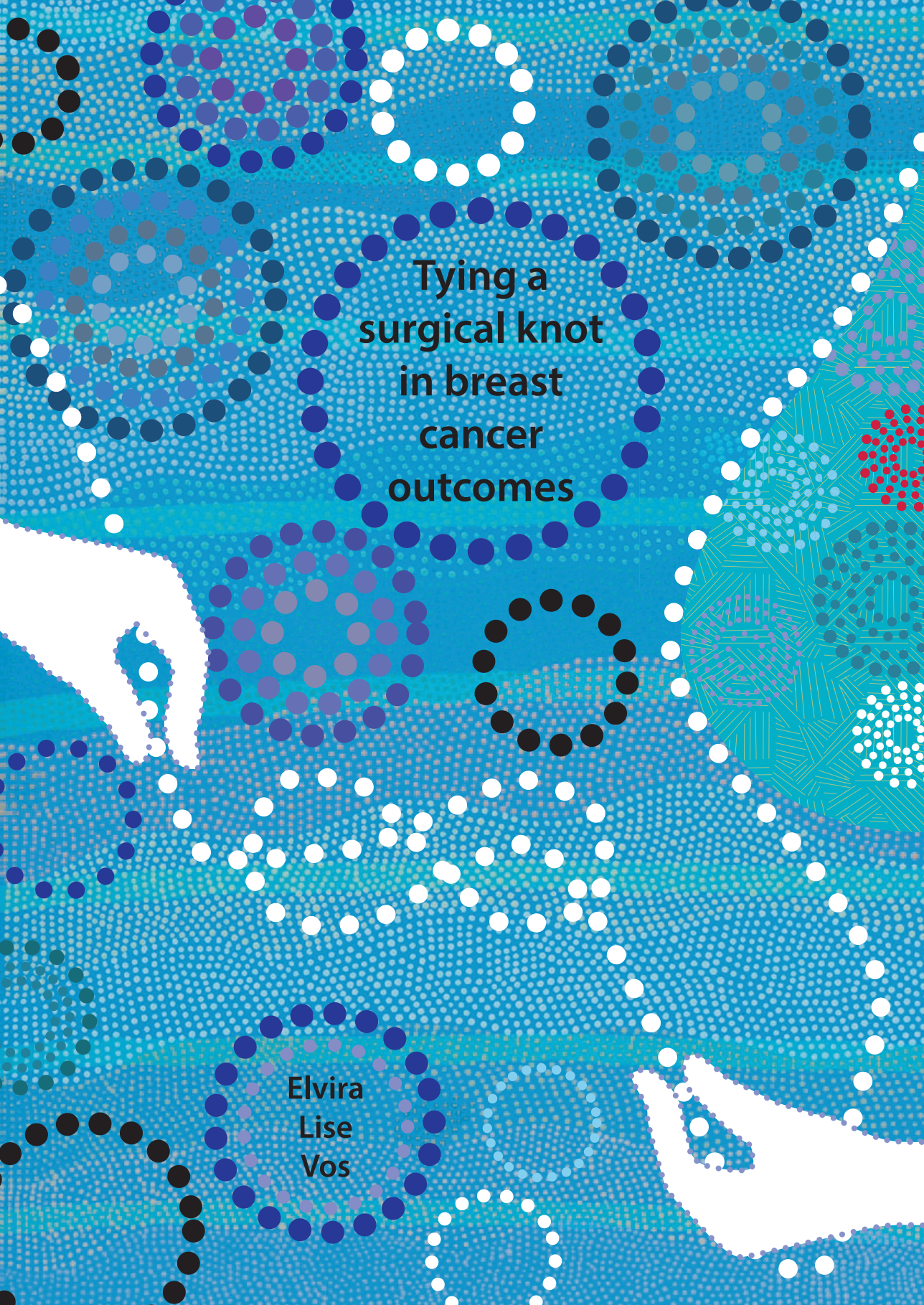
Tying a surgical knot in breast cancer outcomes
Elvira Lise Vos

TYING A SURGICAL KNOT IN BREAST CANCER OUTCOMES

Het leggen van een chirurgische knoop
in de uitkomsten van borstkanker

by
Elvira Lise Vos

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by
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To my parents

PART I

Introduction

CHAPTER 1

General introduction and outline of this thesis

INTRODUCTION

The present thesis focuses on outcomes of breast conserving surgery in early stage breast cancer patients. These outcomes include cosmetic results, quality of life, radicality, reexcision, secondary mastectomy, local recurrence, overall survival and quality of care. This thesis provides insight in how these outcomes are intertwined. To explain the title of this thesis, tying a surgical knot is a metaphor for intertwining. The different breast cancer surgery outcomes represent the surgical sutures.

Breast cancer

Anatomy of the Breast

The breast or so called mammary gland contains skin, adipose tissue, and fibroglandular tissue. Beneath the skin lays the superficial fascia which contains the fibroglandular tissue or so called breast parenchyma. The deep fascia lies anterior to mainly the pectoralis major muscle. Fibrous connective tissue connects the superficial and deep fascia and inserts into the dermis. The breast parenchyma contains 15-20 lobes that are made up of smaller lobules and is connected with the nipple by ducts. There is a network of blood vessels, nerves, lymph vessels, and lymph nodes. The shape, contour, volume, and density of the breasts varies significantly between individuals. For practical reasons, the breast can be divided into four quadrants: upper medial, upper lateral, lower lateral, and lower medial. The upper lateral quadrant usually contain more fibroglandular tissue and therefore is the most frequent location of breast cancer.

Diagnosis

Breast Cancer is the most common type of cancer in woman in the Netherlands. About 1 in 8 woman are diagnosed with breast cancer during her lifetime. In 2016, 14,451 new cases of invasive breast cancer and 2,592 new cases of ductal carcinoma-in-situ (DCIS) were registered by the Netherlands Cancer Registry(1). One-hundred thirty-six cases concerned males. DCIS is a precursor lesion of invasive breast cancer and is therefore also called non-invasive breast cancer. It is found in the ducts of the breast and has not developed the ability to invade outside the ducts into surrounding breast tissue. Invasive breast cancer is most commonly of the ductal type, meaning it arose in the ducts, followed by the lobular type, meaning it arose in the lobules. Other types of breast cancer exist, but are uncommon and not addressed in current thesis. In 80% of the breast cancer patients it is diagnosed at an early stage, i.e., stage I/II as defined by the tumor node metastasis staging (TNM) Classification of Malignant Tumors by the American

Joint Committee on Cancer(2). Imaging consists of mammography and ultrasound in all patients and magnetic resonance imaging (MRI) in some patients. MRI increases the detection of additional disease, but studies also suggest it leads to more mastectomies(3,4). Guidelines give varying recommendations regarding the use of MRI and this is reflected in wide interhospital variation(5). Other imaging modalities are not addressed in current thesis.

Surgical treatment

Surgery remains the primary treatment composing of mastectomy or breast conserving surgery (BCS). Randomized phase III trials have proven that survival is equivalent for mastectomy and BCS followed by radiation therapy for stage I/II patients after 20-years of follow-up even though that local recurrence rates may differ(6-8). Recent retrospective analysis of large population-based data have shown that BCS with radiation therapy may even be preferred over mastectomy regarding survival(9-12). Mastectomy can be followed by immediate or delayed implant-based or autologous breast reconstruction resulting in similar cosmetic satisfaction as compared to breast conservation(13).

Cosmetic outcome and quality of life

Cosmetic outcome influences quality of life (QoL) and plays an important role in the treatment decision(14, 15). BCS should only be offered if no contra-indication exists and if an acceptable cosmetic outcome can be achieved. However judging the feasibility of attaining favorable cosmetic result by BCS is extremely subjective and can be rather difficult. The subjectivity of the treatment decision is reflected in the considerable variation of BCS rates between hospitals(16). Furthermore, no golden standard for measuring cosmetic outcome exists raising a barrier for taking cosmetic outcome into consideration. Larger excision volumes have been correlated to unfavorable cosmetic outcome(17-19). This is important when taking into consideration that complete tumor excision (i.e., radicality) is another outcome of BCS. A larger excision facilitates achieving radicality and a narrow excision benefits cosmetic outcome. However, if the excision is too narrow and turns out to be irradical, then a reexcision may be necessary which again worsens cosmetic result(19). Here is an emerging role for direct oncoplastic reconstruction. That means applying plastic surgical techniques to the BCS attempting to conserve the breast with favorable cosmetic outcome(20, 21). Thereby it can prevent mastectomy or cosmetic deformity following BCS while allowing larger excisions. The indications for direct oncoplastic reconstructions are yet unclear. Another

treatment strategy is neo-adjuvant chemotherapy that can reduce tumor size and increases likelihood of achieving breast conservation with favorable cosmetic outcome. Cosmetic outcome is also influenced by the radiation therapy following BCS. Moderate to severe fibrosis occurs in 26% of irradiated patients(22). Sometimes even a radiation boost dose is added since it has proven to reduce local recurrence risk in some patients, another important outcome after BCS(23). In turn however it increases breast fibrosis and worsens cosmetic outcome(24).

Treatment decision making based on quality of life

Quality-adjusted life years (QALYs) are commonly used outcome measures for comparing effectiveness of treatments. QALYs provide a metric for valuing the impact of treatment on health-related quality of life on a common scale(25). This is achieved by signing a utility value to each health state on a scale from 0 (i.e., dead) to 1 (i.e., full health). A utility is a quantitative measure of the strength of a person's preference for an outcome(26). There are many ways to derive these so-called health state utility values (HSUVs). Commonly used HSUVs are generic preference-based derived by the EuroQol Group with the EQ-5D instrument. This questionnaire has five dimensions each with three levels and thus defines 243 health states. Each state has a value on the 0-1 scale obtained by interviewing a sample of the general population. When the EQ-5D questionnaire is completed by patients it results in a utility value for the patients' health state. In contrast to a condition specific preference-based measure, it may not be sensitive to show quality of life differences between all patient groups.

A treatment decision model can calculate the treatment threshold when to treat for optimal QALYs(26). A decision tree models these different treatment consequences based on certain probabilities. Each endpoint in the decision tree represents a health state to which a utility value is attached. The definition of a treatment threshold is the probability of disease at which the expected value of treatment and no treatment are equal. The threshold can be determined by direct comparison of the benefits and harms of treatment(26).

Oncological outcomes

Radicality, reexcision and secondary mastectomy

As one important outcome of the surgical procedure, the surgical margins of the excised specimen are examined directly postoperatively by the pathologist. The margins can be defined as negative (i.e., radical or 'no tumor touching the inked margins') or positive (i.e., irradical or 'tumor touching the inked margins').

If the margins are positive, the excision is incomplete and residual disease may be left behind in the breast. Worldwide there was no consensus on how wide the cancer-free margin should be until 2014. This controversy was reflected by the large variation of reexcision indications used between hospitals and clinicians from a 10mm negative margin to a tumor positive margin(27). High level evidence about an acceptable margin for BCS is lacking. From the large randomized trials between mastectomy and BCS with radiation therapy, only the NSABP B-06 trial required tumor free resection margins meaning that other trials included patients with incomplete resection margins(6-8). A meta-analysis of retrospective studies showed that positive resection margins independently increased the risk on local recurrence as compared to negative margins(28). This resulted in the recommendation to perform reexcision for positive margins by the Society of Surgical Oncology-American Society for Radiation Oncology (SSO/ASTRO) in 2014(29).

The Dutch national guideline distinguishes between a focally positive margin (i.e., invasive tumor and/or DCIS touching the inked margin over a length of 4mm or less) and an extensively positive margin (i.e., tumor touching the inked margin over a length of more than 4mm). The Dutch guideline already since 2002 does not recommend a reexcision for focally positive margins, but does recommends to apply whole-breast radiation therapy including a radiation boost dose(30). Currently, the choice of treatment (i.e., reexcision or not and radiation boost or not) is provider dependent in the Netherlands. However reexcisions increase healthcare costs, increase burden to the patients, worsen cosmetic outcome and quality of life, and result in secondary mastectomies.

Local recurrence and overall survival

Prognosis, measured in outcomes such as local recurrence and overall survival, has improved due to changes in the multidisciplinary treatment of breast cancer. Patients treated in the 1980s had a 10-year local recurrence rate of 10-20%(31, 32) after BCS. With the introduction of radiation therapy boost, early stage breast cancer patients treated with BCS in the 1990s had a 10-year local recurrence rate of 6.2%(22). As explained earlier, at the cost of cosmetic outcome. Patients treated in the 2000s had a 5-year local recurrence rate of 2.7%(33). The 10-year overall survival rate of patients treated with BCS in 1980s was 65%(32), in the 1990s was 82%(22) and further improved in the 2000s(9, 34). Patients treated between 2006-2012 had an even significant better overall survival as compared to patients treated between 1999-2005 before important changes in the indication and type of systemic therapy in daily practice occurred(35).

Quality of care

Quality of care is an outcome measure generally assessed by quality indicators and classified into structure, process, and outcome type(36). Structure indicators define the characteristics of the hospital in which the care is provided, e.g. hospital patient volume. Process indicators refer to the appropriateness of the delivered care, e.g. proportion of patients who received a full pathology report. Outcome indicators reflect the result as a consequence of care, e.g. proportion of patients with a reexcision. Quality of care information can be used for internal and external purposes. External use involves the public comparison of individual hospitals. Comparison to the average is called benchmarking and the construction of league tables is called ranking(37). Public reporting of quality indicator outcomes stimulates quality improvement activities by hospitals(38). Moreover, the demand for quality assurance and transparency is rapidly increasing worldwide from government agencies, accrediting bodies, medical specialty societies, health care insurance companies, and patient organizations. To prevent misinterpretation of data, it is important that quality indicator differences between hospitals represent real differences in quality of care. Therefore the scientific rigor of quality indicators should be evaluated, i.e., the validity and reliability(39). Reliability refers to the degree to which an indicator is reproducible. It is influenced by data quality, accuracy of indicator definitions, and statistical uncertainty caused by low number of events(40). Validity refers to whether an indicator measures what it claims to measure. Usually quality indicators are defined based on expert opinion and the available evidence by face validity(41). Face validity means subjectively a quality indicator measures what it is intended to measure. Construct validity refers to evaluating the relation between indicators that measure the same underlying concept(42). Validity is influenced by systematic errors, e.g. baseline risk differences between patient populations (i.e., case-mix)(43). A part of the observed differences between hospitals is often explained by statistical uncertainty and case-mix that can be measured. The remaining part of observed differences between hospitals represent unexplained differences. These *might* be due to the quality of care. The percentage of unexplained differences is called rankability and refers to the reliability of ranking hospitals based on quality indicator information(44).

AIMS AND OUTLINE

The main aim of this thesis is to add knowledge on how to improve outcomes of breast cancer surgery.

Part II investigates the value of a new objective tool to predict cosmetic outcome after BCS in early stage breast cancer patients in **Chapter 2**. How this prediction can be used as a treatment decision model between BCS and mastectomy for optimal QoL is studied in **Chapter 3**. Then a randomized controlled trial is proposed in **Chapter 4**. It aims is to improve cosmetic outcome and QoL by use of the treatment decision model in clinical practice.

Part III starts with focusing on radicality, reexcision, and secondary mastectomy after BCS. **Chapter 5** aims to identify subgroups in which the preoperative use of MRI might improve these outcomes. Then it focuses on focally positive margins and the need for a reexcision. Clinicopathological factors associated with focally positive margins and the presence of residual disease are identified in **Chapter 6**. The incidence of residual disease according to negative margins, focally positive margins, and extensively positive margins is studied. **Chapter 7** shines a light on the safety of the Dutch guideline recommending to perform reexcision in case of *extensively* positive margins only. It compares overall survival in patients with a reexcision after BCS to patients without a reexcision. **Chapter 8** describes how often the Dutch recommendation is followed in clinical practice and reexcision is omitted in patients with focally positive margins after BCS. It then studies if local recurrence rate, disease free survival, and overall survival is impaired in this specific patient group.

Part IV studies quality indicators for breast cancer care that are used in the Netherlands. **Chapter 9** quantifies the influence of case-mix and statistical uncertainty and the remaining between hospital differences that may be due to true differences in quality of care. Construct validity between indicators is tested in **Chapter 10**. Quality indicators are then selected for a new case-mix corrected summarizing measure and hospitals are ranked.

Part V includes a summary in **Chapter 11.** The results from previous chapters are discussed and future perspectives are outlined in **Chapter 12**.

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PART II

Cosmetic outcome and quality of life

CHAPTER 2

Preoperative prediction of cosmetic results in breast conserving surgery

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ABSTRACT

Background: Preoperative objective predictions of cosmetic result after breast conserving surgery (BCS) has the potential to aid in surgical treatment decision making. Our aim was to investigate the predictive value of tumor volume in relation to breast volume (TV/BV ratio) for cosmetic result.

Methods: Sixty-nine invasive breast cancer women with preoperative MRI and treated by BCS and radiotherapy in 2007-2012 were prospectively included. Simple excision or basic oncoplastic techniques were used, but no volume-displacement. TV/BV ratio was measured in the MRI while 3D-projected in virtual reality environment (I-Space). Cosmetic result was assessed by patient questionnaire, panel evaluation, and breast retraction assessment (BRA). Quality-of-life was assessed by EORTC QLQ-C30 and BR23.

Results: Intraobserver and interobserver correlation coefficients for tumor and breast volume were all >0.95. Increasing TV/BV ratio correlated with decreasing cosmetic result as determined by patient, panel, and BRA. TV/BV ratio was a significant independent predictor for the panel evaluation (P=0.028), as was tumor location (P<0.05), and together they constituted a good prediction model (AUC 0.83).

Conclusions: TV/BV ratio was a precise and independent predictor for cosmetic result determined by a panel and can be used as preoperative prediction tool to enable more informed surgical treatment decision making.

INTRODUCTION

Since breast conserving treatment has the same prognosis as mastectomy in early stage breast cancer[1, 2], most women prefer breast conserving surgery (BCS). There is an emerging role for direct oncoplastic reconstruction, that is, plastic surgical techniques applied to the BCS which attempts to conserve the breast with favorable cosmetic result and thereby prevent mastectomy or cosmetic deformity following BCS otherwise. Before deciding on a particular surgical treatment, the surgeon needs to inform the patient about the expected cosmetic result which plays an important role in treatment decision and has major influence on quality of life (QoL)[3]. In clinical practice, knowledge of the expected cosmetic result is however limited. Judging the feasibility of attaining good cosmetic result by BCS is extremely subjective and can be rather difficult, especially in high-risk patients for cosmetic deformity. The subjectivity of the treatment decision is reflected in considerable variation in BCS rates between hospitals[4]. Also the indications for direct oncoplastic reconstruction are yet unclear[5]. A preoperative tool that enables objective predictions of cosmetic result after BCS has the potential to aid surgical treatment decision making and improve cosmetic result[6].

It is a well-accepted hypothesis that treatment decision should at least take into account tumor size in relation to breast size (TV/BV ratio). Surprisingly, actual TV/BV ratio has never been estimated in literature and neither its value in treatment decision making. Our goal was to build a preoperative prediction tool for cosmetic result after BCS to aid treatment decision making in breast cancer surgery. Larger excision volumes have frequently been correlated to poor cosmetic result however preoperative available measures are needed[7-11]. TV/BV ratio seems a promising preoperative measure to make objective predictions regarding cosmetic result, yet there is no evidence to support this hypothesis. The availability of the I-Space at our institute, a CAVE™-like virtual reality system that projects a three-dimensional (3D) view of the preoperative magnetic resonance imaging (MRI), created the possibility to perform accurate volume measurements and estimate TV/BV ratio. Former applications of the I-Space in our institute including embryonic volume and yolk sac volumes showed excellent accuracy in volume measurements[12]. The primary aim of this study was to investigate the predictive value of TV/BV ratio and other possible predictors for cosmetic result and QoL after BCS. The secondary aim was to investigate the precision of tumor and breast volume measurements using the I-Space with preoperative MRI.

MATERIALS AND METHODS

Patients

The study population consisted of female breast cancer patients diagnosed between 2007 and 2012 at the tertiary referral Erasmus MC Cancer Institute, Rotterdam, The Netherlands. Women were asked to participate between 2012 and 2013 if the following inclusion criteria were met: (i) invasive breast cancer confirmed by postoperative histological evaluation; (ii) preoperative MRI available; and (iii) BCS performed. Patients were excluded in case of subsequent mastectomy and/or plastic surgery and if the tumor was invisible at MRI. BCS was performed using basic oncoplastic techniques (i.e.,peri-areolar incisions, round block techniques or batwing mastopexy but no volumereplacement techniques) and approximation of the breast parenchyma. The surgery was performed By an oncological surgeon or a surgical resident under supervision of an oncological surgeon. Approval was obtained from the local research ethics board and the procedures followed were in accordance with the Helsinki Declaration.

MRI and I–Space

MRI was performed by standard protocol[13] The preoperative MR images were transferred to the I-Space (Barco NV, Kortrijk, Belgium), at the department of Bioinformatics, Erasmus MC. The I-Space is a four walled CAVE™-like virtual reality system. Eight projectors create 3D images that can be seen using a set of polarizing glasses. The V-Scope volume rendering application creates an interactive "hologram" of the MRI dataset and is used to perform measurements. The dataset can be manipulated (e.g., rotated, resized) using a wireless joystick projecting a virtual pointer (Fig. 1). The advantage of creating 3D views of contrast enhanced MRI data is: (i) detailed visibility of tumor and breast ensuring the observer to measure the entire volume; and (ii) it perfectly suits the V-Scope characteristic of using grey level differences for volume rendering.

Tumor Volume / Breast Volume ratio

Methods of volume measurements are demonstrated in a video that can be found in the supplementary material online. The operator uses the joystick to place a seed point somewhere in tumor or breast. A segmentation algorithm will select the object, filling it visually with contrasting color. This so-called region growing approach uses three thresholds: (i) lower grey level threshold; (ii) upper grey level threshold, meaning only voxels whose grey value lies between the two thresholds

are considered; and (iii) grey level variance threshold, which prevents the inclusion of voxels whose value differ significantly from the neighbouring voxels. In this study the lower threshold was adjusted until the entire intended volume was selected judged by visual inspection. As post contrast images were used, the tumor was directly segmented using this approach. However this does not hold for distinguishing the breast from the chest as the grey values of the tissues are similar. Therefore, the breast was separated from the chest by erasing the chest tissues with a virtual brush. Subsequently, breast volume was determined using the seed fill described above. In case the radiologist suspected ductal carcinoma-in-situ (DCIS) to be present on MRI, it was not included in the tumor volume measurement. Multifocal and multicentric tumor volume was calculated by adding up the individual lesion volumes.

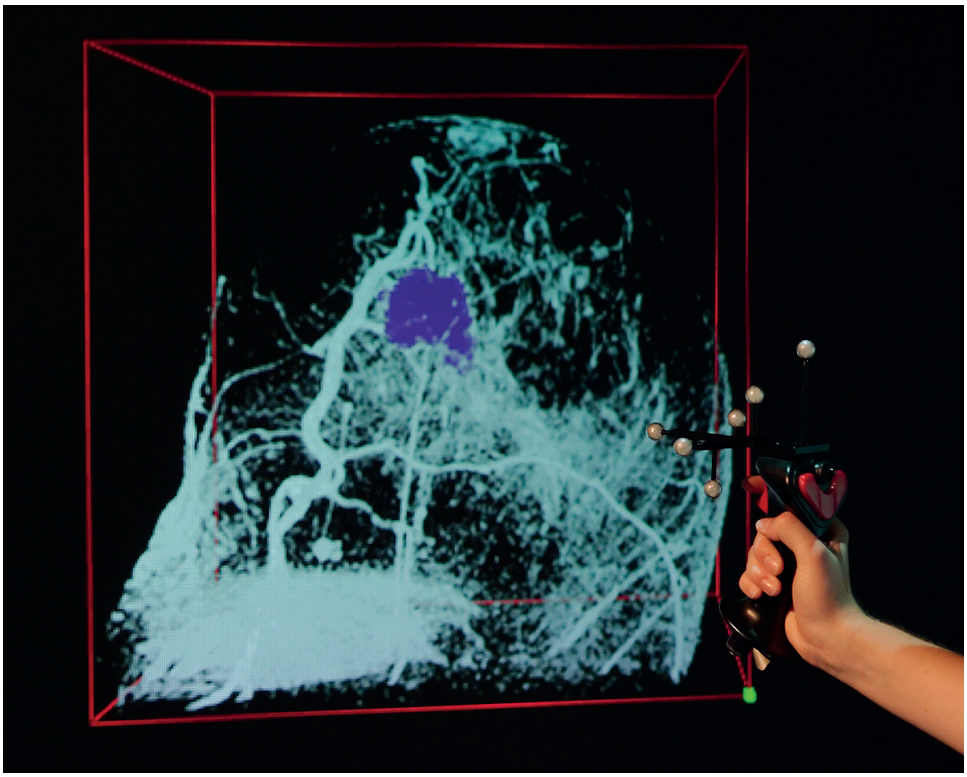

Figure 1. The I-Space creates an interactive three-dimensional (3D) image of the contrast-enhanced preoperative MRI dataset. Automatically the tumor is colored, and the volume is measured by V-Scope volume rendering application based on grey level differences.

Thirty tumor and breast volume measurements were repeated by the same observer after at least one month, as well as by a second observer. The TV/BV ratio was calculated by dividing the average tumor volume in cm^3 by the average breast volume in cm^3. For the convenience, it was multiplied by 1,000.

Cosmetic result and quality of life

Cosmetic result was determined at least after completion of radiotherapy treatment, but preferably one year postoperatively, by patient self-assessment, panel assessment of postoperative photographs,
and relative breast retraction assessment (BRA).

The patient filled in a 9-item questionnaire concerning the following items: overall cosmetic result, appearance of scar, size and shape of breast, nipple position, skin color, asymmetry, satisfaction with appearance of operated breast, and satisfaction with choice of BCS instead of mastectomy (Supplementary Material A). Scoring was performed on a four-point scale defined as follows: 0='excellent', 1='good', 2='moderate' and 3='bad'.

The panel consisted of a plastic surgeon (female), general practitioner (male), patient association member (female), PhD candidate (male), secretary employee (female) and radiotherapist (male). To obtain an evaluation as objective as possible, a six person-panel with various backgrounds, both male and female and both professionals and nonprofessionals, was chosen[14-16]. A professional medical photographer took series of four photographs of the breasts in a standardized manner. The panel members individually scored the photographs on 11-items (Supplementary Material B). The evaluation was based on a four-point scale as defined by Harris et al[17].

The BRA determines asymmetry by measuring the degree of nipple retraction in comparison to the untreated breast[18]. The relative BRA has proven to be as accurate as the absolute BRA and was used in this study[15]. BRA calculations were performed on the frontal view photograph of the patient and by the same observer.

QoL was assessed by the EORTC QLQ C-30 (version 3.0) and BR23 which include a 30-item overall QoL questionnaire and 24-item breast cancer specific module[19].

Information on patient- and tumor characteristics, diagnosis, and treatment that are possible predictors of cosmetic result were extracted from medical records. Tumor location was revised by the radiologist and appointed to one of the four quadrants or to a central position in the breast. Follow-up was defined as time between date of surgery and date of cosmetic result assessment in months.

Excision volume was estimated by specimen weight in gram by histopathological examination divided by breast volume in cm^3 as measured in I-Space[7].

Cosmetic result from patient questionnaire and panel evaluation encompassed the average of multiple items scored between 0 and 3 resulting in a linear scale. To visualize the relationship with TV/BV ratio and QoL, cosmetic result was dichotomized by assuming an average score <1.5 represented an excellent/good and >1.5 represented a moderate/bad cosmetic result. Concerning cosmetic result from BRA, it was dichotomized assuming higher BRA (more asymmetry) versus lower BRA (less asymmetry) than the mean of the study population represented an excellent/good versus moderate/bad cosmetic result. However, to acquire more precise estimation of the influence of TV/BV ratio and other predictors on the outcomes, linear expression of cosmetic result was used instead of dichotomous through linear regression analysis.

Statistical analysis

Intraclass and interclass correlation coefficients (ICC) and Wilcoxon's paired sample tests were calculated for evaluating the precision of I-Space derived volume measurements. Median TV/BV ratio and excision volume according to cosmetic result status were evaluated by Mann-Whitney tests. The QoL questionnaires were processed according to EORTC procedures. By linear regression analyses, unadjusted odds ratios (OR) were estimated to determine the association of TV/BV ratio and other possible predictors with cosmetic result and QoL. Multivariable analyses were performed by stepwise backward linear regression of all univariable predictors of cosmetic result with P <0.05 to calculate adjusted OR's. A prediction model of the panel evaluation was built with the independent preoperative predictors. The models overall performance was indicated by Nagelkerke R2 and the discriminative ability by area under the operating characteristic curve (AUC). Mean QoL differences were compared by Mann-Whitney test. P-values were derived from two-tailed tests and P <0.05 was considered significant. IBM SPSS Statistics 21 was used for all statistical analyses.

RESULTS

A total of 67 patients with 69 breast cancers were included in our analysis. The two patients with bilateral breast cancer were excluded from the analyses with BRA. Patient characteristics are shown in Table I. The reexcisions performed in five patients were for the purpose of invasive cancer on the margin. All patients received adjuvant radiotherapy, but total radiotherapy dose and use of tumor

bed boost was unknown in 11 (15.9%) patients. Median tumor volume was 2.04 (interquartile range (IQR) 0.97-4.37) cm^3, median breast volume was 772 (IQR 561-1111) cm^3 and median TV/BV ratio was 2.47 (IQR 1.25-5.54).

Table I. Patient characteristics.

	n (%)
Histology	
-Ductal	59 (85.5)
- Lobular	2 (2.9)
- Other	8 (11.6)
Right breast	37 (53.6)
Tumor location	
-Upper lateral	33 (47.8)
-Lower lateral	13 (18.8)
- Upper medial	14 (20.3)
-Lower medial	3 (4.3)
-Central	6 (8.7)
Co-existence of carcinoma in-situ	36 (52.2)
Axillary surgery	
-Sentinel node	50 (75.6)
-Axillary dissection	15 (22.4)
-No axillary surgery	2 (3.0)
Re-excision	5 (7.2)
	median (IQR)
Radiological tumor diameter (cm)	1.60 (1.00-2.15)
Pathological tumor diameter (cm)	1.40 (0.90-2.10)
Age (years)	55 (50-62)
Specimen weight (gram)	61.7 (44.8-94.6)
Excision volume (g/cm^3)	8.20 (5.60-11.52)
Radiotherapy total dose (Gray)	65 (65-68)

Interobserver and Intraobserver agreement of volumes measured by I-Space

Thirty tumor volumes were measured twice by the same observer with a median of 1.50 (IQR 0.79-2.97) cm^3 and 2.05 (IQR 0.92-3.39) cm^3 ($p<0.001$) respectively and ICC of 0.95 (95%CI 0.89-0.98). Likewise, 30 breast volumes were measured twice by the same observer with a median of 863 (IQR 594-1262) cm^3 and 929 (IQR 604-1270) cm^3 respectively (P=0.147) and ICC of 0.95 (95%CI 0.90-0.98). A second observer measured 30 tumor and breast volumes with a median of 1.76 (IQR 1.04-6.20) cm^3 (P=0.032) and 788 (IQR 542-1215) cm^3 (P=0.829) respectively. The ICC's

for tumor and breast volume were 0.95 (95%CI 0.90-0.98) and 0.98 (95%CI 0.97-0.99) respectively.

Cosmetic result: patient, panel and BRA

Median time between surgery and cosmetic result assessment (time of follow-up) was 33 months (IQR 18-48). Excellent/good cosmetic result was reported in 56 (81.2%) patients of the self-assessment, 49 (71.0%) patients of the panel evaluation and 42 (64.6%) patients of the BRA. Larger TV/BV ratio was associated with inferior cosmetic result as resulted from all three methods of cosmetic result assessment (Figs. 2 and 3). Likewise, larger excision volume was associated with poorer cosmetic result (Supplementary Material C and D).

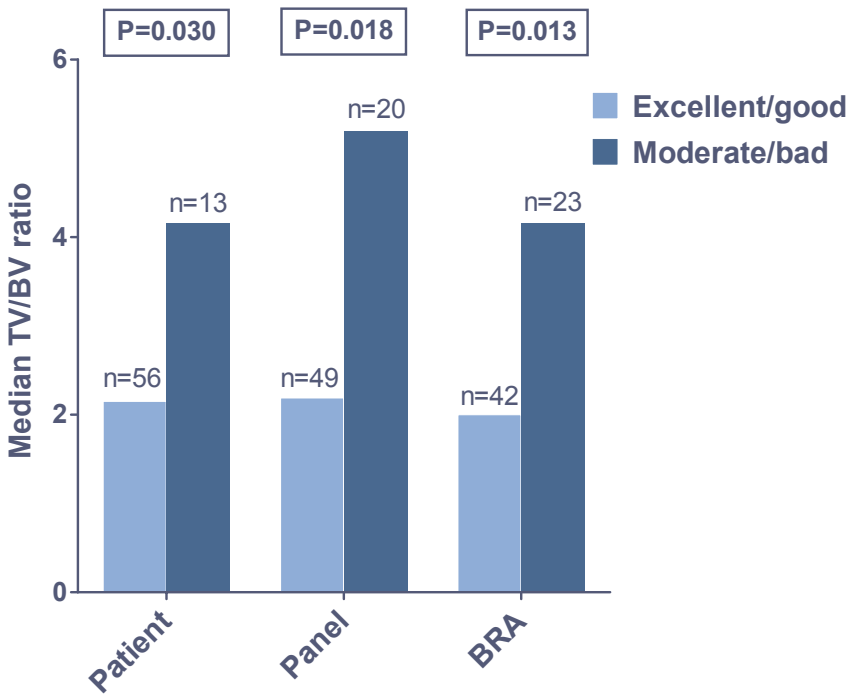

Figure 2. Median tumor volume in relation to breast volume (TV/BV ratio) according to cosmetic result status of the patient questionnaire, panel evaluation of photographs and the breast retraction assessment (BRA) for asymmetry.

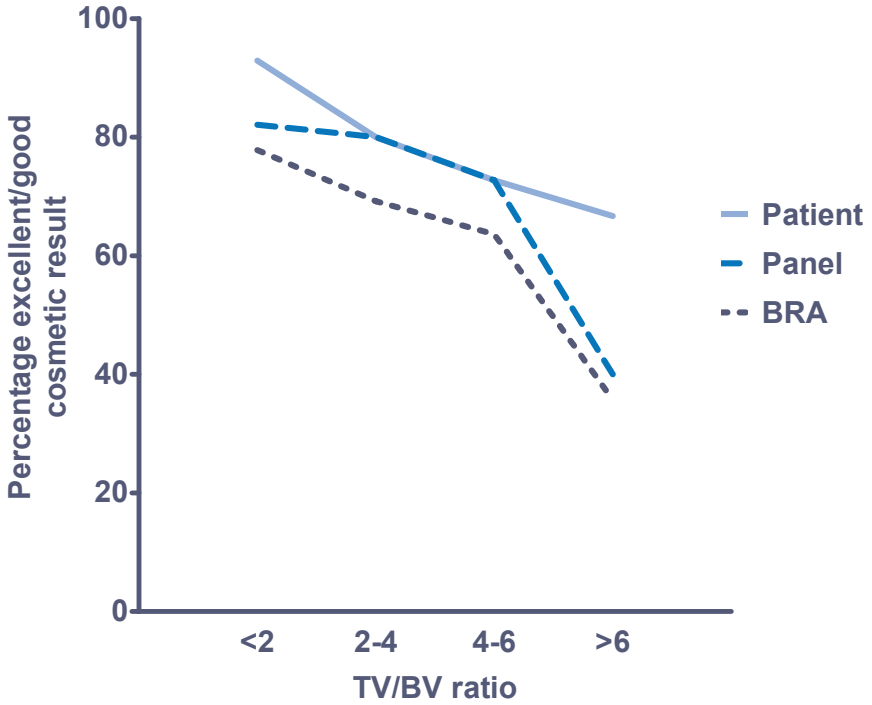

Figure 3. Percentage with excellent/good cosmetic result according to the patient questionnaire, panel evaluation of photographs and the breast retraction assessment (BRA) for asymmetry by tumor volume in relation to breast volume (TV/BV ratio).

After univariable linear regression analysis, continuous TV/BV ratio was a significant predictor for the panel evaluation (OR 0.04 95%CI 0.01-0.07 P=0.017) and BRA (OR 0.37 95%CI 0.12-0.73 P=0.043), but not for the patient self-assessment (OR 0.02 95%CI-0.01-0.05 P=0.238) (Table II). After multivariable linear regression, the independent predictors for cosmetic result as evaluated by the patient were: lower medial tumor location (OR 0.68 95%CI 0.14-1.22 P=0.015) and excision volume (OR 0.04 95%CI 0.01-0.07 P=0.005). Independent predictors for cosmetic result as evaluated by the panel were: TV/BV ratio (OR 0.04 95%CI 0.00-0.07 P=0.028), lower medial and lower lateral tumor location (OR 0.61 95%CI 0.04-1.18 P=0.036 and OR 0.41 95%CI 0.09-0.74 P=0.015), and specimen weight (OR 0.004 95%CI 0.001-0.007 P=0.008). Independent predictor for cosmetic result as determined by the BRA was: specimen weight (OR 0.07 95%CI 0.04-0.11 P<0.001) (Table III).

Table II. Univariable linear regression analysis of all possible predictors of cosmetic result according to the patient questionnaire, panel evaluation of photographs and the breast retraction assessment (BRA) for asymmetry.

	Patient Questionnaire		**Panel Evaluation**		**BRA**	
	OR (95%CI)	**P**	**OR (95%CI)**	**P**	**OR (95%CI)**	**P**
TV/BV ratio (TV/BV*1000)	0.02 (-0.01, 0.05)	0.238	0.04 (0.01, 0.07)	0.017	0.37 (0.12-0.73)	0.043
Radiological tumor diameter (cm)	-0.05 (-0.20, 0.10)	0.515	0.20 (0.04, 0.36)	0.018	1.96 (0.21-3.72)	0.029
Pathological tumor diameter (cm)	-0.03 (-0.19, 0.13)	0.713	0.15 (-0.02, 0.33)	0.090	2.27 (0.33-4.20)	0.022
Tumor location						
- Upper lateral	Reference		Reference		Reference	
- Lower lateral	0.26 (-0.04, 0.55)	0.092	0.51 (0.17, 0.85)	0.004	1.07 (-2.91-5.06)	0.592
-Upper medial	-0.14 (-0.43, 0.15)	0.338	-0.09 (-0.42, 0.24)	0.587	2.76 (-1.12-6.63)	0.159
-Lower medial	0.56 (0.01, 1.11)	0.046	0.47 (-0.16, 1.09)	0.138	1.74 (-6.85-10.3)	0.687
-Central	-0.46 (-0.87,-0.06)	0.026	0.01 (-0.45, 0.47)	0.981	-0.70 (-5.94-4.54)	0.829
Specimen weight (gram)	<0.01 (-0.01, 0.01)	0.105	0.01 (0.002, 0.01)	0.003	0.07 (0.04-0.11)	<0.0001
Excision volume (g/cm3)	0.03 (0.004, 0.06)	0.026	0.05 (0.02, 0.09)	0.001	0.40 (0.04-0.76)	0.029
Co-existence of carcinoma in-situ	0.07 (-0.17, 0.31)	0.547	0.19 (-0.07, 0.46)	0.148	2.67 (-0.16-5.51)	0.064
Age	<0.01 (-0.01, 0.02)	0.937	0.01 (-0.01, 0.03)	0.284	0.07 (-0.11-0.25)	0.430
Reexcision	0.01 (-0.36, 0.38)	0.946	0.27 (-0.25, 0.78)	0.303	5.26 (-0.04-10.5)	0.051
Time of follow-up (months)	<-0.01 (-0.01, 0.002)	0.146	<0.01 (-0.01, 0.01)	0.850	-0.00 (-0.09-0.09)	0.959

Table III. Multivariable linear regression analysis of significant (P<0.05) univariable predictors of cosmetic result according to the patient questionnaire, panel evaluation of photographs and the breast retraction assessment (BRA) for asymmetry.

	Patient Questionnaire		**Panel Evaluation**		**BRA**	
	OR (95%CI)	***P***	**OR (95%CI)**	***P***	**OR (95%CI)**	***P***
TV/BV ratio (TV/BV*1000)			0.04 (0.00, 0.07)	0.028		
Tumor location						
Upper lateral	Reference		Reference			
Lower lateral			0.41 (0.09, 0.74)	0.015		
Lower medial	0.68 (0.14, 1.22)	0.015	0.61 (0.04-1.18)	0.036		
Central	-0.39 (-0.81-0.03)	0.067				
Specimen weight (gram)			0.004 (0.001, 0.007)	0.008	0.07 (0.04, 0.11)	<0.0001
Excision volume (gram/cm3)	0.04 (0.01, 0.07)	0.005				

The prediction model discriminating between excellent/good and moderate/bad panel evaluation including the only preoperative available independent predictors (i.e., TV/BV ratio and tumor location) resulted in a Nagelkerke R^2 of 0.38 and AUC of 0.83.

Quality of Life

Response rate was 79% and mean global health status score was 85.1 (SD 13.7). Larger TV/BV ratio was not associated with decreased QoL as resulted from linear regression analysis (all P>0.05) (Supplementary Material E). Neither for the global health status and functional scales (i.e., physical function, role function, emotional function, cognitive function, social function, body image, sexual functioning, sexual enjoyment, and future perspective). Except sexual enjoyment that decreased with increasing TV/BV ratio, however not significant (OR-1.78 95%CI-5.01-1.45 P=0.268).

Patients self-assessment of cosmetic result was not significantly associated with her QoL. Table IV shows the differences in QoL score between excellent/good and moderate/bad cosmetic self-assessment.

Table IV. Quality of life scores by cosmetic result according to the patient questionnaire.

	Excellent/Good		Moderate/Bad			
	N	**Mean[a] (SD)**	**N**	**Mean[a] (SD)**	**Difference**	***P***
Global health status/QoL[b]	43	86.0 (13.6)	10	80.8 (14.2)	5.2	0.283
Functional scales[c]						
-Physical function	43	89.6 (12.6)	10	89.3 (10.0)	0.3	0.948
-Role function	43	93.0 (13.2)	10	86.7 (15.3)	6.3	0.190
-Emotional function	43	85.2 (21.8)	10	75.8 (27.6)	9.4	0.251
-Cognitive function	43	85.7 (21.8)	10	80.0 (27.0)	5.7	0.446
-Social function	43	89.3 (18.1)	10	83.3 (22.2)	6.0	0.370
-Body image	43	86.6 (17.4)	10	72.5 (36.6)	14.1	0.203
-Sexual functioning	42	24.2 (19.9)	9	24.1 (23.7)	-0.1	0.986
-Sexual enjoyment	22	53.0 (22.2)	5	46.7 (29.8)	6.3	0.591
-Future perspective	43	67.1 (29.7)	10	56.7 (27.4)	10.4	0.317

[a] On a scale from 0-100

[b] High score represents high QoL

[c] High score represents high/healthy level of functioning

DISCUSSION

Tumor volume and breast volume measurements

No universally accepted standard for tumor volume and breast volume measurement exists. Previous studies estimated tumor and breast volumes by mathematical formulae. By definition assumptions on the shape of the tumor and breast had to be made [20,21,22,7,23–25]. The I-Space avoids the need of making assumptions on shape because it includes all contrast enhanced voxels in the volume measurement. In two cases a small area was suspicious for surrounding DCIS on the MRI, however, it was not included in the tumor volume measurement. Volume measurement of DCIS remains a challenge. The inter- and intraobserver agreement for tumor and breast volume measurements showed excellent agreement. This means tumor and breast volume can be measured with excellent precision in I-Space with MRI. Accuracy of the volume measurements, meaning agreement with the real tumor and breast volume, was not addressed in this study but has been proven previously for volume measurements in general in the I-Space (i.e., balloons filled with water)[20]. Concluding, tumor and breast volumes as measured in I-Space with MRI are precise and accurate, thus valid measures. This is an important strength of this study.

Outcome assessment

Although BCS is the most commonly performed procedure in breast cancer, proper standard assessments for cosmetic result are lacking. Therefore, the patient questionnaire and panel evaluation were built by our institute. To visualize our results, linear cosmetic result scores were converted into a binary outcome, and assumptions were made on the cut-off point. Seventy-nine percent of the patient questionnaires had a mean cosmetic result score of <1.5 and thus were classified as excellent/good cosmetic result. Similarly, 76.8% of patients scored the individual item “overall cosmetic result” as excellent/good. This indicates that the cut-off point used was reasonable although it remains arbitrary. Hence, this assumption was avoided by performing regression analyses with cosmetic result on a linear scale.

In the literature, excellent/good satisfaction with aesthetic result after BCS varies between 81%-95% [4,7,9-[11]. This is comparable to 81.2% excellent/good patient self-assessments in the present study, but more favorable than the panel evaluation and BRA. This could be explained by the timing of our outcome assessment, which was at least after completion of the adjuvant radiotherapy treatment and adverse radiotherapy effects influenced the cosmetic result.

Although a relatively long median time of follow-up between surgery and cosmetic assessment was obtained. It is believed that the breast changes until years after treatment, and it is therefore preferred to assess cosmesis at multiple points in time. A limitation of this study is that outcome was evaluated only once and with varying time of follow-up.

This study showed that QoL is not significantly influenced by the TV/BV ratio. This is not surprising as no significant associations between the patients self-assessment of cosmetic result and her QoL were found. On the other hand, substantial differences in absolute QoL scores for excellent/good versus moderate/bad self-assessment were seen. The largest absolute difference was found on the body image scale with 86.6 versus 72.5 on a scale of 0-100. Although these differences were not significant, probably due to small sample size, they are of clinical relevance. Hau et al. presented similar EORTC QoL score differences in patients with excellent/good/normal versus fair/poor cosmesis after BCS[3]. At baseline, 5 years- and 10-years follow-up these absolute differences were 11.0, 17.7, and 12.4 respectively and all $p<0.001$. After multivariable modeling, fair/poor cosmesis was still significantly associated with worse QoL after 5- and 10-years follow-up[3]. In our opinion, a patient questionnaire on cosmetic result should always be combined with a QoL questionnaire to take into account the interaction between self-assessment of cosmetic result and QoL.

Lower medial and lower lateral tumor location in the breast were independent predictors for moderate/bad panel evaluation. Lower medial tumor location was also an independent predictor for moderate/bad patient self-assessment. These findings are consistent with the literature as medial and inferior tumors have been described as worsening patient satisfaction and panel score [7, 10]. Because tumor location is also a preoperative available measure that showed to be an independent significant predictor of panel evaluation it was included in the prediction model. Cosmetic result after breast conserving treatment can be influenced by radiotherapy effects and ideally should be taken into account however radiotherapy effect is yet unpredictable and therefore can not be included in a preoperative prediction model.

Implications

To improve treatment decision making, ideally the cosmetic result should be predicted preoperatively in order to better inform the patient on this aspect and to be used as a treatment indication. In the literature excision volumes by 10%, 20%, and 50 cm–100 cm have been correlated with poor cosmetic result[7-11]. However, this study showed that TV/BV ratio was a better predictor than excision volume.

Moreover, TV/BV ratio is available in the preoperative setting and excision volume is not. A preoperative prediction model including TV/BV ratio and tumor location had good ability in discriminating between excellent/good and moderate/bad panel evaluation. If implemented in clinical practice, this preoperative prediction model results in an expectation of the cosmetic result to aid treatment decision making. In case the expected cosmetic result is inferior to "excellent or good," direct oncoplastic reconstruction could be offered (i.e., breast lift and reduction techniques, volume-displacement and volume-replacement techniques, and/or contralateral asymmetry correction). Mastectomy followed by breast reconstruction can also be an alternative in the absence of oncoplastic options or due to patients' preferences. In the present study, 95.7% of women were (very) satisfied with the choice to conserve the breast yet 18.2% of these women classified the overall result as "moderate/bad." Evidently, cosmesis is not always the driving argument in preferring BCS over mastectomy. However, cosmetic result remains of major importance for QoL[3].

I-Space software runs on a regular linux platform and is owned by the department of Bioinformatics of the Erasmus MC. Projection technology is used from Barco NV, Belgium. I-Space projection technology in a room of 5 x 8 meter in combination with preoperative MRI is quite expensive for routine day-to-day use. Sequel steps need to be taken in contriving an easier clinical applicable method for TV/BV ratio estimation in clinical practice. Therefore, a desktop virtual reality system is being developed by the Erasmus MC department of Bioinformatics. Currently, Erasmus MC is looking for University Medical Centers to collaborate on improvement and roll out of the technology.

