THE BRILLIANCE OF VALUE BASED BREAST CANCER CARE

L.S.E. VAN EGDOM

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Chapter 1

General introduction and outline of this thesis

GENERAL INTRODUCTION

Breast cancer patients are faced with several, often complex, treatment decisions shortly after diagnosis. Decisions that are of great impact on a woman her life course. The cornerstone of the treatment of breast cancer is surgery. Although high survival rates are achieved in breast cancer surgery, irrespective of the type of surgery performed, breast cancer surgery can adversely affect women's psychological health and health-related quality of life outcomes. Anticipation of long-term physical, sexual, and psychosocial outcomes is therefore vitally important in treatment decision-making. In the heat of the healthcare evolution into a more value-based healthcare, this thesis provides insight into obtaining, measuring and improving outcomes that matters most to breast cancer patients. To explain the title of this thesis; the 'bril' (Dutch for glasses) in **bril**liance is a metaphor for the look at the care delivered from the patient's perspective, striving for patient-centred care and more tailor-made treatment, and is furthermore a nod to the three-dimensional glasses that were used in the trials described in this thesis.

Breast cancer

The breast, a mass of lobes, ducts, glandular, adipose and fibrous tissues, is an organ whose structures reflect the special function of lactation. Moreover is the breast part of the female body image and serves as a female sexual characteristic. The breast contour, shape, density, volume, and symmetry varies substantially between individuals. Breast cancer is the most common cancer affecting women worldwide[1]. Even so in the Netherlands, where 1 in 8 women are diagnosed with breast cancer during her lifetime[2]. Over the past year, survival has been increased, which is associated with a decrease in mortality through improved breast cancer therapy and early detection[3]. In Europe, breast cancer patients have a five-year survival of over 80%[3], with rates exceeding 96% for stage I and 86% for stage II breast cancer[4 5]. Female sex, increasing age, reproductive factors, personal or family history of breast and/or ovarian disease, and genetic predisposition are established risk factors for breast cancer[6 7]. A positive family history of breast cancer is the most widely recognized risk factor, particularly if it applies first-degree relatives diagnosed before the age of 50 years[8]. This often reflects the inheritance of a pathogenic *BRCA1* or *BRCA2* gene mutation, which increases the lifetime risk of developing breast cancer up to, respectively, 81% and 85%[9-11]. Among women younger than 40 years sporadic breast cancer is relatively uncommon but increases significantly thereafter[12]. The bimodal pattern of age, with a first peak at about 50 years and a second peak at 70 years, reflects the influence of age within the different subtypes; high-grade, poorly differentiated, disease tend to occur earlier, whereas slow-growing, hormone-sensitive, tumours tend to occur at a more advanced age. Today, due to improved diagnostic imaging, women are frequently diagnosed with non-invasive breast cancer (ductal or lobular carcinoma *in situ*) and early-stage invasive breast cancer (stage I-III). Since the latter are relatively small, mostly node-negative breast tumours, early-stage breast cancer is a potential curable disease and allows for less invasive treatment options.

Evolution of breast cancer workup

Nowadays, breast cancer workup includes a combination of clinical examination, imaging, and cytopathological and/or histopathological evaluation. Mainly early breast carcinomas are asymptomatic. Breast cancer is often first detected on a mammogram. In case of a palpable mass or suggestive lesion on the mammogram, additional breast ultrasonography is performed, sometimes along with a biopsy to complete the diagnostics. If indicated additional imaging is performed to detect possible metastasis, such as ultrasonography of the (ipsilateral) axilla, breast MRI and/or an FDG-PET or CT-scan of the thorax and abdomen in combination with bone scintigraphy. If chemotherapy is given prior to surgery the tumour response is evaluated using breast MRI.

In general, non-metastasized breast cancer is treated by local surgical intervention. Breast cancer surgery has improved substantially over the past decades. Up to the 1980s, the standard treatment was the (modified) radical mastectomy (i.e. removal of all breast tissue), regardless of the stage of the disease. Gradually, the question arose whether the breast could be preserved without compromising for survival. Several randomised trials trying to answer that question followed and have shown that breast-conserving therapy (BCT, i.e. breast-conserving surgery (BCS) followed by whole breast radiotherapy) is as effective as mastectomy for treatment of breast tumours $\leq$5 cm[13-17]. Long-term results of these trials have shown equal survival rates for BCT and mastectomy in early-stage breast cancer patients[18-21]. A recent population-based study amongst T1-2N0-2M0 breast cancer patients in the Netherlands has even shown a superior breast cancer-specific survival and overall survival for BCT patients compared to mastectomy (after correction for all identifiable confounders)[22]. Considering the at least comparable prognosis in early-stage breast cancer after BCT and mastectomy, quality of life should be a focus in treatment decision-making. To improve local control and survival, regional or locoregional radiotherapy, and/or (neoadjuvant) systemic therapy, including chemotherapy, antihormonal therapy or targeted therapy may be indicated. Presently, breast reconstruction is considered an important step in breast cancer care as it not only creates a new breast but restores a woman's body image and quality of life, while reducing the psychological anxiety that a mastectomy procedure causes[23-25]. Breast reconstruction is either applied at the time of mastectomy (immediate breast reconstruction), or at a given point in time after surgery (delayed breast reconstruction). The choice between immediate, delayed, and no breast reconstruction is determined by clinical and treatment characteristics as well as by patients' preferences.