It was not the goal of this study to advocate the use of preoperative MRI in combination with I-Space in clinical practice. The goal was to estimate TV/BV ratio in a precise and accurate manner to enable a proof of principle study to the predictive value of TV/BV ratio. This is the first evidence for TV/BV ratio to be a promising tool in breast cancer surgery. Any 3D-imaging modality (e.g., MRI and 3D-ultrasound) in combination with a volume measurement program can estimate TV/BV ratio and has the potential to facilitate surgery.

CONCLUSIONS

TV/BV ratio can be precisely measured in the I-Space using preoperative MRI. Increasing TV/BV ratio is adversely affecting cosmetic result as assessed by patient, panel, and BRA. After adjustment for excision volume and other possible predictors in linear regression analyses, TV/BV ratio and tumor location are independent significant predictors for cosmetic result after BCS by panel assessment and

constitute a good performing preoperative prediction model. Therefore, TV/BV ratio can be used to enable more informed surgical treatment decision making through objective expectations of cosmetic result following BCS.

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Supplementary Material A

Patient questionnaire

Rate the cosmesis of your treated breast in terms of:

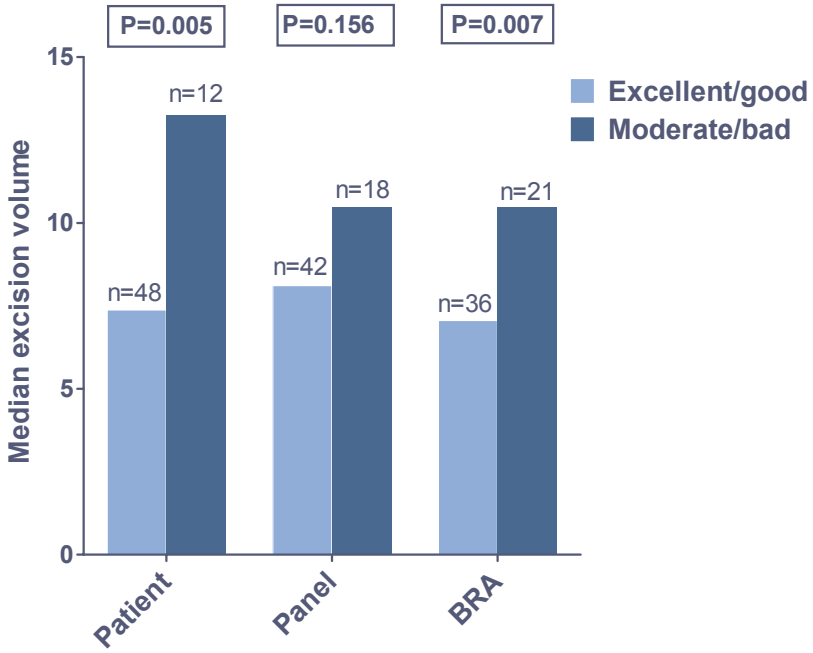
Surgical scar appearance	excellent	good	fair	poor
Breast size	excellent	good	fair	poor
Breast shape	excellent	good	fair	poor
Nipple position	excellent	good	fair	poor
Skin color	excellent	good	fair	poor
Overall cosmetic result	excellent	good	fair	poor
Asymmetry / difference between the treated and untreated breast	none	slight	moderate	very
Satisfaction with the appearance of the breast	excellent	good	fair	poor
Satisfaction with the choice of breast sparing surgery over non breast sparing surgery	extremely	very	moderately	slightly

Supplementary Material B

Panel evaluation				
Overall cosmetic result	0	1	2	3
Appearance of the surgical scar	0	1	2	3
Size of the breast	0	1	2	3
Shape of the breast	0	1	2	3
Position of the nipple-areola complex	0	1	2	3
Size of the nipple-areola complex	0	1	2	3
Color of the nipple-areola complex	0	1	2	3
Position of inframammary fold	0	1	2	3
Color of the skin	0	1	2	3
Teleangiectasia	0	1	2	3
Symmetry	0	1	2	3

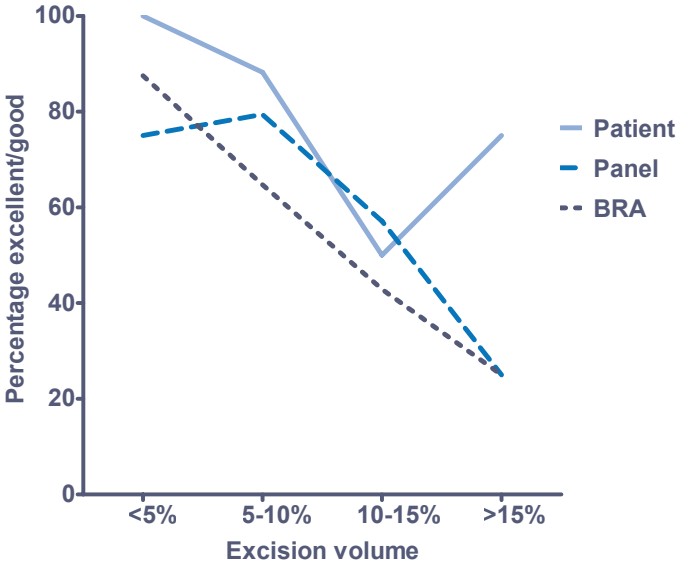
0 = excellent result (without visible treatment sequelae)
1 = good result (slight sequelae with minimal difference between treated and untreated breast)
2 = fair result (obvious difference between treated and untreated breast but without major distortion)
3 = poor result (major aesthetic sequelae)

Supplementary Material C



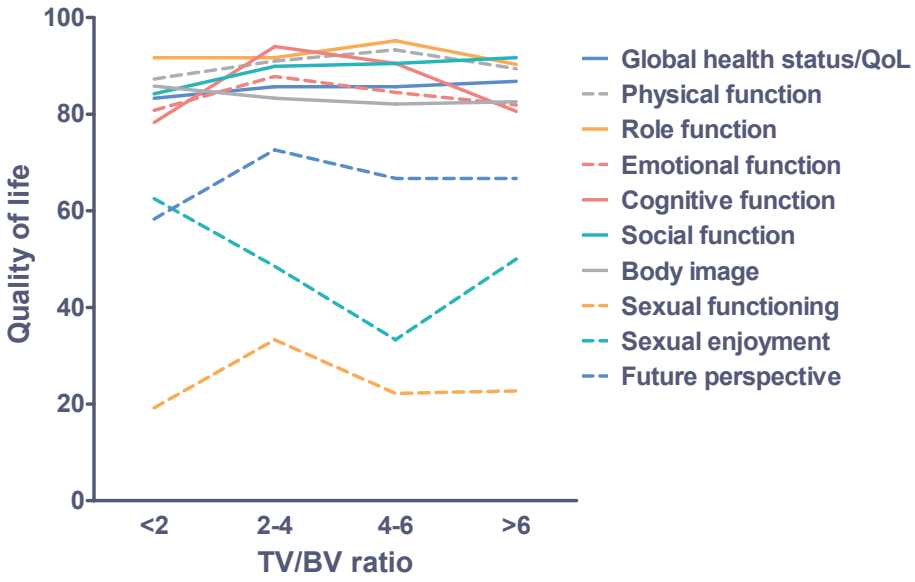
Median excision volume according to cosmetic result status of the patient questionnaire, panel evaluation of photographs and the breast retraction assessment (BRA) for asymmetry.

Supplementary Material D



Percentage with excellent/good cosmetic result according to the patient questionnaire, panel evaluation of photographs and the breast retraction assessment (BRA) for asymmetry by excision volume.

Supplementary Material E



Quality of life scores on a scale from 0 to 100 by tumor volume in relation to breast volume (TV/BV ratio).

CHAPTER 3

A preliminary prediction model for potentially guiding patient choices between breast conserving surgery and mastectomy in early breast cancer patients; a Dutch experience

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ABSTRACT

Purpose To guide early stage breast cancer patients to choose between breast conserving surgery (BCS) and mastectomy (MST) considering the predicted cosmetic result and quality of life (QoL).

Methods A decision model was built to compare QoL after BCS and MST. Treatment could result in BCS with good cosmesis, BCS with poor cosmesis, MST only, and MST with breast reconstruction. QoL for these treatment outcomes were obtained from a previous study and the literature and translated into EuroQoL-5D derived utilities. Chance of good cosmesis after BCS was predicted based on tumor location and tumor/breast volume ratio. The decision model determined whether the expected QoL was superior after BCS or MST based on chance of good cosmesis.

Results The mean utility for the treatments BCS with good cosmesis, BCS with poor cosmesis, MST only, and MST with breast reconstruction were 0.908, 0.843, 0.859, and 0.876, respectively. BCS resulted in superior QoL compared to MST in patients with a chance of good cosmesis above 36%. This 36% threshold is reached in case the tumor is located in the upper lateral, lower lateral, upper medial, lower medial, and central quadrant of the breast with a tumor/breast volume ratio below 21.6, 4.1, 15.1, 3.2, and 14.7, respectively.

Conclusions BCS results in superior QoL in patients with tumors in the upper breast quadrants or centrally and a tumor/breast volume ratio below 15. MST results in superior QoL in patients with tumors in the lower breast quadrants and a tumor/breast volume ratio above 4.

INTRODUCTION

Early stage breast cancer patients and their surgeons are confronted with the complex decision between breast conserving surgery (BCS) with radiotherapy or mastectomy (MST) with or without breast reconstruction. Both have similar overall survival[1-3]. In the absence of an oncological contraindication for BCS, the treatment choice is a matter of expected cosmetic result that influences quality of life (QoL)[4,5]. The surgeon and patient discuss the expected cosmetic result of both BCS and MST, but preoperative prediction of the cosmetic result is typically based on informal assessment by the surgeon. An objective decision aid taking cosmesis and QoL into consideration does not exist.

It is generally believed that the benefit of BCS over MST depends on the cosmetic result after BCS. Good cosmesis after BCS has shown to yield a substantial QoL benefit over poor cosmesis[4]. Therefore it can be hypothesized that BCS is preferable when the chance of a good cosmetic result is high, but MST (with or without breast reconstruction) is preferable when BCS is unlikely to have a good cosmetic result. We have previously demonstrated that a good cosmetic result after BCS can be predicted preoperatively by tumor volume/breast volume ratio (TV/BV ratio) and tumor location[6]. It remains unknown above what specific chance of good cosmetic result, BCS results in higher QoL over MST. If BCS is already performed for a low chance of good cosmesis, too many patients receive BCS increasing the incidence of poor cosmesis and reducing QoL. If BCS is only performed in those patients where good cosmesis is very likely and MST is performed otherwise, too many patients receive MST reducing QoL.

The aim was to guide decision making for patients with early stage breast cancer using a decision model that considers both predicted cosmetic result and QoL after BCS and MST. The treatment threshold – when to treat with BCS or MST – for optimal QoL is calculated. In clinical practice, this decision model could inform the treatment decision by weighing QoL of each treatment option.

METHODS

Study population

Data from a study population of 69 patients previously described in more detail formed the basis for the current analysis[6]. During first year all consecutive patients who came for follow-up visit at the outpatient clinic at the Erasmus MC Cancer Institute were asked to participate. Eligibility criteria included: Females above 18 years old with BCS and adjuvant radiotherapy between 2007 and 2012 for an invasive breast cancer with a preoperative MRI available. Preoperative MRI was an inclusion criterion to allow accurate breast volume measurements. BCS was performed using basic oncoplastic techniques, but no volume replacement techniques or therapeutic reduction mammoplasty. Patients with MST were not eligible since at first we only aimed to build a prediction model for cosmetic result after BCS. Informed consent was obtained from all participants.

The study population from Jagsi et al. consisted of woman aged between 20 and 79 years with stage 0-III breast cancer diagnosed between 2005 and 2007 and treated with MST only (n=263) or MST with reconstruction (both implant and autologous, both immediate and delayed) (n=222) from the Los Angeles and Detroit population based Surveillance, Epidemiology, and End Results registries. These were the patients that responded to a survey including QoL questionnaire at 9 months after diagnosis and approximately 4 years later constituting a 73% and 68% response rate[7]. Patient characteristics of both study populations are shown in Table 1.

Tumor volume/breast volume ratio and tumor location

The preoperative MRI datasets were transferred to a four-walled CAVE™-like virtual reality system (i.e., the I-Space), at the department of Bioinformatics, Erasmus MC. The volume rendering application creates an interactive 'hologram' of the MRI and reliably performs volume measurements based on greyscale differences[8]. Interclass and intraclass correlation coefficients for tumor and breast volumes all exceeded 0.95[6]. Tumor volume/breast volume ratio (TV/BV ratio) was calculated by dividing the tumor volume in cm^3 by the breast volume in cm^3 and multiplied by 1000. Details about the TV/BV ratio were published elsewhere[6]. The tumor location was determined by the radiologist and designated to one of the four quadrants of the breast or a central position.

Table 1. Patient and treatment characteristics of the two study populations from whom the QoL values were translated into EQ-5D derived utilities.

	BCS[a] (n=69)	Mastectomy[b] (n=485)	P-value
Age (years)			0.072
- ≤45	8 (11.6)	99 (20.4)	
- 46-55	28 (40.6)	140 (28.9)	
- ≥56	33 (47.8)	246 (50.7)	
Stage			<0.001
- 0	-	99 (20.4)	
- I	45 (65.2)	133 (27.4)	
- II	20 (29.0)	164 (33.8)	
- III	1 (1.0)	87 (17.9)	
- missing	3 (4.3)	2 (0.4)	
Radiotherapy			<0.001
- yes	69 (100)	144 (29.7)	
- no	-	322 (66.4)	
- missing	-	19 (3.9)	
Chemotherapy			0.054
- yes	31 (44.9)	278 (57.3)	
- no	38 (55.1)	198 (40.8)	
- missing	-	9 (1.9)	

[a]Our study population for the health states BCS with good cosmetic result and BCS with poor cosmetic result

[b]Study population from Jagsi et al.[7] for the health states Mastectomy only and Mastectomy with breast reconstruction

Cosmetic result evaluation

Cosmetic result was determined by panel assessment of post-radiotherapy photographs. The panel consisted of a plastic surgeon, general surgeon, radiotherapist, general practitioner, layperson, and breast cancer patient. They each scored the four photographs taken by a professional medical photographer in a standardized manner. The self-developed 'Erasmus MC Panel questionnaire' (Online Resource 1) consisting of eleven items was scored on a four-point scale (0=excellent, 1=good, 2=moderate, 3=poor)[6]. If the average score of all items and panel members was below or equal to 1.5 it was categorized as a good cosmetic result. In case the average score was above 1.5 it was categorized as a poor cosmetic result.

Cosmetic result prediction model

In the study population of 69 BCS patients, a preoperative prediction model for good cosmetic result after BCS was built[6]. It included the two independent and statistically significant predictors, namely TV/BV ratio (on a continuous scale) and tumor location (categorical variable with upper lateral (reference), upper medial, lower lateral, lower medial quadrant and central). The following parameters were not independently associated with cosmetic result and therefore not included in the prediction model: age, tumor diameter, excision volume, presence of adjacent DCIS, use of re-excision, and time of follow-up. Specimen weight was excluded from the analyses, because it was not preoperatively available. The analysis for cosmetic result predictors can be found in Online Resource 2.

The prediction model result (R) is the chance of a good cosmetic result after BCS. The original formula of R is shown in Online Resource 3, equation 1. The prediction model inherently has true positives (i.e., good cosmesis is predicted which is true), false positives (i.e., good cosmesis is predicted but not true), true negatives (i.e., poor cosmesis is predicted which is true) and false negatives (i.e., poor cosmesis is predicted but not true) (Fig. 1). However, a *threshold* at which BCS is preferred – i.e., at what chance of good cosmesis it is better to perform BCS rather than MST- is unknown. The threshold at which BCS is preferred can be established by modeling the harms and benefits in QoL for each treatment approach.

Treatment decision tree

A treatment decision tree was developed to model the treatment consequences of the prediction model and the prediction model inherent uncertainty (Fig. 2). Patients entered the tree having the diagnosis of invasive breast cancer stage I-II-IA opting for BCS. Each endpoint in the decision tree represents a 'health state', namely the health states BCS with good cosmesis (i.e., true positive result), BCS with poor cosmesis (i.e., false positive result), mastectomy only, and mastectomy with breast reconstruction (i.e., both a negative result). Note that after a MST it is impossible to distinguish between a true negative result (i.e., poor cosmesis if BCS had been performed) and a false negative result (i.e., good cosmesis if BCS had been performed). We assumed good cosmesis after BCS is preferred over MST (± reconstruction) and MST (± reconstruction) is preferred over poor cosmesis after BCS. It was also assumed that QoL after BCS is related to the cosmetic result. The probability of the health state BCS with good cosmesis equaled the prediction model probability for good cosmesis. The opposite from this equaled the probability for BCS with poor cosmesis. The probability of breast reconstruction was esti-

mated from the most recent study with breast reconstruction rate as their primary outcome[9]. The opposite of this equaled the probability for MST only.

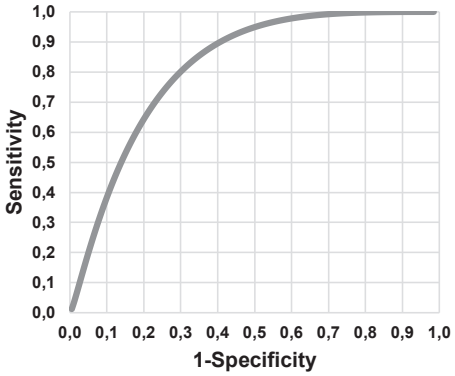

Figure 1. Smooth ROC curve and equation of the prediction model for the chance of a good cosmetic result after breast conserving surgery (BCS). The prediction model combines the individual patient's tumor volume/breast volume ratio and location of the tumor in the breast. Area under the operating characteristic curve (AUC) was 0.83 (95%CI 0.71-0.94)

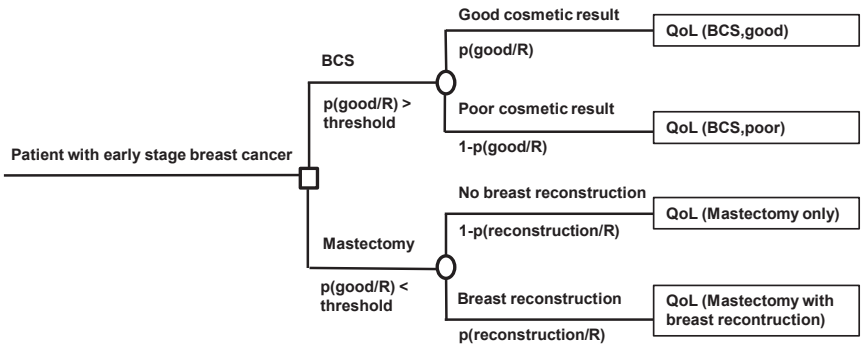

Figure 2. Treatment decision tree in early staged breast cancer patients comparing BCS and MST. The model determines when BCS is superior to MST depending on the chance of a good cosmetic result and the postoperative QoL. The chance of a good cosmetic result is based on the individual patient's tumor volume/breast volume ratio and tumor location which is calculated by our prediction model (R). The treatment threshold for the chance of a good cosmetic result is reached when the QoL of BCS and MST are equal; BCS is preferred for values above the threshold and MST is preferred for values below the threshold. Abbreviations: BCS = breast conserving surgery, p = probability, R = result of prediction model for cosmetic result after BCS, QoL = quality of life.

Quality of life

The primary outcome of each health state in the decision tree was a long-term QoL weight from the patient's perspective. Since life expectancy is equivalent for MST and BCS[1-3], the primary outcome measure QoL was used instead of the quality-adjusted life-years. QoL was defined as a utility, which is a single index-based value between 0 and 1 that enables assessing the effects of interventions on health-related quality of life. In contrast to most patient reported outcome measures, the EuroQoL 5D (EQ-5D) offers utilities[10]. Making use of time trade-off experiments, preference weights (tariffs) have been determined, and each health state of the EQ-5D can be assigned an index score. Freedman et al. describes the largest population (n=1050) with EQ-5D derived utilities at 5 years after BCS in the literature[11]. However, no distinction was made in cosmetic result. To obtain a robust utility for good and poor cosmesis, from our study population the gain and loss in utility for a good and poor cosmesis was added to the mean utility after BCS from Freedman et al. (analysis are shown in Online Resource 4). The EORTC QLQ-C30 values from our study population were converted into EQ-5D compatible utilities making use of the 'map' from Crott et al. (ordinary least squares regression model 3)[12,13]. For the health states involving MST, the most recent and representative QoL values from the literature by Jagsi et al. were used[7]. The FACT-G QoL values from the study population of Jagsi et al. were converted into EQ-5D compatible utilities making use of the map from Teckle et al. (ordinary least squares regression model 2)[14]. All raw QoL values and equations for conversion to EQ-5D utilities can be found in Online Resource 4.

Treatment threshold

The definition of a treatment (treat – do not treat) threshold is the probability of disease at which the expected value of treatment and no treatment are equal[15]. When applied to the current study, the treatment threshold – to perform BCS or not – was defined by the chance of good cosmetic result after BCS at which the QoL after BCS and the QoL after MST (± breast reconstruction) was equal. The threshold can be determined by direct comparison of the benefits and harms of BCS. The benefit is defined as the gain in QoL from living with a good cosmetic result after BCS instead of a MST (±breast reconstruction) (Online Resource 3, equation 2A). The harm is defined by the loss in QoL from living with a poor cosmetic result after BCS instead of a MST (± breast reconstruction) (Online Resource 3, equation 2B).

BCS should be performed when the chance of good cosmesis after BCS exceeds the harm to benefit ratio as presented in the Online Resource 3, equation

3A. Rewriting this expression as probability and substituting Equation 2A-B leads to Equations 3B-C[16]. The treatment threshold was determined by inserting the utilities in the equation.

Data analysis

The prediction model for good cosmetic result after BCS developed in our study population consists of 1) regression coefficients representing the influence of the variables TV/BV ratio and tumor location on the (log odds of the) probability of good cosmesis and 2) an intercept representing the prior probability of good cosmesis in the study population. No random effects were included in the prediction model. The models predictive ability was estimated by area under the operating characteristic curve (AUC). However, the prior probability was assumed to be higher than the actual prevalence of good cosmesis since women with a false negative prediction model outcome (i.e., poor cosmesis is predicted but not true) underwent MST and therefore were not included in the study population. Even though a good cosmetic result was expected if BCS had been performed. The number of false negatives is unknown. Therefore a prior probability slightly larger (2%) than the actual prevalence in the study population was chosen to correct for these false negatives and the intercept of the updated prediction model was recalculated (Online Resource 3, equation 4 and Fig. 1).

A probabilistic sensitivity analysis (PSA) was performed to evaluate the joint effect of uncertainty about all parameters in the model[17]. Parameter uncertainty was expressed by beta probability distributions on the interval [0, 1]. Thereafter, 10,000 times random values from the distributions of all variables were drawn and the model was recalculated for each set (sample) of values using an average patient. Resulting in a probability distribution of the expected outcome (i.e., average expected utility for BCS and MST). The average patient was determined by calculating the study population mean for each parameter included in the prediction model. Subsequently, the expected benefit in utility per patient in the absence of parameter uncertainty (i.e., expected value of perfect information, EVPI) was determined. In each sample the opportunity loss was defined as the difference in utility between the maximum expected benefit of that sample (BCS or MST) and the sample's expected benefit of the baseline optimal treatment (BCS)[17]. P-values were derived from two-tailed tests and $P<0.05$ was considered significant. Microsoft Excel 2010 and IBM SPSS Statistics version 22 were used for all analyses. There was no funding support for this study.

RESULTS

Tumor volume/breast volume ratio and tumor location

In the 69 breast cancer patients with preoperative MRI and treated by BCS, the median TV/BV ratio was 2.47 (IQR 1.25-5.54). Thirty-three (47.8%) tumors were located in the upper lateral quadrant, 14 (20.3%) tumors in the upper medial quadrant, 13 (18.8%) tumors in the lower lateral quadrant, 3 (4.3%) tumors in the lower medial quadrant and 6 (8.7%) tumors in a central position.

Chance of good cosmetic result

Median time between surgery and cosmetic result assessment was 33 months (interquartile range 18–48). The panel evaluation of cosmetic result resulted in 49/69 (71.0%) patients with good cosmesis (i.e., Erasmus MC Panel score ≤1.5) and 20/69 (29.0%) patients with poor cosmesis (i.e., Erasmus MC Panel score >1.5). The median chance of good cosmetic result from the prediction model was 0.84 (interquartile range 0.45-0.92). The formula of the prediction model is depicted in Fig. 1. The prediction model had an area under the operating characteristic curve (AUC) of 0.827 (95%CI 0.71-0.94) meaning that in 82.7% of the cases it correctly discriminated between poor and good cosmesis (Fig. 1). Other patient and treatment characteristics are shown in Table 1. Four oncological surgeons almost exclusively performing breast surgery operated 61/69 (88.4%) of the patients and 8/69 (11.6%) of the patients were operated by general oncological surgeons.

Quality of Life

Of the 69 patients with BCS included, 61 (88.4%) responded to the EORTC QLQ-C30 questionnaire to evaluate their QoL at a median of 38 months (interquartile range 31-54) after surgery. From the respondents, 44 had good cosmetic result and 17 had poor cosmetic result. Utilities are presented in Table 2 and their calculations are shown in Online Resource 4. The mean utility for poor cosmesis and good cosmesis were not statistically significantly different (p=0.055). After linear regression analysis, QoL was not statistically significantly associated with increasing age (coefficient 0.002 95%CI-0.002 to 0.006), higher breast cancer stage (coefficient-0.008 95%CI-0.070 to 0.054), and adjuvant chemotherapy (coefficient -0.018 95%CI-0.080 to 0.044).

Jagsi et al. included 263 patients with MST only and 222 patients with MST plus reconstruction (see patient characteristics Table 1) who completed the FACT-G

that was measured at a mean of 50 months (standard deviation 5) after diagnosis (see utilities in Table 2 and calculations in Online Resource 4).

Table 2. Utilities.

BCS, good cosmetic result	0.908
BCS, poor cosmetic result	0.843
Mastectomy only	0.859
Mastectomy with breast reconstruction	0.876
Mastectomy (±reconstruction)	0.866

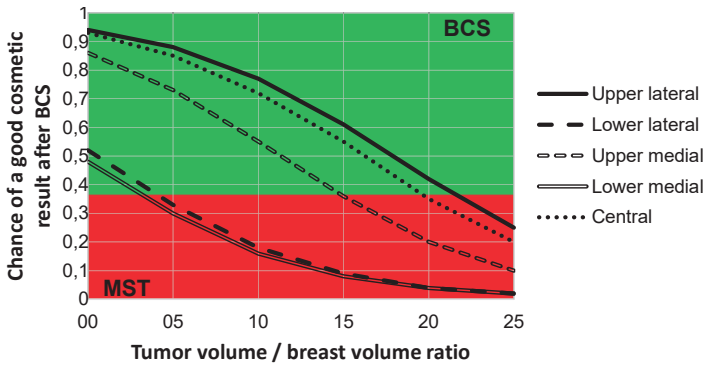

Figure 3. Decision graph to determine whether the expected QoL after surgery is better with BCS (green zone) or MST (red zone). The decision is based on the chance of a good cosmetic result. The decision model demonstrated that QoL after BCS is superior if the chance of a good cosmetic result exceeds 36%. The chance of a good cosmetic result varies between patients and depends on the location of the tumor and the ratio of tumor volume and breast volume. For example, a patient with a lower lateral tumor and a volume ratio of 15 has a low chance of a good cosmetic result after BCS (about 10%) and should therefore consider undergoing MST. On the other hand, a patient with an upper lateral tumor and the same ratio of 15 has a 60% chance of a good cosmetic result after BCS (about 60%) and should consider BCS. Abbreviations: BCS = breast conserving surgery, MST = mastectomy (with or without breast reconstruction).

When to treat with BCS or MST for superior QoL

The benefit in utility from performing BCS with a good cosmetic result rather than a MST (±reconstruction) was: 0.908-0.866 = 0.042 (Table 2) (Online Resource 3, equation 2A). The harm in utility from performing BCS with a poor cosmetic result rather than a MST (±reconstruction) was: 0.866-0.843 = 0.023 (Table 2) (Online Resource 3, equation 2B). BCS should be performed if the chance of a good cosmetic result exceeds 35.8% (Online Resource 3, equation 6) (Fig. 3). For application in

clinical practice the following decision rule can be used. BCS is preferred for an upper lateral, lower lateral, upper medial, lower medial, and central tumor location in case the TV/BV ratio is below 21.6, 4.1, 15.1, 3.2, and 14.7 respectively (Fig. 3). From all 9 patients with a chance of good cosmesis below 35.8% (i.e., negative result) 8/9 had a TV/BV ratio above 5.0 and 7/9 had their tumor located in the lower lateral quadrant.

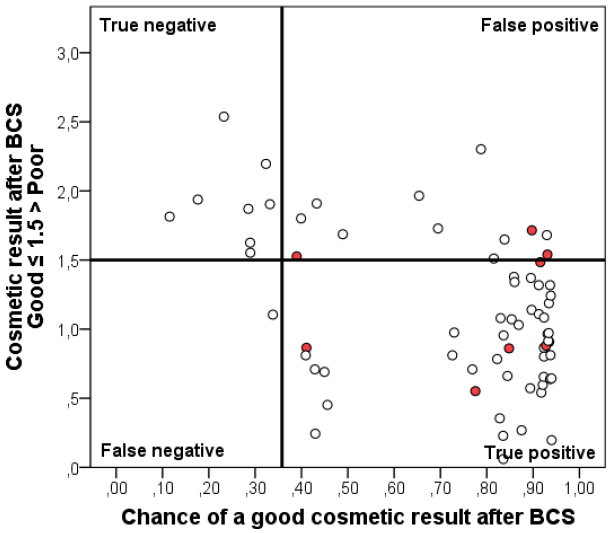

Figure 4. The predicted cosmetic results of the study population on the x-axis are plotted against the cosmetic result as evaluated by the panel on the y-axis. The horizontal line is set at a panel evaluation of cosmetic result cut-off score of 1.5. Values ≤1.5 are defined as good cosmesis and values >1.5 as poor cosmesis. The vertical line is set at the treatment threshold of 0.36 resulting from the decision model. If the predicted cosmetic result is below the threshold, mastectomy (with or without reconstruction) results in the optimal QoL. If the predicted cosmetic result is above the threshold, BCS results in the optimal QoL. This figure shows the number of true positives (good cosmesis after BCS as predicted preoperatively), true negatives (poor cosmesis after BCS as predicted preoperatively), false positives (poor cosmesis after BCS but preoperative prediction was good) and false negatives (good cosmesis after BCS but preoperative prediction was poor) when the prediction model is applied to the study population. The eight patients operated by an - non breast cancer specific - oncological surgeon were colored in red.

Figure 4 shows the number of true positives, true negatives, false positives and false negatives when the prediction model is applied to our study population. Nine out of 69 patients (13.0%) had a chance of good cosmesis below 35.8% (i.e., negative) and would have been advised against BCS had the results of our analysis

been available. Of these 9 patients, 8 indeed had a poor cosmetic result (i.e., true negative) and 1 patient was classified as good cosmetic result (i.e., false negative). The corresponding negative predictive value of the prediction model was 88.9%. The false negative patient had a chance of good cosmesis of 33.8%, which was very close to the threshold. Of the 60 patients with a chance of good cosmesis exceeding 35.8% (i.e., positive), 48 patients indeed had a good cosmetic result (i.e., true positive) and 12 patients were classified as poor cosmetic result (i.e., false positive). The corresponding positive predictive value of the prediction model was 80.0%. The false positive patients had a chance of good cosmesis ranging between 39%-93%.

Parameter uncertainty

The average patient from our study population had a chance of good cosmetic result after BCS of 71%. For example, a patient with a tumor of 3.8 cm^3 in the upper medial quadrant in a breast of 675 cm^3 resulted in a TV/BV ratio of 5.6. Taken into consideration, the parameter uncertainty of our decision model, for this patient on average BCS was the treatment with the largest benefit in QoL and was advised in 61.9% of the 10,000 samples (see probabilistic sensitivity analysis in Online Resource 5). If we reduced our parameter uncertainty, the benefit in QoL would be 0.02 per patient (see expected value of perfect information analysis in Online Resource 5).

DISCUSSION

BCS is the treatment with superior QoL for breast cancer patients with a chance on good cosmetic result exceeding 36%. This 36% threshold is reached in case of an upper lateral, lower lateral, upper medial, lower medial, and central tumor location in combination with a tumor/breast volume ratio below 21.6, 4.1, 15.1, 3.2, and 14.7, respectively. In case of larger tumor/breast volume ratio's, MST (with or without breast reconstruction) will result in higher QoL.

Due to the progress in surgical techniques and improving oncological outcomes, QoL and cosmesis have an increasingly prominent role in breast cancer treatment. Incorporating QoL and cosmesis in a treatment decision model comes with challenges due to their subjective entity. Cosmesis cannot be captured in clear-cut classifications and a (gold) standard for measuring cosmesis after BCS is lacking. Consequently, the validity of this decision model depends on the methodology of measuring and predicting cosmetic result and the definition of good and poor cosmesis. This is a weakness of our study since the validity of our definitions and

self-developed Erasmus MC Panel questionnaire have not been tested extensively. The panel assessment is therefore study specific. How to measure cosmetic result after BCS is still a matter of debate, however, a multiple-person panel evaluation remains the most used and recommended[18]. It does come with disadvantages as it remains a subjective method with low reproducibility results influenced by the type of observers (experts versus non-experts) and the scale used. Consensus increases if the outcome is dichotomized. It could be argued that cosmetic result should be based on a patient-reported outcome measure (PROM). However, PROM's only deliver scores on a continuous scale and their predictive ability is low (eg., TV/BV ratio was not associated with patient evaluation of cosmetic result) [6]. The more efficient BCCT.core software for cosmetic result evaluation might become the future standard, but until today, agreement with panel evaluations differs[19,20]. The 12 patients with false positive result (i.e., model predicted a good cosmetic result but the panel evaluated cosmesis as poor) could be explained by the fact that 8 out of 12 patients had visible radiotherapy fibrosis or skin color changes and retractions around the scar which is not taken into consideration in the predicted cosmetic result. Another explanation could be that 3/12 (25%) of false positive patients were operated by a general oncological surgeon (i.e., not breast cancer specific surgeon) as compared to 8/69 (12%) of the total study population. This suggests that surgeon experience matters for achieving a good cosmetic result. The lack of other significant parameters, like radiotherapy boost, in the prediction model for cosmetic result was a disadvantage. Yet the model proved to discriminate well between poor and good cosmetic result (AUC of 0.83). As far as we know, other prediction models for cosmetic result or other decision models including cosmetic result and/or QoL are not available in the literature. Therefore, our models could not be compared or tested for external validity.

QoL is a complex and multifactorial outcome that is not captured by cosmesis and type of surgery only. For example, age, chemotherapy, and fear of recurrence have been shown to be associated with QoL[21-23]. However fear of recurrence was not considered here and no significant association was seen between QoL and age, stage, or chemotherapy. The lack of adjusted utilities for these factors was a drawback. Future studies should also address fear of recurrence. The mean utility found for poor and good cosmesis after BCS were not significantly different (p=0.055). No sample size calculation was performed for this study and it was not powered to show a significant QoL difference. The nature of our tertiary referral university hospital caused a small study population for BCS. This had multiple implications, like the lack of power to detect QoL differences and large (statistical) uncertainty of the utilities for BCS. To decrease this uncertainty,

the mean utility for BCS in general measured by EQ-5D in 1050 patients from Freedman et al. was used[11]. The results are, however, not directly generalizable beyond our study population and need to be validated. Due to the small sample size, the results of this study are preliminary. Work to validate the results in a larger study is underway.

It was assumed that QoL after BCS would be related to the cosmetic result. However, cosmesis was not significantly associated with EORTC QLQ C-30 and BR-23 scores, although absolute differences were seen (eg., body image score of 87 vs. 73 (0-100) in good versus poor cosmesis, *P*=0.203)[6]. This could be explained by the fact that all the questionnaires are general or disease-specific, not cosmetic result specific. The assessment of cosmesis after BCS by an independent panel, and the lack of a panel assessment after MST (with and without breast reconstruction), could also explain the lack of association with PROM's. Studies with patients' cosmetic evaluation, however, were significantly associated with QoL[4,5]. A larger study population is needed to draw final conclusions about whether EQ-5D is sensitive for breast cancer surgery outcome differences. Promising alternatives for future efficiency analysis are the recently published EORTC Quality of Life Utility Measure-Core 10 dimensions (QLU-C10D)[24], EORTC Quality of Life for women undergoing breast reconstruction (QLQ-BRECON26)[25], and the modernized EORTC BR23 module that is currently under development.

Another disadvantage was the complexity and use of different sources for generating the utilities. Namely, EORTC values with EQ-5D UK tariffs from our study population, EQ-5D values with unknown origin of tariffs from Freedman et al. and FACT values with EQ-5D US tariffs from Jagsi at el. The time of measurement was 38 months after surgery, 60 months after surgery, and 50 months after diagnosis, respectively. We did not correct for these time differences. Neither did we correct for the variety in study population size, but the standard deviations in the PSA show that the uncertainty for most BCS related parameters is larger when compared to the MST related parameters caused by a smaller study population. The mastectomy group had more stage III patients (1% vs. 18%) who underwent less radiotherapy (100% vs. 30%), but this was not unexpected. An alternative for using multiple sources to define the utilities for each health state was not available since, as far as we know, no study has been published presenting EQ-5D derived QoL values for the different surgical treatments of breast cancer. We were the first to compare utilities between BCS and MST.

Whether the differences in utilities found between the treatment options are clinically meaningful can be questioned. The minimally important difference has been estimated to be 0.08 for UK-based EQ-5D scores and 0.06 for US-based

EQ-5D scores by Pickard et al[26]. We found a difference between good and poor cosmetic result after BCS of 0.065. However, Pickard et al. estimated the minimally important differences in advanced stage patients with cancers from all kinds of primary origin. Our study population consists of early stage breast cancer patients that already have a high baseline QoL (towards the maximum of one) which may impede finding large QoL differences. Other studies comparing QoL between treatment options showed comparable ranking order of the treatments to our decision model[7,27,28]. Which is important since our decision model assumes BCS with good cosmesis is preferred over MST (with or without reconstruction) followed by BCS with poor cosmesis. Atisha et al. and Jagsi et al. found that satisfaction with breasts as measured by Breast-Q questionnaire was highest in patients receiving MST with autologous reconstruction and slightly decreased with BCS, followed by MST with implant reconstruction, and was the lowest with MST only[7,27]. Han et al. found that QoL and satisfaction as measured by EORTC QLQ-C30 & BR23 was higher for BCS as compared to MST or reconstructive surgery[28]. These studies suggest that current QoL differences found are clinically meaningful. It has also been found that utility increases by 0.031 if the patient is given a treatment choice versus restricting choice to MST alone[29]. Furthermore, if poor cosmesis is expected, other treatment alternatives are available, namely, neo-adjuvant chemotherapy and oncoplastic surgery including therapeutic mammoplasty. Utility studies are needed regarding these alternatives to enable implementation in a treatment decision model. This study should be interpreted as preliminary and a first step towards a more ideal treatment decision model.

The treatment decision model presented here is currently being studied in a randomized controlled trial in patients who are candidates for both BCS and MST to study the effectiveness in improving cosmetic result and QoL over the present situation[30]. Here, TV/BV ratio is measured by ultrasound instead of MRI since it is less invasive, widely available, and more cost-effective. Validation of the volume measurements is currently awaiting publication. There is a fair amount of QoL benefit (0.02 per patient) that can be expected if more research is performed that decreases parameter uncertainty as shown by our value of information analysis. Currently, we are measuring utilities in a larger study population for all health states to reduce uncertainty and improve the decision model.

CONCLUSIONS

A common goal in breast cancer surgery including breast reconstruction is to pursue shared treatment decision making, which is currently based on informal assessment by the surgeon. We present a preliminary treatment decision model as a first step towards a more ideal treatment decision model applicable in surgical oncology. This treatment decision model can improve shared decision making in breast cancer surgery. With individual patient characteristics, namely tumor/breast volume ratio and tumor location, an expected long-term QoL value is given on a scale between 0-1 for both treatment options. The patient and surgeon can weigh the size of the QoL difference between BCS and MST (with or without breast reconstruction) or choose the surgery with the highest QoL. BCS results in superior QoL in patients with tumors located centrally or in the upper breast quadrants with a tumor volume/breast ratio below 15. MST with or without reconstruction is recommended for all patients with a tumor volume/breast volume ratio above 22 or tumors in the lower breast quadrants with a tumor volume/breast volume ratio above 4. Considering that the model is population-, surgeon-, and panel specific, it is advised to validate the model before introducing it in other countries.

Compliance with Ethical Standards

Approval was obtained from the local research ethics board under registration number MEC-2012-074. Informed consent was obtained from all individual participants included in the study. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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Electronic Supplementary Material

Online resource 1. Erasmus MC Panel questionnaire.

Overall cosmetic result	0	1	2	3
Appearance of the surgical scar	0	1	2	3
Size of the breast	0	1	2	3
Shape of the breast	0	1	2	3
Position of the nipple-areola complex	0	1	2	3
Size of the nipple-areola complex	0	1	2	3
Color of the nipple-areola complex	0	1	2	3
Position of inframammary fold	0	1	2	3
Color of the skin	0	1	2	3
Teleangiectasia	0	1	2	3
Symmetry	0	1	2	3

0 = excellent result (without visible treatment sequelae)

1 = good result (slight sequelae with minimal difference between treated and untreated breast)

2 = fair result (obvious difference difference between treated and untreated breast but without major distortion)

3 = poor result (major aesthetic sequelae)

Online Resource 2. Univariable and multivariable linear regression analysis for predictors of cosmetic result as evaluated by a panel[a.]

	Univariable		**Multivariable[b]**	
	OR (95%CI)	**P**	**OR (95%CI)**	**P**
Age (years)	0.01 (-0.01, 0.03)	0.284		
Radiological tumor diameter (cm)	0.20 (0.04, 0.36)	0.018		
Tumor volume/breast volume ratio (TV/BV ratio)	0.04 (0.01, 0.07)	0.017		
Tumor location			*0.04 (0.00, 0.07)*	*0.028*
-Upper lateral	reference		reference	
-Lower lateral	0.51 (0.17, 0.85)	0.004		
- Upper medial	-0.09 (-0.42, 0.24)	0.587	*0.41 (0.09, 0.74)*	*0.015*
-Lower medial	0.47 (-0.16, 1.09)	0.138		
-Central	0.01 (-0.45, 0.47)	0.981	*0.61 (0.04-1.18)*	*0.036*
Pathological tumor diameter (cm)	0.15 (-0.02, 0.33)	0.090		
Adjacent DCIS (yes versus no)	0.19 (-0.07, 0.46)	0.148		
Specimen weight (gram)	0.01 (0.002, 0.01)	0.003	*0.004 (0.001, 0.007)*	*0.008*
Excision volume (g/cm3)	0.05 (0.02, 0.09)	0.001		
Re-excision (yes versus no)	0.27 (-0.25, 0.78)	0.303		
Time of follow-up (months)	<0.01 (-0.01, 0.01)	0.850		

Abbreviation: TV/BV ratio=tumor volume in relation to breast volume

[a] Cosmetic result was evaluated by the Erasmus MC Panel questionnaire (see Online resource 1). Higher score means reduced cosmetic result.

[b] Multivariable analyses were performed by stepwise backward linear regression of all univariable predictors with P<0.05. Only the significant results are shown.

Online Resource 3. Equations.

Equation 1

$Prediction\ model\ result = probability\ of\ good\ cosmetic\ result\ after\ BCS\ (p(BCS, good/R) = 1/(1 + e\text{^}(-0.157 * TV/BV\ ratio - 2.738 * (lower\ lateral\ quadrant) - 1.026 * (upper\ medial\ quadrant) - 2.886 * (lower\ medial\ quadrant) - 0.262 * (central\ location) - 2.658)\ )$

Equation 2A

The benefit of a true positive result as opposed to a false negative result is the benefit of identifying a patient who will have a good cosmetic result after BCS rather than undergoing mastectomy:

$Benefit = QoL(BCS, good) - QoL(mastectomy \pm reconstruction)$

Equation 2B

The harm of a false positive result as opposed to a true negative result is the harm caused by performing BCS with a poor cosmetic result rather than performing mastectomy: $Harm = QoL(mastectomy \pm reconstruction) - QoL(BCS, bad)$

Equation 3A-C

The odds at the treatment threshold is given by:

$odds(BCS, good/R) > harm/benefit$

Thus, the decision model suggests:

$Perform\ BCS\ if\ test\ result\ p(BCS, good/R) > \frac{\text{Harm}}{\text{Harm+Benefit}}$

Substituting equations B.2A and B.2B in the above yields the optimal cutoff probability:

$\text{p(BCS, good/R)} > \frac{\text{QoL(mastectomy} \pm reconstruction\text{)} - \text{QoL(BCS,poor)}}{\text{QoL(BCS,good)} - \text{QoL(BCS,poor)}}$

Equation 4

Revising Equation 1 with the updated intercept yields:

$Prediction\ model\ result\ (R) = probability\ of\ good\ cosmetic\ result\ after\ BCS\ (p(BCS, good/R) = 1/(1 + e\text{^}(-0.157 * TV/BV\ ratio - 2.738 * (lower\ lateral\ quadrant) - 1.026 * (upper\ medial\ quadrant) - 2.886 * (lower\ medial\ quadrant) - 0.262 * (central\ location) - 2.798)\ )$

Equation 5

$Perform\ BCS\ if: p(BCS, good/R) > \frac{0.023}{0.023+0.042} = 0.358$

Online Resource 4. EQ-5D utility calculations from the source QoL questionnaires (EORTC QLQ-C30 and FACT-G) from the different source populations (Vos et al., Jagsi et al., and Freedman et al.) for the current analysis.

Source study population	Health state, number of patients	Source QoL values										Utilities		
		EORTC QLQ C-30[a]							FACT-G[b]			EQ-5D before correction	EQ-5D difference	EQ-5D after correction
		PF	EF	SF	CO	DI	PA	SL	PWB	FWB	EWB			
Vos et al.[6]	BCS Total, n=61	89.9	83.7	88.8	6.6	3.3	11.7	23.5				0.847[c]		
	BCS Good, n=44	90.5	85.4	88.6	7.6	3.0	8.3	22.7				0.865[c]	+0.018[e]	
	BCS Poor, n=17	88.6	79.4	89.2	3.9	3.9	20.6	25.5				0.800[c]	-0.047[f]	
Jagsi et al.[7]	MST only, n=263								25.8	21.3	20.6	0.859[d]		
	MST + reconstruction, n=222								26.9	22.1	20.8	0.876[d]		
Freedman et al.[11]	BCS Total, n=1050											0.890		
Current analysis	BCS Good													0.908[g]
	BCS Poor													0.843[h]
	MST (± reconstruction)													0.866[i]

Abbreviations: QoL=quality of life, BCS=breast conserving surgery, MST=mastectomy

[a] PF: Physical Functioning, EF: Emotional Functioning, SF: Social Functioning, CO: Constipation, DI: Diarrhoea, PA: Pain, SL: Sleep

[b] PWB: Physical Well-Being, FWB: Funtional Well-Being, EWB: Emotional Well-Being

[c] EQ-5D utility=1-(0.8592777-0.0069693*PF-0.0087346*EF-0.0039935*SF+0.0000355*PF^2+0.0000552*EF^2+0.000029*SF^2+0.0011453*CO+0.0039889*DI+0.0035614*PA-0.0003678*SL-0.000054*DI^2+0.0000117*SL^2

[d] EQ-5D utility=0.391+(0.009*PWB)+(0.008*FWB)+(0.005*EWB) after rescaling FACT-G values on a 0-100 scale

[e] 0.865(BCS Good)-0.847(BCS Total)= +0.018

[f] 0.800(BCS Poor)-0.847(BCS Total)=-0.047

[g] 0.890(BCS Total from Freedman et al.)+0.018(BCS Good EQ-5D difference from Vos et al.)=0.908

[h] 0.890(BCS Total from Freedman et al.)-0.047(BCS Poor EQ-5D difference from Vos et al.)=0.843

[i] reconstruction rate: 41.6%[9] > (0.859*0.584)+(0.876*0.416)=0.866

Online Resource 5. Probabilistic sensitivity analysis (PSA) and expected value of perfect information (EVPI) analysis.