International guidelines state that goals of breast cancer follow-up care are to detect recurrent disease or new malignancies at an early-stage and to detect and intervene in physical and psychosocial (late) effects of therapy[26-29]. Schemes for detecting recurrences often comprise annual physical and mammographic examinations for at least five years, depending on the patient's age, genetic predisposition, and tumour characteristics. Follow-up care also aims to detect and manage (late) effects of treatments[28 29].

Value-based healthcare and outcome measurement

Both the increased incidence of breast cancer and improved breast cancer survival rates have resulted in a rising prevalence of women with breast cancer. This brings new challenges to the medical community, as breast cancer and its treatment can negatively affect the physical-, psychological- and social wellbeing of patients, both during treatment as well as in the long-term after treatment completion. Ideally, a patient-specific fit between patient and disease characteristics and the proposed treatment strategy should be strived for, choosing the least invasive therapy as possible while maintaining optimal cancer control. In this way, overtreatment, as well as undertreatment, may be avoided. With the increased knowledge regarding specific treatment modalities for different sub-groups of patients, more personalized treatment of breast cancer patients can be achieved. Over recent years, a shift from a more generic approach of care towards a more patient-centred approach of care has been seen[30]. With patients-centred care, cancer care has become more focused on the individual needs of breast cancer patients, both in clinical as in personal values[30]. This patients-centred provision of care is the potential of the foundation of value-based healthcare (VBHC). VBHC aims to improve the quality of the care delivered by measuring and improving outcomes that reflect value instead of volume. Value of care is defined as health outcomes per total costs[31]. Since the value in healthcare depends on results, not inputs, value is measured by the outcomes achieved and not the volume of services delivered. Ideally, these outcomes reflect patient-orientated results instead of structure or process measures that do not always reflect the results obtained. In a VBHC-design, outcomes are both provider reported (i.e. breast cancer survival, complications, and hospitalization rates) and patient-reported (PROs)[31]. Inherently, these outcomes are disease-specific and multidimensional to reflect the total cycle of care and quality of life and disease burden in the long run[32 33]. To measure PROs, validated questionnaires can be used, called patient-reported outcome measures (PROMs). PROMs are targeted at either a diseased population in specific or at the population in general. The first is used in comparison across conditions, while the latter is more applicable to general aspects of health and wellbeing[34]. PROMs can be used to measure in absolute terms, such as patient's ratings of the severity of pain, but can also be used to report changes from a previous measure such as a new onset of symptoms following chemotherapy. The patient perspective provides a more holistic interpretation and a comprehensive assessment of the benefits of the treatment when compared to survival rates and disease outcomes. For example, BCS followed by radiotherapy (BCT) may demonstrate good clinical outcomes in terms of locoregional control and breast cancer-free survival, while PROs may identify that breast cancer patients are non-compliant with BCT due to reported adverse side effects, intensity of the daily sessions of radiotherapy, and/or a poor quality of life. The effectiveness of therapy, therefore, has many dimensions, including clinical effectiveness as well as the benefit felt by patients as a direct result of having that specific therapeutic intervention[34]. Specifically in the care for (early-stage) breast cancer patients, the importance of value is increasingly being recognized. Considering the excellent and comparable oncological outcomes and multiple locoregional strategies available, all with different outcomes and costs, there is an increasing need for outcome measurements that accurately differentiate between

treatment strategies. PROM results can be discussed at the outpatient clinic, during consultations, aiming to detect possible health problems that may require further attention. On the other hand, can PROMs also be applied for benchmarking, as routine PROM assessments can reflect the daily care delivered, giving an insight into the effectiveness of care. This insight into a health institution's performance allows providers to improve their quality of care. In the era of increasing healthcare costs and stringent measures to lower costs, these outcomes could increase breast cancer care efficacy, and in addition, could add in future treatment decision-making and/or follow-up regimes.