Sample	p(BCS,-good)	U(BCS,-good)	p(BCS, poor)	U(BCS, poor)	**Benefit (BCS)**	p(MST only)	U(MST only)	p(MST, recon)	U(MST, recon)	**Benefit (MST)**	Treatment Advice	Opportunity Loss in Utilities
1	0.713	0.913	0.316	0.772	0.894	0.540	0.861	0.441	0.878	0.852	BCS	0.000
2	0.761	0.914	0.292	0.862	0.947	0.599	0.853	0.397	0.884	0.862	BCS	0.000
3	0.650	0.917	0.332	0.851	0.879	0.596	0.860	0.417	0.881	0.880	Mastectomy	0.001
4	0.682	0.917	0.209	0.848	0.802	0.623	0.851	0.418	0.890	0.902	Mastectomy	0.100
5	0.719	0.924	0.244	0.817	0.863	0.555	0.841	0.440	0.876	0.852	BCS	0.000
6	0.621	0.906	0.324	0.772	0.813	0.592	0.867	0.401	0.878	0.866	Mastectomy	0.053
7	0.667	0.919	0.335	0.869	0.905	0.618	0.843	0.405	0.871	0.873	BCS	0.000
8	0.719	0.912	0.277	0.832	0.886	0.580	0.880	0.414	0.883	0.876	BCS	0.000
9	0.705	0.920	0.251	0.819	0.854	0.595	0.858	0.394	0.870	0.853	BCS	0.000
10	0.700	0.913	0.364	0.878	0.958	0.562	0.883	0.424	0.878	0.868	BCS	0.000
Average	0.709	0.908	0.290	0.844	0.889	0.584	0.860	0.416	0.876	0.866	**61.9% BCS**	**Total EVPI = 0.020**
SD	0.055	0.014	0.055	0.038	0.069	0.022	0.013	0.022	0.015	0.029		

Abbreviations: BCS=breast conserving surgery, BCS,good=breast conserving surgery with good cosmetic result, BCS,poor= breast conserving surgery with poor cosmetic result, MST=mastectomy with or without breast reconstruction, MST only=mastectomy only, MST,recon=mastectomy with breast reconstruction. From the total of 10,000 randomly drawn values from the beta distributions of each parameter, the first 10 simulated samples are shown in columns 2-5 and 7-10. In column 6 and 11, the net benefit in utility from respectively BCS and MST are shown. The treatment with the largest benefit is the treatment that is advised in that simulated sample (column 12). On average BCS is advised in 61.9% of the 10,000 samples. Ideally, in the presence of large amounts of data, no parameter uncertainty exists (perfect information) whereby on average 0.02 utility could be won per patient.

CHAPTER 4

TUmor-volume to breast-volume RAtio for improving COSmetic results in breast cancer patients (TURACOS); a randomized controlled trial

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ABSTRACT

Background: Cosmetic result following breast conserving surgery (BCS) for cancer influences quality of life and psychosocial functioning in breast cancer patients. A preoperative prediction of expected cosmetic result following BCS is not (yet) standard clinical practice and therefore the choice for either mastectomy or BCS is still subjective. Recently, we showed that tumour volume to breast volume ratio as well as tumour location in the breast are independent predictors of superior cosmetic result following BCS. Implementation of a prediction model including both factors, has not been studied in a prospective manner. This study aims to improve cosmetic outcome by implementation of a prediction model in the treatment decision making for breast cancer patients opting for BCS.

Methods/design: Multicentre, single-blinded, randomized controlled trial comparing standard preoperative work-up to a preoperative work-up with addition of the prediction model. Tumour volume to breast volume ratio and tumour location in the breast will be used to predict cosmetic outcome in invasive breast cancer patients opting for BCS. Three dimensional (3D)-ultrasonography will be used to measure the tumour volume to breast volume ratio needed for the prediction model. Sample size was estimated based on a 14% improvement in incidence of superior cosmetic result one year after BCS (71% in the control group versus 85% in the intervention group). Primarily cosmetic outcome will be evaluated by a 6-member independent panel. Secondary endpoints include; (1) patient reported outcome measured by BREAST-Q, EORTC-QLQ-C30/BR23 and EQ-5D-5 L (2) cosmetic outcome as assessed through the BCCT. core software, (3) radiation-induced reaction (4) surgical treatment performed, (5) pathological result and (6) costeffectiveness. Follow-up data will be collected for 3 years after surgery or finishing radiotherapy.

Discussion: This randomized controlled trial examines the value of a preoperative prediction model for the treatment-decision making. It aims for a superior cosmetic result in breast cancer patients opting for BCS. We expect improvement of patients' quality of life and psychosocial functioning in a cost-effective way.

Trial registration: Prospectively registered, February 17th 2015, at 'Nederlands Trialregister- NTR4997'.

BACKGROUND

For early stage breast cancer patients the goal of therapy is to ensure both local control and breast preservation with an optimal cosmetic outcome. The current standard of care is breast-conserving surgery (BCS) followed by adjuvant whole breast irradiation (1-3). Large randomised clinical trials in the 80's have shown that this treatment is equivalent, in terms of overall and breast-cancer specific survival, to a mastectomy (4). The frequency of BCS performed is estimated at an annual rate of 60% in the Netherlands (5). Oncoplastic surgery, an operation performed jointly by a plastic surgeon and a breast-cancer surgeon specialist, is currently more frequently performed with the goal of obtaining the best cosmetic outcome possible. At time of diagnosis, however, the treatment decision whether to perform a mastectomy (with or without a breast reconstruction) or BCS is often subjective. Unfavourable cosmetic outcome following BCS is significantly associated with decreased quality of life and psychosocial functioning (6, 7). Poor cosmetic outcome following BCS is reported in up to 30% of breast cancer patients (8-11). Pre-operative knowledge of the expected cosmetic outcome would thus be a welcome treatment decision aid.

As previously studied by our group, independent factors for the prediction of cosmetic outcome in BCS are tumour location and tumour volume to breast volume ratio. This volume ratio was obtained through 3-D visualisation of breast MRI images (10). Based on these factors a prediction model is made predicting the expected cosmetic outcome for BCS. The prediction model could aid in the treatment decision by differentiation of patients with an expected favourable cosmetic outcome and thereby improve cosmetic outcome and patients' quality of life.

Within this randomised trial participant will undergo an additional 3-D ultrasonography of the affected breast. Ultrasonography has a broad clinical applicability in breast cancer patients and is not dependent on the use of ionizing radiation. Measurements, obtained by the Automated Breast Volume Scanner (ABVS) and 3-D ultrasonography (3-D US) have previously been compared to MRI and histopathological tumour size with good agreement (12, 13). An additional validation compared volume measurements of the3-D US to those measured by histopathological and 3-D MRI. Both breast and tumour volume showed high agreement (14).

This study aims to improve cosmetic outcome following BCS by using a preoperative prediction model based on 3-D ultrasonography.

Objective

The objective of this randomized controlled trial is to compare cosmetic outcome following a standard preoperative work-up by that of the preoperative prediction model. The hypothesis is that the addition of the preoperative prediction model aids in the treatment-decision making and therefore improves cosmetic outcome and quality of life in patients opting for BCS.

METHODS

Trial design

This single-blinded, multicentre, randomised controlled trial targets women with the diagnosis of primary breast cancer. Patients will randomly be assigned (1:1) to either the intervention or control group after written informed consent is given. The study is in compliance with the Helsinki declaration. Ethical approval has been granted by the Institutional Review Board of the Erasmus University Medical Centre, Rotterdam, the Netherlands (reference-number: MEC-2013-360). This trial is registered before the start of the inclusion on February 17th, 2015 (NTR 4997). Figure 1 present a flow-diagram of the trial design.

Participants

Women with pathologically confirmed primary invasive breast cancer (cT1-3) that are eligible and opt for BCS will be included. Additional inclusion and exclusion criteria are presented in Table 1.

Table 1. Inclusion and exclusion criteria.

Inclusion criteria	Exclusion criteria
Female	Recurrent breast cancer ipsilateral
Aged > 18 years	Previous radiation therapy ipsilateral breast
Primary breast cancer	
Pathologically proven breast cancer TI-III	
Eligible for breast conserving surgery (BCS)	

Interventions

Volumetric measurements

All patients will receive an additional ultrasound performed by the Automated Breast Volume Scanner (ABVS– ACUSON S2000™ ABVS, Siemens Medical Solutions,

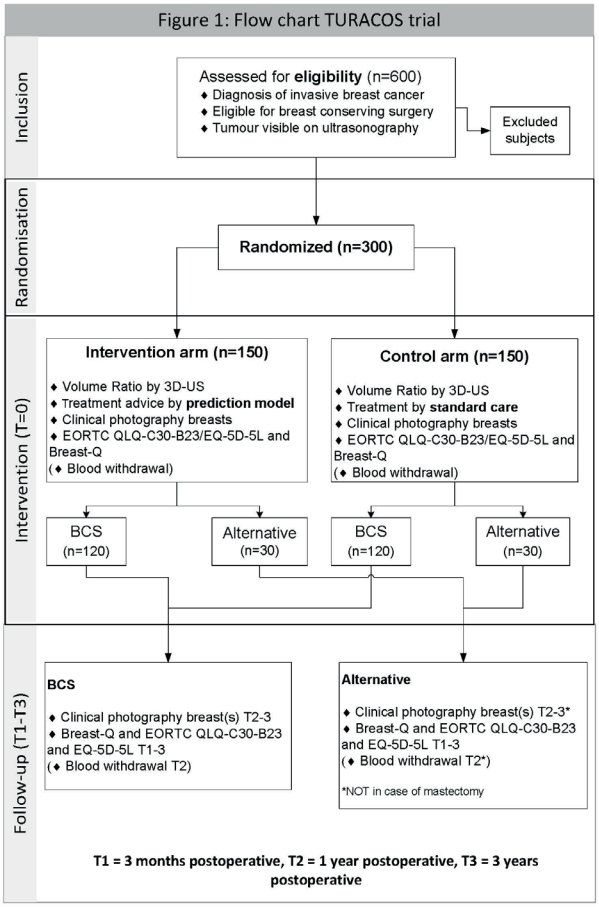

Figure 1. Flow chart TURACOS trial.

Inc, Mountain View, CA) available at the department of Radiology, Erasmus MC Cancer Institute (15). A standardized scanning technique is used where 3 or 5 scans are performed (i.e., anterior-posterior, lateral and medial view or anterior-posterior, upper lateral-, lower lateral-, upper medial- and lower medial-quadrant). Data from the ABVS is visualised by the 'V-scope' software (department of Bioinformatics, Erasmus MC) through an interactive 3-D image on the desktop system. Volume measurements are performed using a tracking system and a wireless joystick (16).

Prediction model

The tumour to breast volume ratio and the location of the tumour in the breast are used in the prediction model to calculate the chance of superior cosmesis in case

of BCS. If the probability exceeds the predefined threshold primary BCS is advised. If the probability is below the predefined threshold an alternative treatment will be advised (i.e., oncoplastic BCS, mastectomy with or without a breast reconstruction or neo-adjuvant chemotherapy). The threshold is defined by modelling the differences in quality of life utilities between the different surgical strategies and the associated cosmetic results.

Pre-operative work-up

For all randomized patients the following characteristics will be collected (if applicable): age, body mass index (BMI), comorbidity, previous operations, smoking status, hormonal status, tumour morphology, TNM stadium, post-operative complications, radiotherapy details, chemotherapy details and hormonal therapy details.

Preoperatively all patients will be asked to complete three questionnaires. This includes the 'Breast Q – preoperative modules' (17), the 'European Organisation of research and Treatment of Cancer quality of life questionnaire (EORTC-QLQ-C30 version 3 and EORTC-QLQ-B23 version 1)' and 'Euro-QoL 5D-5L questionnaire' (EQ-5D-5L-version 2). All patients will preoperatively be discussed in multidisciplinary consultation. For the intervention group, the optimal treatment based on the results of the prediction model will be taken into consideration. All patients will be blinded for the result of the prediction model. Preoperative photographs will be taken by a professional medical photographer. These photographs include the 1) face-view position with the arms down, 2) face-view with arms in the side and 3) lateral view (90°) off the affected breast. The face view photographs will cover the area of chin to the umbilicus protecting the subject's privacy and anonymity.

Follow-up

Three questionnaires will be obtained at all follow-up visits (i.e., 'BREAST-Q postoperative modules', the EORTC-QLQ-C30/B23 and the EQ-5D-5L. Follow-up visits will be scheduled at 3 months (T1), 1 year (T2), and 3 year (T3) postoperatively. Photographs will be obtained both 1 and 3 year following BCS.

Outcomes

Primary outcome

The cosmetic outcome evaluation will be performed by a 6-member, independent panel using the photographs. Each panel consist of 1) a plastic surgeon/breast cancer surgeon, 2) a general practitioner, a medical doctor, 3) a radiation oncologist,

4) a layperson and 5) a breast cancer survivor. Cosmetic outcome will be evaluated using a previously reported in-house developed questionnaire containing 11 aggregating previous recommendations (18) (See supplementary file A 'Erasmus MC panels' questionnaire'). Answers are scored on a four point Harvard cosmetic scale: 0 = 'excellent', 1 = 'good', 2 = 'moderate', and 3 = 'bad' (19).

Table 2. Assessments and used instruments with timeframe indication

Outcome(s)	Instrument(s)	T0	T1	T2	T3
Primary endpoint					
Cosmetic result	Evaluation clinical photos by panel- 'Erasmus MC panels' questionnaire'	x		x	x
Secondary outcome					
Cosmetic result/satisfaction with breast assessed by patient	Breast Q- preoperative module	x			
	Breast Q- postoperative module		x	x	x
Patients' Quality of life	EORTC QLQ-C30/B23 questionnaire	x	x	x	x
	EQ-5D-5L questionnaire	x	x	x	x
Cosmetic result BCCT.core	BCCT.core software (INESC Porto Breast Research Group)	x		x	x
Radiation-induced reaction	RTOG/EORTC			x	x
Surgical strategy performed	Performed surgery/surgeries				x
Pathological result	Data of pathology reports				x
Cost-effectiveness	Quality-Adjusted Life Year (QALY) for direct and indirect costs				x

T0= first visit outpatient clinic, T1= 3 months postoperative, T2= 1 year postoperative, T3= 3 years postoperative

Secondary outcome(s)

1. Patient reported outcome is measured by the 'BREAST-Q', 'EORTC-QLQ-C30/BR23' and 'EQ-5D-5L' questionnaires (T0-3).
2. Cosmetic outcome assessed by the 'BCCT.core software' - INESC Porto Breast Research group (20) based on medical photographs (T0-2-3).
3. Radiation reaction scored by the 'Radiation Therapy Oncology Group/ European Organization for Research and Treatment of Cancer' – 'RTOG/EORTC' (T2-3) (21).
4. Surgeries performed (T3).
5. Pathological results (T3).

Cost-effectiveness; direct costs will include the pre-operative care together with the costs for (surgical) treatment. Indirect costs will generally include adjuvant operation(s) if applicable and costs of outpatient clinic visits or hospitalisation (T4).
6.

Data collection and statistical analysis

Primary study parameter

Cosmetic outcome is calculated by obtaining the mean score for all panel members. The score per panel member is based on the mean score off the 11 scored items combined. Subsequently, the mean panel evaluation will be dichotomized by defining a mean of <1.5 as superior and a mean of >1.5 as inferior. The primary outcome is the incidence of a superior cosmetic outcome in both arms. Difference will be evaluated by using the Chi-square analysis (if normally distributed) or the non-parametric Kruskal-Wallis test (if not normally distributed).

Secondary study parameters

Cosmetic result assessed by the patient (BREAST-Q), cosmetic evaluation through BCCT.core and radiation-induced reaction (RTOG/EORTC) will be analysed by comparing the intervention and control group. For normally distributed categorical data, the Chi-Square test will be used and the Kruskal Wallis test if not normally distributed. Continues variables as the Q-score will be analysed making use of the Student T-test if normally distributed or Mann-Whitney U test if not normally distributed. Pathological result will be analysed by comparing the percentages of incomplete tumour excisions and mean lumpectomy specimen size between the two study arms. The secondary study parameters will be analysed based on the intention-to-treat principle (i.e., including the patients treated with mastectomy). Surgical strategies performed will be analysed by comparing the percentages of the different types of surgery performed by using a Chi-square analysis if normally distributed or Kruskal-Wallis test if not normally distributed. Patients' quality of life, conducted through the EORTC questionnaire/Euro-QoL and BREAST-Q questionnaires will be presented in a quantitative manner. Cost-effectiveness will be calculated by Markov modelling using 'Quality-Adjusted Life Years' (QALY's).

Sample size

In our previously performed retrospective study the incidence of a superior cosmetic result, without intervention, was 71%. An improvement of superior cosmetic outcome to 85% was considered clinically relevant. Expected clinical

relevant difference is a 14% improvement in the incidence of a superior cosmetic result as evaluated by an independent panel. The sample size calculation is based on comparing two proportions in independent groups by the Chi-Square test. With 80% power and 5% significance level we need a study population of 240 patients (120 in each arm). There is a possibility that even after randomization the patient can still undergo mastectomy instead of BCS. We expect this for less than 25% patients in each arm, therefore we aim to include 300 patients in total (150 in each arm).

DISCUSSION

The literature provides limited predictive factors for an expected favourable cosmetic outcome in breast cancer patients opting for BCS. To objectively device a tailor-made treatment plan this study makes use of a prediction model (10). This study aims to provide level 1B evidence for the use of a preoperative prediction model for clinical decision making to improve cosmetic results in patients opting for BCS.

Following the inclusion of the first 30 patients (10%) the patients' experiences tell us that the study is well accepted and appreciated. It is however of great importance that the study is discussed by the treating surgeon at the first or second consultation at the outpatient clinic. By the start of inclusion up to 40% of the approached patients declined participation. This was mainly based on too much burdening in the preoperative phase and an inadequate introduction of the study. If the treating surgeon introduces the study and explains the importance of the study in the preoperative phase the acceptance for participation is higher. With the allocation of multiple including centre's in the region of Rotterdam the inclusion rate has adequately improved with an ongoing high acceptance of participating patients.

Preoperative assessment of patients' quality of life and satisfaction with their breast is currently lacking in the literature available. Only few trials have combined postoperative cosmetic outcome measurements by panel or software with patient reported outcome measures (PROMs) (22-24). Especially an evaluation of cosmetic outcome through time following breast surgery is scarce (22). By preoperatively collecting aesthetics and PROMs a reliable understanding of the relationship between cosmetic results and self-image or quality of life is gained. Comparing overall health-related quality of life (EORTC-QLQ-C30/B23 and EQ-5D-5L) and treatment- or surgery specific outcomes (BREAST-Q) gives a better understanding between overall and disease-specific quality of life (17, 25, 26). With this knowledge, future treatment decision making and cosmetic outcome

evaluation can possibly be based on PROMs. To adequately study cosmetic outcome and their relationship to PROM's, standardized, reproducible and easily available tools are needed (19, 27). Comparing two different panel evaluations within 68 patients following BCS our group found almost perfect inter- and intra-observer agreement. Interclass correlation coefficient showed R=0.93, R=0.9 respectively for the inter- and intra-observer agreement [unpublished data]. When comparing trials differences in panel evaluations found are based on panel size and the use of layperson versus experts (24, 28, 29). Moreover multiple and unstandardized questionnaires are used to obtain cosmetic outcome; making a comparison between different trials difficult. Based on previous recommendations of Cardoso et al our current study uses a questionnaire concerning the different aspect of cosmetic outcome when evaluating the breast by panel members (18). The BCCT. core software is known to evaluate asymmetry, skin colour difference(s) and scar features based on the situation of two identical breasts (30-32). In line with previous literature our group found a moderate agreement (unpublished data) between panel and BCCT core evaluation (23, 24). An independent 6-member panel will therefore assess cosmetic outcome as our primary outcome. In summary, this study aims to improve cosmetic outcome and quality of life through the implementation of a preoperative prediction model for breast cancer patients opting for BCS.

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Online supplementary material Erasmus MC Panels Questionnaire

Overall cosmetic result	0	1	2	3
Appearance of the surgical scar	0	1	2	3
Size of the breast	0	1	2	3
Shape of the breast	0	1	2	3
Position of the nipple-areola complex	0	1	2	3
Size of the nipple-areola complex	0	1	2	3
Color of the nipple-areola complex	0	1	2	3
Position of inframammary fold	0	1	2	3
Color of the skin	0	1	2	3
Teleangiectasia	0	1	2	3
Symmetry	0	1	2	3

0 = excellent result (without visible treatment sequelae)
1 = good result (slight sequelae with minimal difference between treated and untreated breast)
2 = fair result (obvious difference difference between treated and untreated breast but without major distortion)
3 = poor result (major aesthetic sequelae)

PART III

Oncological outcomes

CHAPTER 5

Benefits of preoperative MRI in breast cancer surgery studied in a large population-based cancer registry

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ABSTRACT

Background: Although evidence for the benefits of preoperative MRI in breast cancer is lacking, use of MRI is increasing and characterized by large interhospital variation. The aim of the study was to evaluate MRI use and surgical outcomes retrospectively.

Methods: Women with invasive breast cancer (pT1–3) or ductal carcinoma *in situ* (DCIS), diagnosed in 2011–2013, were selected from the Netherlands Cancer Registry and subdivided into the following groups: invasive cancer, high-grade DCIS, non-palpable cancer, age 40 years **or** less, and invasive lobular cancer. Associations between preoperative MRI use and initial mastectomy, resection margin after breast-conserving surgery (BCS), re-excision after BCS, and final mastectomy were analysed.

Results: In total, 5514 women were included in the study; 1637 (34·1 per cent) of 4801 women with invasive cancer and 150 (21·0 per cent) of 713 with DCIS had preoperative MRI. Positive resection margins were found in 18·1 per cent women who had MRI and in 15·1 per cent of those who did not (adjusted odds ratio (OR) 1·20, 95 per cent c.i. 1·00 to 1·45), with no differences in subgroups. Re-excision rates were 9·8 per cent in the MRI group and 7·2 per cent in the no-MRI group (adjusted OR 1·33, 1·04 to 1·70), with no differences in subgroups. In the MRI group, 38·8 per cent of patients ultimately underwent mastectomy, compared with 24·2 per cent in the no-MRI group (adjusted OR 2·13, 1·87 to 2·41). This difference was not found for patients aged 40 years or less, or for those diagnosed with lobular cancer.

Conclusion: No subgroup was identified in which preoperative MRI influenced the risk of margin involvement or re-excision rate after BCS. MRI was significantly associated with more extensive surgery,except in patients aged 40 years or less and those with invasive lobular cancer. These results suggest that use of preoperative MRI should be more targeted, and that general, widespread use be discouraged.

INTRODUCTION

The primary goal of breast-conserving surgery (BCS) for breast cancer is to obtain complete tumour excision. If the excision is incomplete, re-excision may be necessary, which will increase healthcare costs, the burden to the patient and the risk of a poor cosmetic result. Obtaining a high complete tumour excision rate is important to the patient, as well as to the many healthcare stakeholders that use the re-excision rate as a quality indicator of breast cancer care.

A meta-analysis1[1] has shown that MRI can detect mammographically and clinically occult disease in the ipsilateral breast in around 16 per cent of patients with invasive cancer or ductal carcinoma *in situ* (DCIS). MRI has also been shown[2] to be more accurate than mammography or ultrasonography in determining tumour size and delineating tumour margins. As a consequence, preoperative MRI is believed to improve the surgical planning and likelihood of complete tumour excision at the first attempt. Especially in DCIS with high nuclear grade, MRI complementary to mammography could help improve the ability to diagnose the extent of the DCIS[3,4]. The American College of Radiology guidelines suggest that contrast-enhanced MRI of the breast may be useful to determine both the extent of disease and the presence of multifocality and multicentricity in patients with invasive carcinoma and DCIS. However, currently there is no convincing evidence that preoperative MRI does improve surgical outcomes, such as the rates of positive margins, re-excision or breast conservation, in the average patient with breast cancer[5–7]. An exception to this is the subgroup of patients with lobular cancer, for whom a significantly reduced rate of re-excision has repeatedly been shown following preoperative MRI[5,6,8,9]. This may support the targeted use of preoperative MRI in particular subgroups of patients with breast cancer, as recommended by the European Society of Breast Cancer Specialists (EUSOMA)[10]. Although multiple studies have suggested that MRI is not beneficial in patients with breast cancer in general, and that subgroups must be identified, studies investigating the benefit of MRI in specific subgroups are lacking.

Owing to lack of evidence of the benefits of preoperative MRI regarding short- and long-term treatment outcomes, the value of MRI is heavily debated. Unlike most European countries, guidelines are available in the Netherlands regarding the use of preoperative MRI in women for whom BCS is being considered. In 2011, preoperative MRI was recommended in patients with a (non)-invasive tumour with poorly defined margins, located in dense breast tissue, or with an extensive intraductal component[11]. Since 2012, MRI has been advised in patients with: an invasive tumour and a discrepancy in size between physical examination, mammography and ultrasound imaging; invasive lobular breast cancer; uncertainty regarding the

extent of high-grade DCIS; or suspected (micro)invasive breast cancer in DCIS[12]. Despite these guidelines, extremely wide interhospital variation in the use of preoperative MRI still exists in the Netherlands, with a range of 0–85 per cent for women with invasive cancer[13].

Most studies on the potential benefits of preoperative MRI have described single-centre hospital cohorts, and no European population-based studies have been published. In the present study, the population-based Netherlands Cancer Registry was used to determine the association between preoperative MRI and initial mastectomy rate, surgical margin status after BCS, re-excision rate after BCS, and final mastectomy rate in subgroups of patients with invasive cancer, high-grade DCIS, non-palpable cancer, age 40 years or less, and lobular type of invasive cancer. The aim was to identify subgroups in which the preoperative use of MRI might result in improved surgical outcomes after BCS.

METHODS

The population-based Netherlands Cancer Registry (Eindhoven region) registers all new cancer diagnoses in an area of south-east Netherlands that has 2·4 million inhabitants, and ten large community and teaching (but no academic) hospitals. The registry collects data based on notifications from the automated pathology archive (PALGA) according to international guidelines by specially trained personnel, and meets high-quality standards with completeness exceeding 95 per cent[14,15]. It provides detailed information on patient demographics, tumour characteristics and treatment. Since 2011, the registry has included data commissioned by the National Breast Cancer Audit, which includes information on preoperative MRI and the date it was performed[13]. In each hospital, dynamic contrast-enhanced MRI was performed according to local protocol, using various MRI scanners. Breast radiologists read the images using the Breast Imaging Reporting and Data System (BI-RADS). All patients, including their imaging findings, were discussed in preoperative multidisciplinary meetings.

Patients diagnosed with a new invasive breast cancer or DCIS between 1 January 2011 and 1 January 2014 were selected. Exclusion criteria were: male sex, neoadjuvant chemotherapy or hormone therapy, clinical or pathological tumour stage T4, distant metastasis at presentation, unknown pathological tumour stage or T0, and unknown type of surgery or unknown surgical margin status. Clinical and pathological TNM stage was according to the seventh edition of the TNM staging system[16]. Margin status after the initial surgical procedure was registered in detail as negative, focally positive, or more than focally positive for both the non-invasive and invasive component of the tumour separately.

Statistical analysis

Patients with concurrent contralateral cancer or contralateral new primary cancer later in time were eligible for inclusion. The contralateral breast cancer was analysed as a new patient. The study population was divided into a no-MRI group and an MRI group according to preoperative use of MRI. Differences in patient characteristics between the two groups were tested using the Mann–Whitney *U* test for continuous variables and χ^2 test for categorical variables. The association between MRI and time from diagnosis to surgery (in days) was determined with the Mann–Whitney *U* test. Subsequently, the total study population was allocated to none, one or more of the following subgroups: invasive cancer, purely high-grade DCIS (defined as Bloom and Richardson grade 2 or 3), non-palpable invasive cancer, young patients (40 years or less) at time of diagnosis, and lobular type of invasive cancer. A negative margin was defined as 'no ink on tumour', a focally positive margin as 'tumour at the resection margin over a length of less than 4 mm', and a more than focally positive margin as 'tumour at the resection margin over a length of 4mm or more'. Univariable and multivariable binary logistic regression analysis was used to test the association between MRI and the following outcomes: initial mastectomy rate (*versus* initial BCS), positive margin rate after BCS (*versus* negative margin after BCS), re-excision rate after BCS (*versus* no re-excision after BCS) and final mastectomy rate (*versus* final BCS). The multivariable model was performed by the enter method and included all variables displayed in *Table 1* that were associated with the outcome of interest in univariable analysis with a *P* value of less than 0·100. Both age and tumour size were included as continuous variables in the univariable and multivariable regression analyses. To study the association between surgical margin status after BCS and MRI in more detail, χ^2 analysis was also performed. Statistical tests were two-sided, and $P < 0{\cdot}050$ was considered statistically significant. SPSS® version 20 (IBM, Armonk, New York, USA) was used for all statistical analyses.

Table 1. Patient and tumour characteristics of the 4801 patients with invasive breast cancer of the total study population of 5514.†

	MRI (n = 1637)	**No MRI (n = 3164)**	**P§**
Age (years)			< 0.001
-≤ 40	102 (6.2)	76 (2.4)	
-41–59	767 (46.9)	1096 (34.6)	
-≥ 60	768 (46.9)	1992 (63.0)	
Palpability			0.120
-No	676 (41.3)	1347 (42.6)	
-Yes	920 (56.2)	1764 (55.8)	
-Unknown	41 (2.5)	53 (1.7)	
Histology			< 0.001
-Ductal	1105 (67.5)	2712 (85.7)	
-Lobular	449 (27.4)	231 (7.3)	
-Other	83 (5.1)	221 (7.0)	
DCIS adjacent to tumour			0.006
-No	790 (48.3)	1682 (53.2)	
-Yes	846 (51.7)	1480 (46.8)	
-Unknown	1 (0.1)	2 (0.1)	
Pathological tumour size (mm)*‡	16 (11–23)	15 (9–21)	< 0.001¶
Tumour category			< 0.001
-T1	1126 (68.8)	2397 (75.8)	
-T2	474 (29.0)	731 (23.1)	
-T3	37 (2.3)	36 (1.1)	
Differentiation grade			<0.001
-1	483 (29.5)	1076 (34.0)	
-2	752 (45.9)	1259 (39.8)	
-3	355 (21.7)	754 (23.8)	
-Unknown	47 (2.9)	75 (2.4)	
-Oestrogen receptor status			0.001
-Positive	1,438 (87.8)	2657 (84.0)	
-Negative	184 (11.2)	481 (15.2)	
-Unknown	15 (0.9)	26 (0.8)	
Progesterone receptor status			0.007
-Positive	1200 (73.3)	2185 (69.1)	
-Negative	422 (25.8)	952 (30.1)	
-Unknown	15 (0.9)	27 (0.9)	
Her2/Neu receptor status			0.154
-Negative	1417 (86.6)	2755 (87.1)	
-Positive	189 (11.5)	327 (10.3)	
-Unknown	31 (1.9)	82 (2.6)	

Table 1. Patient and tumour characteristics of the 4801 patients with invasive breast cancer of the total study population of 5514.† *(continued)*

	MRI (n = 1637)	No MRI (n = 3164)	P§
Node category			0.004
-N0	1155 (70.6)	2292 (72.4)	
-N1	348 (21.3)	627 (19.8)	
-N2	71 (4.3)	102 (3.2)	
-N3	36 (2.2)	49 (1.5)	
-Unknown	27 (1.6)	94 (3.0)	

Values in parentheses are percentages unless indicated otherwise; *values are median (i.q.r.). †Details of patients with ductal carcinoma *in situ* (DCIS) alone are described in the main text. ‡Tumour size was not known in five patients in the MRI group and eight in the no-MRI group. §χ^2 test, except ¶Mann–Whitney *U* test.

RESULTS

In 2011–2013, a total of 6685 patients with a new diagnosis of invasive breast cancer or DCIS were registered in the Netherlands Cancer Registry (Eindhoven region). After applying the exclusion criteria, 5514 patients were eligible. Invasive cancer was diagnosed in 4801 women (87·1 per cent), of whom 1637 (34·1 per cent) had preoperative MRI; their characteristics are summarized in *Table 1*. Pure DCIS was diagnosed in 713 patients (12·9 per cent), of whom 150 (21·0 per cent) had preoperative MRI. Of the patients with DCIS in the MRI and no-MRI group, 12 (8·0 per cent) and seven (1·2 per cent) respectively were aged 40 years or less, and 60 (40·0 per cent) and 298 (52·9 per cent) were aged 60 years or over (P <0·001). Furthermore, of the patients with DCIS in the MRI and no-MRI group,12 (8·0 per cent) and 82 (14·6 per cent) respectively had differentiation grade 1 disease, 55 (36·7 per cent) and 217 (38·5 per cent) had differentiation grade 2, and 81 (54·0 per cent) and 261 (46·4 per cent) had differentiation grade 3; the grade was unknown in two (1·3 per cent) and three (0·5 per cent) patients respectively (P =0·089). In the total study population, the incidence of contralateral invasive breast cancer or DCIS diagnosed within 3 months after diagnosis of the first invasive breast cancer or DCIS was 58 (3·2 per cent) in the MRI group and 45 (1·2 per cent) in the no-MRI group. The time between diagnosis and surgery in the total study population was longer for the MRI group: median (i.q.r.) 34 (24–45) days *versus* 22 (15–30) days in the no-MRI group (P <0·001). The median time from MRI to surgery was 24 (15–36) days.

Preoperative MRI and initial mastectomy rate

In the total study population, 1480 patients (26·8 per cent) were initially treated with mastectomy, 651 (36·4 per cent) of the 1787 patients in the MRI group and 829 (22·2 per cent) of the 3727 in the no-MRI group (both unadjusted and adjusted *P* <0·001) (*Table 2*). Likewise, significantly higher initial mastectomy rates were seen in MRI *versus* no-MRI groups in the subgroups of patients with invasive cancer (35·9 *versus* 23·1 per cent respectively), high-grade DCIS (43·4 *versus* 18·2 per cent) and non-palpable cancer (28·8 *versus* 11·8 per cent) (all unadjusted and adjusted *P* <0·001). In contrast, initial mastectomy rates were not significantly different between MRI and no-MRI groups in patients aged 40 years or less (40·4 *versus* 42 per cent), or in patients with lobular type of cancer (41·2 *versus* 40·7 per cent) (all unadjusted and adjusted *P* >0·200) (*Table 2*).

Table 2. Univariable and multivariable logistic regression analysis for initial mastectomy rate, positive margin rate after breast-conserving surgery, re-excision rate after BCS and final mastectomy rate, according to preoperative MRI use.

	Total*	MRI*	No MRI*	Unadjusted OR†	Unadjusted P	Adjusted OR†	Adjusted P
Total study population‡							
-Initial mastectomy (*versus* BCS)	1480 of 5514 (26.8)	651 of 1787 (36.4)	829 of 3727 (22.2)	2.00 (1.77, 2.27)	< 0.001	2.18 (1.92, 2.48)	< 0.001
-Positive margin (*versus* negative)	645 of 4034 (16.0)	206 of 1136 (18.1)	439 of 2898 (15.1)	1.24 (1.03, 1.49)	0.020	1.20 (1.00, 1.45)	0.052
-Re-excision (*versus* no re-excision)	321 of 4034 (8.0)	111 of 1136 (9.8)	210 of 2898 (7.2)	1.39 (1.09, 1.76)	0.008	1.33 (1.04, 1.70)	0.026
-Final mastectomy (*versus* BCS)	1595 of 5514 (28.9)	693of 1787 (38.8)	902 of 3727 (24.2)	1.99 (1.76, 2.24)	< 0.001	2.13 (1.87, 2.41)	< 0.001
Invasive cancer							
-Initial mastectomy (*versus* BCS)§	1318 of 4801 (27.5)	588 of 1637 (35.9)	730 of 3164 (23.1)	1.87 (1.64, 2.13)	< 0.001	1.80 (1.54, 2.09)	< 0.001
Positive margin (*versus* negative)¶	548 of 3483 (15.7)	188 of 1049 (17.9)	360 of 2434 (14.8)	1.26 (1.04, 1.53)	0.020	0.98 (0.79, 1.22)	0.882
-Re-excision (*versus* no re-excision)#	239 of 3483 (6.9)	95 of 1049 (9.1)	144 of 2434 (5.9)	1.58 (1.21, 2.08)	0.001	1.27 (0.94, 1.72)	0.125

Table 2. *(continued)*

	Total*	MRI*	No MRI*	Unadjusted OR†	Unadjusted P	Adjusted OR†	Adjusted P
-Final mastectomy (*versus* BCS)§	1406 of 4801 (29.3)	623 of 1637 (38.1)	783 of 3164 (24.7)	1.87 (1.64, 2.12)	< 0.001	1.74 (1.50, 2.03)	< 0.001
High-grade DCIS							
-Initial mastectomy (*versus* BCS)**	146 of 614 (23.8)	59 of 136 (43.4)	87 of 478 (18.2)	3.44 (2.28, 5.20)	< 0.001	3.18 (2.09, 4.82)	< 0.001
-Positive margin (*versus* negative)‡	90 of 468 (19.2)	18 of 77 (23)	72 of 391 (18.4)	1.35 (0.75, 2.43)	0.314	1.28 (0.70, 2.32)	0.426
-Re-excision (*versus* no re-excision)‡	75 of 468 (16.0)	16 of 77 (21)	59 of 391 (15.1)	1.48 (0.80, 2.73)	0.216	1.38 (0.73, 2.59)	0.320
-Final mastectomy (*versus* BCS)**	171 of 614 (27.9)	66 of 136 (48.5)	105 of 478 (22.0)	3.35 (2.25, 5.00)	< 0.001	3.11 (2.07, 4.66)	< 0.001
Non-palpable invasive cancer							
-Initial mastectomy (*versus* BCS)††	354 of 2023 (17.5)	195 of 676 (28.8)	159 of 1347 (11.8)	3.03 (2.40, 3.83)	< 0.001	2.68 (2.05, 3.50)	< 0.001
-Positive margin (*versus* negative)‡‡	229 of 1669 (13.7)	74 of 481 (15.4)	155 of 1188 (13.0)	1.21 (0.90, 1.64)	0.209	0.92 (0.66, 1.29)	0.645
-Re-excision (*versus* no re-excision)§§	97 of 1669 (5.8)	38 of 481 (7.9)	59 of 1188 (5.0)	1.64 (1.08, 2.50)	0.021	1.33 (0.83, 2.13)	0.234
-Final mastectomy (*versus* BCS)††	380 of 2023 (18.8)	207 of 676 (30.6)	173 of 1347 (12.8)	3.00 (2.38, 3.76)	< 0.001	2.58 (1.99, 3.47)	< 0.001
Age ≤ 40 years							
-Initial mastectomy (*versus* BCS)‡	81 of 197 (41.1)	46 of 114 (40.4)	35 of 83 (42)	0.93 (0.52, 1.65)	0.798	0.68 (0.37, 1.27)	0.226
-Positive margin (*versus* negative)¶¶	24 of 116 (20.7)	16 of 68 (24)	8 of 48 (17)	1.54 (0.60, 3.95)	0.371	1.43 (0.55, 3.76)	0.463
-Re-excision (*versus* no re-excision)##	13 of 116 (11.2)	9 of 68 (13)	4 of 48 (8)	1.68 (0.49, 5.80)	0.414	–	–
-Final mastectomy (*versus* BCS)‡	90 of 197 (45.7)	52 of 114 (45.6)	38 of 83 (46)	0.99 (0.56, 1.75)	0.981	0.75 (0.41, 1.39)	0.358

Table 2. *(continued)*

	Total*	MRI*	No MRI*	Unadjusted OR†	Unadjusted P	Adjusted OR†	Adjusted P
Lobular invasive cancer							
-Initial mastectomy (*versus* BCS)***	279 of 680 (41.0)	185 of 449 (41.2)	94 of 231 (40.7)	1.02 (0.74, 1.41)	0.898	1.00 (0.68, 1.45)	0.977
-Positive margin (*versus* negative)†††	102 of 401 (25.4)	65 of 264 (24.6)	37 of 137 (27.0)	0.88 (0.55, 1.41)	0.603	0.80 (0.47, 1.38)	0.419
-Re-excision (*versus* no re-excision)#	45 of 401 (11.2)	29 of 264 (11.0)	16 of 137 (11.7)	0.93 (0.49, 1.79)	0.835	0.97 (0.44, 2.12)	0.933
-Final mastectomy (*versus* BCS)***	301 of 680 (44.3)	198 of 449 (44.1)	103 of 231 (44.6)	0.98 (0.71, 1.35)	0.903	0.95 (0.65, 1.39)	0.791

Values in parentheses are *percentages and †95 per cent c.i. Adjustment for variables associated with (initial and final) mastectomy, positive resection margin, and re-excision with P <0·100 in univariable analysis: ‡age and differentiation grade, §age, palpability, histology, tumour size, differentiation grade, oestrogen receptor status, progesterone receptor status, Her2/Neu receptor status and regional lymph node status, ¶age, palpability, histology, presence of ductal carcinoma *in situ* (DCIS) component, tumour size, differentiation grade, oestrogen receptor status and regional lymph node status, #age, palpability, histology, presence of DCIS component, tumour size, differentiation grade and regional lymph node status, **age, ††age, histology, presence of DCIS component, tumour size, differentiation grade, oestrogen receptor status, progesterone receptor status, Her2/Neu receptor status and regional lymph node status, ‡‡histology, presence of DCIS component, tumour size, differentiation grade and regional lymph node status, §§histology, presence of DCIS component, tumour size, differentiation grade, progesterone receptor status, Her2/Neu receptor status and regional lymph node status, ¶¶differentiation grade, ##none, ***palpability, tumour size, differentiation grade and regional lymph node status, †††presence of DCIS component, tumour size, Her2/Neu receptor status and regional lymph node status. OR, odds ratio; BCS, breast-conserving surgery.

Preoperative MRI and margin status

BCS was performed in 4034 (73·2 per cent) of the total study population. In theMRI group, a focally positive margin was found more frequently than a more than focally positive margin (P =0·048) (*Table 3*). However, MRI was not significantly associated with a positive margin after adjustment for possible confounders (odds ratio (OR) 1·20, 95 per cent c.i. 1·00 to 1·45; P =0·052) (*Table 2*). In all subgroups, no differences in negative, focally positive, or more than focally positive margin rates were seen between MRI and no-MRI groups in univariable analysis (all P >0·050) (*Table 3*). In addition, in multivariable analysis MRI was not associated with a positive surgical margin (all P >0·050) (*Table 2*). In patients with lobular type of cancer,

preoperative MRI was more frequently associated with a negative margin (75·4 per cent *versus* 73·0 per cent in the no-MRI group), and more rarely with a more than focally positive margin (5·7 and 8·8 per cent respectively) (*Table 3*). However, this difference was not significant in univariable analysis (*P* =0·507) (*Table 3*) or multivariable analysis (OR 0·80, 95 per cent c.i. 0·47 to 1·38; *P* =0·419) (*Table 2*).

Table 3. Surgical resection margin after breast-conserving surgery according to preoperative use of MRI.

Surgical resection margin	MRI	No MRI	*P**
Total study population	*n* = 1136	*n* = 2898	0.048
-Negative	930 (81.9)	2,459 (84.9)	
-Focally positive	147 (12.9)	326 (11.2)	
-More than focally positive	59 (5.2)	113 (3.9)	
Invasive cancer	*n* = 1049	*n* = 2434	0.062
-Negative	861 (82.1)	2074 (85.2)	
-Focally positive	135 (12.9)	264 (10.8)	
-More than focally positive	53 (5.1)	96 (3.9)	
High-grade DCIS	*n* = 77	*n* = 391	0.396
-Negative	59 (77)	319 (81.6)	
-Focally positive	12 (16)	55 (14.1)	
-More than focally positive	6 (8)	17 (4.3)	
Non-palpable invasive cancer	*n* = 481	*n* = 1188	0.312
-Negative	407 (84.6)	1033 (87.0)	
-Focally positive	52 (10.8)	117 (9.8)	
-More than focally positive	22 (4.6)	38 (3.2)	
Age ≤ 40 years	*n* = 68	*n* = 48	0.638
-Negative	52 (76)	40 (83)	
-Focally positive	11 (16)	6 (13)	
-More than focally positive	5 (7)	2 (4)	
Lobular invasive cancer	*n* = 264	*n* = 137	0.507
-Negative	199 (75.4)	100 (73.0)	
-Focally positive	50 (18.9)	25 (18.2)	
-More than focally positive	15 (5.7)	12 (8.8)	

Values in parentheses are percentages. DCIS, ductal carcinoma ***in situ***. *χ^2 test.

Preoperative MRI and re–excision rate

Re-excision after BCS was performed in 111 (9·8 per cent) and 210 (7·2 per cent) patients in the MRI and no-MRI group respectively (unadjusted OR 1·39, 95 per cent c.i. 1·09 to 1·76; *P* =0·008), and remained significantly different after adjustment for age and differentiation grade (OR 1·33, 1·04 to 1·70; *P* =0·026) (*Table 2*). In the subgroup with invasive cancer, re-excision was needed in 9·1 and 5·9 percent of patients in the MRI and no-MRI group respectively (unadjusted P=0·001), and in those with non-palpable cancer re-excision was required in 7·9 and 5·0 per cent respectively (unadjusted P=0·021). However, these differences were not significant after multivariable analysis (OR 1·27, 0·94 to 1·72, *P* =0·125, and OR 1·33, 0·83 to 2·13, *P* =0·234, respectively). The number of re-excisions was not significantly different between the MRI and no-MRI group in patients with high-grade DCIS (21 *versus* 15·1 per cent respectively), patients aged 40 years or less (13 *versus* 8 per cent), and patients with lobular type of cancer (11·0 *versus* 11·7 per cent) (all unadjusted and adjusted *P* >0·200).

Preoperative MRI and final mastectomy rate

Including re-excisions, 1595 (28·9 per cent) of the 5514 patients in the total study population finally had a mastectomy: 693 (38·8 per cent) of the 1787 patients in the MRI group and 902 (24·2 per cent) of 3727 in the no-MRI group (both unadjusted and adjusted *P* <0·001) (*Table 2*). In addition, significantly higher final mastectomy rates were seen in patients with MRI than without MRI in the subgroups of invasive cancer (38·1 *versus* 24·7 per cent respectively), high-grade DCIS (48·5 *versus* 22·0 per cent) and non-palpable cancer (30·6 *versus* 12·8 per cent) (all unadjusted and adjusted *P* <0·001). However, final mastectomy rates were similar in MRI and no-MRI groups in patients aged 40 years or less (45·6 *versus* 46 per cent respectively) and in those with lobular type of cancer (44·1 *versus* 44·6 per cent) (all unadjusted and adjusted *P* >0·300).

DISCUSSION

The hypothesis of this retrospective study in patients with invasive or non-invasive breast cancer was that there are subgroups in which the preoperative use of MRI will result in improved surgical outcomes after BCS. In the total study population, patients who underwent MRI had a small, but significantly higher, positive margin rate (18·1 per cent *versus* 15·1 per cent in those who did not have MRI). However, this does not imply a clinically relevant difference, and in multivariable analysis the difference was no longer significant (*P* =0·052). Preoperative MRI was associated

with neither improved resection margins nor lower re-excision rates after BCS in any of the subgroups studied. However, MRI was associated with higher initial and final mastectomy rates, except in the subgroup of younger patients (aged 40 years or less) and in patients with lobular type of invasive breast cancer.

This is a large, multicentre, population-based analysis of the effect of preoperative MRI on surgical outcomes in Europe. Multivariable analyses were performed, adjusting for multiple patient, tumour and treatment characteristics associated with each outcome separately, which is one of the strengths of the study. Another strength is the large number of patients, which made it possible to focus on patient subgroups, which so far have been studied insufficiently.

The association between preoperative MRI and resection margins after BCS has not been studied in detail before. Contradictory results have been found in multiple small, single-centre studies that have focused on the surgical outcomes of BCS in patients with invasive breast cancer[17–22]. Similar to the findings in the present study, in the only other population-based study, by Fortune-Greeley and colleagues[6], preoperative MRI was not associated with improved surgical outcomes. Only small, single-centre studies with contradictory results have reported on preoperative MRI in patients with pure DCIS[23–27]. In line with the present findings, the only population-based study, performed by Wang and co-workers[7], showed no association between preoperative MRI and positive resection margin and re-excision rates after BCS. To date, only the MONET trial[28] has focused on patients with non-palpable invasive cancer. In contrast to the present findings, the MONET trial (based on 149 patients) found that the addition of preoperative MRI to routine clinical care was associated with an increased re-excision rate.