OUTLINE OF THIS THESIS

The general aim of this thesis is to investigate facilities to obtain, measure and improve outcomes that matter most to breast cancer patients. In **Part I** the focus lies on a new and more patient friendly imaging tool used in the preoperative, neoadjuvant, setting. In **Part II** the focus lies on outcome measurement and improvement. Health-related quality of life outcomes regarding breast cancer and *BRCA1* and *BRCA2* gene mutation are evaluated using PROMs. Furthermore, the implementation of a VBHC-strategy is described. **Part III** focusses on shared decision-making in breast cancer follow-up care. To complete this section an overview is given of delayed breast reconstructive surgery within the Netherlands using a population-based cohort. PROs and patients' experiences were the main sources of information, putting the patient's perspective at the heart of this thesis.

Part I – New breast imaging in tumour response evaluation

Part I of this thesis investigates three-dimensional ultrasonography in breast cancer diagnostics striving to implement diagnostic tools that are minimally burdensome for patients. In **Chapter 2** the Automated Breast Volume Scanner (ABVS – ACUSON S2000TM, Siemens Medical Solutions) is studied for its accuracy for the radiological tumour response evaluation in breast cancer patients who are treated with neoadjuvant chemotherapy (NAC). In this feasibility study, both tumour diameter response and tumour volume responses were evaluated using the (3D) ABVS and compared to (3D) breast MRI, which is considered the gold standard. Additionally, patients' acceptability for ABVS versus breast MRI was evaluated.

Part II – Patient-reported outcome measures

Considering the at least equal oncological outcomes in early-stage breast cancer patients, irrespective of the type of surgery performed, outcomes reflecting the (long-term) quality of life are increasingly important in this group. Therefore the focus in this part lies particularly on early-stage breast cancer patients. Strategies to measure, interpret and improve PROs are evaluated striving to accurately differentiate between different locoregional therapies. The International Consortium for Health Outcomes Measurement (ICHOM) assembled a multidisciplinary international working group that developed a standard set of value-based patient-centred outcomes (PROMs) for breast

cancer. Within this set PROMs are pivotal, accounting for 75% of outcomes. The other 25% is related to clinical outcomes. In **Chapter 3** PROMs as proposed in the ICHOM standard set for breast cancer were administered to breast cancer patients through both regional and national patients' advocate society. Satisfaction and applicability of PROMs were evaluated in addition. **Chapter 4** describes the evaluation of PROMs in breast cancer patients surgically treated in the Erasmus MC Cancer Institute between January 2005 and August 2016. Striving to obtain reference scores for the PROMs used, the relation between PROM scores and patient-, tumour and treatment characteristics were evaluated. **Chapter 5** describes the way a value-based breast cancer strategy, including explicit and longitudinal PROMs, was implemented within the Academic Breast Cancer Centre of the Erasmus MC Cancer Institute. The outline describes both the development and implementation of this initiative, and is meant as a guide for future implementations. It is found that PROMs have been collected and advocated most often in breast cancer patients[35]. However, reviews focusing on methods of PROM administration in specifically breast cancer care has not been published. Therefore, a systematic review was performed. This review, described in **Chapter 6**, provides an overview of PROM collection methods in breast cancer care, giving answer on how PROMs are administered and on what the impact of this administration is on patients, healthcare providers, and health services or processes. Moreover are facilitators and barriers influencing the integration of PROM collection in breast cancer clinical practice evaluated. Little has been done to predict PROs into the future. Therefore, the feasibility of predicting PROs following breast cancer surgery using machine learning techniques is explored in **Chapter 7**.

VBHC embodies outcomes that are disease-specific and multidimensional and reflect the total cycle of care. Naturally, this also regards the women at risk. Women with a pathogenic mutation in the *BRCA1* or *BRCA* 2 gene have a cumulative breast cancer risk to 80 years of 72% and 69% respectively[9]. For managing breast cancer risk *BRCA1/2* gene mutation carriers are offered intensive breast surveillance aimed at early detection of breast cancer, or bilateral prophylactic mastectomy (BPM) aimed at preventing breast cancer. It was hypothesized that PROs differ between women choosing for BPM and women choosing for breast surveillance. The aim in **Chapter 8** was to explore (differences in) PROs of *BRCA1/2* gene mutation carriers after either BPM followed by an immediate breast reconstruction or during breast surveillance to optimize shared decision-making in cancer risk management. In this pilot-study, PROs are collected amongst *BRCA1/2* gene mutation carriers diagnosed within the Erasmus MC Cancer Institute.

Part III – Follow-up care and delayed breast reconstructions

Within the last part of this thesis the focus lies on the period after the initial treatment of breast cancer. Further personalization of the follow-up care may be preferred to meet the individual patient's needs. As treatment strategies depends on patient and tumour characteristics, it is expected that the prevalence and severity of treatment-related health problems vary between patients. To move towards more personalized follow-up care in breast cancer, in **Chapter 9** the evidence on preferences-sensitive decisions and patient involvement in decisions about breast cancer follow-

up is reviewed. Although most decisions about breast reconstructions are made before surgical treatment, sometimes this decision is delayed until after treatment. In **Chapter 10** a nationwide population-based study is performed striving to provide an overview of the application of delayed breast reconstructions in patients with early-stage breast cancer in the Netherlands.

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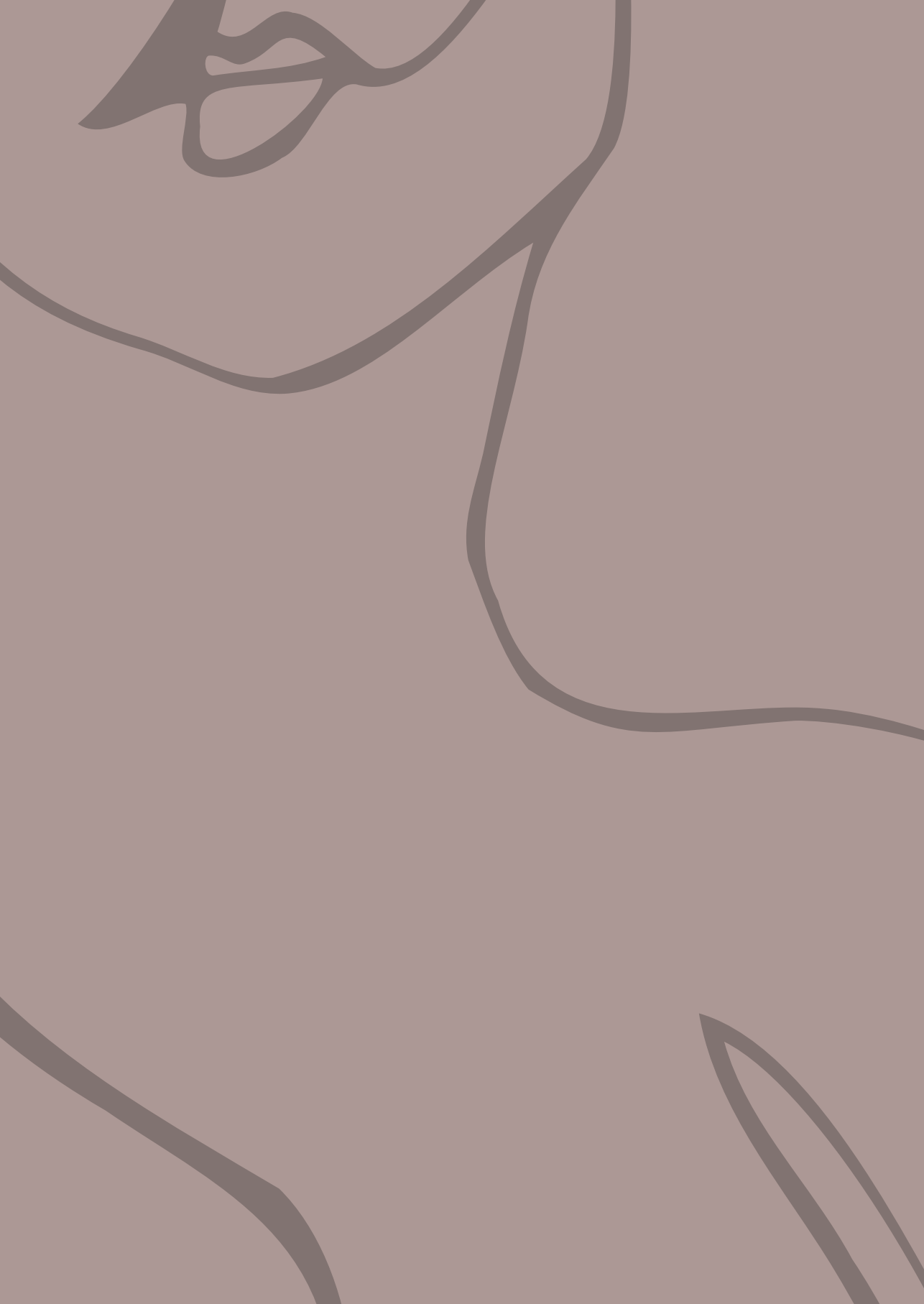

Part I

Preoperative

Chapter 2

Three-dimensional ultrasonography of the breast; an adequate replacement for MRI in neoadjuvant chemotherapy tumour response evaluation – RESPONDER trial

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ABSTRACT

Background

Accurate measurement of tumour response during and after neoadjuvant chemotherapy (NAC) is important and may influence treatment decisions in invasive breast cancer patients. Breast MRI forms the gold standard but is more burdensome, time consuming and costly. In this study response measurement was done with 3-D ultrasound by Automated Breast Volume Scanner (ABVS) and compared to breast MRI. Moreover, patient satisfaction with both techniques was compared.