It is clear from the present findings, and has also been shown frequently in the literature[1,5], that there is a strong association between MRI and mastectomy in all subgroups, except for patients aged 40 years or less and those with invasive lobular breast cancer. A weakness of the study is its retrospective design, and thus the inherent lack of information, such as the presence of multifocality or multicentricity, the indication for performing MRI, the result of The MRI and whether it changed the surgical plan. Recommendations in the Dutch breast cancer guidelines regarding the preoperative use of MRI, described above, can, however, shed some light on the decision-making process underlying the results of this study. The retrospective, non-randomized design of the study also explains the differences in patient characteristics, such as patients undergoing MRI having larger tumours and being more likely to have a DCIS component adjacent to the invasive tumour (*Table 1*). It is known that these factors increase the risk of incomplete excision, and this could have been the reason for performing MRI and thus be a source of

selection bias. Even though factors associated with mastectomy were adjusted for in the multivariable analysis, residual confounding may be present owing to factors not taken into consideration. It must also be noted that the study did not include data from university hospitals, and it is therefore likely that MRI was used for surgical planning rather than screening purposes. The median (i.q.r.) time between MRI and surgery was 24 (15–36) days, supporting the assumption that MRI was used for surgical planning. In addition, the lack of information regarding the incidence of additional occult disease in the ipsilateral breast (estimated to be 16 per cent) detected by MRI prevents firm conclusions from being drawn[1]. The detection rate for contralateral breast cancer by preoperative MRI has been estimated to be 4·1 per cent[29]. In the present study, the incidence of contralateral breast cancer diagnosed within 3 months after diagnosis of the first tumour was 3·2 per cent in patients who had MRI and 1·2 per cent in those who did not. This difference might be larger in patients with lobular cancer and older patients, owing to the higher absolute risk of contralateral breast cancer in these subgroups[30]. Whether preoperative MRI reduces the risk of local and distant recurrence is still a matter of debate[31,32]. Because the cancer registry has included information on preoperative MRI only since 2011, long-term outcomes could not be studied. It can be expected, however, that residual disease in the breast results in positive resection margins that will be treated by re-excision, regardless of the preoperative MRI. It has been shown previously that overall survival is similar in women who have a re-excision and those who do not[33]. Moreover, long-term prognosis has proved to be similar in women having BCS and those undergoing mastectomy[34], and preoperative MRI is therefore unlikely to influence prognosis. Thus, short-term surgical outcomes remain important endpoints for studying the benefits of MRI.

Overall, MRI was used with a relatively high frequency of 32·4 per cent, compared with rates in the above-mentioned population-based studies. In these studies[6,7], which used the US SEER–Medicare-linked database, 6·6–12·2 per cent of patients underwent MRI. The greater use of MRI in the Netherlands could be explained by the more recent time interval, compared with the periods covered in previous studies. It could also be explained by the fact that preoperative staging by MRI has been advised for invasive lobular cancer by the Dutch breast cancer guideline since 2012[12], and by the EUSOMA working group since 2010[10]. There is also a growing body of evidence that the targeted use of MRI in this subgroup improves surgical planning[5,6,8,9]. In the present study, MRI was used in 449 (66·0 per cent) of the 680 patients with invasive lobular breast cancer, and all surgical outcomes were similar for patients with and without MRI. At least these results indicate that MRI is unlikely to have a negative effect in this subgroup. The third

explanation for the more widespread use of MRI in the Netherlands, in comparison with values reported by the studies based on the SEER–Medicare database, could be the younger age of the population. The SEER–Medicare database contains data only for patients aged 65 years or more, whereas the present study included women of all ages, making it the first population-based study to include patients aged less than 65 years. Interestingly, the subgroup analysis of patients aged 40 years or less showed that MRI was significantly associated with neither more extensive surgery (initial and final mastectomy rates) nor the other surgical outcomes studied. However, considering the small number of patients in this subgroup (197), there is a risk of a type II error, and thus the results need to be interpreted with caution. The finding is merely an observation of statistical association and does not provide evidence for a causative relationship.

The present study has shown in a population-based retrospective cohort that preoperative MRI does not result in improved surgical outcomes after BCS, but instead leads to more extensive surgery in patients with breast cancer in general, a finding in line with previous studies. An exception could be in patients aged 40 years or less, and those with invasive lobular breast cancer. Furthermore, MRI may cause a delay in treatment. Large prospective studies are needed urgently to define patient subgroups in which preoperative MRI is of value in short- and long-term outcomes.

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CHAPTER 6

Focally positive margins in breast conserving surgery: predictors, residual disease, and local recurrence

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ABSTRACT

Background: Re-excision after breast conserving surgery (BCS) for invasive breast cancer (IBC) can be omitted for focally positive margins in the Netherlands, but this guideline is not routinely followed. Focally positive and extensively positive margins have rarely been studied separately and compared to negative margins regarding clinicopathological predictors, residual disease incidence, and local recurrence.

Methods: All females with BCS for Tis-T3, without neo-adjuvant chemotherapy between 2005 and 2014 at one university hospital were included. Clinicopathological and follow-up information was collected from electronic patient records. Index tumor samples from all patients with re-excision were reviewed by one pathologist. Margins were classified as negative (≥2 mm width), close (<2 mm width), focally positive (≤4 mm length of tumor touching inked margin), or extensively positive (>4 mm length).

Results: From 499 patients included, 212(43%) had negative, 161(32%) had close, 59(12%) had focally positive, and 67(13%) had extensively positive margins. Increasingly involved margins were associated with lobular type, tumor size, and adjacent DCIS in IBC patients and lesion size in purely DCIS patients. In IBC patients, 17%, 49%, and 77% had re-excision after close, focally positive, and extensively positive margins and residual disease incidence was 55%, 50%, and 70% respectively. In purely DCIS patients, 26(65%), 13(87%), and 16(94%) had re-excision after close, focally positive, and extensively positive margins and residual disease incidence was 39%, 46%, and 90% respectively.

Conclusion: Incidence of residual disease after focally positive margins was not different from close margins, but was significantly higher after extensively positive margins. We recommend quantifying extent of margin involvement in all pathology reports.

INTRODUCTION

After breast conserving surgery (BCS) for invasive breast cancer (IBC) or ductal carcinoma-in-situ (DCIS), a substantial proportion of patients undergoes re-excision(s) aiming to remove residual disease from the breast. The indication for a re-excision is predominantly based on the pathological resection margins. However, in 24-80% of re-excision specimens no residual disease is detected[1-16]. While re-excision comes with disadvantages such as high burden to the patient, impaired cosmetic result, sometimes conversion to mastectomy, and higher health care costs. Therefore re-excision rates need to be reduced as much as possible.

Previously, re-excision was indicated for a variety of margins ranging from a 10 mm negative margin width to a positive margin. This large variety was caused by the lack of international guidelines and randomized controlled trials. Between 2014 and 2016, the Society of Surgical Oncology (SSO) and American Society of Radiation Oncology (ASTRO) published guidelines recommending when to perform re-excision[17,18]. For IBC, re-excision is advised in case of positive margins. For purely DCIS, re-excision is advised for less than 2 mm negative margins. These recommendations are in concordance with The European Society for Medical Oncology (ESMO) guideline published in 2015[19].

The Netherlands' have a national guideline since 2002 that deviates from international guidelines concerning IBC. Re-excision is advised only in case of extensively positive margins (tumor touching the inked margin over a length of more than 4 mm or multiple focally positive foci)[20]. The incidence of residual disease in the breast when a re-excision is omitted for focally positive margins (tumor touching the inked margin over a length of 4 mm or less) is unknown. The local recurrence risk for patients with focally positive margins is also unknown. This lack of knowledge exists since the focally positive margins have rarely been studied separately from the extensively positive margins except for a few small, retrospective studies more than 10 years ago[1,21-30]. Low incidence of residual disease and local recurrences after focally positive margins after BCS could be an argument to omit re-excision. Identifying the clinicopathological factors associated with focally positive and extensively positive margins, could aid in predicting which patients need re-excision.

We aimed to investigate clinicopathological factors associated with focally positive and extensively positive margins, the incidence of residual disease according to margins status, and the clinicopathological parameters associated with residual disease. Finally, the influence of margins and residual disease on prognosis was studied.

METHODS

The Erasmus MC Cancer Institute operation schedules were searched in retrospect for all consecutive female patients with a primary (diagnostic) BCS from January 1st 2005 until April 1st 2014. Patients were eligible if the postoperative pathological report included IBC and/or DCIS and excluded in case of neo-adjuvant chemotherapy and tumor stage T4. The Erasmus MC Cancer Institute is a tertiary referral university hospital where BCS is performed by an oncological surgeon or a surgical resident under supervision of an oncological surgeon. BCS consisted of a lumpectomy including basic oncoplastic techniques. All patients were discussed in a postoperative multidisciplinary meeting where the indication for re-excision was determined. The Dutch national guideline does not recommend a re-excision for focally positive margins after BCS in case of invasive disease, but to continue with radiotherapy. In case of extensively positive margins, a re-excision is recommended. Whole-breast radiotherapy is recommended for all patients, and in case of final (focally) positive margins, an additional tumor bed boost is recommended[20]. Follow-up information was collected until 1st August 2016 by searching the electronic patient records. If there was no report from last year, the general practitioner or patient was contacted. According to the Central Committee on Research involving Human Subjects (CCMO), this type of study does not require approval from an ethics committee in the Netherlands.

Definitions

Resection margin was defined by the most unfavorable margin of the IBC and/or DCIS component. Negative margin was defined as tumor at 2 mm width or more from the inked margin. Close margin was defined as tumor less than 2 mm width from the inked margin. Focally positive margin was defined as tumor touching the inked margin over a length of 4 mm or less. Extensively positive margin was defined as tumor touching the inked margin over a length of more than 4 mm. The definitions for focally and extensively positive margins are standard in Dutch clinical practice and written in the national guideline. In case of multiple sites of tumor touching the inked margin the length of each individual site was added up to define margin length. In case of multifocality, the largest tumor was used to define tumor size. Re-excision was defined as a subsequent BCS or mastectomy where breast tissue was excised performed by an oncological surgeon in the same breast within 6 months of primary surgery.

Pathological revisions

From all patients who underwent re-excision- except in case of negative margin – the tumor samples of the primary (index) surgery were reviewed by one pathologist (J.G). The margin status of both the IBC and DCIS components were reviewed including the width of negative margins and the length of positive margins. Even though not part of the standard pathology report, the growth pattern of the invasive component (i.e., diffuse versus circumscript) and growth pattern of adjacent DCIS (i.e., within, close, or diffusely surrounding the invasive component) were evaluated[38]. If the tissue was missing or could not be revised, the original pathology report was used or variables were classified as missing. The detection of residual disease in the re-excision specimen was not reviewed, but abstracted from the original pathology report.

Statistical analysis

Clinicopathological characteristics were compared by Chi-square test for proportions and Mann-Whitney U test for medians. Odds ratios (OR) were estimated by 1) linear regression analysis to determine predictors for an increasingly involved resection margins and 2) logistic regression analysis to compare the incidence of residual disease and to determine predictors for residual disease. Multivariable analysis included all factors with $p < 0.1$ in univariable analysis. To provide insight into the clinicopathological characteristics considered for the re-excision indication, the group without re-excision and the group with re-excision were compared. Time of follow-up was defined as time between primary surgery and local recurrence as first event, date of last report, or censoring. Pathological proven recurrence in ipsilateral breast, in scar or pectoral muscle was defined as local recurrence. Local recurrence rate (LR) distributions were compared by the log-rank test. Statistical tests were two-sided and p-value <0.050 was considered statistically significant. SPSS® version 21 (IBM, Armonk, New York, USA) was used for all statistical analyses.

Table 1. Clinicopathological characteristics and margins status after primary surgery including linear regression analysis in the total study population. (n=499)

	Negative	Close	Focally positive	Extensively positive	OR 95%CI	P
Invasive breast cancer (n=391)	178 (45.5)	118 (30.2)	43 (11.0)	52 (13.3)		
Age:						
- >60 years	58 (32.6)	36 (30.5)	13 (30.2)	19 (36.5)	reference	
- 51-60 years	56 (31.5)	40 (33.9)	17 (39.5)	19 (36.5)	0.05 (-0.21;0.30)	0.713
- ≤50 years	64 (36.0)	42 (35.6)	13 (30.2)	14 (26.9)	-0.12 (-0.37;0.14)	0.367
Multifocality:						
- Unifocal	169 (94.9)	102 (86.4)	38 (88.4)	45 (86.5)	reference	
- Multifocal	9 (5.1)	16 (13.6)	5 (11.6)	7 (13.5)	*0.39 (0.03;0.74)*	*0.032*
Tumor type:						
- Ductal	157 (88.2)	97 (82.2)	36 (83.7)	41 (78.8)	reference	
- Lobular	6 (3.4)	11 (9.3)	5 (11.6)	7 (13.5)	*0.57 (0.17;0.96)*	*0.005*
- Other	14 (7.9)	10 (8.5)	2 (4.7)	4 (7.7)	-0.01 (-0.40;0.38)	0.948
- Unknown	1 (0.6)	-	-	-	-	
Grade:						
- 1	51 (28.7)	22 (18.6)	8 (18.6)	12 (23.1)	reference	
- 2	69 (38.8)	52 (44.1)	21 (48.8)	23 (44.2)	0.27 (-0.04;0.58)	0.082
- 3	58 (32.6)	44 (37.3)	14 (32.6)	17 (32.7)	0.21 (-0.11;0.52)	0.197
Tumor size in mm[a]:	13 (8-18)	13 (8-19)	15 (10-21)	15 (11-23)	*0.02 (0.01;0.03)*	*0.001*
Surrogate subtype:						
- ER+/Her2neu-	100 (56.2)	67 (56.8)	25 (58.1)	30 (57.7)	reference	
- ER+/Her2neu+	12 (6.7)	10 (8.5)	4 (9.3)	3 (5.8)	0.00 (-0.41;0.40)	0.995
- ER-/Her2neu+	5 (2.8)	4 (3.4)	-	-	-0.49 (-1.19;0.21)	0.170
- Triple negative	29 (16.3)	21 (17.8)	3 (7.0)	5 (9.6)	-0.21 (-0.51;0.09)	0.176
- Unknown	32 (18.0)	16 (13.6)	11 (25.6)	14 (26.9)	0.16 (-0.11;0.44)	0.246
Mitotic activity index[b]:	6 (3-12)	8 (3-14)	7 (2-9)	4 (2-11)	-0.00 (-0.01;0.01)	0.417
Lymfovascular invasion:						
- No	79 (44.4)	56 (47.5)	18 (41.9)	19 (36.5)	reference	
- Yes	32 (18.0)	23 (19.5)	8 (18.6)	10 (19.2)	0.08 (-0.21;0.37)	0.590
- Unknown	67 (37.6)	39 (33.1)	17 (39.5)	23 (44.2)	0.11 (-0.13;0.34)	0.368

Table 1 Clinicopathological characteristics and margins status after primary surgery including linear regression analysis in the total study population. (n=499) *(continued)*

	Negative	Close	Focally positive	Extensively positive	OR 95%CI	P
Axillary lymph nodes:						
- Negative	134 (75.3)	84 (71.2)	31 (72.1)	29 (55.8)	Reference	
- Positive	39 (21.9)	29 (24.6)	10 (23.3)	21 (40.4)	0.29 (0.05-0.53)	0.017
- No axillary surgery performed	5 (2.8)	5 (4.2)	2 (4.7)	2 (3.8)	0.23 (-0.33-0.79)	0.413
Adjacent DCIS:						
- No	56 (31.5)	31 (26.3)	6 (14.0)	13 (25.0)	reference	
- Yes	122 (68.5)	87 (73.7)	37 (86.0)	39 (75.0)	0.10 (-0.02;0.22)	0.090
Pre-operative MRI:						
- No	86 (48.3)	62 (52.5)	21 (48.8)	27 (51.9)	reference	
- Yes	92 (51.7)	56 (47.5)	22 (51.2)	25 (48.1)	-0.05 (-0.26;0.16)	0.661
Purely DCIS (n=108)	34 (31.5)	43 (39.8)	16 (14.8)	15 (13.9)		
Age:						
- >60 years	11 (32.4)	7 (16.3)	3 (18.8)	5 (33.3)	reference	
- 51-60 years	8 (23.5)	18 (41.9)	7 (43.8)	5 (33.3)	0.16 (-0.35;0.67)	0.536
- <50 years	15 (44.1)	18 (41.9)	6 (37.5)	5 (33.3)	-0.05 (-0.55;0.44)	0.829
Grade:						
- 1	12 (35.3)	5 (11.6)	5 (31.2)	1 (6.7)	reference	
- 2	10 (29.4)	18 (41.9)	5 (31.2)	6 (40.0)	0.40 (-0.13;0.92)	0.135
- 3	12 (35.3)	20 (46.5)	6 (37.5)	8 (53.3)	0.44 (-0.07;0.94)	0.092
Lesion size in mm[c]:	10 (6-17)	18 (10-37)	20 (13-43)	20 (15-33)	*0.01 (0.00;0.03)*	*0.039*
Pre-operative MRI:						
- No	19 (55.9)	13 (30.2)	9 (56.2)	14 (93.3)	reference	
- Yes	15 (44.1)	30 (69.8)	7 (43.8)	1 (6.7)	*-0.44 (-0.82;-0.06)*	*0.022*

[a] median (interquartile range), missing in n=9
[b] median (interquartile range), missing in n=28
[c] median (interquartile range), missing in n=34

RESULTS

Margins after primary surgery

A total of 482 patients fulfilled the inclusion and exclusion criteria of whom 17 with bilateral breast cancer resulting in 499 cases. IBC (with or without adjacent DCIS) was found in 391 (78.4%) patients and purely DCIS in 108 (21.6%) patients. In the original pathology reports, negative margins, close margins, focally positive margins, and extensively positive margins were reported in 212 (42.5%), 161 (32.3%), 59 (11.8%), and 67 (13.4%) patients respectively. Table 1 shows clinicopathological characteristics according to the margins status. After univariable linear regression in IBC patients, margins were significantly increasingly involved in case of multifocality, lobular tumor type, larger tumor size, and positive axillary lymph nodes (Table 1). After multivariable analysis, lobular tumor type (OR 0.69 95%CI 0.28;1.11 p=0.001), tumor size (OR 0.02 95%CI 0.00;0.03 p=0.016), and adjacent DCIS (OR 0.15 95%CI 0.03;0.27 p=0.014) were independently associated with increasingly involved margins. After univariable linear regression in patients with purely DCIS, margins were significantly increasingly involved in case of larger lesion size and the lack of a pre-operative MRI (Table 1). After multivariable analysis, only lesion size was significantly associated (OR 0.01 95%CI 0.00;0.03 p=0.020).

Re-excision

A re-excision was performed in 149 from the total of 499 (29.9%) patients of whom 107 (71.8%) by mastectomy and 42 (28.2%) by BCS and all were performed at the Erasmus MC Cancer Institute. Fig. 1 shows the number and type of re-excisions according to the margins status after primary surgery in patients with IBC (Fig. 1A) and purely DCIS (Fig. 1B). Fourteen secondary mastectomies were performed after negative margins of which eight preventative mastectomies in BRCA mutation carriers, four mastectomies due to contra-indications for radiotherapy, and two mastectomies to fulfill the patient's wish. Table A in the online supplementary file shows the clinicopathological characteristics for the group without re-excision and the group with re-excision. In the IBC patients, significant differences between the groups were multifocality (7.6% versus 15.9%, p=0.019) and lymphovascular invasion (20.5% versus 12.5%, p=0.016). In the patients with purely DCIS, the median lesion size was significantly different (12 mm versus 23 mm, p=0.037).

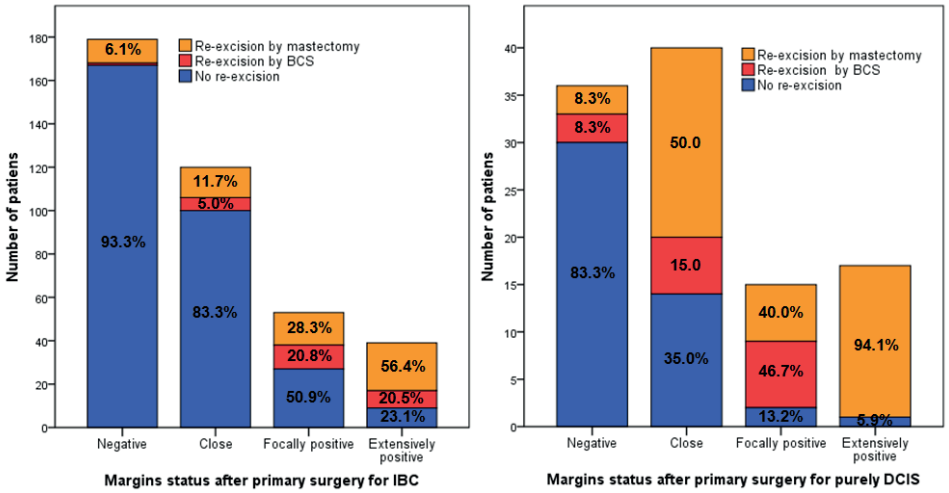

Figure 1 A,B. The performance of a re-excision and type of re-excision (by BCS or mastectomy) according to the (unrevised) resection margins after the primary surgery. A: patients with invasive breast cancer (n=391), B: patients with purely DCIS (n=108).

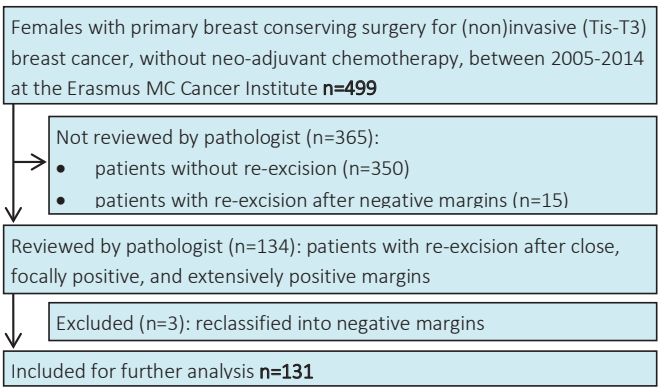

Figure 2. Flowchart of the pathology revisions.

Residual disease

After reviewing the 134 tumor samples obtained at the primary (index) surgery of the patients who had a re-excision due to close or positive margin, three were reclassified as negative margins and therefore excluded from further analysis resulting in 131 cases (Fig. 2). Twelve tumor samples were missing and 13 samples

could not be reviewed and the original pathology report was used. After pathology review of these 131 index samples, 46 (35.1%) had close margins, 39 (29.8%) had focally positive margins, and 46 (35.1%) had extensively positive margins. Residual disease was detected in the re-excision specimens of 76 (58.0%) patients of which 21 (45.7%) after close margins, 19 (48.7%) after focally positive margins, and 36 (78.3%) after extensively positive margins. Fig. 3 shows the incidence of residual disease according to the reviewed margins status for IBC (Fig. 3A) and purely DCIS (Fig. 3B) separately. The incidence of residual disease was not significantly different after focally positive margins as compared to close margins in all patients (Table 2). However after extensively positive margins, the odds of residual disease was significantly increased as compared to close margins (OR 4.29 95%CI 1.73;10.60 P=0.002) and as compared to focally positive margins (OR 3.79 95%CI 1.48;9.71 p=0.006). The area under the curve (AUC) for margin status as predictor for residual disease was 0.65 (95%CI 0.56;0.75 P=0.003). In the patients with IBC and residual disease, the residual disease included an invasive component in 7/11 after close margins, 4/13 after focally positive margins, and 7/19 after extensively positive margins. In the patients with purely DCIS and residual disease, the residual disease included an invasive component in 0/10, 1/6, and 1/17 respectively. When screening the re-excision specimen for residual disease, the pathologist had evaluated a median of 12 versus 13 slices in the group without and with residual disease respectively (p=0.289).

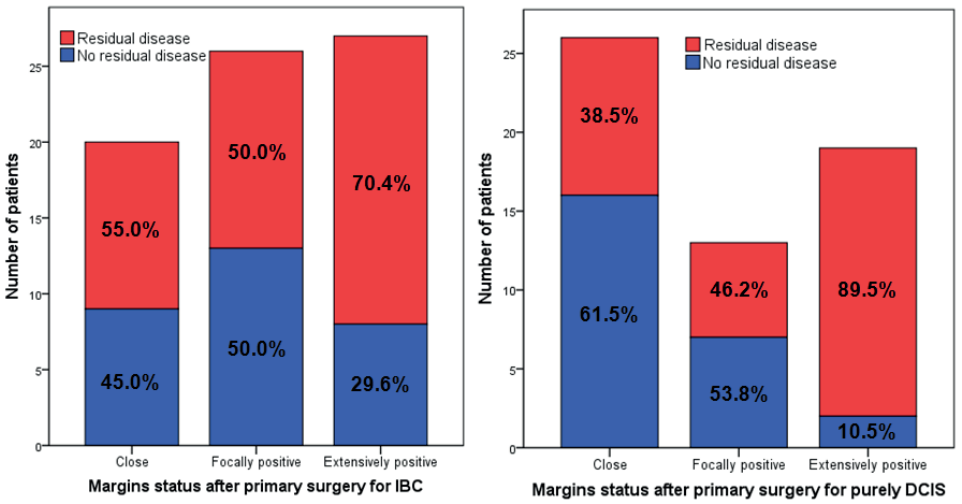

Figure 3 A,B. The incidence of residual disease in the re-excision specimen according to the margins status after primary surgery. A: patients with invasive breast cancer (IBC) (n=73), B: patients with purely ductal carcinoma-in-situ (DCIS) (n=58).

Table 2. Clinicopathological characteristics and the detection of residual disease including logistic regression analysis in the patients with pathology review. (n=131)

	No residual disease	**Residual disease**	**OR 95%CI**	**P**
All patients (n=131)	55 (42.0)	76 (58.0)		
Positive margin length in mm[a]:	3 (2-7)	6 (3-10)	*1.14 (1.00;1.29)*	*0.045*
Margin status				
- Close	25 (45.5)	21 (27.6)	Reference	
- Focally positive	20 (36.4)	19 (25.0)	1.13 (0.48;2.66)	0.778
- Extensively positive	10 (18.2)	36 (47.4)	*4.29 (1.73;10.6)*	*0.002*
Grade:				
- 1	12 (21.8)	20 (26.3)	reference	
- 2	19 (34.5)	31 (40.8)	0.98 (0.39;2.45)	0.964
- 3	24 (43.6)	25 (32.9)	0.63 (0.25;1.55)	0.311
Tumor/lesion size in mm[b]:	15 (8-25)	15 (8-27)	0.99 (0.97;1.02)	0.620
Pre-operative MRI:				
- No MRI	24 (43.6)	45 (59.2)	reference	
- MRI	31 (56.4)	31 (40.8)	0.53 (0.26;1.08)	0.078
Age:				
- >50 years	35 (63.6)	54 (71.1)	reference	
- ≤50 years	20 (36.4)	22 (28.9)	0.71 (0.34;1.49)	0.370
Invasive (± adjacent DCIS) (N=73)	30 (41.1)	43 (58.9)		
Multifocality:				
- Unifocal	29 (96.7)	37 (86.0)	reference	
- Multifocal	1 (3.3)	6 (14.)	4.70 (0.54;41.3)	0.162
Tumor type:				
- Ductal	26 (86.7)	36 (83.7)	reference	
- Lobular	4 (13.3)	7 (16.3)	1.26 (0.34;4.77)	0.730
Growth pattern invasive tumor:				
- <50% diffuse (>50% circumscript)	16 (53.3)	16 (37.2)	reference	
- >50% diffuse (<50% circumscript)	12 (40.0)	22 (51.2)	1.83 (0.68;4.92)	0.229
- Unknown	2 (6.7)	5 (11.6)	2.50 (0.42;14.8)	0.313

Table 2. Clinicopathological characteristics and the detection of residual disease including logistic regression analysis in the patients with pathology review. (n=131)*(continued)*

	No residual disease	**Residual disease**	**OR 95%CI**	**P**
Grow pattern adjacent DCIS:				
- No adjacent DCIS present	6 (21.4)	7 (18.4)	reference	
- DCIS within invasive cancer	1 (3.6)	6 (15.8)	5.14 (0.48;55.6)	0.178
- DCIS close from invasive cancer (<2mm)	5 (17.9)	5 (13.2)	0.86 (0.16;4.47)	0.855
- DCIS diffusely surrounding invasive cancer	16 (57.1)	20 (52.6)	1.07 (0.30;3.83)	0.915
- Unknown	2 (6.7)	5 (11.6)	2.14 (0.30;15.4)	0.448
Surrogate subtype:				
- ER+/Her2neu-	13 (43.3)	26 (60.5)	reference	
- ER+/Her2neu+	3 (10.0)	1 (2.3)	0.17 (0.02;1.76)	0.137
- ER-/Her2neu+	1 (3.3)	-	-	
- Triple negative	6 (20.0)	2 (4.7)	*0.17 (0.03;0.94)*	*0.043*
- Unknown	7 (23.3)	14 (32.6)	1.00 (0.32;3.08)	1.000
Estrogen receptor				
- Positive	22 (73.3)	38 (88.4)	reference	
- Negative	8 (26.7)	2 (4.7)	0.15 (0.03;0.74)	0.021
- Unknown	-	3 (7.0)	-	
Mitotic activity index[c]:	6 (3-13)	3 (2-8)	*0.93 (0.86;1.00)*	*0.036*
Lymphovascular invasion:				
- No	10 (33.3)	14 (32.6)	reference	
- Yes	4 (13.3)	6 (14.0)	1.07 (0.24;4.82)	0.928
- Unknown	16 (53.3)	23 (53.5)	1.03 (0.37;2.88)	0.960
Axillary lymph nodes:				
- Negative	22 (73.3)	25 (58.1)	reference	
- Positive	8 (26.7)	15 (34.9)	1.65 (0.59;4.63)	0.341
- No axillary surgery performed	-	3 (7.0)	-	

[a] median (interquartile range). The length of positive margin was evaluated in all patients with a positive margin hence it was evaluable in n=23/30 of the no residual disease group and in n=42/55 of the residual disease group.
[b] median (interquartile range), missing in n=14
[c] median (interquartile range), missing in n=11

Prognosis

After a median follow-up time of 57 months (interquartile range 28-83) in 391 IBC patients, LR occurred in four patients with negative margins, two patients with close, none in patients with focally positive, and one in patients with extensively positive margins after primary surgery(p=0.704). In 108 patients with purely DCIS, no LR occurred after negative, close, and focally positive margins after primary surgery, as compared to one LR after extensively positive margin. After classifying all patients according to the type of re-excision, LR was found in 6 out of 350 patients without a re-excision, in 1 out of 42 patients with a re-excision by BCS, and 1 out of 107 patients with a re-excision by mastectomy (p=0.467). After classifying all patients according to the detection of residual disease, the 5-year LRR rate was 2.4% in the group without residual disease and 2.7% in the group with residual disease (p=0.655).

DISCUSSION

Focally positive margins were found in 12% of the patients which was similar to the 11% in a nationwide Dutch pathology study[31]. Lobular tumor type, adjacent DCIS, and larger tumor or lesion size independently increased the risk of involved tumor margins. In multiple other studies, the same factors were found to be associated with positive margins (not differentiating between focally and extensively) or re-excision[16,24,32-39]. The size of invasive tumor differed only a few millimeters between the margins, but the effect on more involved margins was stronger (OR 0.02) as compared to the bigger differences in DCIS lesion size between the margins, but with a smaller effect size (OR 0.01) (Table 1). The lack of a pre-operative MRI, univariable increased the risk of involved margins in patients with purely DCIS. However, this was not confirmed by a large Dutch population-based study[40]. Young age has been described as predictor for involved margins, but was not seen here[32,38,39]. These risk factors could be considered at time of treatment decision making and during primary surgery to reduce re-excision rates.

Extensively positive margins resulted in a significant four-times higher odds of residual disease as compared to close margins. Focally positive margins did not. Residual disease was previously detected in 7-78% after close margins[1-3,8-13,21-23,41-44], 22%-76% after focally positive margins[1,21-23], and 30%-84% after extensively positive margins[1,21-23]. It must be noted that the definition of margins differed, details of these articles and their definitions for focally positive margins are outlined in Table B in the online supplementary file. Multiple studies show a trend in increasing residual disease with increasing margin involvement[1,2,5,9,12,21,41-43].

We were the first to study tumor growth pattern as a predictor for residual disease. Concerning the invasive component, a trend was seen between more diffusely growing tumor and more frequent residual disease, but not significant (OR 1.83 95%CI 0.68;4.92). Concerning adjacent DCIS, the hypothesis was that more diffuse growth was associated with more residual disease, but this was rejected. Others did find that only the *presence* of adjacent DCIS and extensive intraductal component was associated with residual disease, but the extent of adjacent DCIS was not determined[3,16,22,23]. Lymfovascular invasion, tumor size, her2-neu positive receptor status, multifocality, and young age have also been described as predictors for residual disease, but were not confirmed here. The most frequently found (independent) predictor of residual disease remains to be the extent of margin involvement[3,9,11,16,23,45].

In case the presence of residual disease could be predicted accurately and is expected to be unlikely, can it be used as an argument to omit re-excision? The answer is yes, if the presence of residual disease at the site of primary tumor is associated with LR. However, we found that LR rate is not different between the group with and without residual disease. This was supported by multiple studies[1,4,15,46]. One LR occurred after a re-excision by mastectomy favoring the idea that LR is not purely a result of residual disease. Low incidence of residual disease after close margins has been used as an argument to adapt the re-excision indication[43]. However, not detecting any residual disease does not prove absence of disease either. Since subclinical foci of disease can be present at large distance from the resected tumor[47]. Furthermore, the pathologist only evaluates a selection of the re-excision specimen and disease can be missed due to sampling error. The risk of sampling error is highest in the mastectomies which represent the majority of re-excisions. The secondary mastectomy rate of 72% was higher than 54%-62% found in recent Dutch population-based studies which could be explained by the complexity of the patient population in our tertiary referral university hospital[48,49]. Nevertheless, the number of tissue slices evaluated by the pathologist was not effecting the incidence of residual disease since it was comparable in the group with residual disease and without.

Moreover, the question is whether re-excision will improve LR rates in IBC patients with focally positive margins that are meant to undergo radiotherapy. A few studies performed in the previous century, although with small differences in the definition for focally positive (as summarized in Table B in the online supplementary file), found that LR rates after focally positive margins were not different from negative margins[24-30]. This was confirmed in a recent large national cohort covering all 91 Dutch hospitals including our academic hospital[49]. From the 1078

IBC patients with focally positive margins, re-excision was omitted in 45.6% for unknown reasons with a 5-years LR rate of 2.9% versus 1.1% in patients with re-excision. We found that from the 53 IBC patients with focally positive margins, re-excision was omitted in 27 for unknown reasons and 26 did had re-excision, but no LR occurred. Even though the patients included were not all treated according to the Dutch guideline, the findings of this study support the recommendation to accept focally positive margins for IBC, omit the re-excision, and continue with whole breast radiotherapy including a tumor bed boost.

Surprisingly, no local recurrences occurred in patients with purely DCIS and negative, close, or focally positive margins in contrast to one LR purely DCIS in patients with extensively positive margins after primary surgery. The low number of events impairs drawing conclusions about margins. Residual disease was detected in 33/58 (56.9%) of the patients with purely DCIS, but only two had an invasive component. The low number of events and invasive components found question the need for the strict re-excision indication of 2 mm negative margin width, assuming that whole-breast radiotherapy is given. In contrast, the meta-analysis of Morrow et al. showed that 0 or 1 mm negative margins and 2 mm negative margins resulted in a significantly reduced risk of ipsilateral breast tumor recurrence[18].

A disadvantage of our study was the unknown indications for performing or omitting the re-excision. Previously we have shown that the guideline not recommending re-excision after focally positive margins in case of invasive disease is ignored in 54% of the Dutch patients[48]. In those situations most likely other clinicopathological characteristics of the patients are considered in the decision making since the evidence for omitting re-excision is scarce and international guidelines recommend otherwise. The omission of re-excision after extensively positive margins can be explained by posterior margin involvement[50]. This may have caused a selection bias for performing re-excision based on unmeasured characteristics besides the association shown with multifocality, lymphovascular invasion, and DCIS lesion size (Table A, online supplementary file). Another limitation was the low number of patients in each margin status subgroup complicating the interpretation of the comparisons. Although it was a strength of our study to separate positive margins into focally and extensively positive. It is a clinically relevant distinction in the Netherlands and may be in the near future for others. We recommend to quantify the extent of margin involvement in all pathology reports in order to predict residual disease and guide treatment. Future studies should investigate focally and extensively positive margins separately. This will add fruitful evidence to the discussion on adequate margins and re-excisions and may further change guidelines worldwide.

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Online Supplementary File

Table A. Clinicopathological characteristics and the performance of a re-excision after primary surgery in the total study population. (n=499)

	No re-excision	**Re-excision**	**P**
Invasive breast cancer (n=391)	**303 (77.5%)**	**88 (22.5%)**	
Age:			0.786
- >60 years	95 (31.4)	31 (35.2)	
- 51-60 years	104 (34.3)	28 (31.8)	
- ≤50 years	104 (34.3)	29 (33.0)	
Multifocality:			*0.019*
- Unifocal	280 (92.4)	74 (84.1)	
- Multifocal	23 (7.6)	14 (15.9)	
Tumor type :			0.080
- Ductal	262 (86.5)	69 (78.4)	
- Lobular	17 (5.6)	12 (13.6)	
- Other	23 (7.6)	7 (8.0)	
- Unknown	1 (0.3)	-	
Grade:			0.286
- 1	67 (22.1)	26 (29.5)	
- 2	133 (43.9)	32 (36.4)	
- 3	103 (34.0)	30 (34.1)	
Tumor size in mm[a]:	14 (9-19)	12 (7-19)	0.099
Surrogate subtype:			0.342
- ER+/Her2neu-	173 (57.1)	49 (55.7)	
- ER+/Her2neu+	25 (8.3)	4 (4.5)	
- ER-/Her2neu+	8 (2.6)	1 (1.1)	
- Triple negative	46 (15.2)	12 (13.6)	
- Unknown	51 (16.8)	22 (25.0)	
Mitotic activity index[b]:	7 (3-13)	5 (2-13)	0.116
Lymfovascular invasion:			*0.016*
- No	139 (45.9)	33 (37.5)	
- Yes	62 (20.5)	11 (12.5)	
- Unknown	102 (33.7)	44 (50.0)	

Table A. Clinicopathological characteristics and the performance of a re-excision after primary surgery in the total study population (n=499)*(continued)*

	No re-excision	**Re-excision**	**P**
Invasive breast cancer (n=391)	**303 (77.5%)**	**88 (22.5%)**	
- No	84 (27.7)	22 (25.0)	
- Yes	219 (72.3)	66 (75.0)	
Pre-operative MRI:			0.830
- No	151 (49.8)	45 (51.1)	
- Yes	152 (50.2)	43 (48.9)	
Purely DCIS (n=108)	**47 (43.5)**	**61 (56.5)**	
Age:			0.161
- >60 years	14 (29.8)	12 (19.7)	
- 51-60 years	12 (25.5)	26 (42.6)	
- <50 years	21 (44.7)	23 (37.7)	
Grade:			0.303
- 1	13 (27.7)	10 (16.4)	
- 2	17 (36.2)	22 (36.1)	
- 3	17 (36.2)	29 (47.5)	
Lesion size in mm[c]:	12 (9-20)	23 (9-40)	*0.037*
Pre-operative MRI:			0.452
- No	22 (46.8)	33 (45.1)	
- Yes	25 (53.2)	28 (45.9)	

Table B. Studies from the literature describing patients with focally positive margins after breast conserving surgery.

First author	Year of publication	Years of treatment	Definition of focally positive margins	Number of patients[a]	Incidence of residual disease	Local recurrence rate
Swanson[1]	2002	1985-1996	two or fewer microscopic foci[b]	59	17/55 (31%)	2/55 at 4.7 years
Kotwall[21,c]	2007	-	-	132	22%	-
Smitt[22]	2003	1972-1992	not given	132	100/132 (76%)	-
Wazer[23]	1997	1983-1994	less than or equal to four low-power field and/or limited to 7 sections at one geographic edge	117	63/117 (54%)	-
Schnitt[24]	1994	1982-1985	three or fewer low-power microscopic fields using a 4X objective	48	-	5/48 at 5 years
Park[25]	2000	1976-1987	three or fewer low-power microscopic fields (using a x4 objective and x10 ocular lens, which has a diameter of 5 mm per low-power microscopic fields)	122	-	14% at 8 years
Dibiase[26]	1998	1978-1994	one positive margin	56	-	9% at 5 years and 26% at 10 years
Peterson[28]	1999	1977-1992	one or two foci	124	-	7%-10% at 8 years
Park[29]	2011	1994-2004	single area of carcinoma, 0.4 cm in size	28	-	15% at 5 years
Solin[30]	1999	1977-1985	positive microscopic pathology margins	57	-	0%-2.0% at 5 years
Vos[49]	2017	2003-2008	length of 4 mm or less[d]	1078	-	1.1%-2.9% at 5 years

[a] With focally positive margins

[b] The subgroups focal, minimal, and moderate are added together

[c] Full article not available

[d] Translated from the definition three or less low-power microscopic fields using a x10 ocular lens

CHAPTER 7

Overall survival in patients with a re-excision following breast conserving surgery compared to those without in a large population-based cohort

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ABSTRACT

Aim To investigate the overall survival of invasive breast cancer patients with primary breast conserving surgery (BCS) followed by re-excision compared to those with primary BCS only. The Dutch re-excision indications are less stringent compared to other European and Northern American countries (Society of Surgical Oncology-American Society for Radiation Oncology (SSO/ASTRO) guideline).

Methods Retrospective analyses in women <75 years with breast cancer stage pT1–T3 treated by BCS and radiotherapy between 1999 and 2012 from a population-based database. The national guideline recommends to reserve re-excision for invasive tumours showing 'more than focally positive' margin since 2002. Patients were divided into 'primary BCS only', 're-excision by BCS', and 're-excision by mastectomy'. Multivariable Cox regression analysis was adjusted for patient and systemic treatment characteristics.

Results A total of 11,695 patients were included of which 2156 (18.4%) underwent re-excision. Median time of follow-up was 61 months (interquartile range (IQR) 26–101). The 5-year overall survival rates in the 'primary BCS only', 're-excision by BCS' and 're-excision by mastectomy' group were 92%, 95% and 91%, respectively. The 10-year overall survival rates were 81%, 82% and 79%, respectively (P = 0.20). After multivariable analyses no significant association was observed between use of and type of re-excision and overall survival.

Conclusions The overall survival of breast cancer patients with a re-excision did not significantly differ from the survival of women who underwent primary BCS only. Advising re-excision only for those tumours showing 'more than focally positive' resection margin appears safe, supposing the long-term safety of the recent SSO/ASTRO guideline that more cautiously recommended re-excision for tumours showing 'ink on tumour'.

INTRODUCTION

Randomised controlled trials comparing breast conserving surgery (BCS) followed by radiotherapy and mastectomy for breast cancer have shown no significant differences in overall survival after 20 years of follow-up(1-3). As compared to mastectomy, patients undergoing BCS have a higher risk of tumour-positive resection margin. This is the strongest predictive factor for developing local recurrence and has also been associated with an increased risk of distant recurrence and a decreased disease specific survival(4-7)(4-6). Re-excision for a tumour-positive resection margin after BCS is therefore the current standard of care.

Despite multiple studies there is no consensus on how wide the cancer-free margin should be to improve prognosis(8-10). This controversy is reflected by the large variation of re-excision indications used between hospitals and clinicians(11). Recently, the Society of Surgical Oncology-American Society for Radiation Oncology (SSO/ASTRO) published a consensus guideline on margins for BCS with whole breast irradiation in stage I and II invasive breast cancer. It recommends 'no ink on tumour' as the standard for an adequate margin and advises to perform re-excision for 'focally positive' (i.e., foci of tumour touching ink, but over a length of less than 4 mm) and 'more than focally positive' margin(12). Thereby it leaves the discussion of the ideal negative margin width behind. This is an attempt to reduce re-excision rates, improve cosmetic outcomes, and decrease health care costs. The guideline is developed based on data of margin width and ipsilateral breast tumour recurrence. Surprisingly, long-term prognosis (i.e., overall survival) has not been addressed.

In contrast to North America and Europe, the Netherlands have always used less stringent indications for re-excision after BCS. Unlike most European countries, comprehensive national treatment guidelines are in use since 2002 which have proven to be strictly followed(13). Before 2002, a margin was considered to be involved only if ductal carcinoma in situ (DCIS) or invasive ductal carcinoma was microscopically present at the surface of the specimen(14). Already since the first national guideline in 2002 it is recommended to perform a re-excision only in case of 'more than focally positive' resection margin(15). In other words, no re-excision is recommended in case the resection margin is 'focally positive', close negative or wide negative.

In a large population based database, women diagnosed with invasive breast cancer between 1999 and 2012 and primarily treated by BCS were studied retrospectively. Information on margin status was not available. But we investigated the long-term prognosis after the use of re-excision in accordance to the Dutch

indications. This might shed light on the safety of omitting a re-excision for 'focally positive' resection margin.

The aim of the present study is to compare overall survival in breast cancer patients with a re-excision following their primary BCS and those with primary BCS only in Dutch clinical practice. We hypothesised that there is no difference, since treatment with adjuvant systemic therapy has a large impact on survival (16).

METHODS

Study population

The Comprehensive Cancer Center South registers all new cancer diagnoses in an area covering 2.4 million inhabitants and ten large community hospitals in southeast Netherlands. This population-based registry collects data according to international guidelines by specially trained personnel and meets high-quality standards with data completeness exceeding 95%(17). It provides detailed information on patient demographics, tumour characteristics, treatment and co-morbidity.

Females under the age of 75 diagnosed with a unilateral, invasive breast cancer between 1st January 1999 and 1st October 2012 were extracted from the database. Patients were excluded in the case of uncertainty concerning their tumour stage, surgical treatment, radiotherapy, or systemic therapy. Other exclusion criteria are shown in Fig. 1.

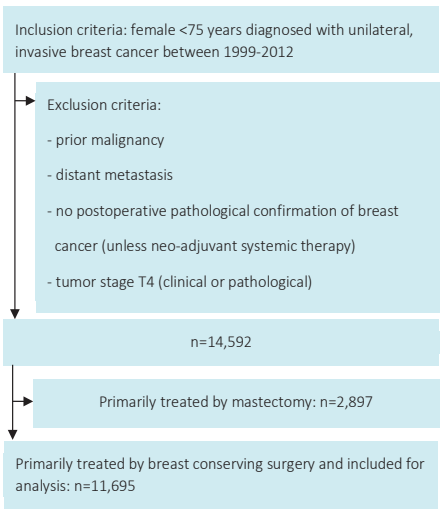


Figure 1. Inclusion and exclusion criteria.

Re-excision status was classified as 'primary BCS only' for patients who underwent BCS without a re-excision assuming that their BCS was radical. Patients who had a re-excision were classified as 're-excision' irrespective of the amount and nature of re-excision(s). Re-excision was further classified into 're-excision by BCS' and 're-excision by mastectomy' according to the ultimate surgical treatment. Patients who received neo-adjuvant or adjuvant chemotherapy were both classified as having had chemotherapy. Patients receiving neo-adjuvant or adjuvant endocrine treatment were both classified as having had endocrine treatment. The Clinical and pathological tumour node metastasis staging (TNM) used was similar to the international TNM classification in use during the year of diagnosis. Tumour stadium (T) was equivalent to the clinical tumour stadium (cT) in case patients that received neo-adjuvant systemic therapy, otherwise pathological tumour stadium (pT) was used. The same holds for the lymph node stadium (N). Axillary staging was defined as sentinel lymph node biopsy, axillary lymph node dissection or the examination of at least 10 axillary lymph nodes. Co-morbidity was expressed by the cumulative number of co-morbidities irrespective of their nature. Histology was classified as ductal, lobular (including mixed ductal–lobular types) and other. Tumour biology markers that were recorded included: differentiation grade, oestrogen receptor status, progesterone receptor status and HER2neu receptor status.

The effectiveness of adjuvant systemic treatment has improved immensely over the last decades. In 2005, the Dutch national guideline adopted major changes regarding chemotherapy based on evidence showing superiority of anthracycline-containing regimens over CMF and the benefit of taxane-containing regimens and trastuzumab-containing regimens(18-21). The increased effectiveness of these modern (neo-)adjuvant chemotherapy altered the breast cancer treatment considerably. Therefore the effect of re-excision was studied separately in the pre-modern chemotherapy period (1999–2005) and modern chemotherapy period (2006–2012).

Statistical analysis

Survival time was defined as the time difference in months between date of diagnosis and date of last follow-up. Date of last follow-up was first available in order of: date of death, date of emigration, 1st January 2012 (if diagnosed before 1st January 2012) or date of diagnosis plus 6 months (if diagnosed after 1st January 2012). Primary endpoint was death from any cause. Overall survival was determined by Kaplan–Meier method and distributions between subgroups were compared by the log-rank test. Hazard ratios (HR) were estimated by Cox

proportional hazards regression analysis. Comparisons were made with respect to whether or not receiving re-excision (definition 1) and according to the type of re-excision (definition 2) (i.e., BCS or mastectomy). Multivariable Cox proportional hazards regression was performed with definition 2 to determine the effect size of the co-variables. The proportional hazards assumption was tested by graphing the log(-log(survival)) versus log of survival time of each predictor and was considered proportional when parallel curves were observed. Statistical tests were two-sided, and P-values <0.05 were considered significant. IBM SPSS Statistics 20 was used for all statistical analyses.