Methods and materials

A single-institution, prospective observational pilot study evaluating tumour response by ABVS in addition to breast MRI (standard care) was performed in 25 invasive breast cancer patients receiving NAC. Tumour response was evaluated comparing longest tumour diameters as well as tumour volumes at predefined time points using Bland-Altman analysis. Volume measurements for breast MRI were obtained using a fully immersive virtual reality system (a Barco I-Space) and V-Scope software. Same software was used to obtain ABVS volume measurements using an in-house developed desktop VR system. Inter- and intra-observer agreement was evaluated by Intraclass Correlation Coefficient (ICC).

Results

Twenty-five patients were eligible for baseline measurement, 20 for a mid-NAC response evaluation, and five for a post-NAC response evaluation. MRI and ABVS showed absolute concordance in 73% of patients for the mid-NAC evaluation, with a 'good' correlation for the difference in longest diameter measurement (ICC 0.73, $p<0.01$) as compared to baseline assessment. Concerning difference in volume measurement in the mid-NAC response evaluation showed a 'fair' correlation (ICC 0.52, $p<0.01$) and in the post-NAC response evaluation an 'excellent' correlation (ICC 0.98, $p<0.01$). 'Excellent' inter- and intra-observer agreement was found (ICC 0.88, $p<0.01$) with comparable limits of agreement (LOA) for observer 1 and 2 in both diameter and volume measurement. Patient satisfaction was higher for ABVS compared to breast MRI, 93% versus 12% respectively.

Conclusion

ABVS showed 'good' correlation with MRI tumour response evaluation in breast cancer patients during NAC with 'excellent' inter- and intra-observer agreement. ABVS has patients' preference over breast MRI and could be considered as alternative to breast MRI, in case results on an on-going prospective trial confirm these results (NTR6799).

INTRODUCTION

The use of neoadjuvant chemotherapy (NAC) for invasive breast cancer patients has increased in the Netherlands from 13% (6,262/49,073) in 2011-2014 to 20% in 2017[1]. Systemic therapy can be administered preoperatively to downstage a tumour and allow for less extensive breast surgery. NAC generates the ability of in vivo response evaluation[2]. Tumour response evaluation therefore directly influences treatment decisions, i.e. immediate surgery or change of regime in case of progression.

Internationally tumour response is evaluated according to 'Response Evaluation Criteria in Solid Tumours' (RECIST)[3], stating that tumour responses should be evaluated by changes in the longest diameter of the (pre-specified) target lesion(s). Magnetic resonance imaging (MRI) is the preferred modality to evaluate longest tumour diameter and considered gold standard[3]. Reported concordance for tumour size measured by MRI or on histopathological specimen however varies in studies of breast cancer patients with[2 4-7] and without NAC[8 9].

RECIST does not support handheld 2-D ultrasonography (US) response evaluation since it is an observer-dependent modality [3]. Although currently not recommended, we hypothesized that whole breast ultrasound with standardized imaging, the Automated Breast Volume Scanner (ABVS), can be applied for breast cancer response evaluation.

ABVS is an observer-independent automated standardized ultrasound imaging technique with access to images at any point in time[10]. ABVS was more accurate than handheld 2-D US in predicting histological tumour size[10-13]. ABVS has the opportunity to calculate volume using 3-D ABVS imaging software, quite similar to MRI with 3-D MRI imaging software. A previous 3-D ABVS volume study within our institute showed an excellent association with histopathological tumour volume[14].

Multiple studies showed that tumour *volume* response (using 3-D MRI) mid and post NAC showed higher correlation with histopathologic tumour regression compared to diameter response[15-17]. We hypothesized that tumour volume response could be a more accurate than diameter response.

ABVS is known to be advantageous over breast MRI with regard to cost, time, ease of interpretation by multiple clinicians, accessibility and avoidance of contrast agents[18-20]. We questioned whether the ABVS is as accurate as breast MRI and performed a feasibility study. Tumour diameter response as well as tumour volume response evaluation was done by ABVS and compared to breast MRI at predefined time points with two independent observers. Moreover, patient satisfaction was measured.

METHODS

Patient population

This prospective observational pilot study was conducted at the Academic Breast Cancer Centre/ Erasmus MC Cancer Institute, Rotterdam the Netherlands. Twenty-five patients were included from October 2015 to October 2017. Approval of the medical ethics committee was obtained prior to start of the study (MEC 2015-647). Women aged over 18 years, scheduled to undergo NAC and after written informed consent were eligible. Patients with cT4 breast cancer were excluded, because lesions growing outside breast tissue (i.e. chest wall or skin) cannot be discriminated by ultrasonography precisely enough. Lesions were classified according to the TNM classification system (7th edition)[21]. Tumour differentiation grade was assessed at time of final histopathological evaluation or in pre-NAC biopsies in case of pathological complete response. Surrogate subtypes were defined according to the St. Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer[22].