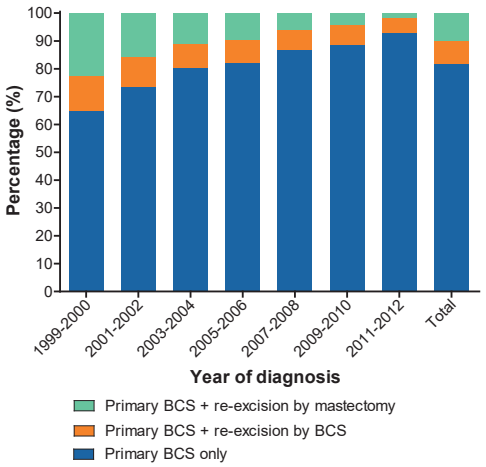


Figure 2. Re-excision rates and type of re-excision in the total study population.

RESULTS

Because the omission of adjuvant radiotherapy in patients treated by BCS strongly interacted with re-excision on overall survival, these patients were excluded (n = 287). Patients with adjuvant radiotherapy after re-excision by mastectomy had a strong negative influence on prognosis and were also excluded (n = 341) (Fig. 1). Of the 14,592 patients in the Eindhoven Cancer Registry who met the inclusion criteria and exclusion criteria, 2897 (19.9%) underwent mastectomy as their primary surgical treatment. A total of 11,695 patients had undergone BCS as their primary surgical treatment and were included in the analyses.

Re-excision was performed in 2156 (18.4%) patients of which 984 (45.6%) by BCS. Fig. 2 shows that re-excision rates decreased over time from 35.3% in 1999–2000 to 7.2% in 2011–2012. Simultaneously the proportion of re-excisions by mastectomy fell from 22.5% to 1.9%. Patient and treatment characteristics are shown in Table 1.

Table 1. Patient and treatment characteristics.

	Primary breast conserving surgery (BCS) only	Primary BCS + Re-excision by BCS	Primary BCS + Re-excision by mastectomy	P^a	P^b	P^c
Total no. of patients	9539	984	1172			
Time cohort				<0.001	<0.001	<0.001
- 1999-2005	4165 (43.7)	568 (57.7)	868 (74.1)			
- 2006-2012	5374 (56.3)	416 (42.3)	304 (25.9)			
Age, median (interquartile range (IQR))	58 (50-65)	55 (48-64)	54 (46-64)	<0.001	<0.001	0.098
Histology				0.002	0.002	0.014
- ductal	7950 (83.3)	780 (79.3)	886 (75.6)			
- lobular	1077 (11.3)	148 (15.0)	231 (19.7)			
- other	512 (5.4)	56 (5.7)	55 (4.7)			
Differentiation grade				<0.001	<0.001	<0.001
- 1	2612 (27.4)	229 (23.3)	156 (13.3)			
- 2	3464 (36.2)	359 (36.5)	358 (30.5)			
- 3	2036 (21.3)	195 (19.8)	307 (26.2)			
- unknown	1427 (15.0)	201 (20.4)	351 (29.9)			
Primary tumour stadium				0.672	<0.001	<0.001
- T1	7150 (75.0)	750 (76.2)	756 (64.5)			
- T2	2344 (24.6)	230 (23.4)	399 (34.0)			
- T3	45 (0.5)	4 (0.4)	17 (1.5)			
Regional lymph node stadium				<0.001	<0.001	<0.001
- N0	5988 (62.8)	554 (56.3)	658 (56.1)			
- N1	2339 (24.5)	250 (25.4)	374 (31.9)			
- N2	238 (2.5)	28 (2.8)	7 (0.6)			
- N3	99 (1.0)	9 (0.9)	3 (0.3)			
- unknown	875 (9.2)	143 (14.5)	130 (11.1)			
Oestrogen receptor status				<0.001	<0.001	<0.001
- negative	952 (10.0)	62 (6.3)	73 (6.2)			
- positive	5588 (58.6)	479 (48.7)	376 (32.1)			
- unknown	2999 (31.4)	443 (45.0)	723 (61.7)			

Table 1. Patient and treatment characteristics.*(continued)*

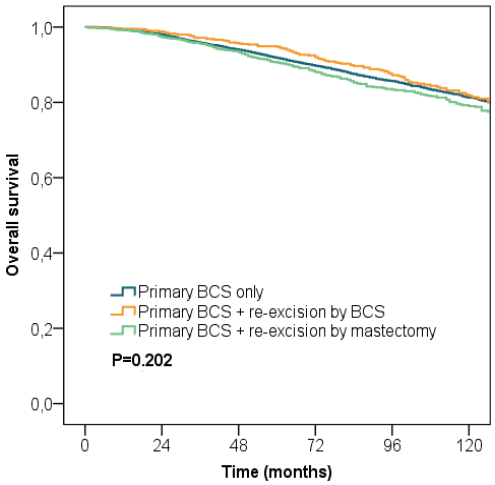
	Primary breast conserving surgery (BCS) only	Primary BCS + Re-excision by BCS	Primary BCS + Re-excision by mastectomy	P^a	P^b	P^c
Progesteron receptor status				<0.001	<0.001	<0.001
- negative	1763 (18.5)	154 (15.7)	134 (11.4)			
- positive	4618 (48.4)	376 (38.2)	306 (26.1)			
- unknown	3158 (33.1)	454 (46.1)	732 (62.5)			
Her2Neu receptor status				<0.001	<0.001	<0.001
- negative	5063 (53.1)	393 (39.9)	295 (25.2)			
- positive	644 (6.8)	51 (5.2)	62 (5.3)			
- unknown	3832 (40.2)	540 (54.9)	815 (69.5)			
Systemic therapy	4982 (52.2)	499 (50.7)	613 (52.3)	0.365	0.961	0.461
- chemotherapy[d]	3280 (34.4)	334 (33.9)	395 (33.7)	0.781	0.643	0.907
- neoadjuvant[d]	379 (4.0)	17 (1.7)	14 (1.2)	<0.001	<0.001	0.300
- adjuvant[d]	2948 (30.9)	318 (32.3)	383 (32.7)	0.541	0.372	0.645
- hormonal therapy[d]	3706 (38.9)	375 (38.1)	455 (38.8)	0.650	0.985	0.735
- neoadjuvant[d]	64 (0.7)	2 (0.2)	2 (0.2)	0.077	0.039	0.861
- adjuvant[d]	3655 (38.3)	373 (37.9)	453 (38.7)	0.801	0.824	0.723
Co-morbidity				0.415	<0.001	<0.001
- none	5551 (58.2)	574 (58.3)	693 (59.1)			
- one	2078 (21.8)	217 (22.1)	194 (16.6)			
- two or more	932 (9.8)	82 (8.3)	89 (7.6)			
- unknown	978 (10.3)	111 (11.3)	196 (16.7)			

[a] Comparing 'primary BCS only' and 're-excision by BCS'.

[b] Comparing 'primary BCS only' and 're-excision by mastectomy'.

[c] Comparing 're-excision by BCS' and 're-excision by mastectomy'.

[d] Numbers and percentages are given from the total of patients with systemic therapy.



Patients at risk, time (months)	Start	24	48	72	96	120
Primary BCS only	9539	7065	5354	3711	2345	1195
Primary BCS + re-excision by BCS	984	827	681	517	369	222
Primary BCS + re-excision by mastectomy	1172	1070	947	765	580	348

Figure 3. Crude overall survival according to re-excision status in the total study population.

Re–excision in overall survival

Of the whole study population, 1214 (10.4%) patients died. Median time of follow-up was 61 months (interquartile range (IQR) 26–101). The 5-year overall survival rates in the 'primary BCS only', 're-excision by BCS', and 're-excision by mastectomy' group were 92%, 95%, and 91%, respectively. The 10-year overall survival rates were 81%, 82%, and 79%, respectively (P = 0.20) (Fig. 3). Patients with a re-excision had a similar risk of death compared to patients without a re-excision (HR 1.01 95% confidence interval (CI) 0.89–1.15 P = 0.86). Both 're-excision by BCS' and 're-excision by mastectomy' did not significantly influence overall survival. In multivariable analysis no statistically significant association was observed between use of and type of re-excision and overall survival (Table 2).

Table 2. Cox proportional hazards regression analysis of overall survival in all patients.

	Univariable			**Multivariable[a]**		
	Hazard ratio (HR)	**95% confidence interval (CI)**	***P***	**HR**	**95% CI**	***P***
Age	1.03	1.03-1.04	<0.001	1.04	1.03-1.04	<0.001
Histology						
- ductal	reference			Reference		
- lobular	0.94	0.80-1.12	0.485	0.96	0.80-1.14	0.633
- other	0.67	0.51-0.89	0.006	0.77	0.58-1.03	0.075
Differentiation grade						
- 1	Reference			Reference		
- 2	1.80	1.47-2.19	<0.001	1.59	1.30-1.94	<0.001
- 3	2.52	2.06-3.07	<0.001	2.04	1.65-2.53	<0.001
- unknown	1.84	1.50-2.26	<0.001	1.63	1.32-2.02	<0.001
Primary tumour stadium						
- T1	Reference					
- T2/T3	1.65	1.46-1.85	<0.001	1.40	1.23-1.58	<0.001
Regional lymph node stadium						
- N0	Reference			Reference		
- N1	1.70	1.49-1.93	<0.001	1.83	1.58-2.13	<0.001
- N2/N3	4.59	3.66-5.74	<0.001	4.34	3.41-5.52	<0.001
- unknown	1.11	0.94-1.31	0.229	1.09	0.91-1.29	0.353
Oestrogen receptor status						
- negative	Reference			Reference		
- positive	0.36	0.29-0.44	<0.001	0.64	0.48-0.87	0.004
- unknown	0.48	0.39-0.58	<0.001	0.58	0.31-1.08	0.083
Progesteron receptor status						
- negative	Reference			Reference		
- positive	0.41	0.34-0.50	<0.001	0.67	0.52-0.88	0.004
- unknown	0.61	0.51-0.72	<0.001	1.05	0.58-1.90	0.873

Table 2. Cox proportional hazards regression analysis of overall survival in all patients. *(continued)*

	Univariable			**Multivariable[a]**		
	Hazard ratio (HR)	**95% confidence interval (CI)**	***P***	**HR**	**95% CI**	***P***
Her2Neu receptor status						
- negative	Reference					
- positive	0.96	0.67-1.37	0.820			
- unknown	1.08	0.92-1.26	0.342			
Chemotherapy	1.08	0.95-1.22	0.231			
Hormonal therapy	1.19	1.06-1.34	0.003	0.83	0.72-0.96	0.013
Co-morbidity						
- none	Reference			Reference		
- one	1.39	1.21-1.60	<0.001	1.21	1.04-1.40	0.013
- two or more	2.47	2.09-2.92	<0.001	1.97	1.66-2.35	<0.001
- unknown	0.94	0.79-1.13	0.502	0.94	0.78-1.12	0.480
Re-excision(1)						
- primary breast conserving surgery (BCS) only	Reference			Reference		
- primary BCS + re-excision	1.01	0.89-1.15	0.859	1.05	0.92-1.20	0.434
Re-excision(2)						
- primary BCS only	Reference			Reference		
- primary BCS + re-excision by BCS	0.89	0.73-1.08	0.245	0.94	0.77-1.15	0.543
- primary BCS + re-excision by mastectomy	1.10	0.94-1.28	0.239	1.14	0.97-1.33	0.116

[a] Adjusted for factors with p<0.1 in univariable analyses: age at time of diagnosis, histology type, differentiation grade, tumour and lymph node stadium, oestrogen and progesterone receptor status, hormonal therapy and comorbidity at diagnosis.

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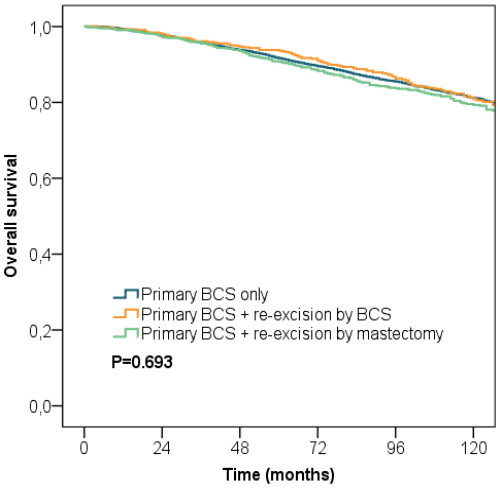
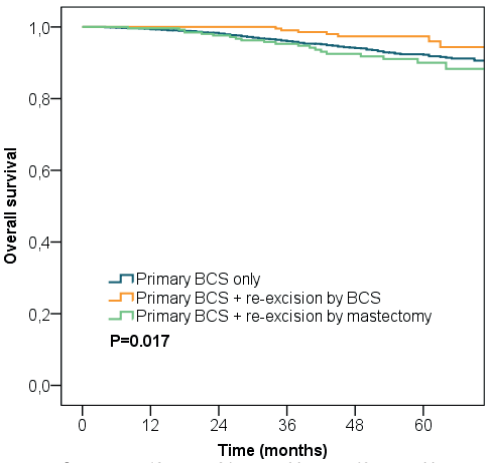


Patients at risk, time (months)	Start	24	48	72	96	120
Primary BCS only	4165	4073	3896	3711	2345	1195
Primary BCS + re-excision by BCS	568	556	537	517	369	222
Primary BCS + re-excision by mastectomy	868	844	809	764	580	348

B



Patients at risk, time (months)	Start	12	24	36	48	60
Primary BCS only	5374	3879	2992	2226	1458	712
Primary BCS + re-excision by BCS	416	332	271	207	144	74
Primary BCS + re-excision by mastectomy	304	272	226	186	138	76

Figure 4. Crude overall survival according to re-excision status of patients diagnosed in (A) the pre-modern chemotherapy time cohort (1999-2005) and (B) the modern chemotherapy time cohort (2006-2012).

Time cohort specific effect of re-excision in overall survival

Thereafter patients were stratified into two time cohorts with respect to chemotherapy guidelines, including the pre-modern chemotherapy period between 1999 and 2005 and the modern chemotherapy period between 2006 and 2012. Of the 5601 patients diagnosed between 1999 and 2005, 992 (17.7%) patients died. Median time of follow-up was 102 months (IQR 83–127). In the 'primary BCS only', 're-excision by BCS', and 're-excision by mastectomy' group, the 5-year overall survival rates were 92%, 94%, and 91%, respectively. The 10-year overall survival rates were 81%, 81%, and 79%, respectively (P = 0.69) (Fig. 4a). Both in the univariable and multivariable analyses, use and type of re-excision were not associated with overall survival (Table 3).

Of the 6094 patients diagnosed between 2006 and 2012, 222 (3.6%) patients died. Median time of follow-up was 30 months (IQR 11–51). Five-year overall survival rates in the 'primary BCS only', 're-excision by BCS', and 're-excision by mastectomy' group were 92%, 97%, and 90% respectively (P = 0.02) (Fig. 4b). A statistically significant decrease in the risk of death was seen in patients with 're-excision by BCS' compared to patients with 'primary BCS only' (HR 0.39 95%CI 0.18–0.83 P = 0.02). After adjustment for potential confounders in the multivariable analysis, patients with 're-excision by BCS' still had a decreased hazard ratio but not significant (HR 0.49 95%CI 0.23–1.04 P = 0.07). In patients with 're-excision by mastectomy' a higher risk of death was observed compared to those with 'primary BCS only', however not statistically significant (univariable HR 1.31 95%CI 0.83–2.05 P = 0.25 and multivariable HR 1.32 95%CI 0.83–2.11 P = 0.24) (Table 3).

DISCUSSION

Current results showed that between 1999 and 2012 the adjusted overall survival was comparable for women with primary BCS only, those who underwent a re-excision by BCS, and those who underwent a re-excision by mastectomy. No association was found between the need for and type of re-excision and overall survival. Thus our hypothesis that there is no difference in overall survival after a re-excision following primary BCS and primary BCS only in Dutch clinical practice was found to be true. Therefore the recommendation to perform re-excision for those tumours showing 'ink on tumour' as stated in the SSO/ASTRO guideline on margins for BCS is certainly supported by these data. We therefore agree with the proposal to terminate the search for an ideal negative margin width. This is supported by recent reviews concluding that there is no evidence that a specific margin beyond 'no ink on tumour' is ideal(8-10, 22).

Table 3. Cox proportional hazards regression analysis of overall survival according to re-excision status. Patients were stratified with respect to diagnosis in the pre-modern chemotherapy time cohort (1999-2005) and modern chemotherapy time cohort (2006-2012).

	1999-2005 (n = 5601)		**2006-2012 (n = 6094)**	
	Univariable	Multivariable[a]	Univariable	Multivariable[b]
	Hazard ratio (HR) (95% confidence interval (CI)) *P*	HR (95% CI) *P*	HR (95% CI) *P*	HR (95% CI) *P*
Re-excision(1)				
- primary breast conserving surgery (BCS) only	Reference	Reference	Reference	Reference
- primary BCS + re-excision	1.03 (0.90-1.18) 0.685	1.07 (0.93-1.23) 0.352	0.82 (0.55-1.23) 0.338	0.92 (0.62-1.38) 0.694
Re-excision(2)				
- primary BCS only	Reference	Reference	Reference	Reference
- primary BCS + re-excision by BCS	0.97 (0.79-1.20) 0.788	1.01 (0.82-1.25) 0.902	0.39 (0.18-0.83) 0.015	0.49 (0.23-1.04) 0.065
- primary BCS + re-excision by mastectomy	1.07 (0.90-1.26) 0.448	1.11 (0.93-1.31) 0.239	1.31 (0.83-2.05) 0.248	1.32 (0.83-2.11) 0.238

a Adjusted for univariable p<0.1: age at diagnosis, histology type, differentiation grade, tumour and lymph node stadium, oestrogen and progesterone receptor status, hormonal therapy and comorbidity at diagnosis.

b Adjusted for univariable p<0.1: age at diagnosis, differentiation grade, tumour and lymph node stadium, oestrogen and progesterone receptor status, chemotherapy and comorbidity at diagnosis.

The rate of re-excisions gradually declined over time and was three to four times lower in 2011–2012 compared to 1999–2000. Improvement in patient selection for BCS, preoperative imaging, localisation techniques, surgical techniques and pathological evaluation might have played a role in the drop in re-excision rates. But most likely this is caused by the introduction of the guideline recommending to restrict re-excision to 'more than focally positive' resection margin in 2002, which makes it interesting to investigate the role of re-excision since 2003. Similar overall survival rates were observed as compared to those without re-excision because of negative or 'focally positive' resection margin. It can be argued that *if* the patients with 'focally positive' margin within the group 'primary BCS only' would have had a re-excision the survival might have been superior. This seems unlikely since the already excellent 5-year and 10-year overall survival rates of 92% and 81%, respectively in the total study population. Also this is significantly better than the 5-year and 10-year overall survival in the patients who met the inclusion and exclusion criteria, but were primarily treated by mastectomy, with 86% and 72%, respectively (P,0.001). We think that advising re-excision only for those tumours showing 'more than focally positive' resection margin is safe.

The ultimate aim of the multimodality treatment of primary breast cancer is to prolong the life expectancy, therefore overall survival was chosen as our primary endpoint. Most studies have addressed the correlation between re-excision and local recurrence. Often no differences in local recurrence rate were reported(23-28). Sometimes re-excision was associated with an increased local recurrence rate(29, 30), however after multivariable analyses no statistically significant difference remained(30-32). Local recurrence could not be addressed in this study because of lack of data on local recurrence. Although local control is very important, in particular differences in survival will guide practice changing recommendations. Until now only one single institution study (n = 902) with high re-excision rates (64%) investigated the impact of re-excision on survival in an era before modern chemotherapy was available (1977–2000). No difference in overall and disease specific survival between patients with re-excision and patients without re-excision was reported(30). Our study describes a large multicenter study population in the era of modern chemotherapy including multivariable survival analyses adjusting for patient and treatment characteristics.

Since chemotherapy eradicates micrometastases within and outside the local breast cancer region, modern and more effective chemotherapy may have decreased the need of a microscopic radical resection(9). Somewhat surprisingly in our modern chemotherapy cohort, women re-excised by BCS had significant increased overall survival in comparison to women with primary BCS only. However,

after multivariable analysis this favourable effect of re-excision by BCS was no longer significant (HR 0.49 95%CI 0.23–1.04 P = 0.07). Nevertheless, it cannot be concluded that wider margins caused an improved overall survival trend due to the fact that the 're-excision by mastectomy' group did not show the same trend.

There are limitations to this study. The time cohort 2006–2012 by definition had a short median time of follow-up since most distant metastases occur >5 years after diagnosis. Furthermore it was assumed that women in need of a re-excision indeed had a re-excision and women not in need of a re-excision had primary BCS only. Unfortunately this assumption could not be verified due to the lack of information about margin status. This lack of details on initial margin status also prevents us from defining the incremental benefit of re-excision for each possible margin status. It also complicates drawing firm conclusions about the relative benefit of re-excision, or the lack thereof. However, the percentage of patients whose treatment adhered to the guidelines about surgical therapy has been found to be 99.5% in a study population of 24,959 patients between 2005 and 2008 in the Netherlands(13). It should also be noted that all patients in this study of whom the breast was conserved had adjuvant whole-breast radiotherapy. These results cannot be extrapolated to those without radiotherapy.

We present the largest study population in which the role of re-excision in overall survival has been studied to date. The Dutch guidelines created the opportunity to retrospectively investigate the long-term prognosis in a treatment setting in which less re-excisions are performed due to less stringent re-excision indications compared to other European and Northern American countries. This issue has not been emphasised previously.

CONCLUSION

Women with a re-excision have excellent overall survival which did not statistically significantly differ from the survival of women who underwent primary BCS only. Advising re-excision only for those tumours showing 'more than focally positive' resection margin appears safe. Therefore, these data definitively support the long-term safety of adhering to the recent SSO/ASTRO guideline that more cautiously recommended to reserve re-excision for tumours showing 'ink on tumour'.

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CHAPTER 8

Omitting re-excision for focally positive margins after breast conserving surgery does not impair disease-free and overall survival

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ABSTRACT

Purpose In contrast to other countries, the Dutch breast cancer guideline does not recommend re-excision for focally positive margins after breast-conserving surgery (BCS) in invasive tumor and does recommend whole-breast irradiation including boost. We investigated whether omitting re-excision as compared to performing re-excision affects prognosis with a retrospective population-based cohort study.

Methods The total cohort included 32,119 women with primary BCS for T1–T3 breast cancer diagnosed between 2003 and 2008 from the nationwide Netherlands cancer registry. The subcohort included 10,433 patients in whom the resection margins were registered. Outcome measures were 5-year ipsilateral breast tumor recurrence (IBTR) rate, 5-year disease-free survival (DFS) rate, and 10-year overall survival (OS) rate.

Results In the total cohort, 25,878 (80.6%) did not have re-excision, 2368(7.4%) had re-excision by BCS, and 3873(12.1%) had re-excision by mastectomy. Five-year IBTR rates were 2.1, 2.8, and 2.9%, respectively($p = 0.001$). In the subcohort, 7820(75.0%) had negative margins without re-excision, 492(4.7%) had focally positive margins without re-excision, 586(5.6%) had focally positive margins and underwent re-excision, and 1535(14.7%) had extensively positive margins and underwent re-excision. Five-year IBTR rate was 2.3, 2.9, 1.1, and 2.9%, respectively($p = 0.099$). Compared to omitting re-excision, performing re-excision for focally positive margins was associated with lower risk of IBTR (adjusted HR 0.30, 95%CI 0.11–0.82), but not with DFS (adjusted HR 0.83 95%CI 0.59–1.17) nor with OS (adjusted HR 1.17 95%CI 0.87–1.59).

Conclusion Omitting re-excision in breast cancer patients for focally positive margins after BCS does not impair DFS and OS, provided that whole-breast irradiation including boost is given.

INTRODUCTION

For breast-conserving surgery (BCS), the minimally accepted resection margin above which a re-excision will be advised has been debated extensively since high level of evidence is lacking. For many years, the international debate has been predominated by finding the ideal negative margin width, whereby it was compared to positive margins in general. A meta-analysis concluded that there is no evidence that increasing the tumor-free margin width significantly reduces the odds of local recurrence[1]. Since a tumor-positive margin did increase the odds of local recurrence, the Society of Surgical Oncology and the American Society for Radiation Oncology (SSO-ASTRO) and European Society for Medical Oncology (ESMO) recently published guidelines recommending *no ink on tumor* as an adequate margin for invasive breast cancer. Re-excision is only advised in case the tumor is touching the inked resection margin[2,3]. No distinction was made, however, between focally and extensively positive margins.

The next question in the debate is whether a focally positive margin is a risk factor for local recurrence and therefore an indication for re-excision. Six out of seven studies previously investigating local recurrence rate in patients with focally positive margins after final surgery found it was not different from negative margins[4-10]. In the last decade, the risk of local recurrence has decreased even more through improvements in radiotherapy and systemic treatment[11]. The impact of margin status on local relapse was also investigated in the European Organisation for Research and Treatment of Cancer (EORTC) boost versus no boost trial. Margin status had no significant influence, suggesting that radiotherapy boost on the tumor bed negates the prognostic significance of positive margins[12,13].

Uniquely, since 2002, the Dutch national guideline does not recommend a re-excision for focally positive margins after BCS in case of invasive disease and does recommends to apply whole-breast radiotherapy including a boost on the tumor bed in this situation[14]. As far as we know, the Netherlands is the only country with such a liberal approach. How often re-excision is indeed omitted in clinical practice is unknown[15]. The aim of the current study was to describe the implementation of the recommendation in clinical practice and investigate whether omitting re-excision for focally positive margins affects ipsilateral breast tumor recurrence (IBTR), disease-free survival (DFS), and overall survival (OS) in a nationwide cancer registry.

METHODS

In this retrospective population-based cohort study, all female invasive breast cancer patients diagnosed between 2003 and 2008 with BCS as their primary surgical treatment in the Netherlands were included. Data were retrieved from the Netherlands Cancer Registry that includes all new cancer diagnoses in the Netherlands since 1989 covering 17 million inhabitants. The main source of information is the national pathology archive and in addition the registry is linked with the national discharge register. Specially trained registration clerks from the Netherlands Cancer Registry are located in each hospital in the Netherlands, both academic and non-academic, and independently collect data on patient demographics, tumor characteristics, and breast cancer treatment. Data completeness exceeds 95%[16]. The registration clerks follow a strict coding manual of which the majority is mandatory to register. Registration of resection margins was optional and it was not collected by all registration clerks. Death certificates are not available, due to privacy regulations. Vital status and date of death are obtained by a yearly linkage to the Municipal Personal Records Database and are complete up to December 31, 2014. Information on local, regional, and contralateral recurrence as well as distant metastasis is not collected routinely by the cancer registry. On a project basis, it was collected retrospectively by the local registration clerks up to 5 years after primary breast cancer diagnosis for the cohort diagnosed between 2003 and 2008. The exclusion criteria are shown in Fig. 1.

Definitions

Clinical and pathological tumor node metastasis staging (TNM) was in accordance with the sixth edition of TNM Classification of Malignant Tumors by the American Joint Committee on Cancer (AJCC). Surgical treatment was classified as ‘primary BCS only’ for patients who underwent BCS not followed by a re-excision. Patients who underwent BCS followed by a re-excision were classified as ‘re-excision by BCS’ or ‘re-excision by mastectomy’ according to the type of final re-excision. Margin status was classified as ‘negative’ defined as no invasive tumor component and/or adjacent DCIS component touching the inked margin, ‘focally positive’ defined as foci of invasive tumor component and/or adjacent DCIS component touching the inked margin over a length of four mm or less, or ‘extensively positive’ defined as foci of invasive tumor component and/or adjacent DCIS component touching the inked margin over a length of more than four mm. The four mm cut-off is a translation from the previous definition of three low-power microscopic fields (using a x10 ocular lens). All Dutch pathologists are obliged to report the margin

status by this classification. The use of radiotherapy was registered as yes or no, but details about the total dose, anatomical fields, and use of boost were not included in the registry.

The first recurrence that occurred at least 3 months from primary breast cancer diagnosis was registered by the Netherlands Cancer Registry. Other recurrence(s) within 3 months from the first recurrence were also included. IBTR rate was defined as the percentage of patients with ipsilateral local recurrence of breast carcinoma. DFS rate was defined as the percentage of patients being alive without having had any breast cancer recurrence (i.e., local, regional, contralateral, or distant). OS rate was defined as the percentage of patients being alive.

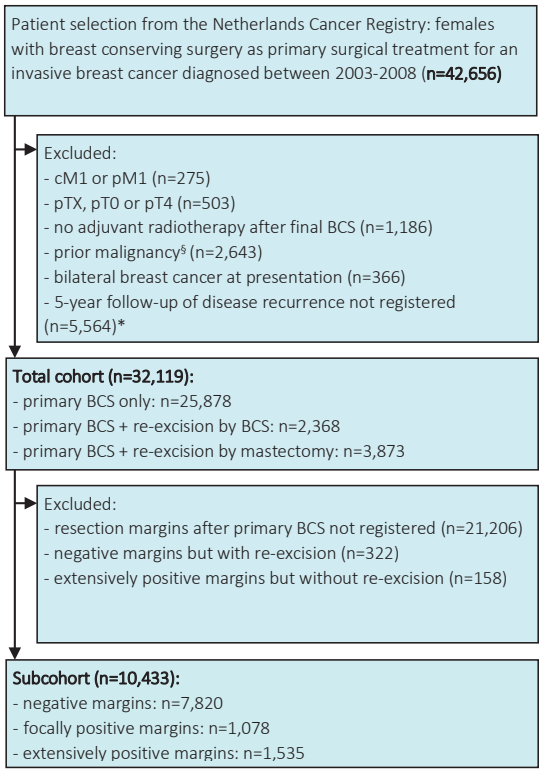

Figure 1. Patient selection. cM1 clinically suspect distant metastasis, pM1 pathologically confirmed distant metastasis, pTX primary tumor cannot be assessed or is unknown, pT0 no evidence of primary tumor, pT4 tumor with direct extension to the chest wall and/or to the skin, BCS breast-conserving surgery. §Except for basal-like skin cancer. *Follow-up information on disease recurrence was assembled for all patients diagnosed in 2003–2006, and for 44% of the patients diagnosed in 2007–2008 due to lack of funding for some hospitals. †All patients of whom the breast was conserved had adjuvant radiotherapy. From all patients with a re-excision by mastectomy, 873 (22.5%) had adjuvant radiotherapy. ‡Since it was an optional item in the coding manual, some registration clerks did not code margins

Table 1. Clinicopathological and treatment characteristics according to the performance of re-excision in the total cohort. (n = 32119)

	Primary BCS only	Primary BCS + re-excision by BCS	Primary BCS + re-excision by mastectomy	P-value[a]
No. of patients	25878 (80.6)	2368 (7.4)	3873 (12.1)	
Age				<0.001
- >60 years	10505 (40.6)	718 (30.3)	1185 (30.6)	
- 51-60 years	7946 (30.7)	780 (32.9)	1113 (28.7)	
- 41-50 years	5795 (22.4)	681 (28.8)	1152 (29.7)	
- ≤40 years	1632 (6.3)	189 (8.0)	423 (10.9)	
Histology				<0.001
- ductal	20148 (77.9)	1797 (77.9)	2548 (65.8)	
- lobular[b]	2841 (11.0)	325 (13.7)	901 (23.3)	
- other	2889 (11.2)	246 (10.4)	424 (10.9)	
Differentiation grade				<0.001
- 1	6657 (25.7)	550 (23.2)	606 (15.6)	
- 2	10726 (41.4)	985 (41.6)	1611 (41.6)	
- 3	7086 (27.4)	657 (27.7)	1281 (33.1)	
- unknown	1409 (5.4)	176 (7.4)	375 (9.7)	
pT				<0.001
- T1	19289 (74.5)	1730 (73.1)	2164 (55.9)	
- T2	6463 (25.0)	631 (26.6)	1493 (38.5)	
- T3	51 (0.2)	6 (0.3)	216 (5.6)	
- ypT0	75 (0.3)	1 (0.0)	-	
pN				<0.001
- N0	18200 (70.3)	1589 (67.1)	1998 (51.6)	
- N1	5944 (23.0)	620 (26.2)	1284 (33.2)	
- N2	1045 (4.0)	104 (4.4)	375 (9.7)	
- N3	432 (1.7)	35 (1.5)	183 (4.7)	
- unknown	257 (1.0)	20 (0.8)	33 (0.9)	
Oestrogen receptor				<0.001
- positive	13508 (52.2)	1267 (53.5)	1803 (46.6)	
- negative	2720 (10.5)	230 (9.7)	422 (10.9)	
- unknown	9650 (37.3)	871 (36.8)	1648 (42.6)	

Table 1. Clinicopathological and treatment characteristics according to the performance of re-excision in the total cohort. (n = 32119) *(continued)*

	Primary BCS only	Primary BCS + re-excision by BCS	Primary BCS + re-excision by mastectomy	P-value[a]
Progesteron receptor				<0.001
- positive	10836 (41.9)	996 (42.1)	1414 (36.5)	
- negative	4874 (18.8)	424 (17.9)	725 (18.7)	
- unknown	10168 (39.3)	948 (40.0)	1734 (44.8)	
Her2Neu receptor				<0.001
- negative	13282 (51.3)	1220 (51.5)	1647 (42.5)	
- positive	1761 (6.8)	183 (7.7)	404 (10.4)	
- unknown	10835 (41.9)	965 (40.8)	1822 (47.0)	
Systemic therapy[c]				<0.001
- none	13128 (51.1)	1114 (47.0)	1321 (34.1)	
- chemotherapy only	3173 (12.3)	286 (12.1)	565 (14.6)	
- hormonal therapy only	4038 (15.6)	332 (14.0)	616 (15.9)	
- chemotherapy and hormonal therapy	5449 (21.1)	636 (26.9)	1371 (35.4)	

Abbreviations: pT=pathological tumor stage, pN=regional lymph nodes stage. [a]Chi-square test. [b]Includes mixed ductal and lobular tumors. [c]Both neo-adjuvant and adjuvant.

Dutch national breast cancer guideline

The Dutch guideline is evidence-based and complemented with expert opinion written by a multidisciplinary team and is regularly updated. The goal is to advise and guide clinical practice. In the timeframe studied, it recommended whole-breast irradiation with a doses equivalence of 50 Gy followed by a 14–16 Gy boost in case of negative margins. Boost could be omitted in patients older than 60 years. In case of focally positive margins or patients being 40 years or younger with negative margins, a 20–25 Gy boost was recommended. Post-mastectomy chest wall irradiation was recommended in case of positive margins, tumor growth into the pectoral muscle, and should be considered for T3 tumors, with a doses equivalence of 45–50 or 60–70 Gy in case of macroscopic residual tumor. Regional lymph node irradiation was indicated in case of pN2 or if the highest axillary medial node was positive.

Statistical analysis

To avoid noise in the comparisons between groups that are defined by the patient's margin status and surgical treatment, patients were excluded if they had re-excision for negative margins and if they did not had re-excision for extensively positive margins (Fig. 1). Primary outcome was IBTR and secondary outcomes were DFS and OS. The effect of re-excision and type of re-excision (i.e., BCS or mastectomy) on the outcomes was studied in the total cohort (32,119 patients), irrespective of the resection margins after primary BCS. Subsequently, the effect of resection margins on the outcomes was studied in a subcohort (10,433 patients) of whom the resection margins after primary BCS were registered (Fig. 1). Time of follow-up was defined as the time between the latest re-excision and the event or censoring. Patients were censored in case of emigration, 5 years after the latest breast cancer operation concerning IBTR and DFS, or at the December 31, 2014 concerning OS. Differences in patient characteristics were tested using the $\chi 2$ test. IBTR rate, DFS rate, and OS rate were determined by Kaplan–Meier method and distributions between subgroups were compared by the log-rank test. Hazard ratios (HR) were estimated by Cox proportional hazards regression analysis. In the total cohort, comparisons were made with respect to whether or not a re-excision was performed. In the subcohort, comparisons were made with respect to resection margins including whether or not a re-excision was performed. Due to the prognostic importance of systemic therapy, the effect of margin status on IBTR was also studied after stratification for use of (neo)adjuvant systemic therapy (none versus endocrine therapy and/or chemotherapy). Multivariable models were performed by the enter method (i.e., including all covariates at the same time in the model and no forward or backward selection) and included all clinicopathological and treatment variables with a maximum degrees of freedom of ten events per covariate included. Missing values were classified as unknown. In spite of missing values, all patients were included in the analyses to prevent bias in IBTR, DFS, and OS rate estimates. Interaction was tested between all variables and margin status for IBTR. The proportional hazards assumption was tested by graphing the log(-log(IBTR)) versus log of IBTR time of each variable in Table 1 and was considered proportional when parallel curves were observed. Statistical tests were two-sided, and p-value <0.050 was considered statistically significant. SPSS® version 21 (IBM, Armonk, New York, USA) was used for all statistical analyses.

RESULTS

Re–excision in total cohort

Of the total of 42,656 women with invasive breast cancer diagnosed between 2003 and 2008 and primarily treated with BCS in the Netherlands, 32,119 met the eligibility criteria. Patient selection is displayed in Fig. 1. Patients in whom no 5-year follow-up was collected due to lack of funding did not differ from the total cohort in terms of clinicopathological and treatment characteristics. Re-excision was performed in 6241 (19.4%) patients of whom 3873 (62.1%) underwent a mastectomy. The frequency of mastectomy as the re-excision decreased over time from 65.9% in 2003 to 52.5% in 2008. Clinicopathological and treatment characteristics are shown in Table 1. All patients with primary BCS only and re-excision by BCS have had radiotherapy. From the 3873 patients with re-excision by mastectomy, 873 (22.5%) had radiotherapy. Median follow-up time for IBTR, DFS, and OS was 60 months (interquartile range (IQR) 57–60), 60 months (IQR 57–60), and 106 months (86–123), respectively. After testing the proportional hazards assumption for all variables as shown in Table 1, a constant relative hazard was seen for IBTR risk and therefore time was not included in the multivariable models. The 5-year IBTR rate in the primary BCS only, re-excision by BCS, and re-excision by mastectomy group was 2.1, 2.8, and 2.9%, respectively (p = 0.001) (Table 2). Multivariable analysis showed that IBTR rates after re-excision by BCS and re-excision by mastectomy were not statistically significantly different as compared to primary BCS only (HR 1.31 95%CI 1.00–1.71 and HR 0.89 95%CI 0.57–1.40, respectively). DFS rates and OS rates are shown in Table 2 and were statistically significantly decreased in patients with re-excision by mastectomy as compared to primary BCS only after multivariable analyses.

Table 2. Ipsilateral breast tumor recurrence (IBTR), disease free survival (DFS), and overall survival (OS) rates from Kaplan-Meier analysis and adjusted hazard ratio (HR) from multivariable Cox regression analysis according to the performance of re-excision in the total cohort. (n = 32119)

	IBTR		**DFS**		**OS**		
	5-year	**Adjusted[a] HR (95%CI)**	**5-year**	**Adjusted[a] HR (95%CI)**	**5-year**	**10-year**	**Adjusted[a] HR (95%CI)**
Primary BCS only (N=25878)[b]	2.1%	reference	89.0%	reference	92.7%	82.1%	reference
Primary BCS + re-excision by BCS (N=2368)[b]	2.8%	1.31 (1.00-1.71)	87.7%	1.13 (1.00-1.28)	94.5%	85.3%	0.89 (0.80-1.00)
Primary BCS + re-excision by mastectomy (N=3873)[c]	2.9%	0.89 (0.57-1.40)	82.9%	*1.38 (1.19-1.61)*	89.9%	78.7%	*1.16 (1.01-1.34)*

[a]Adjusted for: age (continuous), histology (ductal, lobular, or other), differentiation grade (1, 2, 3, or unknown), pT stage (1, 2, 3, or ypT0), pN stage (1, 2, 3, or unknown), oestrogen receptor status (positive, negative, or unknown), her2neu receptor status (positive, negative, or unknown), use of systemic therapy (any or none), and radiotherapy (yes or no). [b]All patients had radiotherapy (100%). [c]Radiotherapy was performed in 873 (22.5%) of the patients.

Resection margins in subcohort

The subcohort consisted of 10,433 (32.5%) patients (Fig. 1). The registration of resection margin in the cancer registry was not associated with the occurrence of IBTR (OR 1.12 95%CI 0.95–1.31 P = 0.180). Clinicopathological and treatment characteristics are shown in Table 3. Negative margins were observed in 7820 (75.0%) patients, focally positive margins in 1078 (10.3%) patients, and extensively positive margins in 1535 (14.7%) patients. After focally positive margins, in 492 (45.6%) patients re-excision was omitted (i.e., primary BCS only) and in 586 (54.4%) patients re-excision was performed. The frequency of omitting the re-excision varied non-linearly over time ranging between 32.8 and 58.4% and the proportional hazards assumption for IBTR was not violated. Figure 2 shows the use of re-excision in the patients with focally positive margins according to whether the invasive component and/or the adjacent DCIS component were focally touching the inked margins. Of the 586 patients with focally positive margins and re-excision, 268 (45.7%) underwent a re-excision by BCS followed by adjuvant radiotherapy and 318 (54.3%) underwent a re-excision by mastectomy of whom 84 (26.4%) had post-mastectomy radiotherapy. The type of re-excision varied non-linearly over time with the frequency of BCS ranging between 40.7 and 53.3%.

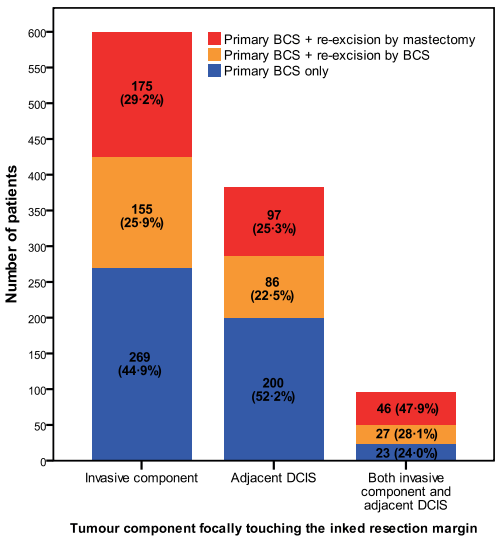

Figure 2. Re-excisions according to the tumor component focally touching the inked margin. Figure only shows the patients with focally positive margins after primary BCS from the subcohort (n = 1078). Re-excision was omitted in 492 (45.6%) patients (total of blue bars) and was performed in 586 (54.4%) patients (total of orange and red bars). The frequency and type of re-excision is shown according to which component of the tumor was focally touching the inked margin.

Table 3 Clinicopathological and treatment characteristics according to resection margin after primary BCS and the performance of re-excision in the subcohort. (n = 10433)

	Negative margin and primary BCS only	**Focally positive margin and primary BCS only**	**Focally positive margin and primary BCS + re-excision[a]**	**Extensively positive margin and primary BCS + re-excision[b]**	**P-value**
Total no. of patients	7820 (75.0)	492 (4.7)	586 (5.6)	1535 (14.7)	
Age					<0.001
- > 60 years	2695 (34.5)	210 (42.7)	149 (25.4)	374 (24.4)	
- 51-60 years	2346 (30.0)	120 (24.4)	169 (28.8)	417 (27.2)	
- 41-50 years	2258 (28.9)	145 (29.5)	218 (37.2)	583 (38.0)	
- ≤ 40 years	521 (6.7)	17 (3.5)	50 (8.4)	161 (10.5)	
Histology					<0.001
- ductal	6233 (79.7)	379 (77.0)	427 (72.9)	1046 (68.2)	
- lobular[c]	783 (10.0)	69 (13.8)	110 (18.8)	317 (20.6)	
- other	804 (10.3)	45 (9.1)	49 (8.4)	172 (11.2)	
Differentiation grade					<0.001
- 1	1766 (22.6)	105 (21.3)	94 (16.0)	254 (16.5)	
- 2	3114 (39.8)	202 (41.1)	229 (39.1)	618 (40.3)	
- 3	2440 (31.2)	149 (30.3)	217 (37.0)	506 (33.0)	
- unknown	500 (6.4)	36 (7.3)	46 (7.8)	157 (10.2)	
pT					<0.001
- T1	5576 (71.3)	345 (70.1)	347 (59.2)	866 (56.4)	
- T2	2123 (27.1)	145 (29.5)	227 (38.7)	593 (38.6)	
- T3	15 (0.2)	2 (0.4)	12 (2.0)	76 (5.0)	

Table 3 Clinicopathological and treatment characteristics according to resection margin after primary BCS and the performance of re-excision in the subcohort ,(n = 10433) *(continued)*

	Negative margin and primary BCS only	Focally positive margin and primary BCS only	Focally positive margin and primary BCS + re-excision[a]	Extensively positive margin and primary BCS + re-excision[b]	P-value
- ypT0	34 (0.4)	-	-	-	
pN					<0.001
- N0	5166 (66.1)	316 (64.2)	297 (50.7)	816 (53.2)	
- N1	2231 (27.4)	117 (23.8)	214 (36.5)	503 (32.8)	
- N2	344 (4.4)	40 (8.1)	47 (8.0)	142 (9.3)	
- N3	120 (1.5)	17 (3.5)	25 (4.3)	61 (3.9)	
- unknown	67 (0.9)	2 (0.4)	3 (0.5)	13 (0.8)	
Oestrogen receptor					<0.001
- positive	3292 (42.1)	217 (44.1)	245 (41.8)	531 (34.6)	
- negative	710 (9.1)	42 (8.5)	55 (9.4)	124 (8.1)	
- unknown	3818 (48.8)	233 (47.4)	286 (48.8)	880 (57.3)	
Progesteron receptor					<0.001
- positive	2662 (34.0)	176 (35.8)	182 (31.1)	410 (26.7)	
- negative	1253 (16.0)	81 (16.5)	103 (17.6)	227 (14.8)	
- unknown	3905 (49.9)	235 (47.8)	301 (51.4)	898 (58.5)	
Her2Neu receptor					<0.001
- negative	3890 (37.0)	188 (38.2)	196 (33.4)	392 (25.5)	
- positive	980 (12.5)	68 (13.8)	96 (16.4)	233 (15.2)	
- unknown	3950 (50.5)	236 (48.0)	294 (50.2)	910 (59.3)	

Table 3 Clinicopathological and treatment characteristics according to resection margin after primary BCS and the performance of re-excision in the subcohort. (n = 10433) *(continued)*

	Negative margin and primary BCS only	**Focally positive margin and primary BCS only**	**Focally positive margin and primary BCS + re-excision[a]**	**Extensively positive margin and primary BCS + re-excision[b]**	**P-value**
Systemic therapy[d]					<0.001
- none	3214 (41.1)	183 (37.2)	179 (29.0)	468 (30.5)	
- chemotherapy only	1011 (12.9)	53 (10.8)	82 (14.0)	225 (14.7)	
- hormonal therapy only	1168 (14.9)	83 (16.9)	79 (13.5)	180 (11.7)	
- chemotherapy and hormonal therapy	2427 (31.0)	173 (35.2)	255 (43.5)	662 (43.1)	
Radiotherapy	7820 (100)	492 (100)	352 (60.1)*	786 (51.2)†	<0.001

Abbreviations: pT=pathological tumor stage, pN=regional lymph nodes stage. [a]Re-excision by BCS in 268 (45.7%) patients of whom all had radiotherapy (100%) and re-excision by mastectomy in 318 (54.3%) patients of whom 84 (26.4%) had radiotherapy. [b]Re-excision by BCS in 516 (33.7%) patients whom all had radiotherapy (100%) and re-excision by mastectomy in 1016 (66.3%) patients of whom 270 (26.5%) had radiotherapy.[c]Includes mixed ductal and lobular tumors. [d]Both neo-adjuvant and adjuvant.

Table 4 Ipsilateral breast tumor recurrence (IBTR), disease free survival (DFS), and overall survival (OS) rates from Kaplan-Meier analysis and adjusted hazard ratio (HR) from multivariable Cox regression analysis according to resection margins after primary BCS and the performance of re-excision in the subcohort. (n = 10433)

	IBTR		DFS		OS		
	5-year	Adjusted[a] HR (95%CI)	5-year	Adjusted[a] HR (95%CI)	5-year	10-year	Adjusted[a] HR (95%CI)
Negative margins and primary BCS only (n=7820)[b]	163 (2.3%)	0.76 (0.43-1.35)	89.2%	0.81 (0.63-1.04)	93.1%	82.9%	1.07 (0.85-1.34)
Focally positive margins							
- primary BCS only (n=492)[b]	13 (2.9%)	Reference	86.0%	Reference	92.7%	81.1%	Reference
- primary BCS + re-excision (n=586)[c]	6 (1.1%)	***0.30 (0.11-0.82)***	87.1%	0.83 (0.59-1.17)	92.1%	82.1%	1.17 (0.87-1.59)
- by BCS (n=268)[b]	3 (1.3%)	0.39 (0.11-1.38)	90.7%	0.66 (0.42-1.06)	94.8%	86.0%	1.01 (0.68-1.49)
- by mastectomy (n=318)[d]	3 (1.0%)	***0.23 (0.06-0.89)***	84.0%	0.98 (0.66-1.47)	89.9%	78.7%	1.34 (0.93-1.91)
Extensively positive margins and primary BCS + re-excision (n=1535)[e]	40 (2.9%)	0.75 (0.37-1.51)	84.7%	0.97 (0.72-1.31)	91.8%	81.1%	1.22 (0.94-1.59)

[a]Adjusted for: age (continuous), histology (ductal, lobular, or other), differentiation grade (1, 2, 3, or unknown), pT stage (1, 2, 3, or ypT0), pN stage (1, 2, 3, or unknown), oestrogen receptor status (positive, negative, or unknown), her2neu receptor status (positive, negative, or unknown), use of systemic therapy (any or none), and radiotherapy (yes or no). Complete table can be found in the Online Resource 1, Table 1. [b]Radiotherapy was performed in all patients with BCS (100%). [c]Radiotherapy was performed in 352 (60.1%) of the patients since all 268 patients with re-excision by BCS (100%) and 84 (26.4%) of the patients with re-excision by mastectomy had radiotherapy. [d]Radiotherapy was performed in 84 (26.4%) patients. [e]Adjuvant radiotherapy was performed in 786 (51.2%) patients since all 516 patients with re-excision by BCS (100%) and 270 (26.5%) of the patients with re-excision by mastectomy had radiotherapy.

Ipsilateral breast tumor recurrence (IBTR)

After a median follow-up time of 60 months (IQR 59–60), 222 IBTR's occurred. Five-year IBTR rate was 2.3% in patients with negative margin and primary BCS only, 2.9% in patients with focally positive margin and primary BCS only, 1.1% in patients with focally positive margin and re-excision, and 2.9% in patients with extensively positive margin and re-excision (p = 0.099) (Table 4). Interaction between all clinicopathological and treatment characteristics with margin status was tested but none interacted statistically significantly. Multivariable analyses showed that performing re-excision in patients with focally positive margins was statistically significantly associated with a lower IBTR rate as compared to omitting re-excision (adjusted HR 0.30 95%CI 0.11–0.82); however the absolute difference in 5-year IBTR rate was low 1.8% (2.9–1.1%).

Disease-free survival (DFS)

After a median follow-up time of 60 months (IQR 59–60), 1181 patients developed recurrent disease. Five-year DFS rates are shown in Table 4. Multivariable analyses showed that performing re-excision in patients with focally positive margins was not associated with improved DFS as compared to omitting re-excision (adjusted HR 0.83 95%CI 0.59–1.17).

Overall survival (OS)

After a median follow-up time of 110 months (IQR 78–135), 1709 deaths of any cause occurred. Five- and 10-year OS rates are shown in Table 4. Multivariable analyses showed that performing re-excision in patients with focally positive margins was not associated with improved OS as compared to omitting re-excision (adjusted HR 1.17 95%CI 0.87–1.59).

Systemic therapy

Stratifying the subcohort into patients who did (6398 patients) and did not (4035 patients) had (neo)adjuvant systemic therapy showed that 5-year IBTR rate was always lower than 4.0% independent of margin status and use of re-excision (see Online Resource 1, Table 2). In patients with systemic therapy, performing re-excision for focally positive margins was not statistically significantly associated with lower IBTR as compared to omitting re-excision (unadjusted HR 0.28 95%CI 0.08–1.06). In patients without systemic therapy, performing re-excision for focally positive margins was not statistically significantly associated with lower

IBTR as compared to omitting re-excision (unadjusted HR 0.61 95%CI 0.15–2.56). After selecting patients with focally positive margins and primary BCS only, use of systemic therapy was not statistically significantly associated with lower IBTR compared to no use of systemic therapy (unadjusted HR 0.92 95%CI 0.30–2.81).

DISCUSSION

Omitting re-excision for focally positive margins was associated with statistically significantly higher IBTR rate as compared to performing re-excision (adjusted HR 0.30 95%CI 0.11–0.82), but the absolute difference was small (1.8% at 5-years), the absolute number of events was already low in both groups (2.9% versus 1.1% at 5-years), and the odds ratio was not significantly different from negative margins. Moreover, omitting re-excision in case of focally positive margins did not adversely affect DFS and OS. In the total study population (n = 32119) irrespective of the margins, IBTR rate was similar for patients with primary BCS only and patients with re-excision. Therefore, it can be concluded that omitting re-excision for focally positive margins does not impair DFS and OS. It could be argued that the difference found in IBTR rate is not clinically relevant; however, more evidence is needed to confirm this. Introducing the policy to omit re-excision for focally positive margins could potentially prevent large numbers of mastectomies which accounted for over 50% of the re-excisions. Interestingly, comparing IBTR, DFS, and OS rates between the re-excision by BCS group and re-excision by mastectomy group in the total study population (Table 2), it suggests that mastectomy is not preferred over BCS. Less mastectomies and attendant breast reconstructions will reduce burden to the patient and health-care costs that have been estimated to be $1055 per patient attempting BCS[17]. The same holds for the costly procedure of cavity shaving that has recently been introduced since our high rate of local control in patients with involved margins suggests it is unnecessary[18,19].

Both the SSO/ASTRO guideline and the meta-analysis that was the guideline's primary evidence base do not separate positive margins into focally or extensively positive. Six studies that did describe prognosis in patients with focally positive margins previously were all unicenter, predominantly from the 1980s, and margin status was defined *after* the final surgery and not after the *first* surgery[5,4,6,7,9,10]. They included only between 10 and 124 patients with focally positive margins who had whole breast irradiation with a total dose range 55–65 Gy. Five and eight-year local recurrence rates were reported by four studies and two studies, respectively, and ranged between 2 and 15% and 10–14%, respectively. Five out of six studies found that margin status after final excision was *not* sta-

tistically significantly associated with local recurrence after unadjusted analyses. These studies were too small to compare their findings to ours.

Our hypothesis is that radiotherapy boost reduces IBTR rates and nullifies the prognostic influence of focally positive margins. Jones et al. showed that a positive margin after BCS not followed by a re-excision was *not* a risk factor for local relapse in the boost versus no boost trial[12]. All patients with final BCS in our study population underwent adjuvant whole-breast radiotherapy, since no radiotherapy after BCS was an exclusion criterion. Unfortunately, what patients actually received and if boost was included was not registered by the Netherlands Cancer Registry. The Dutch guideline has strict recommendations, however, regarding radiotherapy (see methods), but whether they were strictly followed is unknown. To estimate the frequency and height of boost received in our study population, all 21 radiotherapy institutes in the Netherlands were contacted and radiation oncologists were questioned about their institute's treatment policy in 2003–2008. Sixteen (76.2%) responded and all reported to have used a boost in patients with focally positive margins in whom re-excision was omitted with a median of 20 Gy (range 14–26 Gy). In patients with focally positive margins in whom re-excision was performed, one institute reported never to have used a boost after 2004, seven institutes always used boost, and eight institutes omitted boost in older patients and/or took into account grade and lymphovascular invasion. If boost was given, the median dose was 16 Gy (range 14–26 Gy). Radiotherapy boost is not without costs both financial and cosmetic and often additional hospital visits are needed. Increasing dose is associated with increasing incidence of fibrosis[20]. However, no evidence is available determining if boost or re-excision is the least harmful or preferred by the patient.

The safety of omitting re-excision in case of focally positive margins could also be explained by increasing systemic therapy use and effectiveness over time which significantly improved local control after breast-conserving therapy. The 5-year local recurrence rate decreased from 9.8% in 1988–1998 to 3.3% in 2006–2010 in early stage breast cancer patients ≤40 years[21]. Moreover, in patients with focally positive margins, Park et al. described a local recurrence risk of 7% with systemic therapy as compared to 18% without systemic therapy[5]. Other studies evaluating the effect of systemic therapy in patients with focally positive margins do not exist as far as we know. In our study, 5-year IBTR rates in patients with focally positive margins in whom re-excision was omitted were low and not statistically significantly different both in the presence and absence of systemic therapy (2.8 and 3.2%, respectively), but the confidence intervals were wide due to low number of events. Progress in breast cancer screening and treatment

including use of modern radiotherapy techniques, more effective systemic therapy, accurate radiological tumor localization, inking of surgical specimens, and adequate pathological examination of resection margins may explain why omitting re-excision for focally positive margins appears to be safe nowadays.

Firm conclusions cannot be drawn, since limitations apply to our retrospective study. Registration of resection margins was not mandatory for the registration clerks of the Netherlands Cancer Registry and was only available in 32.5% of the total study population. The availability of resection margins was not associated to a time period, hospitals, pathologists, or IBTR. Moreover, patients in whom resection margins was registered were comparable as far as patient, tumor and treatment characteristics are concerned (data not shown) and the incidence of focally positive margins was equal to a study of all breast-conserving surgeries for invasive cancer in 2012–2013 in the Netherlands (10.3 and 11.0[22]. This confirms that the subcohort is a random selection from the total study population. The caregivers motives for omitting or performing re-excision were unknown, which could have led to confounding. However, patients who did and who did not underwent re-excision for focally positive margins were comparable as far as patient, tumor and treatment characteristics are concerned (Table 3) and adjustment for all these possible confounders was performed in the multivariable analyses. This makes selection bias less likely, although unknown residual confounding may be present. A survey evaluating surgeons' preferences for margins and re-excision found that—even though the new SSO-ASTRO guideline advises *against* re-excision in case of negative margin—12% would re-excise for triple-negative tumor within 1 mm, 50% would re-excise when imaging and pathology are discordant, when tumor was within 1 mm of multiple margins, and when multiple foci of DCIS extended to within 1 mm of multiple margins[23]. Similar considerations will apply to the Dutch clinical practice. Another limitation was the limited number of events impairing to study the effect of omitting re-excision in clinically relevant subgroups. Furthermore, the orientation of the involved margins was unknown, but it can be assumed that re-excision was omitted for anterior and posterior margin involvement if the standard full thickness breast tissue excision was performed which previously has been shown to result in satisfactory local control[24]. Another important issue is the incidence of a first IBTR after 5years of follow-up, especially in the estrogen-receptor-positive tumors, and the changes in prognostic factors for IBTR related to the time of follow-up[25],[26]. This emphasizes the importance of longer follow-up to estimate effect of re-excision accurately.

Since a randomized controlled trial of surgical margins has never been performed and is unlikely to be realizable, reliance on observational data is an accept-

able approach. No studies have been performed comparing prognosis in patients in whom the focally positive margin is defined after the *first* surgery and thus comparing a group without re-excision to a group with re-excision after first surgery. Moreover, this is the first nationwide population-based analysis on a detailed cancer registry database including all hospitals, enabling adjustment for confounders. We describe a 10–100 times larger study population as compared to previous studies even in an era with lower incidence of positive margins, an important strength our study. It is the first cohort completely treated in the 21st century approaching current daily practice in which large improvements in breast cancer treatment and overall prognosis have been accomplished.

Omitting re-excision in invasive breast cancer patients with focally positive margins after BCS does not impair DFS and OS. Provided that adjuvant whole-breast irradiation is given including boost to the tumor bed, more evidence is needed to confirm that IBTR is not impaired either. Adoption of this recommendation will lead to less re-excisions and mastectomies which have considerable clinical implications reducing patient discomfort, health-care costs, and possibly improvement of cosmetic result.

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Online resource

Table 1. Ipsilateral breast tumor recurrence (IBTR), disease free survival (DFS), and overall survival (OS) rates from Kaplan-Meier analysis and adjusted hazard ratio (HR) from multivariable Cox regression analysis. (n = 10,433)

	IBTR	**DFS**	**OS**
	Adjusted[a] HR (95%CI)	**Adjusted[a] HR (95%CI)**	**Adjusted[a] HR (95%CI)**
Resection margins and surgical treatment			
- negative margins and primary BCS only	0.76 (0.43-1.35)	0.81 (0.63-1.04)	1.07 (0.85-1.34)
- focally positive margins			
- primary BCS only	reference	reference	reference
- primary BCS + re-excision	***0.30 (0.11-0.82)***	0.83 (0.59-1.17)	1.17 (0.87-1.59)
- extensively positive margins and primary BCS + re-excision	0.75 (0.37-1.51)	0.98 (0.73-1.32)	1.22 (0.94-1.59)
Age	***0.98 (0.97-1.00)***	1.00 (0.99-1.01)	***1.05 (1.05-1.06)***
Histology			
- ductal	reference	reference	reference
- lobular	0.87 (0.54-1.39)	1.17 (0.98-1.40)	0.93 (0.80-1.08)
- other	0.86 (0.54-1.36)	0.97 (0.80-1.19)	0.94 (0.80-1.11)
Differentiation grade			
- 1	reference	reference	reference
- 2	1.26 (0.84-1.91)	***1.59 (1.31-1.92)***	***1.38 (1.19-1.60)***
- 3	2.63 (1.67-4.15)	2.62 (2.13-3.22)	2.02 (1.71-2.37)
- unknown	1.45 (0.78-2.63)	***1.50 (1.14-1.97)***	***1.40 (1.14-1.74)***
pT			
- T1	reference	reference	reference
- T2	1.30 (0.95-1.77)	***1.60 (1.40-1.82)***	1.56 (1.40-1.74)
- T3	1.48 (0.45-4.91)	1.49 (0.94-2.35)	***1.89 (1.30-2.75)***
- ypT0	-	1.49 (0.47-4.67)	1.54 (0.57-4.15)
pN			
- N0	reference	reference	reference
- N1	1.23 (0.85-1.78)	***1.41 (1.20-1.65)***	***1.37 (1.21-1.57)***
- N2	2.32 (1.34-4.01)	3.16 (2.57-3.89)	2.61 (2.18-3.13)
- N3	4.19 (2.15-8.17)	5.51 (4.31-7.06)	4.45 (3.55-5.58)
- unknown	1.11 (0.27-4.54)	1.19 (0.62-2.32)	***1.98 (1.34-2.94)***

Table 1. Ipsilateral breast tumor recurrence (IBTR), disease free survival (DFS), and overall survival (OS) rates from Kaplan-Meier analysis and adjusted hazard ratio (HR) from multivariable Cox regression analysis. (n = 10,433)*(continued)*

	IBTR	DFS	OS
	Adjusted[a] HR (95%CI)	**Adjusted[a] HR (95%CI)**	**Adjusted[a] HR (95%CI)**
Estrogen receptor			
- positive	reference	reference	reference
- negative	2.32 (1.49-3.59)	1.63 (1.33-2.00)	1.53 (1.26-1.86)
- unknown	2.43 (0.85-6.95)	1.48 (0.96-2.29)	1.12 (0.79-1.60)
Her2Neu receptor			
- negative	reference	reference	reference
- positive	1.10 (0.71-1.72)	0.85 (0.70-1.04)	*0.78 (0.64-0.94)*
- unknown	0.60 (0.21-1.74)	0.86 (0.55-1.34)	1.04 (0.73-1.50)
Systemic therapy (yes vs no)	0.30 (0.20-0.44)	0.48 (0.41-0.58)	0.81 (0.71-0.93)
Radiotherapy (yes vs no)	0.67 (0.38-1.27)	0.97 (0.76-1.23)	1.11 (0.90-1.36)

[a]Adjusted for: age (continuous), histology (ductal, lobular, or other), differentiation grade (1, 2, 3, or unknown), pT stage (1, 2, 3, or ypT0), pN stage (1, 2, 3, or unknown), estrogen receptor status (positive, negative, or unknown), her2neu receptor status (positive, negative, or unknown), use of systemic therapy (any or none), and radiotherapy (yes or no).

Table 2. Ipsilateral breast tumor recurrence (IBTR) rate from Kaplan-Meier analysis and unadjusted hazard ratio (HR) from univariable Cox regression analysis stratified for systemic therapy (chemotherapy and/or hormonal therapy) and according to resection margins after primary BCS and the performance of re-excision in the subcohort. (n = 10,433)

	No systemic therapy			**Systemic therapy**		
	n	**5-year**	**HR (95%CI)**	**n**	**5-year**	**HR (95%CI)**
Negative margins and primary BCS only	3214	2.7%	0.87 (0.35-2.14)	4606	2.0%	0.70 (0.34-1.45)
Focally positive margins						
- primary BCS only	183	3.2%	reference	309	2.8%	reference
- primary BCS + re-excision	170	1.9%	0.61 (0.15-2.56)	416	0.8%	0.28 (0.08-1.06)
Extensively positive margins and primary BCS + re-excision	468	4.0%	1.34 (0.49-3.63)	1067	2.3%	0.85 (0.38-1.91)

PART IV

Quality of care

CHAPTER 9

The effect of case-mix and random variation on breast cancer care quality indicators and their rankability

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ABSTRACT

Background: Hospital comparisons are increasingly common as an approach to improve quality of care, but require valid and reliable quality indicators. We aimed to test the validity and reliability of six breast cancer care process and outcome indicators by quantifying the influence of case-mix and random variation.

Methods: The population-based database included 79,690 breast cancer patients from all 91 Dutch hospitals between 2011-2016. The indicator scores calculated were: 1) irradical breast conserving surgery (BCS) for invasive disease, 2) irradical BCS for ductal carcinoma-in-situ, 3) breast contour preserving treatment, 4) MRI before neo-adjuvant chemotherapy, 5) radiotherapy for locally advanced disease, and 6) surgery within 5 weeks from diagnosis. Between-hospital variation was expressed with (interquartile) ranges. Case-mix and random variation adjustment were performed with multivariable fixed effect and random effect logistic regression models. Rankability was calculated to quantify the part of between-hospital variation representing unexplained differences that might be due to quality of care.

Results: All indicators showed between-hospital variation with wide (interquartile) ranges. Case-mix adjustment reduced variation in indicator 1 and 3 to 5. Random variation adjustment (further) reduced variation for all indicators. Case-mix and random variation adjustment influenced the individual hospitals scores of all indicators. Rankability for indicator 1-6 was 22%, 20%, 68%, 63%, 23%, and 71% respectively.

Conclusion: Although measuring quality indicators may stimulate quality improvement in general. Comparisons and judgments of individual hospital performance should be made with caution if based on indicators that were not tested for validity and reliability. Especially in the public domain.

INTRODUCTION

Public reporting of quality indicator outcomes stimulates quality improvement activities by hospitals(1). An increasing demand for monitoring and comparing (i.e., benchmarking) the quality of breast cancer care of individual hospitals has been seen worldwide. Wide reaching parties desire transparency about this quality of care; governmental agencies, accrediting bodies, medical specialty societies, health care insurance companies, and patient organizations.

In the Netherlands, breast cancer care quality improvements efforts are led by the National Breast cancer working group Netherlands (NABON) Breast Cancer Audit (NBCA). A set of structure, process and outcome indicators are defined and regularly updated by multidisciplinary group consensus including surgeons, medical oncologists, radiation oncologists, pathologists, radiologists, health care insurers, and patient representatives(2). Indicators are adapted or removed when considered redundant and new indicators are developed based on new insights. In 2011 the set included 30 quality indicators which evolved into a set of 19 indicators in 2017. Previously, the between-hospital variation of individual quality indicators have been published(3-5). Data quality is high due to the use of unique cancer registry data to a large extent. Completeness of patient records in the NBCA database from each hospital in the country is high with a median of 99% in 2014(2). The NBCA provides feedback to the individual hospitals on their quality indicator scores in relation to national levels and other (anonymously presented) hospitals.

Quality improvement based on indicators can be broadly distinguished into internal and external quality improvement. Internal improvement does not require benchmarking between hospitals while external improvement does. Comparing and public reporting requires that quality indicators measure what they claim to measure and thus are valid and reliable. Valid and reliable quality indicators require that differences actually represent true differences in quality of care. Between-hospital differences may be explained by other issues than differences in actual quality of care. Firstly, they can be caused by baseline risk differences between the patient populations (i.e., case-mix) influencing the validity of the indicator(6, 7). Which case-mix factors (e.g. patient and tumour characteristics) are relevant can be different for each individual quality indicator. Secondly, low numbers of patients per hospital, and more specifically low numbers of events may cause differences that are due to variation by chance i.e., statistical uncertainty or random variation(8). Random variation prevents an indicator to produce the same result on repeated measurements thereby making the indicator less reliable. Whether it is fair to rank hospitals according to their performance after adjustment

for case-mix and random variation can be addressed by rankability. Rankability quantifies the remaining 'true' between hospital differences that may be due to differences in quality of care. Thirdly, other elements that determine reliability and validity are indicator definitions and data quality. Other aspects of quality indicators that are more relevant for internal quality improvement are relevance, feasibility, and usability, which have been addressed earlier and are not topic of the current study(2).

If data is misinterpreted the consequences can be major for all parties involved. To pursue fair hospital comparisons and ranking it is crucial to evaluate quality indicators for validity and reliability(9). These comprise the scientific rigor of a quality indicator and is statistically analysed in the current study. The aim of this study was to quantify the influence of case-mix and random variation on process and outcome measures that are used as quality indicators for breast cancer care in the Netherlands. Three outcome indicators and three process indicators were studied. Furthermore, the remaining true between hospital differences that may be due to differences in the quality of care were quantified.

METHODS

Data collection

From the NBCA, patient level data were retrieved of primary invasive breast cancer or ductal carcinoma-in-situ (DCIS) patients whom were surgically treated and diagnosed in 91 different hospitals between January 1st 2011 and August 1st 2016 in the Netherlands. The NBCA gathers information from all Dutch hospitals on breast cancer care and outcomes in the Netherlands since 2011. Hospitals choose to register the data themselves or have it registered by the Netherlands Comprehensive Cancer Organisation (IKNL). Self-registering hospitals (20-30% of all hospitals) enter the data directly into a web-based system using a manual to secure uniform data acquisition. The IKNL hosts the Netherlands Cancer Registry (NCR) that registers all new malignancies on a national level since 1989. It has specially trained registration clerks located in each hospital in the Netherlands that follow a strict coding manual. All hospitals review the data for inconsistencies and make corrections before the data is transferred by IKNL to the NBCA database. A third party anonymised all data before it was made available for this study.

The following general patient-, tumor-, and treatment characteristics have been collected: gender, age, World Health Organization (WHO) performance status, history of breast surgery, method of tumor detection, palpability, type of surgery, multifocality, histology, tumor size in mm, Bloom and Richardson differentiation

grade, hormone and her2neu receptor status, clinical and pathological tumor node metastasis staging (TNM) according to the sixth edition of TNM Classification of Malignant Tumors by the American Joint Committee on Cancer, radiotherapy use, chemotherapy use and type, and hormonal therapy use.

Quality indicators (QI)

The definitions of the NBCA quality indicator set of 2017 were used for calculating the indicator scores with the data from 2011-2016 described above. For the purpose of current analysis we could only study a limited number of indicators. Since outcome indicators are often seen as the most valuable, all outcome indicators were calculated, namely: QI 1) irradical breast conserving surgery for invasive disease defined as more than focally positive according to the Dutch national guideline (tumour touching the inked margin over a length of 4mm or more)(10), QI 2) irradical breast conserving surgery for DCIS defined as tumour-on-ink, and QI 3) breast contour preserving treatment. Breast contour preserving treatment was a composite measure for a) the percentage of patients with breast conserving surgery, including re-lumpectomies, without neo-adjuvant chemotherapy and followed by radiation treatment, b) the percentage of patients with breast conserving surgery, including re-lumpectomies, after neo-adjuvant chemotherapy and followed by radiation treatment, and c) the percentage of patients with a mastectomy and direct breast reconstruction.

Concerning the process indicators, three measures were chosen that address different specialties for which a general believe in their representation of quality of care exists, that show considerable hospital variation, and have room for improvement (i.e., not already scoring 100%), namely: QI 4) MRI in neo-adjuvant chemotherapy, QI 5) radiotherapy for locally advanced breast cancer, and QI 6) surgery within 5 weeks of breast cancer diagnosis. No evidence or guidance exists for which process indicators to use.

Quality indicator scores were calculated based on the NBCA manual defining the numerators and denominators of each indicator (Table 1). Indicator scores presented here can deviate from the reports published by the NBCA. We chose not to make missing indicator variables an advantage likewise the NBCA. In case indicator information was missing, it was assumed that this indicator was not met. This can only lead to an underestimation of the indicator scores.

Table 1A. Between-hospital variation in breast cancer quality indicator scores in 2015 only.

QI	Name	Definition	Type	N	Median	IQR	Range
1	Irradical BCS in invasive disease	Numerator: number of patients with more than focally positive margins[a] after first breast conserving surgery. Denominator: Number of patients treated with breast conserving surgery for invasive non-metastasized breast cancer and without neo-adjuvant chemotherapy.	O	82	2.8%	0.8-4.6	0-15
2	Irradical BCS in DCIS	Numerator: number of patients with positive margins (tumor-on-ink) after first breast conserving surgery. Denominator: Number of patients treated with breast conserving surgery for DCIS.	O	82	19%	11-29	0-100
3	Breast contour preserving treatment	Numerator: number of patients with i) breast conserving surgery including re-lumpectomies (both without and with neo-adjuvant chemotherapy) and ii) mastectomy with direct breast reconstruction[d]. Denominator: number of patients with invasive non-metastasized breast cancer, both patients treated without and with neo-adjuvant chemotherapy.	O	82	68%	61-76	45-94
4	MRI in neo-adjuvant chemotherapy	Numerator: number of patients with breast MRI prior to start of neo-adjuvant chemotherapy. Denominator: number of patients with invasive breast cancer and treated with neo-adjuvant chemotherapy.	P	82	94%	86-100	18-100
5	Radiotherapy for locally advanced	Numerator: number of patients treated with radiotherapy. Denominator: number of patients with invasive non-metastasized locally advanced[b] breast cancer and treated with mastectomy	P	79	79%	69-92	0-100
6	Surgery within 5 weeks	Numerator: number of patients receiving surgery within 5 weeks of diagnosis[c]. Denominator: number of patients without breast reconstruction. invasive breast cancer and treated with neo-adjuvant chemotherapy. Transit time ≤ 5 weeks between diagnosis and primary surgery (without immediate reconstruction).	P	82	85%	76-92	29-100

QI=quality indicator, N=number of hospitals IQR=interquartile range, O=outcome, P=process, DCIS=ductal carcinoma-in-situ, MRI=magnetic resonance imaging.

[a] Extensively positive margins is defined as tumour touching the inked margin over a length of 4mm or more.

[b] Clinical T3, T4, any N, M0 and T, N2-3,M0. with ≥cT3 or ≥pT2 (except for pT3N0).

[c] Date of diagnosis=date of biopsy.

[d] Including secondary mastectomies and including both prosthesis and autologous breast reconstruction.

Table 1B. Between-hospital variation in breast cancer quality indicator scores between 2011 to 2016.

QI	Name	Definition	Type	N	Median	IQR	Range
1	Irradical BCS in invasive disease	Numerator: number of patients with more than focally positive margins[a] after first breast conserving surgery. Denominator: Number of patients treated with breast conserving surgery for invasive non-metastasized breast cancer and without neo-adjuvant chemotherapy.	O	91	3.1%	2.1-4.2	0-9

QI=quality indicator, N=number of hospitals IQR=interquartile range, O=outcome.

[a] Extensively positive margins is defined as tumour touching the inked margin over a length of 4mm or more.

Statistical analysis

Throughout the results section hospital variation refers to *between*-hospital differences. W*ithin*-hospital trends over the years or between caregivers were not studied. Between-hospital variation was expressed as median, interquartile range (IQR), and range of the quality indicator. To assess the effect of the number of events, we calculated hospital variation of the indicators with one year of data only (2015) and with five years of data combined (2011-2016).

Missing values of the above mentioned available data which could be considered to be possible case-mix factors were imputed if less than 20% was missing in the total study population. Data imputation was performed by multiple imputation by chained equations (MICE) approach (5 times) based on the case-mix factors themselves and the following predictors: WHO performance status, clinical tumor and axillary lymph node stage, type of surgery, pathologically confirmed positive axillary lymph nodes, radiotherapy use, chemotherapy use, hormonal therapy use. The predictors also included missing values. To confirm that imputation did not change the data, hospital variation in case-mix factors before and after imputation was calculated.

The associations between possible case-mix factors and quality indicators were identified by univariable fixed effects logistic regression analyses. Factors with p-value <0.1 were considered as case-mix factors and included in the multivariable fixed effects logistic regression analyses. Age was always included in the multivariable models. Continuous variables were added to the model as quadratic term in case it significantly improved the models in Nagelkerke R square. Case-mix model performance was evaluated by the area under the curve (AUC) with a 95% confidence interval (CI). The AUC value lies between 0 and 1 and resembles the ability to predict the quality indicator outcome based on the case-mix variables. Whereby an AUC of 0.5 is no better than chance, 0.5-0.6 is very poor, 0.6-0.7 is poor, 0.7-0.8 is fair, 0.8-0.9 is good, and >0.9 is excellent.

To quantify the effect of case-mix and random effect correction, standardized rate was used. The standardized rate (SR) is a ratio between the observed number of events and the expected number of events in an individual hospital. A standardized rate larger than 100 (>100) means excess events and a standardized rate smaller than 100 (<100) means less events than expected. The standardized rate was calculated in the following three models: i) crude fixed effect model, ii) case-mix corrected fixed effect model, iii) crude random effect model, and iv) case-mix corrected random effect model. In the fixed effects models (i and ii), the observed number of events is the individual hospital quality indicator score. The expected number of events is the mean from all hospitals for the crude model

(i) and the predicted probability for an individual hospital for the case-mix corrected model (ii). In the random effects models (iii and iv), the observed number of events is the overall intercept plus the hospital specific random intercept from the crude random effects models transformed into a probability. Multiplying this probability by the total number of patients in that hospital gives the observed number adjusted for variation by chance. The effect of case-mix correction is quantified by comparing the standardized rate in model ii to that of model i. The additional effect of random effect correction is quantified by comparing the standardized rate in model iiii to that of model ii. Whereby an effect is present in case the between-hospital variation becomes smaller (i.e., smaller IQR) or when there is a substantial shift in individual hospital standardized rate scores (i.e., shift in standardized rate).

Rankability addresses the reliability of ranking hospitals on their quality of care. It is a percentage expressing the part of heterogeneity between hospitals that is represented by unexplained differences that might be due to the quality of care. Rankability was calculated by relating the variance of the random effects after case-mix correction with the variance of the fixed-effect individual-hospital effect estimates after case-mix correction (see formula in Figure 1). To assess the effect of the number of events, we calculated the rankability with one year of data only (2015) and with five years of data combined (2011-2016).

Statistical tests were two-sided and p-value<0.050 was considered statistically significant. Statistical analyses were performed by IBM SPSS Statistics version 21.0 (IBM, Armonk, New York, USA) and R statistical software 3.4.0 (R Foundation for Statistical Computing, Vienna, Austria).

$$\rho = \frac{\tau^2}{(\tau^2 + \text{median}(s_i^2))}$$

ρ= rankability, τ^2= variance of the random effects, $s^2_{i=}$ variance of the fixed-effect individual-hospital effect estimates

Figure 1. Rankability formula.

RESULTS

Between January 2011 and August 2016, a total of 91 hospitals with 79,690 newly diagnosed breast cancer patients were surgically treated and included in the NBCA. Using data of 2015 only, the median number of patients per hospital was 156 (range 50-612) (Table 1A). The hospital variation was large for QI 2 ('irradical BCS in DCIS') and QI 4-6 ('MRI in neo-adjuvant chemotherapy', 'radiotherapy for locally advanced', 'surgery within 5 weeks') which was especially pronounced in the range. In QI 3 ('breast contour preserving treatment') there was less hospital

variation, but the least variation was seen in QI 1 ('irradical BCS in invasive disease') (Table 1A). To illustrate the effect of larger hospital volume, Table 1B shows the hospital variation of QI 1 ('irradical BCS in invasive disease') in the years 2011 to 2016 combined. The median number of patients per hospital treated between 2011 to 2016 was 746 (range 43-3114). In contrast to 2015 only, the hospital variation was smaller due to larger number of patients per hospital (Table 1B).

WHO performance status was the only case-mix factor with more than 20% missing values and therefore no imputation was performed for it (Table 2). The data before and after imputation was very comparable. All case-mix factors showed quite some variation between hospitals, especially the case-mix factors history of breast surgery, WHO status, multifocality, histology, tumor size, tumor and lymph node stadium, estrogen receptor status, number of screen detected tumors, and palpability.

Table 2. Descriptive information and between-hospital variation on possible case-mix factors between 2011 to 2016.

	Before data imputation			After data imputation		
	Number of patients (%)	**Hospital IQR (%)**	**Hospital range (%)**	**Total (%)**	**Hospital IQR (%)**	**Hospital range (%)**
Number of patients	79690	575-1048	43-3114	79690	575-1048	43-3114
Gender						
- Female	79228 (99)	99-100	98-100	79239 (99)	99-100	98-100
- Male	451 (0.6)	0.4-0.8	0-1.8	451 (0.6)	0.4-0.8	0-1.8
- Missing values	11 (0.0)	0-0	0-0.4			
Age						
- Mean (years)	61	61-62	54-65	61	61-62	54-64
- Missing values	28 (0.0)					
WHO performance status*						
- 0	17598 (22)	7.0-31	0.0-59	17598 (22)	7.2-31	0-59
- 1	3010 (3.8)	1.0-6.0	0-23	3010 (3.8)	1.0-6.1	0-23
- 2-4	452 (0.6)	0.1-0.5	0-10	452 (0.6)	0.1-0.5	0-10
- Missing values	58630 (74)	64-91	34-100	58630 (74)	64-91	34-100
History of breast surgery						
- No	72081 (91)	89-93	76-96	72354 (91)	89-93	84-96
- Benign	5201 (6.5)	5.2-7.8	1.9-11	5220 (6.6)	5.2-7.8	1.9-11
- Malignancy	2109 (2.6)	1.3-3.5	0-8.0	2116 (2.7)	1.3-3.5	0-8.0
- Missing values	299 (0.4)	0-0.4	0-13			
Screen detected tumor						
- No	45117 (57)	55-60	45-95	45317 (57)	54-59	38-95
- Yes	34255 (43)	40-45	4.7-55	34372 (43)	41-46	4.7-63
- Missing values	318 (0.4)	0-0.5	0-9.0			
Palpability						
- No	33609 (42)	39-45	23-59	34173 (43)	39-45	24-60
- Yes	44893 (56)	54-60	39-68	45517 (57)	55-61	40-76
- Missing values	1188 (1.5)	0.4-2.0	0-9.3			
Multifocality						
- No	67024 (84)	83-88	62-96	67873 (85)	84-89	65-96
- Yes	11646 (15)	11-16	4.1-35	11817 (15)	11-16	4.1-35
- Missing values	1020 (1.3)	0.2-1.1	0-26			
Histology						
- Ductal	65761 (80)	81-85	57-90	66666 (84)	82-86	69-90
- Lobular (or mixed)	9841 (12)	10-14	5.3-24	9959 (12)	11-14	5.3-26
- Other	3006 (3.7)	3.0-4.6	0-21	3065 (3.8)	3.1-4.7	0-21
- Missing values	3185 (3.9)	0.6-1.6	0-15			

Table 2. *(continued)*

	Before data imputation			After data imputation		
	Number of patients (%)	Hospital IQR (%)	Hospital range (%)	Total (%)	Hospital IQR (%)	Hospital range (%)
Primary tumor stadium						
- pT1	44214 (56)	53-58	37-67	44382 (56)	53-58	39-68
- pT2	18645 (23)	21-27	14-44	18784 (24)	21-27	14-44
- pT3	2285 (2.9)	2.1-3.5	0-7.0	2506 (3.1)	2.3-3.7	1.0-7.3
- pT4	588 (0.7)	0.5-0.9	0-2.5	594 (0.7)	0.5-1.0	0-2.6
- pT0	2014 (2.5)	1.1-3.1	0-8.3	2340 (2.9)	1.3-3.6	0-8.4
- pTis (DCIS)	10826 (14)	12-14	7.0-22	11119 (14)	12-15	7.0-22
- Missing values	1118 (1.4)	0.7-1.9	0.1-7.9			
Postoperative tumor size						
- Mean (mm)	18	17-20	13-26	19	18-20	13-26
- Missing values	6350 (8.0)					
Differentiation grade						
- 1	17506 (22	19-25	13-37	18677 (23)	20-26	14-38
- 2	33423 (42)	39-46	26-57	36403 (46)	43-49	27-58
- 3	22064 (28)	24-31	19-56	24609 (31)	27-34	19-58
- Missing values	6697 (8.4)	4.7-11	1.1-30			
Oestrogen receptor status						
- Negative	11602 (15)	12-15	4.4-43	17004 (21)	18-22	10-49
- Positive	55149 (69)	68-73	33-80	62686 (79)	78-82	51-90
- Missing values	12939 (16)	13-17	11-38			
Progesteron receptor status						
- Negative	21561 (27)	23-29	19-41	29016 (36)	32-38	27-52
- Positive	45279 (57)	55-61	29-68	50674 (64)	62-68	48-73
- Missing values	12850 (16)	13-17	11-33			
Har2 receptor status						
- Negative	55893 (71)	71-76	34-82	66817 (84)	84-86	76-89
- Positive	8587 (11)	10-12	4.6-18	12873 (16)	14-16	11-24
- Missing values	14210 (18)	14-18	7.0-61			
Regional lymph nodes stadium						
- pN0(i)	53752 (68)	65-70	57-75	56916 (71)	69-73	63-78
- pN1	16820 (21)	20-23	15-27	17457 (22)	21-23	16-27
- pN2	3197 (4.0)	3.4-4.9	0-14	3333 (4.2)	3.5-5.1	0.6-14
- pN3	1830 (2.3)	1.6-2.8	0-4.8	2070 (2.6)	1.9-3.1	0-5.4
- Missing values	4091 (5.1)	3.3-6.8	0-16			
Distant metastasis						
- No (cM0 or pM0)	79328 (100)	99-100	97-100	79366 (100)	100-100	99-100
- Yes (cM1 and/or pM1)	320 (0.4)	0.1-0.5	0-1.5	324 (0.4)	0.1-0.5	0-1.5
- Missing values	42 (0.1)	0-0	0-1.6			

* 0=asymptomatic, 1=symptomatic but completely ambulatory, 2-4=symptomatic, < 50% in bed during the day, and bedbound

Table 3. Multivariable fixed effects logistic regression analyses with odds ratio (95% CI) after data imputation between 2011 to 2016.

	Outcome indicators						**Process indicators**					
	Surgery						**Radiology**		**Surgery**		**Radiology**	
	1: Irradical BCS in invasive disease	p-value	2: Irradical BCS in DCIS	p-value	3: Breast contour preserving treatment	p-value	4: MRI in neo-adjuvant chemotherapy	p-value	5: Radiotherapy for locally advanced	p-value	6: Surgery within 5 weeks	p-value
Number of patients	36562		7437		68135		7599		5257		20577	
Male gender (vs female)					0.02 (0.01-0.03)	<0.001						
Age (years)	1.00 (0.99-1.00)	0.085			1.09 (1.07-1.10)	<0.001	1.10 (1.05-1.15)	<0.001	1.12 (1.08-1.17)	<0.001	1.04 (1.01-1.06)	0.006
WHO performance status												
- 0	1.00 (ref)		1.00 (ref)		1.00 (ref)		1.00 (ref)		1.00 (ref)		1.00 (ref)	
- 1	1.07 (0.79-1.45)	0.671	-		0.72 (0.66-0.79)	<0.001	0.71 (0.55-0.93)	0.012	0.76 (0.56-1.01)	0.062	1.01 (0.84-1.24)	0.953
- 2-4	1.52 (0.78-2.98)	0.221	-		0.70 (0.56-0.87)	0.001	0.45 (0.21-0.98)	0.044	0.36 (0.21-0.63)	<0.001	0.64 (0.45-0.91)	0.013
- Missing values	0.91 (0.79-1.06)	0.220	2.53 (0.97-6.61)	0.058	0.92 (0.88-0.96)	<0.001	0.55 (0.48-0.63)	<0.001	0.66 (0.55-0.80)	<0.001	1.00 (0.91-1.11)	0.934
History of breast surgery												
- No	1.00 (ref)				1.00 (ref)				1.00 (ref)		1.00 (ref)	
- Benign	1.22 (0.97-1.54)	0.083			1.00 (0.94-1.09)	0.835			1.13 (0.81-1.58)	0.466	1.02 (0.87-1.19)	0.831
- Malignancy	2.16 (1.44-3.24)	<0.001			0.21 (0.19-0.23)	<0.001			0.45 (0.26-0.77)	0.004	0.84 (0.72-0.98)	0.024
Screen detected (vs not)	0.79 (0.69-0.91)	0.001	0.74 (0.65-0.85)	<0.001	1.72 (1.64-1.80)	<0.001					1.01 (0.92-1.10)	0.913
Palpable tumor (vs not)	0.84 (0.72-0.97)	0.016	1.14 (0.95-1.36)	0.169	0.89 (0.85-0.94)	<0.001					1.36 (1.23-1.50)	<0.001
Multifocal (vs unifocal)	2.19 (1.84-2.61)	<0.001	1.89 (1.47-2.44)	<0.001	0.29 (0.27-0.30)	<0.001					0.87 (079-0.94)	0.001
Histology												
- Ductal	1.00 (ref)				1.00 (ref)						1.00 (ref)	
- Lobular (or mixed)	2.11 (1.82-2.45)	<0.001			0.66 (0.63-0.70)	<0.001					0.90 (0.81-0.99)	0.033
- Other	1.29 (0.94-1.75)	0.111			1.02 (0.92-1.13)	0.704					0.83 (0.69-0.99)	0.039

Table 3. Multivariable fixed effects logistic regression analyses with odds ratio (95% CI) after data imputation between 2011 to 2016. *(continued)*

	Outcome indicators						**Process indicators**					
	Surgery						**Radiology**		**Surgery**		**Radiology**	
	1: Irradical BCS in invasive disease	p-value	2: Irradical BCS in DCIS	p-value	3: Breast contour preserving treatment	p-value	4: MRI in neo-adjuvant chemotherapy	p-value	5: Radiotherapy for locally advanced	p-value	6: Surgery within 5 weeks	p-value
Primary tumor stadium												
- pT1	1.00 (ref)				1.00 (ref)		1.00 (ref)		1.00 (ref)		1.00 (ref)	
- pT2	2.49 (2.17-2.87)	<0.001			0.53 (0.50-0.56)	<0.001	1.08 (0.90-1.29)	0.412	1.26 (0.95-1.66)	0.107	0.99 (0.90-1.08)	0.765
- pT3	19.3 (13.9-26.6)	<0.001			0.21 (0.18-0.25)	<0.001	0.74 (0.58-0.95)	0.018	1.88 (1.26-2.80)	0.002	0.91 (0.77-1.08)	0.284
- pT4	7.08 (3.44-14.6)	<0.001			0.21 (0.16-0.28)	<0.001	0.32 (0.22-0.48)	<0.001	1.31 (0.89-1.93)	0.174	0.70 (0.53-0.93)	0.014
- pT0	2.64 (0.62-11.3)	0.189			0.47 (0.42-0.53)	<0.001	1.03 (0.87-1.22)	0.705	2.56 (1.63-3.70)	<0.001	0.50 (0.19-1.35)	0.172
- pTis (DCIS)	1.34 (0.22-8.03)	0.749			0.67 (0.35-1.28	0.192	1.27 (0.48-3.35)	0.619	2.95 (0.65-13.4)	0.162	0.64 (0.57-0.73)	<0.001
Tumor size (mm)			1.05 (1.04-1.07)	<0.001	0.98 (0.98-0.98)	<0.001			0.97 (0.96-.98)	<0.001		
Differentiation grade												
- 1	1.00 (ref)		1.00 (ref)		1.00 (ref)				1.00 (ref)			
- 2	1.45 (1.07-1.46)	0.006	1.52 (1.26-1.84)	<0.001	0.89 (0.85-0.94)	<0.001			1.35 (1.01-1.82)	0.047		
- 3	1.30 (1.07-1.57)	0.007	1.76 (1.47-2.11)	<0.001	0.91 (0.85-0.97)	0.003			1.44 (1.05-1.98)	0.026		
Positive ER (vs negative)	1.58 (1.28-1.94)	<0.001			1.14 (1.07-1.23)	<0.001						
Positive PR (vs negative)					1.10 (1.05-1.16)	<0.001						
Positive HR (vs negative)					0.76 (0.72-0.80)	<0.001						
Lymph nodes stadium												
- pN0(i)	1.00 (ref)				1.00 (ref)				1.00 (ref)		1.00 (ref)	
- pN1	1.42 (1.23-1.63)	<0.001			0.59 (0.57-0.62)	<0.001			4.72 (3.68-6.05)	<0.001	1.00 (0.91-1.10)	0.911
- pN2	3.05 (2.33-3.98)	<0.001			0.26 (0.24-0.29)	<0.001			11.0 (8.71-14.0)	<0.001	0.92 (0.78-1.07)	0.261
- pN3	2.93 (2.02-4.25)	<0.001			0.24 (0.21-0.27)	<0.001			12.4 (9.35-16.3)	<0.001	0.90 (0.75-1.07)	0.234
Distant metastasis (vs no)												

Abbreviations: DCIS=ductal carcinoma-in-situ, ER=oestrogen receptor, PR=progesteron receptor, HR=her2neu receptor

Case–mix and random effect adjustment

For each of the six quality indicators, a separate case-mix model was build. The case-mix factors included in each model were displayed in Table 3. All factors with a p-value <0.1 in the univariable analysis and 'age at diagnosis' were included in the case-mix fixed effect models (ii) (online supplementary material Table A). The AUC (95%CI) was fair for QI 1 with 0.71 (0.70-0.73), poor for QI 2 with 0.67 (0.66-0.69), good for QI 3 with 0.80 (95% CI 0.80-0.81), poor for QI 4 with 0.65 (0.63-0.66), fair for QI 5 with 0.78 (0.76-0.79), and very poor for QI 6 with 0.56 (0.55-0.58).

After case-mix adjustment, hospital variation became generally smaller, but the extent varied between the indicators (Table 4). Hospital variation became moderately smaller for QI 3 and QI 4, slightly smaller for QI 1 and QI 5, but did not narrow down for QI 2 and QI 6. For the individual hospitals, their standardized rate changed substantially for QI 1 to 3 and QI 5, moderately for QI 4, and limited for QI 6. After adjustment for random variation, hospital variation further narrowed down substantially for all six indicators (Table 4). For individual hospitals, their standardized rate further changed substantially for QI 1 and QI 2, moderately for QI 3 to 5, and limited for QI 6. To illustrate the effect of lower hospital volume, hospital variation for QI 1 using data from 2015 only was added to Table 4. In contrast to the 2011 to 2016 combined, the hospital variation was larger, but the effect of case-mix and random variation was similar (Table 4).

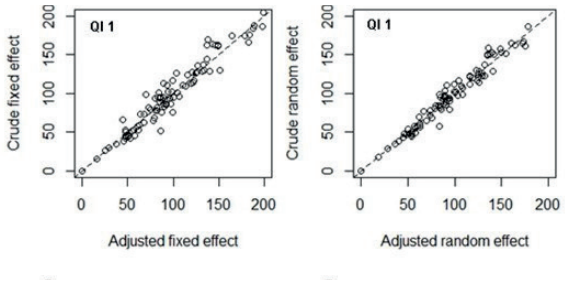
To illustrate the shift in standardized rate of individual hospitals after case-mix adjustment in the fixed effect(A) and random variation(B) models, the standardized rates were shown in scatterplots (Figure 2). The deviation from the diagonal illustrates the effect of case-mix adjustment. The spread on the diagonal line in Figure B as compared to Figure A illustrates the effect of random variation adjustment. For QI 1-2, there was a large effect of case-mix adjustment since substantial deviation from the diagonal is present. For QI 3 to 5, hospital variation was mostly affected by random variation and not by case-mix. This is illustrated by the limited deviation from the diagonal line and decreasing diagonal spread between the random and fixed effect model. For QI 6, there was no effect of case-mix adjustment since all hospitals remain on the diagonal line in the random variation model.

Table 4 Between-hospital variation in breast cancer quality indicator scores between 2011 to 2016.