Study procedures

Breast MRI and 3-D breast MRI

Dynamic contrast-enhanced breast MRI was performed on a 1.5 T system (Siemens Medical Solutions – Erlangen, Germany), with the patient prone in a dedicated breast coil. Pre-contrast injection imaging protocol included a low resolution localizing sequence, a transversal T2-weighted fat-suppressed (FS) sequence (TE/TR 42/67000, FOV 34 cm, slice thickness 5.0 mm, matrix 32 x 224). Than a pre- and post-contrast injection (with intravenous 7.5 cc Gadovist or 15 cc ProHance, 2 cc/s) VIBRANT (T1) transversal 3-D sequence were performed (TE/TR 1.0/34, FOV 34 cm, slice thickness 2.2 mm, flip angle 10°, matrix 388 x 388), and a final post-contrast sagittal VIBRANT sequence (TE/TR 1.0/34, FOV 34 cm, slice thickness 3 mm, flip angle 10°, matrix 388 x 388). All patients were investigated in prone position with breast pending in a dedicated double breast surface coil. Premenopausal women were scanned on day 5-15 of the menstrual cycle. Subtraction images were obtained with the use of a software subtraction function. All MRI examinations were evaluated on a dedicated breast MRI workstation. Longest tumour diameter measurements were based on the dynamic T1 w sequences using digital rulers on the imaging workstation. For volume measurements on 3-D MRI a fully immersive virtual reality system (a Barco, Kuurne Belgium) I-Space was used. The Erasmus MC was the first university medical centre to install this system in which data can be visualized and manipulated using virtual reality, details of which have been described elsewhere[23-25]. The breast is projected as a hologram viewed with 3-D glasses and the observer can select the region of the breast with the targeted lesion. The selected image can be sized, turned and cropped with a wireless joystick (Online video I-Space)[24]. The driving V-scope software was developed by the department of Bioinformatics[23] and enables calculation of volume based on differences in grey-levels[25].

Using the V-scope software, specific thresholds for the grey-level of the voxels can be chosen to calculate the volume. Longest diameter measurements are obtained by measuring the distance between two specified points in a 3-D space.

ABVS and 3-D ultrasonography

The ABVS (Siemens ACUSON S2000$_{TM}$) is designed to acquire ultrasound images using a linear transducer that scans the entire breast in an automated fashion[10]. The resulting volume can be evaluated in three imaging-planes simultaneously (i.e. axial, coronal and sagittal plane) and measured repeatedly off-line. The transducer scans volume slabs while acquiring 0.5 mm thick images in the transverse plane[10]. The whole examination takes about 10 min. For ABVS, digital rulers were used to measure the longest tumour diameter, using the ABVS workstation. The measure the longest tumour diameter has to be obtained. The V-Scope software as used in the I-Space was also used for the 3-D visualization of ABVS data on a desktop system (further defined as 3-D ABVS). Volume was measured based on differences in echogenicity similarly to the measurement in the 3-D MRI, Fig. 1.

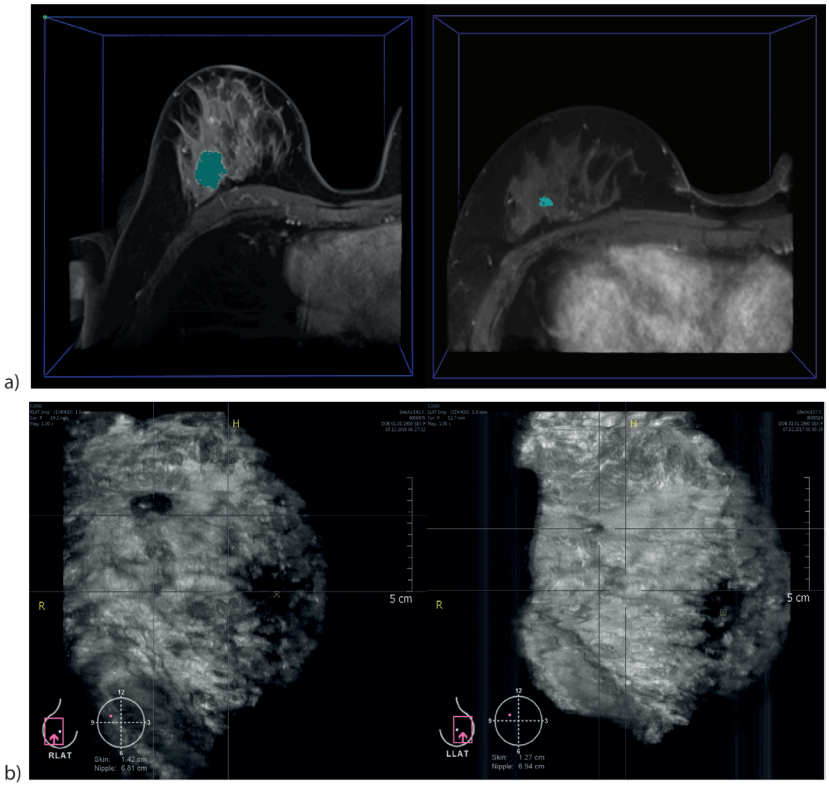

Figure 1. Example of the ABVS used for response evaluation, compared to breast MRI.