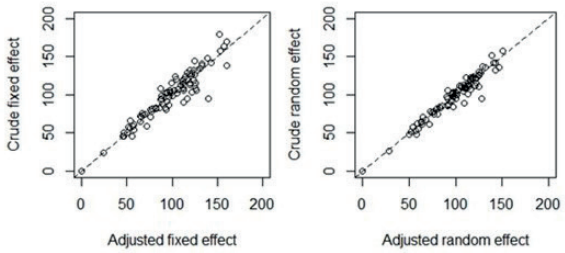
	Before case-mix correction, absolute score			**After case-mix correction, absolute score**		**Crude fixed effect SR**	**Case-mix corrected fixed effect SR**	**Individual hospital shifts in SR**	**Case-mix corrected random effect SR**	**Individual hospital shifts in SR**
	N	IQR	Range	IQR	range	IQR	IQR	Range	IQR	Range
QI 1	91	2.1-4.2	0-8.9	3.0-3.6	2.0-4.9	62-128	63-127	-41, 31	68-126	-28, 23
QI 2	91	16-24	0-36	20-22	14-29	80-120	77-120	-45, 27	84-116	-32, 14
QI 3	91	57-72	46-88	65-68	53-76	88-110	90-107	-15, 15	93-103	-12, 6
QI 4	90	73-94	0-100	83-86	78-89	91-117	88-110	-2, 12	94-106	-6, 1
QI 5	89	77-88	52-100	80-84	65-92	94-108	94-106	-33, 12	95-104	-11, 3
QI 6	91	79-92	42-100	83-84	82-84	95-110	96-111	-2, 0	94-106	-1, 1
QI 1*	82	0.8-4.6	0-15	2.9-3.5	1.9-4.9	26-151	26-139	-55, 73	33-141	-30, 56

Abbreviations: QI=quality indicator, N=number of hospitals, IQR=interquartile range, SR=standardized rate

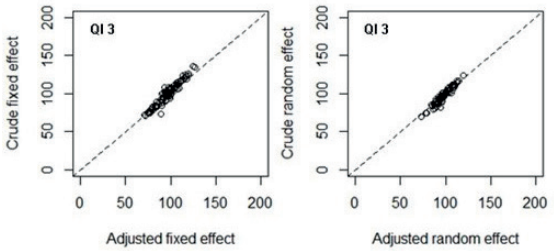
* in data of 2015 only



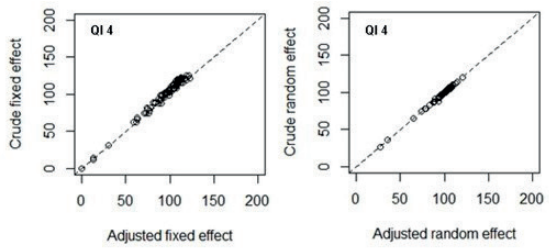
QI 1 Irradicality in invasive disease in fixed effect (A) and random effect model (B)



QI 2 Irradicality in DCIS in fixed effect (A) and random effect model (B)

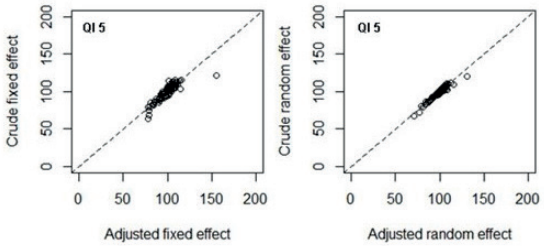


QI 3 Breast contour preserving treatment in fixed effect (A) and random effect model (B)

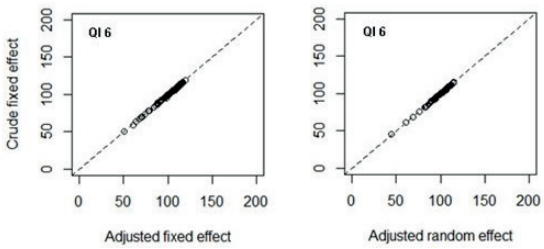


QI 4 MRI in neo-adjuvant chemotherapy in fixed effect (A) and random effect model (B)

9



QI 5 Radiotherapy for locally advanced breast cancer in fixed effect (A) and random effect model (B)



QI 6 Surgery within 5 weeks in fixed effect (A) and random effect model (B)

Figure 2. The effect of case-mix adjustment in the fixed effect and random effect models for individual hospitals. Each dot represents a hospital. Both axis show the standardized rate of the quality indicator, the y-axis before adjustment and the x-axis after adjustment for case-mix. The deviation from the diagonal illustrates the effect of case-mix adjustment. If dots deviate from the diagonal line, effect from case-mix adjustment is present. The spread on the diagonal line in Figure B as compared to Figure A illustrates the effect of random variation adjustment. If the spread on the diagonal line reduces, effect form random variation adjustment is present.

Rankability

Rankability can be interpreted as the percentage of observed hospital differences due to other causes than the known case-mix factors and random variation, possibly quality of care. A high rankability indicates that a large part of the variation may be 'true' differences compared to noise. A low rankability indicates that most of the observed differences are noise. Rankability was 22% for QI 1 'irradical BCS in invasive disease', 20% for QI 2 'irradical BCS in DCIS', 68% for QI 3 'breast contour preserving treatment', 63% for QI 4 'MRI in neo-adjuvant chemotherapy', 23% for QI 5 'radiotherapy for locally advanced', and 71% for QI 6 'surgery within 5 weeks'.

DISCUSSION

The aim of this study was to address the validity and reliability of quality indicators used for breast cancer care in the Netherlands. We quantified the effect of adjustment for case-mix and random variation on three process and three outcome measures and calculated the rankability expressing the part of the between-hospital difference that may be due to quality of care. The analyses were performed in a large national population based cohort of around 80,000 patients from a total of 91 hospitals. Both case-mix and/or random variation adjustment had influence on the between-hospital variation and the scores of individual hospitals of the three process and three outcome indicators studied. Rankability showed that the residual hospital variation that is possibly due to differences in quality of care varied between the quality indicators from 20% to 71%. The most valid and reliable quality indicators are QI 3 'breast contour preserving treatment', QI 4 'MRI in neo-adjuvant chemotherapy', and QI 6 'surgery within 5 weeks' since they have the highest rankability and are the least influenced by case-mix and random variation.

For each quality indicator analyzed in the current study, the results can be interpreted in general as follows. A lower AUC may indicate 1) the indicator is not strongly determined by patient characteristics and thus case-mix correction is not of major importance or 2) missed case-mix factors are present that may lead to unobserved confounders and thereby overestimate the validity. Furthermore if a large effect can be seen from case-mix and/or random variation adjustment this will result in a low rankability. A low rankability means case-mix and random variation explain the majority of between-hospital differences and a minority could possibly be explained by quality of care. It can be concluded that such an quality indicator tell us very little about quality of care and is not reliable (i.e., a large random variation) or valid (i.e., a large case-mix effect). A high rankability also does not necessarily represent true hospital differences since it may include residual confounding like unmeasured case-mix (eg. comorbidity) or other unknown differences between hospitals. Rankability also increases by increasing number of events and/or by increasing hospital variation. To illustrate this, the number of events per hospital strongly influenced the reliability of QI 1 score and the amount of its between-hospital variation. Since the incidence of irradicality after BCS is low this causes a low number of events with little hospital variation when evaluating one year of data only. The choice for presenting one year versus multiple years of data depends on the purpose. In case of hospital feedback on irradicality after BCS scores, using more years of data resulting in a more reliable estimate seems fair. However, using more years of data for providing feedback to hospitals results in

delay and reduces usability to quickly take action. Another consideration is to give quality indicators with low number of events or low number of eligible patients less priority, because quality improvement efforts affects less patients and thus have lower potential for public health benefit(11). Even if a large part of the remaining hospital variation represents true differences, whether it is *fully* explained by quality of care is unknown. However better evaluation methods do not yet exist.

Concerning the outcome QI 1 'irradical BCS for invasive tumor' and QI 2 'irradical BCS for DCIS', the between-hospital differences could largely – for almost 80% - be explained by case-mix and random variation. We have to judge these indicators as not valid and not reliable and therefore unsuitable for comparison purposes. That does not mean they are not informative for hospital monitoring, with or without adjustment. In the Netherlands, the monitoring and providing feedback of these indicators has resulted in improvement of the outcome in the past. It still gives a fair impression of daily practice. Simple case-mix adjustment to re-excision rates has been presented in one study with data from 16 hospitals and found remaining between-hospital variation, however this effect was not quantified(7). The third outcome indicator 'breast contour preserving treatment' had a good performing case-mix adjustment model (AUC 0.80) but it should be noted that the model included a substantial amount of case-mix variables (n=15). Case-mix and random variation adjustment had moderate effect on the between-hospital differences and individual hospitals scores. The rankability was 68% making it a fairly reliable and valid indicator. Naturally, a 100% score is not required due to patient preferences for mastectomy only over breast contour preserving treatment. However hospital variation can give insight in differences in quality of care. Furthermore usability needs to be investigated since it is a composite measure of BCS rate (including re-lumpectomy) and mastectomy followed by direct breast reconstruction rate and therefore not easy to interpret. 'Breast contour preserving treatment' is a promising quality indicator provided that case-mix and random effect correction is performed. Concerning the process indicators, QI 4 'MRI prior to neo-adjuvant chemotherapy' had a poor performing case-mix model (AUC 0.65) with a rankability of 63%. The low AUC may indicate that this process indicator is not strongly determined by patient characteristics and thus case-mix correction is not of major importance, in contrast to outcome indicators. Then the reliability and validity is reasonable. On the other hand the high rankability could also be explained by unobserved confounders and thereby overestimate the validity. For QI 5 'radiotherapy for locally advanced breast cancer' it can be concluded that both case-mix and random variation explain the majority of between-hospital differences and it is not a reliable or valid indicator. QI 6 'surgery within 5 weeks'

was not effected by case-mix adjustment which could be explained by the poor case-mix adjustment model (AUC 0.56). However, neither was an substantial effect seen from random variation adjustment. It may be concluded that surgery within 5 weeks is a relatively reliable and valid measure with 71% of true between-hospital differences that may be explained by quality of care.

A weakness of this study was the completeness of case-mix variables with i.e., up to 18% of missing values for the hormone receptor status. Since data completeness of the NCR is high, most likely the missing values concern patients from the self-registering hospitals. However due to the privacy of hospitals we could not determine whether this was the case. This could have been avoided using data from the NCR completely, but since the aim was validate indicators based on data used for external purposes, data from the NBCA including self-registering hospitals was used. On the other hand, completeness of patient records in each hospital is high with a median of 99% in 2014(2). One hospital only treated 43 patients in 2011, a possible explanation could be the merging of this hospital with another hospital since 2012, but again this information was unknown due to hospital privacy. All missing case-mix variables (except for WHO classification since >20% was missing) were imputed to enable building optimal case-mix adjustment models. This did not influence the results since the data before and after imputation were similar. Imputation is a good method for research purposes. Whether imputation should be applied in regular benchmark initiatives is debatable as it does not encourage hospitals to deliver complete data and data is imputed based on the case-mix of other hospitals. Ideally, few case-mix factors as possible are needed. Therefore, the additional effect of each individual case-mix factor for each individual quality indicator should be investigated. In daily practice correction for the most important case-mix factors only needs to be performed thereby reducing registration burden.

A strength of this study was the fact that the data covered all hospitals and was specifically gathered for the purpose of quality control and not for instance a financial reason(9). Another strength of this study was that case-mix was studied very thoroughly, which has rarely been performed. Random variation and rankability have never been studied for breast cancer care quality indicators at all. Moreover, the scientific rigor of process types of indicators has never been studied in any disease type. Although the quality indicators studied are specific for the Netherlands, the lessons learned are widely applicable. Indicators with validity and reliability issues might not be useful for benchmarking, but can be used internally for monitoring or reflection on observed differences to stimulate improvement, which is the ultimate aim of quality of care monitoring.

CONCLUSIONS

Worldwide quality indicators are increasingly being collected and used for benchmarking between hospitals. From the results presented in this study it can be concluded that there is a risk of making false comparisons if the influence of case-mix and random variation is not investigated and - if present - adjusted for. This is the first study to show this is not only true for outcome indicators, but even so for process indicators. The number of events per hospital must be considered and increased by i.e., aggregating years if necessary. Although measuring quality indicators and comparing hospitals based on indicators which were not tested for validity or reliability may stimulate quality improvement in general, judgments on the performance of individual hospitals should be made with caution, especially in the public domain.

Acknowledgements

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CHAPTER 10

From multiple quality indicators of breast cancer care towards hospital variation of a summary measure

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ABSTRACT

Background: In breast cancer care, large amounts of quality indicators are being collected and published, leading to large numbers of – sometimes unreliable or invalid- indicator scores per hospital. Potentially, the understanding and impact of quality of care information could be increased by a summary measure capturing multiple indicators. The aim of this study was to create and test a summary measure for quality of breast cancer care.

Methods: The population-based database used for this study included all 79,690 (non-)invasive breast cancer patients surgically treated between 2011-2016 in all 91 hospitals in the Netherlands. Construct validity of the single indicators was tested by Spearman's rho of hypothesized associations between indicators measuring the same underlying construct. A summary measure 'textbook outcome' was created including all valid indicators. Patients had a 'textbook outcome' if they scored positive on all indicators. Case-mix adjusted standardized 'textbook outcome' rates (observed/expected score) were calculated as above(>100) or below(<100) expected. Hospitals were outliers if the confidence interval excluded 100.

Results: Twenty-one indicators were calculated and their between hospital variation was expressed by interquartile range. Twenty indicators were represented in 14 hypothesized correlations of which 10 showed weak to strong construct validity. Thirteen indicators were included in 'textbook outcome'. The median percentage of patients with 'textbook outcome' was 49% (42%-54%) before and 49% (48%-51%) after case-mix adjustment. Three hospitals were positive and nine hospitals were negative outliers.

Conclusions: The majority of Dutch breast cancer care quality indicators showed good construct validity. Hospital variation in 'textbook outcome' was present, also after case-mix adjustment, and negative and positive outlier hospitals could be identified. The summary measure is promising in maximizing benefit of monitoring hospital quality performance.

INTRODUCTION

There is a growing demand for transparency of quality of care to drive quality improvement[1]. Therefore quality indicators are increasingly being collected and published. Monitoring and reporting of indicator information has led to quality improvement[2-4]. Further quality improvement is expected from comparing and ranking hospitals[5,6]. However, hospitals can score high on one indicator, but low on another indicator, resulting in a complex web of information. Moreover, between-hospital variation may be influenced by case-mix[7-10]. Hospital performance data is difficult to understand and until now has small impact on both health care providers and consumers[11-15]. Greater alignment is needed between the reporting of data and its audience to maximize its benefit[16]. Also there is no consensus regarding which of the many quality indicators are the most important. The challenge is how to identify priority indicators for quality improvement[17,18] or even generate a summarizing measure being able to describe quality with one value.

One important prerequisite for quality indicators is their validity. Validity means that indicators measure what they claim to measure[19]. One type of validity is construct validity, which evaluates the relation between indicators that measure the same underlying concept[20]. Construct validity has been studied in for example colorectal cancer and hip replacement, but not in yet for breast cancer[21,22]. Testing construct validity can identify indicators that can be removed from indicators sets because they capture the same information as other indicators or because they are invalid. Thereby it can help prioritize which quality indicators to focus on for monitoring, quality improvement efforts or constructing a summary measure.

Studies revealed that patients prefer a summary measure to have insight in the performance of a hospital [23-25]. This is most likely also true for other parties making use of performance data as health care providers, health insurance companies, governmental agencies, and medical specialty societies. A commonly used approach to construct a summary measure is the 'textbook outcome'[26,27]. It is a multidimensional summary measure representing patients in whom optimal ('text book') health outcomes are realized. Between-hospital variation can then be evaluated by comparing the in 'textbook outcome' scores of individual hospitals. This can even been done taking into account the underlying population of the individual hospitals (i.e., case-mix) resulting in an expected 'textbook outcome' score for all individual hospitals. This makes comparison between the expected and observed 'textbook outcome' score fair and without influence of underlying case-mix.

Breast cancer care quality improvements efforts in the Netherlands are led by the National Breast cancer working group Netherlands (NABON) Breast Cancer Audit (NBCA). Since 2011 a set of structure, process and outcome indicators are defined and regularly updated by multidisciplinary group consensus including surgeons, medical oncologists, radiation oncologists, pathologists, radiologists, health care insurers, and patient representatives[28]. The NBCA provides feedback on the quality indicator scores to the individual hospitals. The aim of this study was to create and test a summary measure for quality of breast cancer care.

METHODS

Data

From the NBCA, patient level data were retrieved of primary invasive breast cancer or ductal carcinoma-in-situ (DCIS) patients whom were surgically treated and diagnosed in 91 different hospitals between January 1st 2011 and August 1st 2016 in the Netherlands. In this time period, hospitals may have fused, resulting in a different total number of hospitals per year. The NBCA collects information on breast cancer care and outcomes from all hospitals in the Netherlands since 2011. Hospitals choose to register the data themselves directly into a web-based system (20-30% of all hospitals) or have it registered by the Netherlands Comprehensive Cancer Organisation (IKNL) as part of the Netherlands Cancer Registry (NCR). The IKNL hosts the NCR, in which all new malignancies are registered on a national level since 1989. All hospitals review the data for inconsistencies and make corrections before the data is transferred by IKNL to the NBCA database. A third party anonymised all data before it was made available for this study.

The data included the following general patient-, tumor-, and treatment characteristics: gender, age, World Health Organization (WHO) performance status, method of tumor detection, palpability, type of surger(y)(ies), multifocality, histology, tumor size in mm, Bloom and Richardson differentiation grade, hormone and her2neu receptor status, clinical and pathological tumor node metastasis staging (TNM)[29], radiation treatment, chemotherapy, and hormonal therapy.

Table 1. Definition of Quality Indicators.

	Short name	Type*	Definition
	Radiology		
QI 1	BI-RADS classification	P	Numerator: number of patients with BI-RADS category reported in diagnostic phase on mammography, ultrasound or breast MRI. Denominator: number of patients surgically treated for invasive breast cancer or DCIS.
QI 2	MRI in neo-adjuvant chemotherapy	P	Numerator: number of patients with breast MRI prior to start of neo-adjuvant chemotherapy. Denominator: number of patients with invasive breast cancer treated with neo-adjuvant chemotherapy.
	Pathology		
QI 3	Full pathology report as defined	P	Numerator: number of patients with standard pathology report including information about ER% , PR%, HER2, grade, tumor size, resection margin and number of positive lymph nodes. Denominator: number of patients with a pathology report of invasive breast cancer of at least 1cm without neo-adjuvant therapy.
	Surgery / Plastic Surgery		
QI 4	Irradicality after BCS in invasive disease	O	Numerator: number of patients with more than focally positive margins[a] after first BCS. Denominator: Number of patients treated with BCS for invasive non-metastasized breast cancer and without neo-adjuvant chemotherapy.
QI 5	Irradicality after BCS in DCIS	O	Numerator: number of patients with positive margins after first BCS. Denominator: number of patients treated with BCS for DCIS.
QI 6	Reexcision after BCS for invasive disease	O	Numerator: number of patients with re-excision. Denominator: number of patients with BCS for invasive non-metastasized breast cancer without neo-adjuvant chemotherapy.
QI 7	Reexcision after BCS for DCIS	O	Numerator: number of patients with re-excision. Denominator: number of patients with BCS for DCIS.
QI 8	Breast contour preserving treatment	P	Numerator: number of patients with i) breast conserving surgery including re-lumpectomies without neo-adjuvant chemotherapy and ii) with neo-adjuvant chemotherapy, and iii) mastectomy with direct breast reconstruction. Denominator: number of patients with invasive non-metastasized breast cancer with and without neo-adjuvant chemotherapy.
QI 9	Immediate breast reconstruction in DCIS	P	Numerator: number of patients with immediate breast reconstruction. Denominator: number of patients with a primary mastectomy for DCIS.
QI 10	Immediate breast reconstruction in invasive disease	P	Numerator: number of patients with immediate breast reconstruction. Denominator: number of patients with a primary mastectomy for invasive breast cancer.

Table 1. Definition of Quality Indicators. *(continued)*

	Short name	Type*	Definition
	Surgery / Plastic Surgery		
	Radiotherapy		
QI 11	Seen by radiation oncologist prior to neo-adjuvant chemotherapy	P	Numerator: number of patients seen by radiation oncologist prior to neo-adjuvant chemotherapy. Denominator: number of patients with invasive breast cancer treated with neo-adjuvant chemotherapy, surgery and postoperative radiotherapy.
QI 12	Radiotherapy for locally advanced	P	Numerator: number of patients treated with radiotherapy. Denominator: number of patients with invasive non-metastasized locally advanced[b] breast cancer and treated with mastectomy.
	General		
QI 13	Pre-operative MDT meeting	P	Numerator: number of patients of whom the information in the registry is complete and are discussed in a pre-operative MDT meeting. Denominator: number of surgically treated patients with primary invasive breast cancer or DCIS.
QI 14	Postoperative MDT meeting	P	Numerator: number of patients of whom the information in the registry is complete and are discussed in a postoperative MDT meeting. Denominator: number of surgically treated patients with primary invasive breast cancer or DCIS.
QI 15	Neo-adjuvant chemotherapy within 5 weeks of diagnosis	P	Numerator: number of patients receiving neo-adjuvant chemotherapy within ≤5 weeks after diagnosis. Denominator: number of patients with neo-adjuvant chemotherapy for invasive non-metastasized breast cancer.
QI 16	Surgery within 5 weeks (without reconstruction) of diagnosis	P	Numerator: number of patients receiving surgery within 5 weeks of diagnosis. Denominator: number of patients with primary surgery without immediate breast reconstruction for invasive non-metastasized breast cancer or DCIS and without neo-adjuvant chemotherapy.
QI 17	Surgery with breast reconstruction within 5 weeks of diagnosis	P	Numerator: number of patients receiving surgery within 5 weeks of diagnosis. Denominator: number of patients with primary surgery with breast reconstruction[c] for invasive non-metastasized breast cancer or DCIS and without neo-adjuvant chemotherapy.
	General		
QI 18	Radiotherapy within 5 weeks of final operation	P	Numerator: number of patients receiving radiotherapy within ≤5 weeks after surgery. Denominator: number of patients with invasive non-metastasized breast cancer or DCIS treated with surgery and radiotherapy (without chemotherapy between the two treatments).
QI 19	Radiotherapy within 5 weeks of last chemotherapy	P	Numerator: number of patients receiving radiotherapy within ≤5 weeks after chemotherapy. Denominator: number of patients with invasive non-metastasized breast cancer with chemotherapy and radiotherapy.

Table 1. Definition of Quality Indicators. *(continued)*

	Short name	Type*	Definition
QI 20	Chemotherapy within 5 weeks of final operation	P	Numerator: number of patients receiving chemotherapy within ≤5 weeks after surgery. Denominator: number of patients with invasive non-metastasized breast cancer with surgery and chemotherapy (without radiotherapy between the two treatments).
QI 21	Chemotherapy within 5 weeks of last radiotherapy	P	Numerator: number of patients receiving chemotherapy within ≤5 weeks after radiotherapy. Denominator: number of patients with invasive non-metastasized breast cancer with radiotherapy and chemotherapy.

* S, structure; P, process, O, outcome
Abbreviations: QI=quality indicator, DCIS=ductal carcinoma-in-situ, MRI=magnetic resonance imaging, BCS=breast conserving surgery, MDT=multidisciplinary team
[a] More than focally positive margins is defined as tumor touching the inked margin over a length of 4mm or more.
[b] Clinical T3, T4, any N, M0 and T, N2-3,M0. with ≥cT3 or ≥pT2 (except for pT3N0).
[c] Including both primary and secondary mastectomies and both prosthesis and autologous breast reconstruction.

Quality indicators

The NBCA quality indicator set changed over the years and all indicators used between 2011-2017 were considered[28]. Only quality indicators were studied in which a higher or lower score is believed to represent better quality of care from 2011-2017. For example, the indicators 'percentage of patients with chemotherapy' and 'percentage of patients with MRI' were unsuitable since a higher or lower score is not associated with better quality of care. Per patient an indicator could be positive or negative. Quality indicator scores were calculated based on the publically available NBCA manual defining the numerators (i.e., the number of patients with the process or outcome of interest) and denominators (i.e., the number of patients under consideration) of each indicator (Table 1)[30]. Patients with distant metastasis at time of diagnosis were excluded in all denominator definitions. For example for the indicator 'immediate breast reconstruction in DCIS', all patients with a primary mastectomy for DCIS (denominator) could score a 0 or a 1 based on whether they received immediate breast reconstruction or not (numerator). Per hospital the indicator score was calculated by dividing the patients scoring positive in the numerator by the denominator. Indicator scores presented here can however deviate from the NBCA reports.

Statistical analysis

Whether the patient-, tumor-, and treatment characteristics differed between hospitals was tested by one-way ANOVA test for continuous variables and Chi-square test for categorical variables. Hospital variation referred to *between*-hospital variation and *within*-hospital variation was not studied. Indicator scores and hospital variation were presented by median, interquartile range (IQR), and range. To assess the effect of the number of events on hospital variation, we presented results from one year of data only (i.e., 2015 was chosen being the most recent year, 2016 only included data till August 1st) and from the total cohort (2011-2016).

Construct validity

Based on rationale we hypothesized that some indicators measure the same underlying construct and they were associated with each other. This resulted in 14 associations representing 20 out of the 21 indicators. The direction of association (i.e., negative or positive) was defined on beforehand. Construct validity was tested by Spearman correlation coefficient and 95% confidence interval (CI) was obtained by bootstrapping (1000 random replicas). Construct validity was considered present if statistically significant in the expected direction of association. A Spearman's rho <0.40 was defined as a weak correlation, 0.40-0.59 was defined as a moderate correlation and >60 as a strong correlation[31].

Textbook outcome

Valid indicators representing an optimal ('textbook') health care process or outcome were included in the summary measure 'textbook outcome'. Note that the NBCA set majorly includes process types of indicators. In each individual patient, the achievement of these indicators was studied. If a patient scored positive on all indicators, a so-called 'textbook outcome' was achieved in that patient. For each indicator a different patient selection (i.e., the denominator) applied. If a patient was not included in the denominator of the indicator of interest, the patient however did score positive. For example, a patient with DCIS only was not included in the denominator for the indicator 'Irradicality in invasive disease'. That patient however did score 1 for that indicator and could still achieve a 'textbook outcome'. 'Textbook outcome' was presented as a continuous score (i.e., the median number of indicators with a positive score out of the maximum) and as a 'all-or-none' score (i.e., the percentage of patients scoring positive on all indicators thus achieving 'textbook outcome').

Case-mix adjustment was performed by multivariable linear regression analysis for the continuous textbook outcome and by logistic regression analysis for the all-or-none 'textbook outcome'. All general patient- and tumor characteristics were used as case-mix factors: age, histology, pathological tumor and node stage, differentiation grade, multifocality, oestrogen and her2neu receptor status. For each individual hospital, the standardized rate and 95% confidence interval (CI) for textbook outcome was calculated by dividing the observed score by the expected score. The expected score was the mean from all hospitals for the none case-mix adjusted model and the predicted probability for an individual hospital for the case-mix adjusted model. A standardized rate larger than 100 means more textbook outcomes (i.e., better achieving hospital) and a standardized rate smaller than 100 means less textbook outcomes (i.e., poorer achieving hospital) as compared to the average or expected. The standard error of the standardized rate was calculated by dividing the standardized rate by the root of the number of events.

Statistical analysis was performed by IBM SPSS Statistics version 22.0 (IBM, Armonk, New York, USA). A p-value of <0.05 was considered statistically significant. For this type of study approval from a Medical Ethical committee was not required.

RESULTS

A total of 79.690 patients had invasive breast cancer or DCIS and were surgically treated in 91 different hospitals between January 1st 2011 and August 1st 2016 in the Netherlands (Table 2). In 2015 only, 15.101 patients were treated in 82 hospitals. Hospital variation was present for all quality indicators (QI), but the magnitude of the variation differed per indicator (Table 3).

Table 2. Descriptive information and between-hospital variation on possible case-mix factors between 2011-2016.

	Number of patients (%)	**Between hospital IQR**	**Between hospital range**	**P-value#**
Number of patients (median)	79690 (746)	575-1048	43-3114	
Gender				P<0.001
- Female	79228 (99)	99-100	98-100	
- Male	451 (0.6)	0.4-0.8	0-1.8	
- Missing values	11 (0.0)	0-0	0-0.4	
Age				P<0.001
- Mean (years)	61	61-62	54-65	
- Missing values	28 (0.0)			
WHO performance status*				P<0.001
- 0	17598 (22)	7.0-31	0.0-59	
- 1	3010 (3.8)	1.0-6.0	0-23	
- 2-4	452 (0.6)	0.1-0.5	0-10	
- Missing values	58630 (74)	64-91	34-100	
Screen detected tumor				P<0.001
- No	45117 (57)	55-60	45-95	
- Yes	34255 (43)	40-45	4.7-55	
- Missing values	318 (0.4)	0-0.5	0-9.0	
Palpability				P<0.001
- No	33609 (42)	39-45	23-59	
- Yes	44893 (56)	54-60	39-68	
- Missing values	1188 (1.5)	0.4-2.0	0-9.3	
Multifocality				P<0.001
- No	67024 (84)	83-88	62-96	
- Yes	11646 (15)	11-16	4.1-35	
- Missing values	1020 (1.3)	0.2-1.1	0-26	
Histology				P<0.001
- Ductal	65761 (80)	81-85	57-90	
- Lobular (or mixed)	9841 (12)	10-14	5.3-24	
- Other	3006 (3.7)	3.0-4.6	0-21	
- Missing values	3185 (3.9)	0.6-1.6	0-15	

Table 2. Descriptive information and between-hospital variation on possible case-mix factors between 2011-2016.*(continued)*

	Number of patients (%)	**Between hospital IQR**	**Between hospital range**	**P-value#**
Primary tumor stadium				P<0.001
- pT1	44214 (56)	53-58	37-67	
- pT2	18645 (23)	21-27	14-44	
- pT3	2285 (2.9)	2.1-3.5	0-7.0	
- pT4	588 (0.7)	0.5-0.9	0-2.5	
- pT0	2014 (2.5)	1.1-3.1	0-8.3	
- pTis (DCIS)	10826 (14)	12-14	7.0-22	
- Missing values	1118 (1.4)	0.7-1.9	0.1-7.9	
Postoperative tumor size				P<0.001
- Mean in mm	18	17-20	13-26	
- Missing values	6350 (8.0)			
Differentiation grade				P<0.001
- 1	17506 (22	19-25	13-37	
- 2	33423 (42)	39-46	26-57	
- 3	22064 (28)	24-31	19-56	
- Missing values	6697 (8.4)	4.7-11	1.1-30	
Oestrogen receptor status				P<0.001
- Negative	11602 (15)	12-15	4.4-43	
- Positive	55149 (69)	68-73	33-80	
- Missing values	12939 (16)	13-17	11-38	
Progesteron receptor status				P<0.001
- Negative	21561 (27)	23-29	19-41	
- Positive	45279 (57)	55-61	29-68	
- Missing values	12850 (16)	13-17	11-33	
Her2neu receptor status				P<0.001
- Negative	55893 (71)	71-76	34-82	
- Positive	8587 (11)	10-12	4.6-18	
- Missing values	14210 (18)	14-18	7.0-61	

Table 2. Descriptive information and between-hospital variation on possible case-mix factors between 2011-2016.*(continued)*

	Number of patients (%)	Between hospital IQR	Between hospital range	P-value#
Regional lymph nodes stadium				P<0.001
- pN0(i)	53752 (68)	65-70	57-75	
- pN1	16820 (21)	20-23	15-27	
- pN2	3197 (4.0)	3.4-4.9	0-14	
- pN3	1830 (2.3)	1.6-2.8	0-4.8	
- Missing values	4091 (5.1)	3.3-6.8	0-16	
Distant metastasis				P<0.001
- No (cM0 or pM0)	79328 (100)	99-100	97-100	
- Yes (cM1 and/or pM1)	320 (0.4)	0.1-0.5	0-1.5	
- Missing values	42 (0.1)	0-0	0-1.6	

P-value after testing whether the case-mix factor was statistically significantly different between the 91 hospitals

* 0=asymptomatic, 1=symptomatic but completely ambulatory, 2-4=symptomatic, < 50% in bed during the day, and bedbound

Construct validity

From the total of 14 correlations hypothesized to measure the same underlying construct, 9 correlations were found to be significant in the cohort of 2015 only and 11 in the total cohort of 2011-2016 (Table 4). Representing the quality of patient reports, a weak correlation was present between having a 'BI-RADS classification' reported and a 'Full pathology report' in the total cohort. Whether a patient was discussed in both the 'Pre-operative multidisciplinary team meeting' and 'Postoperative multidisciplinary team meeting' was moderately correlated. Representing the quality of care around neo-adjuvant chemotherapy, having a 'MRI' and 'Visiting a radiotherapist prior to treatment' was weakly correlated in the total cohort, but was not associated in 2015 only. Representing the quality of surgery, an 'irradical BCS for invasive disease' and 'irradical BCS for DCIS' was moderately correlated. Since an irradical resection is generally followed by a reexcision, a strong correlation was present between 'irradicality' and 'reexcision' both for invasive disease and DCIS. As expected 'Reexcision after BCS in invasive disease' and 'Reexcision after BCS in DCIS' was correlated. Representing timely surgical treatment, 'Surgery within five weeks from diagnosis without breast reconstruction' and 'Surgery within five weeks from diagnosis with breast reconstruction' was moderately correlated. The composite indicator 'Breast contour sparing surgery' was significantly correlated with 'Direct breast reconstruction', but not with 'Irradicality after BCS'. Representing the practice of plastic surgery, 'Immediate

breast reconstruction in invasive disease' was strongly correlated with 'Immediate breast reconstruction in DCIS'. The indicators representing timely chemotherapy and radiation treatment were not correlated and thus do not possess construct validity.

Table 3. Between-hospital variation in quality indicator scores.

	2015 only (n=15,101 patients)				Total cohort (2011-2016) (n=79,690 patients)			
	N	**Median (%)**	**IQR**	**Range**	**N**	**Median (%)**	**IQR**	**Range**
QI1	82	100	100-100	94-100	91	99	98-100	92-100
QI 2	82	94	86-100	18-100	90	87	73-94	0-100
QI 3	82	97	95-98	68-100	91	93	90-96	41-98
QI 4	82	2.8	0.8-4.6	0-15	91	3.1	2.1-4.2	0-9
QI 5	82	19	11-29	0-100	91	21	16-24	0-36
QI 6	82	6.1	4.2-9.0	0-18	91	7.8	5.0-8.9	0-20
QI 7	82	14	5-22	0-100	91	15	11-19	0-46
QI 8	82	68	61-76	45-94	91	65	57-72	46-88
QI 9	81	45	25-62	0-100	90	39	29-51	0-83
QI 10	82	25	12-33	0-80	91	17	6-27	0-69
QI 11	82	66	25-93	0-100	89	45	20-76	0-100
QI 12	79	79	69-92	0-100	89	84	77-88	52-100
QI 13	82	99	98-100	91-100	91	97	94-99	44-100
QI 14	82	99	98-100	89-100	91	99	99-100	72-100
QI 15	82	87	75-95	40-100	90	82	72-91	50-100
QI 16	82	90	84-94	32-98	91	91	85-94	55-100
QI 17	78	57	40-77	0-100	88	54	38-76	0-100
QI 18	78	67	48-81	0-100	89	55	36-66	0-92
QI 19	67	80	67-100	0-100	88	78	66-85	25-100
QI 20	66	75	50-100	0-100	88	73	54-83	0-95
QI 21	78	100	91-100	50-100	89	95	90-97	57-100

Abbreviations: QI=quality indicator, IQR=interquartile range, N=number of hospitals

Table 4. Construct validity of hypothesized correlations between indicators and statistical direction of association.

		Direction	2015 only n= 82 hospitals		2011-2016 n=91 hospitals	
			Spearman's rho (p value)*	95% CI	Spearman's rho (p value)*	95% CI
1	Full pathology report & BI-RADS classification	Positive	0.17 (P 0.131)	-0.03-0.35	0.31 (P 0.002)	0.09-0.52
2	Pre-operative multidisciplinary team meeting & Postoperative multidisciplinary team meeting	Positive	0.36 (P=0.002)	-0.19-0.27	0.48 (P<0.001)	0.30-0.62
3	Seen by radiation oncologist prior to neo-adjuvant chemotherapy & MRI in neo-adjuvant chemotherapy	Positive	0.18 (P=0.110)	-0.07-0.43	0.28 (P=0.007)	0.09-0.46
4	Irradicality after BCS in invasive disease & Irradicality after BCS in DCIS	Positive	0.35 (P=0.001)	0.14-0.54	0.44 (P<0.001)	0.26-0.60
5	Reexcision after BCS in invasive disease & Reexcision after BCS in DCIS	Positive	0.24 (P=0.033)	0.04-0.,42	0.37 (P<0.001)	0.18-0.56
6	Irradicality after BCS in invasive disease & Reexcision after BCS in invasive disease	Positive	0.61 (P<0.001)	0.44-0.76	0.60 (P<0.001)	0.43-0.75
7	Irradicality after BCS in DCIS & Reexcision after BCS in DCIS	Positive	0.63 (P<0.001)	0.46-0.75	0.52 (P<0.001)	0.34-0.68
8	Surgery (without reconstruction) within 5 weeks of diagnosis & Surgery with breast reconstruction within 5 weeks of diagnosis	Positive	0.49 (P<0.001)	0.29-0.67	0.51 (P<0.001)	0.30-0.67
9	Irradicality in invasive disease & Breast contour preserving treatment	Negative	-0.07 (P=0.554)	-0.31-0.16	-0.004 (P=0.971)	-0.23-0.22
10	Breast contour preserving treatment & Immediate breast reconstruction in invasive disease	Positive	0.58 (P<0.001)	0.38-0.70	0.62 (P<0.001)	0.45-0.75
11	Immediate breast reconstruction in invasive disease & Immediate breast reconstruction in DCIS	Positive	0.52 (P<0.001)	0.31-0.67	0.77 (P<0.001)	0.66-0.86
12	Neo-adjuvant chemotherapy within 5 weeks of diagnosis & Surgery within 5 weeks (without reconstruction) of diagnosis	Positive	0.26 (P=0.017)	0.03-0.48	0.22 (P=0.040)	-0.01-0.43
13	Radiotherapy within 5 weeks of final operation Radiotherapy within 5 weeks of last chemotherapy	Positive	0.08 (P=0.527)	-0.16-0.31	-0.07 (P=0.523)	-0.26-0.14
14	Chemotherapy within 5 weeks of final operation & Chemotherapy within 5 weeks of last radiotherapy	Positive	0.07 (P=0.566)	-0.20-0.33	0.06 (P=0.607)	-0.17-0.27

*Spearman's rho, <0.40 weak, 0.40-0.59 moderate, >0.60 strong **Control

Abbreviations: CI=confidence interval, MRI=magnetic resonance imaging, BCS=breast conserving surgery

Table 5. Textbook outcome in total cohort (N=79,690 patients).

	Quality indicator short name	N patients in denominator	N patients scoring positive (numerator)
1	BI-RADS classification	79,520	78,499
2	MRI in neo-adjuvant chemotherapy	7,599	6,487
3	Full pathology report	45,317	40,605
4	Irradicality in invasive disease	36,748	1,207
5	Irradicality in DCIS	7,559	1,541
6	Breast contour preserving treatment	68,135	45,383
7	Seen by radiation oncologist prior to neo-adjuvant chemotherapy	5,564	3,159
8	Radiotherapy for locally advanced	5,257	4,346
9	Pre-operative MDT meeting	79,690	75,344
10	Postoperative MDT meeting	79,690	77,520
11	Neo-adjuvant chemotherapy within 5 weeks of diagnosis	7,860	6,413
12	Surgery (without reconstruction) within 5 weeks of diagnosis	63,200	54,616
13	Surgery with breast reconstruction within 5 weeks of diagnosis	6,030	3,306

Abbreviations: BI-RADS= Breast Imaging Reporting and Data System, MRI=magnetic resonance imaging, DCIS=ductal carcinoma-in-situ, MDT=multidisciplinary team, N=number of patients

Textbook outcome

All indicators showing a weak or moderate construct validity were included in the textbook outcome. From the indicators with a strong construct validity, one of the two was included in the textbook outcome. Indicators lacking construct validity were excluded.

Only three patients scored positive on seven out of thirteen indicators from the 'textbook outcome', 21 patients scored positive on eight indicators, 276 (0.3%) patients scored positive on nine indicators, 1,979 (2.5%) patients scored positive on ten indicators, 9,313 (11.7%) patients scored positive on eleven indicators, 29,142 (36.6%) patients scored positive on twelve indicators, and 38,956 (48.9%) scored positive on all thirteen indicators and thus achieved 'textbook outcome'. The three patients with the lowest score had varying age and tumor stage, but many missing indicators explaining their low score. Hospital volume was hardly correlated with achieving 'textbook outcome' (Pearson correlation of 0.05) and did not reach significance (p-value=0.404). Median (interquartile range) of the continuous 'textbook outcome' score was 12.3 (12.2-12.4) before and 12.3 (12.3-

12.3) after case-mix adjustment (Table 5). Median (interquartile range) all-or-none 'textbook outcome' score was 49% (42%-54%) before and 49% (48%-51%) after case-mix adjustment. Besides reduction of hospital variation after case-mix adjustment, also individual hospital scores increased or decreased (Figure 1). From the continuous 'textbook outcome', no outliers were identified before and after case-mix adjustment(Figure 2). From the all-or-none 'textbook outcome', three hospitals were identified as positive outliers and nine hospitals were identified as negative outliers both before and after case-mix adjustment(Figure 2). They had a statistically significantly higher or lower adjusted rate of 'textbook outcomes' respectively as compared to the expected average.

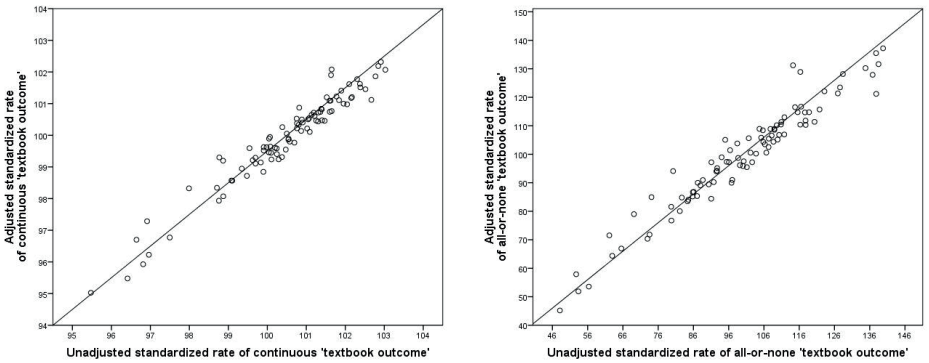

Figure 1. The effect of case-mix adjustment on the standardized rate of 'textbook outcome' in 91 hospitals (2011-2016) with on the X-axis: unadjusted standardized rate and on the Y-axis: case-mix adjusted standardized rate. A: continuous 'textbook outcome'. B: all-or-none 'textbook outcome'.

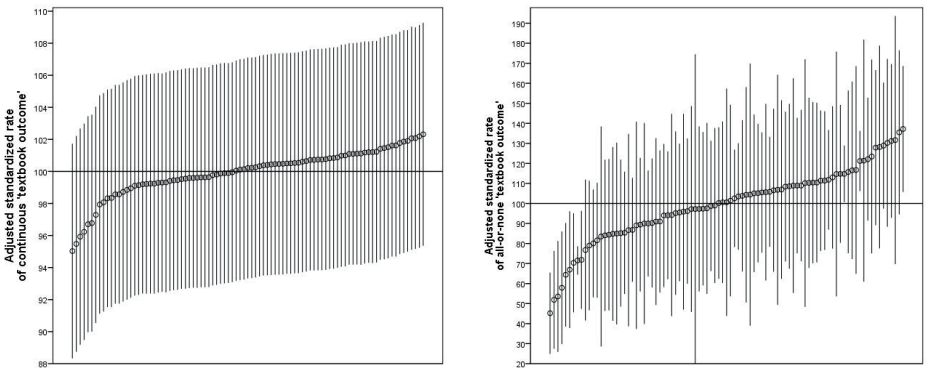

Figure 2. The case-mix adjusted standardized rate of 'textbook outcomes' (on the Y-axis) with a reference line at the expected mean of 100. The hospitals are sorted on the x-axis in order of 'textbook outcome' score with 95% confidence interval. A: continuous 'textbook outcome'. B: all-or-none 'textbook outcome'.

DISCUSSION

The majority of Dutch breast cancer care quality indicators showed good construct validity. Thirteen process and outcome indicators were included in the summary measure 'textbook outcome'. Hospital variation in 'textbook outcome' was present and significant negative and positive outliers were identified.

Regarding construct validity, the strength of associations was variable. In case of a strong association, monitoring and reporting both indicator scores is superfluous. For example, 'irradicality after BCS' and 'reexcision after BCS' was strongly associated and monitoring both indicators is minimally informative. Which to select should be discussed. In the NBCA set of 2017, the indicator 'reexcision after BCS' has been removed, but now evidence is provided. In case of a moderate or weak association, it is under discussion whether one of the two indicators is superfluous. They do address the same underlying concept, but still provide some complimentary information[22]. For example, 'pre-operative multidisciplinary team meeting' and 'postoperative multidisciplinary team meeting' were weakly associated in 2015 only and moderately associated in 2011-2016. The same pattern was seen for 'irradicality after BCS in invasive disease' and 'irradicality after BCS in DCIS'. It can also be concluded that the lack of a strong correlation here means that achieving radical margins cannot be explained by surgical performance only. Other patient or tumour factors might be of influence. A reason to give these indicators less priority.

A lack of construct validity (i.e., quality indicators hypothesized to measure the same underlying construct do not show an association) could have multiple explanations. First of all, it could be a result of low number of events. For example the correlation between 'seen by radiation oncologist prior to neo-adjuvant chemotherapy' and 'MRI in neo-adjuvant chemotherapy' was not significant in the data from 2015 only, but a significant association was seen when the number of events increased in the data from 2011-2016. Second, it could mean the indicators are simply not valid and don't measure what they intent to measure. For example, 'start of chemotherapy within 5 weeks after final operation' was not associated with 'start of chemotherapy within 5 weeks after last radiotherapy.' The same was true for 'radiotherapy within 5 weeks of final operation' and 'radiotherapy within 5 weeks of last chemotherapy'. We suggest to use these indicators only for internal purposes or remove them.

Another important lesson can be learned from the composite indicator 'breast contour sparing surgery' that was strongly associated with 'immediate breast reconstruction' and not at all associated with 'irradicality after BCS'. The indicator 'breast contour sparing surgery' was designed to replace the indicator

'irradicality after BCS' that is thought to falsely stimulate performing mastectomy to keep irradicality percentages low. However testing construct validity showed that 'breast contour sparing surgery' is driven by 'immediate breast reconstruction rates and merely influenced by 'irradicality after BCS rates'. In the literature, construct validity was often found to be limited, in contrast to our findings[21,22]. This could be explained by the high reliability of the NBCA data which is an important strength of this study. The data is relatively complete, accurate, consistent and reproducible with clear indicator definitions[32-34]. The completeness of patient records from each hospital was 99% in 2014[28]. This is the result of the national population-based nature of the data and the registration being performed by the National Cancer Registry.

A summary measure has multiple advantages. It reduces the visible size of the indicator set without losing underlying information[35]. Hospital indicator scores can be communicated simple and quick. Patients can more easily understand the information and increase the so far limited impact of comparative information on patient's hospital choice[11-15,23-25]. Care-givers and hospitals can quickly see how they perform compared to expected and average. If necessary, individual items can be investigated and care can be improved where necessary. Our summary measure was named 'textbook outcome' and presented as continuous score and all-or-none score. The all-or-none method has previously been found to be the most useful since it sets a high benchmark and more often has good discriminative ability[27,36]. A median of 12.3 desired indicators were met in all patients and 49% of patients achieved all 13 desired indicators and thus achieving 'textbook outcome'. It is known that the all-or-none method results in low scores[25,27]. More informative is the between hospital variation and ranking since this is the focus of current study. Large between hospital variation was present that reduced after case-mix adjustment. Moreover, individual hospitals changed in the ranking. This emphasizes the importance of case-mix adjustment when comparing hospitals. The ranking of hospitals by continuous score was comparable to the ranking of hospitals by all-or-none score. Three positive and nine negative outlier hospitals were identified by the all-or-none 'textbook outcome'. Quality improvement efforts should focus on these hospitals. The positive outliers can function as examples of best practices.

Disadvantage of the proposed 'textbook outcome' is that not all individual items apply to all breast cancer patients. For a patient with purely DCIS, only 8 out of 13 desired indicators apply. A high score does not necessarily means better quality of care, because it can be misleading in the following cases. If a hospital rarely uses neo-adjuvant chemotherapy, it does receive points for the indicators

'MRI in neo-adjuvant chemotherapy' and 'seen by radiation oncologist prior to neo-adjuvant chemotherapy', and 'neo-adjuvant chemotherapy within 5 weeks of diagnosis' and can achieve 'textbook outcome'. This is also true in case a hospital more frequently performs mastectomy. It does receive points for 'radical BCS in invasive disease' and 'radical BCS in DCIS' and can achieve 'textbook outcome'. Further research into the individual items of the hospitals ranking low and high is needed to discover whether the summary measure really is misleading or not. The selection of indicators included in the 'textbook outcome' was based on rationale and could be discussed. Also the addition of weights could be discussed. It is true that the indicators are not equal with respect to their influence on quality of care. However, the relative contribution of each indicator needs to be studied and the simplicity of unweighted measures encourages implementation[25]. Patients may also prefer other items. Hence it has been found that there is no such thing as the typical patient: different patients make different choices in different situations[37].

Current study had multiple strengths. First of all, the large national population-based database with almost 80,000 patients treated in more than 90 hospitals provides relatively reliable results. Second, construct validity has not been tested before in breast cancer. Third of all, a summary measure or 'textbook outcome' has not been constructed before in breast cancer. Furthermore, the addition of case-mix adjustment increased the validity of hospital comparisons and ranking performed[7]. Our findings can aid the current challenge of prioritizing quality improvement efforts[1].

CONCLUSIONS

We found good construct validity for the majority of breast cancer care quality indicators used in the Netherlands. Suggestions were made about selecting indicators to be removed or continued. The lessons learned are valuable for improving the Dutch indicator set, but are also widely applicable as a method to prioritize quality improvement efforts. We constructed a summary measure 'textbook outcome' including thirteen desirable multidisciplinary indicators out of 21 indicators. Large between-hospital variation was present, also after case-mix adjustment and both positive and negative outliers were identified. The summary measure seemed promising since it reduces the visible size of the indicator set without losing information, it is easier to understand, and has discriminative ability. This can possibly increase the impact of publishing hospital performance data. Patients can choose their hospital and quality improvements efforts can target outlier hospitals. However more research into the validity and interpretation of the summary measure is needed before implementation.

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PART V

Summary and discussion

CHAPTER 11

Summary in English and Dutch

SUMMARY

This thesis focused on the different outcomes after breast conserving surgery (BCS). Ranging from cosmetic result, quality of life, radicality, reexcision, secondary mastectomy, local recurrence, overall survival and quality of care. These outcomes are however intertwined, as outlined in this thesis.

Part II Cosmetic outcome and quality of life

Cosmetic outcome plays an important role in the treatment decision between mastectomy (MST) and BCS being the topic of Part II. The feasibility of achieving a good cosmetic result *if* BCS is performed should be discussed with the patient. However the feasibility judgment is subjective and can be difficult.

In **Chapter 2** the value of tumor volume in relation to breast volume (TV/BV ratio) for predicting cosmetic results after BCS was investigated. The TV/BV ratio was measured in the preoperative MRI while 3D-projected in a virtual reality environment (I-Space) of 69 breast cancer patients. Increasing TV/BV ratio was independently associated with decreasing cosmetic result as evaluated by a six-member panel. TV/BV ratio and location of the tumor in the breast constituted a good performing prediction model with an area under the curve of 0.83. In clinical practice this can be used for more informed treatment decision making.

The literature has shown that better cosmetic results are also important for a better quality of life (QoL). In **Chapter 3** it was assumed that BCS results in a better QoL when the chance of a good cosmetic result is high. MST (with or without breast reconstruction) results in better QoL when a good cosmetic result is unlikely after BCS. The treatment threshold- when to treat with BCS or MST (with or without breast reconstruction) - for optimal QoL was established by modeling the harms and benefits in QoL for each treatment approach. EuroQoL-5D derived utilities were obtained as QoL weight from the patient's perspective to enable comparative analyses. BCS resulted in superior QoL compared to MST whenever the chance of a good cosmetic result exceeded 36%. This 36% threshold was reached in case the tumor was located in the upper lateral, lower lateral, upper medial, lower medial, and central quadrant of the breast with a TV/BV ratio below 21.6, 4.1, 15.1, 3.2, and 14.7, respectively. The effectiveness of this treatment decision model in improving cosmetic results and QoL needs to be proven in clinical practice.

Therefore a multicenter and single-blinded randomized controlled trial (TURACOS trial) was designed and its study protocol presented in **Chapter 4**. The TURACOS trial is currently ongoing and randomizes invasive breast cancer patients between standard preoperative work-up and preoperative work-up with addition

of the prediction model. Three dimensional ultrasonography is used for measuring TV/BV ratio. The results of the prediction model are presented in the preoperative multidisciplinary meeting and taken into consideration for the treatment advice. Primary aim is to improve the incidence of a superior cosmetic result one year after BCS with 14%. Based on an incidence of 71% in the control group as was found in the study presented in Chapter 2. A total of 300 patients need to be randomized.

Part III Oncological outcomes

Although cosmetic outcome is important, the primary goal of BCS is complete tumor excision. If the excision is incomplete, re-excision may be necessary. Re-excision increases healthcare costs, increases burden to the patient, increases risk of poor cosmetic result, increases risk of secondary mastectomy, and impairs quality indicator scores. **Chapter 5** describes a retrospective investigation whether preoperative magnetic resonance image (MRI) use is associated with less positive margins after BCS, less re-excisions after BCS, and less mastectomies (both primary and secondary). A population-based cohort was abstracted from the Netherlands Cancer Registry including 5514 women with invasive breast cancer or ductal carcinoma in situ (DCIS) diagnosed between 2011–2013. The prevalence of positive margins (18% versus 15%) and the performance of re-excision (9.8% versus 7.2%) were not significantly different in the MRI and no-MRI group respectively, nor in subgroups. Patients in the MRI group underwent statistically more frequently mastectomy (39% versus 24%), except in patients aged 40 years or less and those with invasive lobular cancer. These results suggested that use of preoperative MRI should be more targeted, and that general, widespread use should be discouraged.

The Dutch guideline deviates from other European and American countries concerning what surgical margin it accepts as adequate. It advises re-excision only in case of extensively positive margins (i.e., tumor touching the inked margin over a length of more than 4 mm or multiple focally positive foci). In case of focally positive margins (i.e., 4 mm or less) it is advised to continue with whole-breast radiotherapy including a boost dose. Chapter 6-8 aimed to shed a light on the safety of the Dutch guideline.

After the performance of a re-excision often no residual disease is detected. Low incidence of residual disease after focally positive margins could be an argument to support the Dutch guideline and omit the re-excision. Therefore in **Chapter 6**, all index tumor samples from all 134 BCS patients with a re-excision between 2005 and 2014 at Erasmus MC were reviewed by one pathologist. In case of re-excision for invasive breast cancer, incidence of residual disease was not different after focally positive margins (50%) as compared to close (<2mm

negative) margins (55%), but was higher after extensively positive margins (70%). After multivariable analysis an increasing margin involvement was significantly associated with lobular type of cancer, increasing tumor size, and adjacent DCIS. These risk factors could be considered at time of treatment decision making or surgery to reduce re-excision rates.

To answer the question whether it is safe to omit re-excision for focally positive margins it is important to study prognosis which is the focus of **Part IV**. In **Chapter 7** we included 11,695 invasive breast cancer patients <75 years of age, treated between 1999-2012 from a population-based database of the Netherlands Cancer Registry. Overall survival was compared after primary BCS followed by re-excision to those with primary BCS only. It was assumed that the re-excision group only included patients with extensively positive margins. Ten-year overall survival rates were 81% after 'primary BCS only', 82% after 're-excision by BCS', and 79% after 're-excision by mastectomy' (p-value=0.20). Overall survival was not significantly different after extensive adjustment for multiple patient-, tumor-, and treatment characteristics. This study adds that undergoing reexcision does not impair overall survival.

A drawback of this study was the lack of data on the actual surgical margin. Therefore in **Chapter 8** another population-based retrospective cohort study with patients treated between 2003-2008 was performed. It was found that the Dutch guideline was not routinely followed. From the 1,078 invasive breast cancer patients included with focally positive margins after BCS, 54% underwent re-excision. Compared to omitting re-excision, performing re-excision was associated with lower 5-years risk of local recurrence. However the absolute difference was small (1.8%) and the absolute number of events was already low in both groups (2.9% versus 1.1%). Besides, the local recurrence rate for negative margins (also 2.9% after 5-years) was not significantly different from focally positive margins without re-excision. Moreover, omitting re-excision in case of focally positive margins did not adversely affect disease free survival and overall survival. It was concluded that de Dutch guideline seems safe. Provided that adjuvant whole-breast irradiation is given including boost dose according to the Dutch guideline.

Part IV Quality of care

Processes and outcomes of breast cancer care can be used for measuring quality of breast cancer care. Worldwide there is a growing demand for transparency about quality of care to drive quality improvement. Monitoring and reporting of indicator information has led to quality improvement. However hospital performance data is easily misinterpreted and comparisons and rankings may be unfair. To prevent

this it is crucial to evaluate quality indicators for their scientific rigor (i.e., validity and reliability).

In **Chapter 9** the validity and reliability were tested of three process and three outcome indicators from the Dutch breast cancer working group (NABON) Breast Cancer Audit (NBCA). Case-mix and random variation adjustment were applied and hospital variation studied. The national population-based database from the NBCA included 79,690 surgically treated breast cancer patients from all 91 Dutch hospitals between 2011-2016. All indicators were not valid and/or reliable since both case-mix and/or random variation adjustment had large influence on between-hospital variation and the scores of individual hospitals. The remaining true between-hospital variation that may be due to differences in the quality of care were quantified by rankability that varied between 22%-71%. It was advised not to publically present hospital quality indicator scores before testing validity and reliability and perform adjustments if necessary to prevent unfair comparisons and rankings.

Potentially, the understanding and impact of quality of care information could be increased by a summary measure capturing multiple indicators. **Chapter 10** aimed to create and test a summary measure for quality of breast cancer care. Twenty indicators were represented in 14 hypothesized correlations that measure the same underlying concept. Eleven correlations showed weak to strong construct validity. Meaning that the majority of Dutch breast cancer care quality indicators showed good construct validity. The summarizing measure was defined as 'textbook outcome' including thirteen indicators with construct validity present. The median percentage of patients who scored positive on all thirteen indicators and therefore achieved 'textbook outcome' was 49% (interquartile range 42%-54%) before and 49% (interquartile range 48%-51%) after case-mix adjustment. Three hospitals were positive outliers and nine hospitals were negative outliers. The summary measure is promising in maximizing benefit of monitoring hospital quality performance.

SAMENVATTING

Dit proefschrift richt zich op de verschillende uitkomsten na mammasparende therapie (MST). Variërend van cosmetiek, radicaliteit, heroperatie, lokaal recidief, overleving tot kwaliteit van leven. Deze uitkomsten zijn met elkaar verbonden zoals dit proefschrift laat zien.

Deel II Cosmetisch resultaat en kwaliteit van leven

Het cosmetisch resultaat speelt een belangrijke rol in de behandelkeuze tussen een ablatio en MST, het onderwerp van **deel II**. De haalbaarheid van een goed cosmetisch resultaat indien er gekozen wordt voor MST zou besproken moeten worden met de patiënt. Echter het inschatten van deze haalbaarheid is subjectief en kan moeilijk zijn.

In **hoofdstuk 2** wordt de waarde van tumorvolume in relatie tot borstvolume (TV/BV ratio) onderzocht als voorspeller voor het cosmetisch resultaat na MST. Deze TV/BV ratio werd bepaald bij 69 mammacarcinoom patiënten in een preoperatieve MRI terwijl deze 3D geprojecteerd werd in een virtuele omgeving (I-Space). Een hogere TV/BV ratio was onafhankelijk geassocieerd met verminderd cosmetisch resultaat zoals beoordeeld door een zes persoons panel. TV/BV ratio en de tumorlocatie vormde samen een accuraat predictiemodel met een area-under-the-curve van 0.83. In de praktijk kan dit predictiemodel gebruikt worden voor het maken van beter geïnformeerde behandelkeuzes.

We weten uit de literatuur dat een beter cosmetisch resultaat ook belangrijk is voor een betere kwaliteit van leven. In **hoofdstuk 3** werd verondersteld dat MST resulteert in een betere kwaliteit van leven als de kans op een goed cosmetisch resultaat hoog is, maar dat ablatio (met of zonder borstreconstructie) resulteert in een betere kwaliteit van leven als de kans op een goed cosmetisch resultaat na MST laag is. De behandel drempel – wanneer te behandelen met MST of ablatio (met of zonder borstreconstructie) – voor een optimale kwaliteit van leven was bepaald door het modeleren van de voor- en nadelen van elke behandeling. EuroQol-5D afgeleide utiliteiten werden verzameld en fungeerde als kwaliteit van leven waarderingen vanuit het perspectief van de patiënt. MST resulteerde in superieure kwaliteit van leven ten opzichte van een ablatio als de kans op een goed cosmetisch resultaat boven de 36% was. Deze drempel van 36% werd behaald indien de tumor gelokaliseerd was in het boven-buiten, onder-buiten, boven-binnen, onder-binnen en centrale kwadrant van de borst met een TV/BV ratio onder de 21.6, 4.1, 15.1, 3.2 en 14.7 respectievelijk. De effectiviteit van dit behandelmodel in het verbeteren van het cosmetisch resultaat en de kwaliteit van

leven in de praktijk moet nog bewezen worden. Daarom was de gerandomiseerde, gecontroleerde en multicenter studie TURACOS ontworpen die gepresenteerd werd in **hoofdstuk 4**.

De TURACOS studie loopt momenteel en randomiseert patiënten met mammacarcinoom tussen de standaard preoperatieve work-up enerzijds en de standaard preoperatieve work-up met het predictiemodel anderzijds. Drie-dimensionale echo word ingezet om de TV/BV ratio te meten. Het resultaat van het predictiemodel word gepresenteerd tijdens de preoperatieve multidisciplinaire bespreking en meegenomen in het behandeladvies. Het primaire doel is het verbeteren van het cosmetisch resultaat één jaar na de MST met 14%. Waarbij vanuit wordt gegaan van een incidentie van 71% in de controle groep zoals gevonden in het onderzoek gepresenteerd in hoofdstuk 2. Totaal zullen er 300 patiënten gerandomiseerd gaan worden.

Deel III Oncologische uitkomsten

Ofschoon het cosmetisch resultaat belangrijk is, het primaire doel van MST is excisie van de gehele tumor. Als de excisie incompleet is kan een heroperatie nodig zijn en dat is de focus van deel III. Heroperaties verhogen de kosten van de gezondheidszorg, de lasten van de patiënt, het risico op een slecht cosmetisch resultaat, het risico op een secundaire ablatio en benadelen de scores van kwaliteitsindicatoren. **Hoofdstuk 5** beschrijft een retrospectief onderzoek naar de waarde van preoperatieve MRI in het verlagen van positieve marges, heroperaties en ablatio's. Uit de Nederlandse Kankerregistratie was een op een populatie gebaseerd cohort gedefinieerd met 5514 vrouwen gediagnosticeerd met invasief mammacarcinoom of ductaal carcinoma-in-situ (DCIS) tussen 2011-2013. De prevalentie van een positieve marge (18% versus 15%) en het ondergaan van een heroperatie (9.8% versus 7.2%) was niet significant verschillend tussen de MRI groep en geen MRI groep respectievelijk, ook niet in subgroepen. Patiënten in de MRI groep ondergingen wel vaker een ablatio (39% versus 24%), behalve in patiënten jonger dan 40 jaar en met een lobulair type mammacarcinoom. Deze resultaten suggereerde dat preoperatieve MRI niet bij iedereen, maar doelgericht ingezet moet worden.

De Nederlandse richtlijn wijkt af van de rest van Europa en Amerika wat betreft de definitie van een adequate chirurgische marges na MST. De richtlijn adviseert een heroperatie alleen in het geval van meer dan focaal positieve marge (tumor aan de geïnkte marge over een lengte van meer dan 4mm of meerdere focaal positieve foci). In het geval van een focaal positieve marge (4mm of minder) wordt geadviseerd om de behandeling te continueren met radiotherapie inclusief

een boost dosis. Het doel van hoofdstuk 6-8 was om een licht te schijnen op de veiligheid van dit advies.

In het geval van een heroperatie wordt er vaak geen resttumor meer gevonden. De lage incidentie van resttumor na een heroperatie voor een focaal positieve marge kan een argument zijn om het beleid in de Nederlandse richtlijn te ondersteunen en de heroperatie in dat geval achterwege te laten. Daarom zijn alle index tumorweefsels van 134 patiënten met MST en een heroperatie in het Erasmus MC tussen 2005-2014 gereviseerd door de patholoog in **hoofdstuk 6**. In het geval van een heroperatie voor invasief mammacarcinoom was de incidentie van resttumor na focaal positieve marge (50%) niet verschillend ten opzichte van negatieve marge <2mm (55%). De incidentie was wel hoger na meer dan een focaal positieve marge (70%). Na multivariabele analyse bleek dat meer betrokkenheid van tumor in de marge significant geassocieerd was met: lobulair type mammacarcinoom, toenemende tumorgrootte en bijkomend ductaal carcinoma-in-situ (DCIS). Deze risicofactoren kunnen meegewogen worden ten tijde van de behandelkeuze of preoperatief om het aantal heroperaties te verminderen.

Om een antwoord te krijgen op de vraag of het veilig om de heroperatie achterwege te laten na een focaal positieve marge is het belangrijk om ook de prognose te bestuderen. Dit is het doel van deel IV. In **hoofdstuk 7** werden 11695 mammacarcinoom patiënten geïncludeerd onder de 75 jaar oud en behandeld tussen 1999-2012 uit de database van de Nederlandse Kankerregistratie. De overleving van patiënten met mammasparende chirurgie gevolgd door een heroperatie werd vergeleken met patiënten zonder heroperatie. De aanname was dat de heroperatie alleen plaats vond in het geval van meer dan focaal positieve marge. Na 10 jaar leefde nog 81% van de patiënten zonder heroperatie, 82% van de patiënten met een mammasparende heroperatie en 79% van de patiënten met een ablatio als heroperatie. Dit verschilde statistisch gezien niet significant, ook niet na uitgebreide correctie voor meerdere patiënt-, tumor- en behandelkarakteristieken. Deze studie toonde aan dat het ondergaan van een heroperatie de overleving niet nadelig beïnvloed.

Een nadeel van de studie was het gebrek aan data over de chirurgische marge. Daarom werd in **hoofdstuk 8** een nieuwe retrospectieve cohort studie uitgevoerd over patiënten behandeld tussen 2003-2008. Van de 1078 mammacarcinoom patiënten met focaal positieve marge na mammasparende chirurgie onderging 54% alsnog een heroperatie. Vergeleken met het achterwege laten van een heroperatie was het uitvoeren van een heroperatie geassocieerd met een lager 5-jaars lokaal recidief risico. Echter het absolute verschil was laag (1.8%) en het absolute risico was al laag in beide groepen (2.9% versus 1.1%). Daarnaast

was het 5-jaar lokaal recidief percentage in patiënten met negatieve marge (2.9%) niet significant verschillend ten opzichte van patiënten met focaal positieve marge zonder heroperatie. Daarbovenop, het achterwege laten van de heroperatie in het geval van focaal positieve marge beïnvloedde de (ziektevrije) overleving niet nadelig. De conclusie was dat de Nederlandse richtlijn veilig lijkt. Op voorwaarde dat adjuvant radiotherapie wordt gegeven inclusief boost dosis.

Deel IV Kwaliteit van zorg

Processen en uitkomsten van de borstkanker behandeling kunnen gebruikt worden om de kwaliteit van de borstkankerzorg te meten. Wereldwijd is er toenemende vraag naar transparantie in kwaliteit van zorg om kwaliteitsverbetering te stimuleren. Het meten en publiceren van kwaliteitsindicatoren heeft in het verleden geleid tot kwaliteitsverbetering. Echter misinterpretatie van data en oneerlijke ziekenhuis vergelijkingen en ranglijsten liggen op de loer. Om dit te voorkomen is het cruciaal om de validiteit en betrouwbaarheid van de kwaliteitsindicatoren te evalueren.

Hoofdstuk 9 testte de validiteit en betrouwbaarheid van drie proces en drie uitkomst indicatoren van Nationaal Borstkanker Overleg Nederland (NABON) Breast Cancer Audit (NBCA). Case-mix en toevalsvariatie correctie werden toegepast en verschillen tussen ziekenhuizen werden bestudeerd. De NBCA database bevatte 79690 chirurgisch behandelde patiënten met mammacarcinoom behandeld in alle 91 Nederlandse ziekenhuizen die borstkanker behandelen tussen 2011-2016. Alle zes de indicatoren bleken niet valide en/of betrouwbaar doordat zowel case-mix als toevalsvariatie grote invloed hadden op de variatie tussen ziekenhuizen en op de scores van individuele ziekenhuizen. De overgebleven werkelijke verschillen tussen ziekenhuizen dat mogelijk te verklaren is door kwaliteit van zorg varieerde tussen de 22%-71%. Het advies luidde om niet publiekelijk kwaliteitsindicatoren scores van ziekenhuizen te publiceren zonder het testen van validiteit en betrouwbaarheid en eventueel hiervoor te corrigeren. Dit om oneerlijke ziekenhuis vergelijkingen en ranglijsten te voorkomen.

Er is potentie om de impact van kwaliteitsinformatie te verbeteren middels een samengestelde maat die meerdere indicatoren omvat. **Hoofdstuk 10** beoogde om een samengestelde maat voor de kwaliteit van borstkankerzorg te creëren en deze te testen. Veertien correlaties tussen een totaal van 20 indicatoren werden verondersteld op basis van redenatie die de hetzelfde onderliggende concept meten. Zwakke tot sterke construct validiteit was aanwezig in 11 correlaties. Dit betekent dat de meerderheid van de NBCA kwaliteitsindicatoren construct validiteit bezitten. De samengestelde maat was gedefinieerd als ‘tekstboek uitkomst’ en includeerde dertien indicatoren die construct validiteit bevatte. Het

mediane aantal patiënten die positief scoorde op alle 13 indicatoren en dus een 'tekstboek uitkomst' behaalde was 49% (interkwartielafstand 42%-54%) voor case-mix correctie en in 49% (interkwartielafstand 48%-51%) na case-mix correctie. Drie ziekenhuizen waren positieve uitschieters en negen ziekenhuizen waren negatieve uitschieters. Deze samengestelde maat is veelbelovend en de voordelen van kwaliteitsmonitoring maximaliseren.

CHAPTER 12

General discussion and future perspectives

GENERAL DISCUSSION AND FUTURE PERSPECTIVES

Cosmetic outcome and quality of life

This thesis found that a good/excellent cosmetic outcome after breast conserving surgery (BCS) can be predicted by preoperative tumor volume in relation to breast volume (TV/BV) ratio and tumor location[1]. Based on this cosmetic outcome prediction, we build a treatment decision model that results in the treatment with superior quality of life (QoL)[2]. BCS resulted in superior QoL as compared to mastectomy in case the tumor was located in the upper lateral, lower lateral, upper medial, lower medial, and central quadrant of the breast with a TV/BV ratio below 21.6, 4.1, 15.1, 3.2, and 14.7, respectively. The proposed TURACOS trial will investigate if objectifying the treatment decision by this treatment model increases the incidence of a superior cosmetic outcome from the current 71% to 85%. If so, the model needs to be implemented in clinical practice to improve informed treatment decision making and improve cosmetic outcome and QoL.

Future perspectives

At time of the diagnosis of breast cancer the patients priority is the oncological outcome. Many patients do not question the cosmetic outcome and *if* questioned by the surgeon these patients are little concerned by it. Since the expected survival of early stage breast cancer patients is excellent[3], cosmetic outcome will become more important later in life and it also influences QoL[4,5]. Therefore the surgeon should guard the cosmetic outcome and QoL at the time of treatment decision making.

However in contrary to the few studies available in the literature we found no association between the patients self-assessment of cosmetic outcome and QoL[1]. This lack of association was explained by the limited sample size. Hence substantial differences in absolute QoL scores for excellent/good versus moderate/bad self-assessment were seen. The association between cosmetic outcome and QoL needs to be further clarified and quantified. This challenge is complicated by the lack of a golden standard for measuring cosmetic outcome. Beyond this thesis, our research group advised to use a panel evaluation or the BCCT.core software in combination with the BREAST-Q for studying cosmetic outcome and QoL[6]. Evaluation of cosmetic outcomes and QoL should be essential in any institution performing breast cancer treatment[7].

The prediction model for cosmetic outcome could be improved by including predictors for radiotherapy related toxicity as breast fibrosis. Moderate to severe fibrosis occurs in 26% of irradiated patients reducing QoL and sometimes

requiring reoperation[8]. However, there are large inter-individual variations in radiation sensitivity. The genetic, patient and treatment related predictors are yet to be discovered. The ability to identify in advance highly radiosensitive patients allows better informed decision making. These patients can be recommended to undergo mastectomy with or without direct reconstruction instead of breast conserving surgery followed by radiation therapy. An important step in identifying predictors of radiation toxicity is the evaluation of cosmetic outcomes and QoL (which includes radiation toxicity related questions) in all hospitals.

The treatment decision model for optimal QoL can further be improved by adding more treatment alternatives and more reliable QoL predictions. In case the expected cosmetic outcome after BCS is inferior, other alternatives then mastectomy can be offered like direct oncoplastic reconstruction and neo-adjuvant chemotherapy followed by BCS. There is a fair amount of QoL benefit that can be expected if more research is performed to acquire more accurate QoL values that decreases parameter uncertainty. As shown by our value of information analysis[2]. For that purpose utilities have been measured in a larger study population for more different treatment options in our institute. An improved treatment decision tree will be developed and the effect of individual patient and tumor characteristics on the treatment with optimal QoL will be studied. Ideally, a webbased decision aid is available to patients. The Dutch guideline has already been translated into a webbased guide/app based on decision trees[9]. An extension can be implemented whereby tumor characteristics (e.g. tumor volume and tumor location) and personal characteristics (e.g. age, smoking status, breast size, socio-economic status) can be inserted resulting in an output of expected QoL values per treatment strategy. The treatment strategies should be more extensive and include BCS, oncoplastic surgery, neo-adjuvant chemotherapy followed by BCS, mastectomy only, and mastectomy with (immediate or delayed, implant or flap) breast reconstruction. This means that not only the oncological breast cancer surgical options, but also the possible plastic surgical breast reconstruction options are taken into consideration at time of breast cancer diagnosis. To realize this change in treatment decision management, intensive collaboration between oncological surgeon and plastic surgeon needs to be pursued.

We suggest cosmetic outcome to be a quality indicator of the official National Breast cancer working group Netherlands (NABON) Breast Cancer Audit (NBCA) set. The aim is to stimulate improving cosmetic outcome and its associated QoL. Monitoring and reporting of the quality indicator score to individual hospitals in comparison to (anonymous) national data has previously shown to increase quality of care[10]. Reporting hospital performance data is further discussed in

the paragraph 'Quality of care'. The optimal time for cosmetic outcome evaluation can be discussed. It is known that the cosmetic outcome worsens over time[11]. From a feasibility and usability point of view, at one year postoperative it should be evaluated to obtain relevant information as soon as possible. An objective method of evaluation alongside a patient self-evaluation should be used. This objective method should be efficient to guarantee feasibility and data quality. The most evidence based methods would then be the bcct.core software evaluation of a photograph[12].

Oncological outcomes

Cosmetic result and QoL are majorly influenced by undergoing reexcision due to irradicality which involves a secondary mastectomy in 38%-46%[13,14]. The use of preoperative MRI was found not to improve radicality and reexcision rate and even increased mastectomy rate[15]. Even if woman needed to undergo a reexcision, this was however not associated with decreased overall survival[13]. A reexcision was omitted in 54% of the invasive breast cancer patients with focally positive margins after BCS between 2003-2008[14]. The results of this thesis provides supportive evidence for the safety of this. The 10-year disease-free survival and overall survival were not impaired. The 5-year local recurrence rate was statistically significantly higher if reexcision was omitted as compared to performing reexcision, but considered as a non-relevant difference[14]. Furthermore, we showed that the incidence of residual disease in the reexcision specimen after focally positive margins was not different from the incidence of residual disease after close margins. However it was higher after extensively positive margins[16]. As the Dutch guideline advises, the patient can continue with radiation therapy including a boost dose. This not only reduces reexcision rates and secondary mastectomy rates, it also improves cosmetic outcome and QoL.

Focally positive margins after breast conserving surgery for invasive breast cancer: Omission of surgical re-eXcision and radiation boost (FOX); a single-arm clinical trial

A radiation boost increases long-term radiation toxicity and detoriates cosmetic outcome and QoL[17]. Evidence for the radiation boost in case of focally positive margins is however lacking. It is generally hypothesized that increased local recurrence risk results from tumor biology, not positive margins, and should not be targeted with boost[18]. A trial should be performed aiming to show that treating patients with focally positive margins with whole-breast radiation therapy only is non-inferior to current standard of care. The design can be a prospective,

two-arm, non-randomised, non-inferiority, multicenter trial. Eligibility criteria include: primary T1-2N0 invasive breast cancer, aged >50 years and BCS with focally positive margins. In the absence of risk factors, patients receive standard whole-breast radiation therapy conform their institutes protocol, without boost. In case of any of the following risk factors, a low boost dose is given; tumor size >3cm, grade 3, triple negative Her2neu positive, lymphovascular invastion, and neo-adjuvant chemotherapy. Quality control includes central pathology review of the margins from all patients and central radiation protocol review of 10% of patients at each study center. Primary outcome is 5-year IBTR rate in the first arm of patients without risk factors and without boost. The expected 5-year IBTR rate is 2.9% conform our previous findings with an upper margin of 4%[14]. The current true rate of 2.1% confirms the MINDACT trial[19]. The number of patients required is 395. Secondary outcomes are measured at 5- and 10-year and include: overall survival, breast cancer specific survival, disease free survival, cosmetic result by bcct.score software evaluation of photographs, surgeon-reported radiation fibrosis on 4-point scale, satisfaction with breasts measured by Breast-Q, patient reported radiation fibrosis measured by EORTC BR23, and QoL measured by EORTC QLQ C30. The patient is expected to benefit from reduced reexcision rates, reduced radiation toxicity, improves cosmetic outcome, and improves QoL. If this single-arm trial shows a 5-year local recurrence rate that is non-inferior to current standard of care. The majority of patients with focally positive margins after BCS for invasive breast cancer can only be treated with whole-breast radiation therapy; the re-excision and radiation boost dose can be omitted. This could be guideline changing.

Other future perspectives

For patients with focally positive margins not fulfilling the eligibility criteria of the trial proposed above. It would be interesting to study what the preferable treatment is in terms of cosmetic outcome and QoL; surgical reexcision or radiation boost. This has never been investigated.

For patients with ductal carcinoma-in-situ (DCIS) only, it might be interesting to study whether reexcision rates can be reduced. Currently the American guideline defines a 2 mm negative margin as acceptable[20]. In 58 patients with DCIS only and a reexcision, we found residual disease in 39% after close margins, 46% after focally positive margins, and 90% after extensively positive margins. In only two patients the residual disease included an invasive component[16]. Only one local recurrence occurred from the total of 108 patients with DCIS only after a median of 57 months. That patient had extensively positive margins. These findings question

the need for the strict reexcision indication, assuming that whole-breast radiation therapy is given. A first step could be a large retrospective analysis of DCIS only patients with ≤2mm negative margins after BCS. Whereby the local recurrence rates are compared in patients with a reexcision (according to current guidelines) to patients without a reexcision (the experimental group). Assuming that a considerable number of patients did not have a reexcision. In this thesis that was the case in 35% of patients treated at a single institute between 2005-2014[16].

To facilitate future studies we recommend to quantify the extent of margin involvement in all pathology reports. Future studies addressing margins should investigate focally and extensively positive margins separately. This will add fruitful evidence to the discussion on adequate margins, the need for reexcisions, and the radiation boost dose.

Quality of care

The outcomes radicality, reexcision and a derivative of secondary mastectomy make up the outcome types of quality indicators in the Dutch Breast Cancer Audit. All other quality indicators are process types. This thesis found that construct validity was present for the majority of indicators used in the Netherlands. Case-mix and/or random variation influenced the variation between hospitals and the individual hospitals scores. The part of residual hospital variation that is possibly due to differences in quality of care varied between 20% to 71%. Reliability however increased by increasing number of events. The summary measure included 13 indicators. It showed between hospital variation and had discriminative ability. There is a risk of making false comparisons and drawing wrong conclusions if the influence of case-mix and random variation is not investigated and - if present - adjusted for. Although reporting hospital performance data may stimulate quality improvement in general. Judgments on the performance of individual hospitals should be made with caution. Quality improvements efforts can target the negative outlier hospitals and use the positive outlier hospitals as best practice examples. The proposed summary measure has the potential to increase the impact of publishing hospital performance data, but further research is needed.

Future perspectives

Since the methodology of studying between hospital differences is relatively new and emerging. A manual for validity and reliability testing should be written by methodologists and made available to the scientific committees monitoring quality indicators. Concerning case-mix adjustment, ideally few case-mix factors as possible

are needed. Therefore, the additional effect of each individual case-mix factor for each individual quality indicator should be investigated. Consequently, only correction for the most important case-mix factors needs to be performed and that will reduce the number of case-mix factors registered and thus reduce registration burden. We also believe quality indicators should be divided into those suitable for internal monitoring purposes and those suitable for external comparison purposes. The indicators 'irradical margin after BCS for invasive tumor' and 'irradical margin after BCS for DCIS' were not valid and not reliable and therefore unsuitable for comparison purposes, but informative for monitoring purposes. One of the causes for their lack of reliability is the low number of events per hospital. These two indicators also showed to be only moderately associated assuming that achieving radical margins cannot be fully explained by surgical performance. As this thesis has shown, other clinicopathological factors are of influence[16]. A reason to give these indicators less priority.

The quality indicator 'breast contour preserving treatment' was found to be fairly reliable and valid and suitable for comparison purposes. However it was majorly driven by the direct breast reconstruction rate and therefore underrepresenting BCS rate. This is important information to add when comparing hospitals and it may be a reason for splitting up this composite measure into separate indicators for monitoring hospitals. Note that breast contour preserving treatment does not necessarily means a good cosmetic outcome. It is important to prevent falsely stimulating performing mastectomies to keep irradicality percentages low or to falsely stimulate performing direct breast reconstructions at high risk for complications to keep breast contour preserving treatment percentages high. Therefore we advocate including a quality indicator addressing cosmetic outcome as discussed above.

To achieve maximum impact of quality of care information, the best understandable method of presentation needs to be studied to prevent misinterpretation. To identify this preferable method, qualitative research should be performed with the different internal and external stakeholders in focus groups. The demand for transparency about quality of care is an unavoidable health care development for which we as professionals better lead the way and ensure it is in the patients benefit.

The surgical knot of breast cancer outcomes

This thesis added information how to improve outcomes after breast cancer surgery. Due to the relatively good survival of early stage breast cancer, other outcomes besides survival have become important, making it a challenging disease entity to treat. Going through this thesis you find how these outcomes are intertwined which adds to the treatment challenge. One cannot improve one outcome without affecting other outcomes. First of all, improving cosmetic outcome can improve QoL. Second of all, improving radicality rate decreases reexcision rates and decreases secondary mastectomy rates. Consequently, the cosmetic outcome will improve and thus QoL improves. The quality indicator scores for "irradical BCS", "reexcision after BCS" and "breast contour preserving treatment" will improve. Thirdly, the reexcision rate can be decreased by omitting the reexcision. Again this will improve the two latter quality indicator scores, but the first "irradical BCS" remains unchanged. Whether cosmetic outcome and QoL will be improved or even worsened depends on the radiation therapy dose and the patients sensitivity for radiation induced toxicity. Survival will not be influenced, but the hypothesized non-inferior change in local recurrence risk has yet to be proven. Another example is the treatment model between BCS and mastectomy proposed in this thesis to improve the decision making, it may increase mastectomy (with breast reconstruction) rates. This is hypothesized to improve cosmetic outcome and QoL, but may reduce the quality indicator score for "breast contour preserving treatment". Regarding survival, recent retrospective analysis of large population-based data have shown that BCS with radiation therapy may be preferred over mastectomy. The many difficult decisions in breast cancer treatment remains to be made by shared decision making between patient and physician preferably and advised by a multidisciplinary team.

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APPENDICES

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Dan zijn er de bijrijders die frequent een paar kilometer meereden op die lange weg. Ze draaiden aan de knop van de autoradio; naar *lounge* muziek om te ontspannen en te genieten van het gezelschap en landschap, naar *calm vibes* voor een goed gesprek, maar meestal naar *happy tunes* voor een dansje en een lach. Allen, heel veel dank! Mijn paranimf Annemarie, is een oersterke vrouw die alle ballen soepel in de lucht houdt en ook nog verschrikkelijk attent en lief is, zo knap! Wij delen onze ambities en heel veel meer en ik weet dat geen barrière (afstand) ons zal tegenhouden om daarmee door te gaan. Zij heeft mij New York voor het eerst laten zien, dat zal ik nooit vergeten. Kim, nog zo'n sterke, knappe vrouw

die mij voor de tweede keer heeft meegenomen naar New York. Ze is bereisd, maar heeft Hollandse nuchterheid en daarom voel je je altijd op je gemak bij haar. De woorden “plezier maken” passen bij ons en wij hebben een soort magische *sisterhood*. Nina Liza, de derde sterke vrouw die vaak wordt aangezien voor mijn zus! Ze is authentiek, onafhankelijk, heeft een warme persoonlijkheid en is een onwijs goede danseres (om jaloers op te zijn). Je weet nooit hoe onze wegen gaan lopen, maar ik weet wel zeker dat ze blijven kruisen, want *history repeats itself*. Zoals de lezer inmiddels weet, omring ik mijzelf met sterke vrouwen, en dat is ook stoere Nelleke. Ik bewonder haar rustige uitstraling, ze biedt iedereen een luisterend oor en geeft indien gevraagd ook goed advies. Sterker dan ik is Monika, dat laat ze mij elke keer weer zien in *the gym*. Maar behalve onze spieren, laten we vooral onze tanden zien, *because she makes me laugh*. Mijn avontuur naar Australië eindigde op Schiphol, en daar stond mijn jeugdvriendin Mirjam mij op te wachten, dat zal ik nooit vergeten.

Mijn familie bedank ik: Opa en Oma Bakker, Frank en Marjan, Marjan en Cees, Koen en Derk, Tessa en Leon, Ingrid, Gideon en Birgit. Emil, jij bracht humor en weer een hond in ons gezin, waarvoor ik je nog steeds dankbaar ben. En jij was overal bij, dat zal ik nooit vergeten.

Mijn paranimf en zus Githa, wat kennen wij elkaar toch goed, het is een privilege om een zus te hebben en dat gevoel te kennen. Jij was altijd mooier en in alles beter, maar dat vond ik helemaal niet erg, want ik gun jou alles! Heel veel geluk *in life*.

Mama en papa, jullie gaven de karaktereigenschappen, opvoeding en kansen die mij hebben gemaakt tot wie ik ben. En ik ben er trots op! Ik schrijf dit stuk tekst met uitzicht op ons huis aan de Rijksstraatweg. Het geeft mij een groot geluksgevoel en duizend-en-één prachtige herinneringen. Van de hond en pony, radslagen in de tuin, vakanties met ski’s of vouwwagen… Het was een voorrecht, daarom wil ik dit proefschrift opdragen aan jullie, eeuwig dank!!

PHD PORTFOLIO

Name PhD student:	**PhD period:**
Elvira Lise Vos	March 2013 – March 2018
Erasmus MC department:	**Promotors:**
Surgery	Prof.dr. C. Verhoef and Prof.dr. S. Siesling
Research School:	**Supervisor:**
Medicine	Dr. L.B. Koppert

1. PhD training

	Year	Workload (ECTS)
General academic courses		
- Research Integrity Course, Erasmus MC	2014	0.3
- Basic course for clinical investigators (BROK®)	2013	1.5
- Basic didactics "Teach the teacher", Erasmus MC	2012	0.3
- Erasmus MC Female Career Development Program	2017	4.0
- Microsoft Access 2010: Basic, Erasmus MC	2013	0.3
Research courses		
- Master of Science in Clinical Research, NIHES	2011-2014	120
- Advanced Topics in Decision-making in Medicine, NIHES	2014	2.4
Seminars and workshops		
- Research meetings at the Department of Surgery, Erasmus MC	2012-2015	1.0
- ECCO-AACR-EORTC-ESMO Workshop: Methods in Clinical Cancer Research	2017	5.0
- ESO-ESMO Oncology course for medical students	2014	2.0
- Annual Course on Molecular Medicine, Postgraduate school, Erasmus MC	2015	0.7

Presentations

Oral	**Year**	**Workload (ECTS)**
- Esser Course on Oncoplastic Breast Surgery, Rotterdam	2017	1.0
- European Society of Surgical Oncology (ESSO) congress, Krakau, Poland	2016	1.0
- Society of Surgical Oncology (SSO) congress, Boston, USA	2016	1.0
- European Cancer Organisation (ECCO) congress, Vienna, Austria	2015	1.0
- Regional breast cancer symposium, Erasmus MC	2018	1.0
- Borstkanker Behandeling Beter, Rotterdam, the Netherlands	2014	1.0
- Dutch Breast Surgeons Course, Dutch Society of Surgical Oncology	2014	1.0
- Daniel Den Hoed Day, Erasmus MC	2013	1.0
- NVvH Chirurgendagen	2013	1.0
Posters		
- European Breast Cancer Conference (EBCC), Barcelona, Spain	2018	0.5
- European Breast Cancer Conference (EBCC), Amsterdam, the Netherlands	2016	0.5
- San Antonio Breast Cancer Symposium (SABCS), Houston, USA	2014	0.5
- European Breast Cancer Conference (EBCC), Glasgow, UK	2014	0.5
- Society of Surgical Oncology (SSO), Phoenix, USA	2014	0.5
National and international conferences		
- EORTC Breast Cancer Group biannual meetings	2017-2018	2.0
- Erasmus MC Surgery “Stafdag”	2012-2014	0.9
- Borstkanker Behandeling Beter, Rotterdam, the Netherlands	2015-2017	0.9
- Scholingscursus Mammcarcinoom, Tiel, the Netherlands	2012-2014	0.9

2. Teaching

	Year	Workload (ECTS)
Lecturing		
- Methodology lectures at the National Cancer Registry	2015-2018	2.0
- Breast cancer lecture for last year medical students	2014-2015	1.0
- Medical lectures for nurses and allied health professions	2009-2014	4.0
- Breast cancer lecture for the general public at Summerlab	2016	0.3
Supervising and tutoring		
- Supervising Msc Medicine thesis of Karishma Ramlakhan	2015	4.0
- Supervising Msc Medicine thesis of Krista Brouwer	2014	4.0
- Supervising Bsc Medicine students writing a systematic review	2012	1.5
- Erasmus Anatomy Research Project (EARP)	2009-2012	9.0
Other		
- Peer review for Medical Decision Making (IF 2.4)	2018	0.5
- Peer review for Breast Cancer Research & Treatment (IF 3.6)	2015	0.5

LIST OF PUBLICATIONS

Vos EL, Koppert LB, van Lankeren W, Verhoef C, Groot Koerkamp B, Hunink MGM. A preliminary prediction model for potentially guiding patient choices between breast conserving surgery and mastectomy in early breast cancer patients; a Dutch experience. Qual Life Res 2018; 27:545-553.

Vos EL, Gaal J, Verhoef C, Brouwer K, van Deurzen CHM, Koppert LB. Focally positive margins in breast conserving surgery: predictors, residual disease, and local recurrence. Eur J Surg Oncol 2017; 43:1846-1854.

Vos EL, Siesling S, Baaijens MHA, Verhoef C, Jager A, Voogd AC, Koppert LB. Omitting re-excision for focally positive margin after breast conserving surgery does not impair disease free and overall survival. Breast Cancer Res Treat 2017; 164:157-167.

Vos EL*, Lagendijk M*, Koning AHJ, Hunink MGM, Pignol JP, Corten EML, de Monye C, van Deurzen CHM, van Dam JH, Vrijland WW, Contant CME, Verhoef C, van Lankeren W, Koppert LB. TUmor-volume to breast-volume RAtio for improving COSmetic results in breast cancer patients (TURACOS); a randomized controlled trial. BMC Cancer 2017; 17:336-343.

Vos EL, Voogd AC, Verhoef C, Siesling S, Obdeijn IM, Koppert LB. Benefits of preoperative MRI in breast cancer surgery studied in a large population-based cancer registry. Br J Surg 2015; 102:1649-1657.

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Vos EL, Koning AH, Obdeijn IM, van Verschuer VM, Verhoef C, van der Spek PJ, Menke-Pluijmers MB, Koppert LB. Preoperative prediction of cosmetic results in breast conserving surgery. J Surg Oncol 2015; 111:178-184.

Vos E, Seynaeve C, Obdeijn IM, Mureau MA, Verhofstad MH, Rothbarth J. Curatieve resectie van solitaire claviculametastase. Ned Tijdschr Geneeskd 2014; 158:A7296.

Vos EL, Lingsma HF, Jager A, Schreuder K, Spronk PE, Vrancken Peeters MTFD, Siesling S, Koppert LB. The effect of case-mix and random variation on breast cancer care quality indicators and their rankability. Submitted.

Vos EL, Koppert LB, Jager A, Vrancken Peeters MTFD, Siesling S, Lingsma HF. Construct validity of breast cancer care quality indicators and hospital variation of a composite measure. Submitted.

Lagendijk M, Vos EL, Verhoef C, Koning AHJ, van Lankeren W, Koppert LB. Breast volume and tumour volume measurements in breast cancer patients using 3-D Ultrasound Automated Breast Volume Scanner images. World J Surg 2018; 42:2087-2093.

Lagendijk M, Vos EL, Nieboer D, Verhoef C, Corten EML, Koppert LB. Evaluation of cosmetic outcome following breast conserving therapy in trials: panel versus digitalized analysis and the role of PROMs. Breast J 2018; 24:519-525.

van Verschuer VM, Mureau MA, Gopie JP, Vos EL, Verhoef C, Menke-Pluijmers MB, Koppert LB. Patient Satisfaction and Nipple-Areola Sensitivity After Bilateral Prophylactic Mastectomy and Immediate Implant Breast Reconstruction in a High Breast Cancer Risk Population: Nipple-Sparing Mastectomy Versus Skin-Sparing Mastectomy. Ann Plast Surg 2016; 77:145-152.8.

Verseveld M, Barendse RM, Dawson I, Vos EL, de Graaf EJ, Doornebosch PG. Intramucosal carcinoma of the rectum can be safely treated with transanal endoscopic microsurgery. Surg Endosc 2014; 28:3210-3215.

ABOUT THE AUTHOR

Elvira Vos was born and raised in Ridderkerk, the Netherlands on May 2nd 1989. After finishing high school she took a gap year to travel and work her way around Australia. She returned and started medical school in 2008 at the Erasmus University in Rotterdam. She was one of the best first year students and selected to simultaneously study for a master degree in Clinical Research at the Netherlands Institute of Health Sciences on a full scholarship. Some courses were followed at the Johns Hopkins Bloomberg School of Public Health in Baltimore, USA and University of Cambridge in Cambridge, UK. She also actively participated as teacher/tutor in a student organization for peer-to-peer teaching of surgical anatomy masterclasses for excellent students (Erasmus Anatomy Research Project). Here she found her passion for surgery. For her master degree in Clinical Research, she initiated a research project at the Department of Surgery, Erasmus MC Cancer Institute in 2012. The thesis was rewarded with a score 9 out of 10 and the 'Best first-author research paper of the academic year' award. She wrote a number of grant proposals that were awarded by the Theia foundation – Zilveren Kruis and Dutch Cancer Society (KWF). In 2013 she got the opportunity to continue her research as a PhD candidate under the supervision of Dr. Linetta Koppert, Prof.dr. Kees Verhoef, and Prof.dr. Sabine Siesling. She initiated multiple collaborations with other departments and institutes, amongst others the Netherlands Comprehensive Cancer Organisation (IKNL) and Dutch Institute for Clinical Auditing (DICA). She held multiple presentations at (inter) national congresses and was invited as member of the EORTC Breast Cancer Group for Young Investigators. In 2015 she continued her medical training with clinical rotations. She received her medical degree in 2017 and gained work experience as a surgical intern at the IJsselland Hospital in Capelle a/d IJssel. Soon she will start a new adventure overseas as a Surgical Outcomes Research Fellow at Memorial Sloan Kettering Cancer Center in New York, USA (Dr. Vivian Strong).