a) Transversal coupes of breast-MRI scans of the right breast. The left picture shows the tumour (coloured green) pre-NAC. The right picture shows the same patient mid-NAC with a smaller tumour (coloured green).

b) Frontal view (anterior-posterior) of the right breast. The left picture shows the tumour (upper left corner) pre-NAC. The right picture shows the same patients mid-NAC with a smaller tumour (upper left corner).

Response evaluation

According to standard care all patients underwent breast MRI prior to NAC and a second MRI following 3 courses of chemotherapy (mid-NAC), Fig. 2. If applicable a final MRI was obtained preoperatively after the completion of NAC (post-NAC) (Fig. 2). Only if the breast MRI showed residual tumour ABVS was applied.

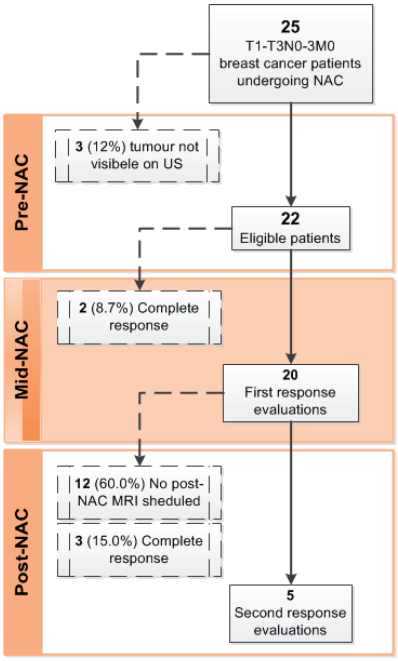

Figure 2. Flow chart patient inclusion and response evaluation.
NAC = Neo-adjuvant chemotherapy. US = ultrasonography

Response was calculated as percentage difference compared to baseline assessment (pre-NAC). Response was evaluated comparing the longest diameters using both breast MRI and ABVS. Additionally, response was evaluated by comparing the tumour volumes using both the 3-D MRI and 3-D ABVS. Changes in the RECIST criteria (Supplementary Table S1) were evaluated comparing the longest diameter of the breast MRI to the longest diameter using ABVS. Response was measured mid-NAC and post-NAC (if applicable).

Readings

Two observers performed repetitive measurements under identical conditions evaluating both tumour diameter and volume. The time-interval between two identical measurements was at least 3 months. To evaluate the intra-observer and inter-observer agreement for both the mid-NAC and

post-NAC response evaluation all diameter responses were performed twice using the ABVS. Tumour diameter measurements on MRI were only evaluated by a radiologist. To evaluate the intra-observer and inter-observer agreement of the tumour volume response evaluation all measurements were performed twice using the ABVS and the MRI.

Patient satisfaction

Patient satisfaction, i.e. acceptability for breast MRI and ABVS, was measured with the use of rating scale following the Likert Scale principle[26] (Supplementary Fig. S1). Acceptability was scored on a 5-point scale (i.e. 5 resembles a 'high acceptability', 4 'acceptable', 3 'neutral', 2 'moderately acceptable' and 1 being 'not acceptable'). The acceptability questionnaire was administered to all patients during all the study visits.

Statistical analysis

Longest diameter response was scored based on the RECIST guidelines (PD $\geq$20% increase, SD <20% increase to < 30% decrease, PR $\geq$30% decrease in longest diameter and CR if no tumour is visible), see Supplementary Table S1. Response evaluations using (3-D) MRI were compared to (3-D) ABVS by calculating the Intraclass Correlation Coefficient (ICC), which determines the variation between the clusters as a proportion of the total variance. The level of clinical significance evidence of the ICC was judged according to Cichetti and colleagues; an ICC of <0.40 was rated as 'Poor', ICC of 0.40-0.59 as 'Fair', ICC of 0.60-0.74 as 'Good' and ICC of 0.74-1.00 as 'Excellent'[27]. The longest diameter and volume response obtained by (3-D) MRI were compared to the longest diameter and volume response obtained by (3-D) ABVS (both in observer 1 and 2). Intra-observer agreement was evaluated comparing the first and second (3-D) ABVS measurement for longest diameter and tumour volume. Bland-Altman plots were used to graphically display the pairwise agreement in measuring the lesion size reduction (% longest diameter decrease) by breast MRI and ABVS. Agreement was expressed as the average difference in measurements together with 95% limits of agreement (LOA), i.e. the range of agreement within 95% of the difference between the measurements[28]. A p value $\leq$0.01 was considered statistically significant. Data analyses were performed using IBM SPSS Statistics (version 21).

RESULTS

Twenty-five patients undergoing NAC were eligible for participation in the study. In three patients the tumour was not visible on ultrasonography, resulting in 22 patients eligible for evaluation (Fig. 2). Patient and tumour characteristics are shown in Table 1. All carcinomas evaluated were invasive ductal carcinomas. MRI showed an average longest diameter of 27.5 mm, 17.0 mm and 17.0 mm for the pre-NAC, mid-NAC and post-NAC evaluation (Table 2). This was 21.6 mm, 14.4 mm and 23.5 mm respectively using ABVS (observer 1). Tumour volume in MRI was 3.8 cm^3, 0.7 cm^3, 1.0 cm^3 respectively for the first observer pre-NAC, mid-NAC and post-NAC (Table 2). Using 3-D ABVS tumour volume was 2.5 cm^3, 1.0 cm^3 and 1.6 cm^3 respectively for the first observer pre-NAC, mid-NAC and post-NAC.

Table 1. Baseline characteristics of 25 eligible patients, n (%).

Median age in years (IQR)	40.0 (29.0-52.5)
Laterality	
Left	14 (56.0)
Morphology	
Invasive ductal carcinoma	25 (100)
Invasive lobular carcinoma	.0
cT-stage	
T1	4 (16.0)
T2	17 (68.0)
T3	4 (16.0)
Molecular subtype	
Luminal A	8 (32.0)
Luminal B	6 (24.0)
Triple negative/ basal like	9 (36.0)
HER2-enriched	2 (8.0)
cN-stage	
Negative	18 (72.0)
Positive	7 (28.0)
pN-stage (SNB)	
pN0	15 (60)
pNo(itc+)	1 (4.0)
pN1	2 (8.0)
Not applicable*	7 (28.0)
ypT-stage	
ypT0/Complete pathological response	14 (56.0)
ypT1	9 (36.0)
ypT2	3 (12.0)
ypN-stage	
ypN0	20 (80.0)
ypN1	4 (16.0)
ypN2	1 (4.0)
DCIS present	
Yes	7 (28.0)
No	18 (72.0)

SNB = sentinel lymph node biopsy, itc = isolated tumour cells, pNstage = pathological nodal stage, ypTstage = histopathological tumour stage following NAC, ypNstage = histopathological nodal stage following NAC, micro = micro metastasis,
*If by histopathological or cytopathological biopsy a lymph node metastasis is diagnosed no pre-NAC SNB was performed.

Table 2. Median longest diameter (mm) and tumour volume (cm^3) pre-NAC, mid-NAC and post-NAC.

	Pre-NAC (n=22)	Mid-NAC (n=20)	Post-NAC (n=5)
	Longest diameter (mm)		
MRI (radiologist)	27.5 (18.8-34.0)	17.0 (10.0-28.5)	17.0 (9.0-29.0)
ABVS (observer 1)	21.6 (16.2-32.3)	14.4 (11.0-23.5)	23.5 (12.8-31.4)
ABVS (observer 2)	23.1 (16.0-32.1)	15.9 (11.1-23.5)	26.2 (14.0-32.9)
	Tumour volume (cm^3)		
3-D MRI (observer 1)	3.8 (2.7-7.0)	0.7 (0.5-2.6)	1.0 (0.5-10.8)
3-D MRI (observer 2)	3.8 (2.8-7.0)	0.8 (0.5-2.6)	3.1 (0.5-10.5)
3-D US (observer 1)	2.5 (1.1-5.5)	1.0 (0.4-2.3)	1.6 (0.6-5.6)
3-D US (observer 2)	2.4 (1.1-5.1)	0.9 (0.4-2.2)	1.3 (0.4-5.3)

NAC = neoadjuvant chemotherapy

Mid-NAC response evaluation

MRI and ABVS (observer 1) showed an absolute concordance in 16/22 (73%) patients according to RECIST response (Table 3). Two patients showed a complete radiological response on MRI and were excluded for a diameter and volume response comparison. The Intraclass Correlation Coefficient (ICC) showed a significant and 'good' correlation for the longest diameter response for the MRI and ABVS, ICC 0.71 [95% CI (0.41-0.88)] and 0.73 (0.43-0.88), $p<0.01$ (Table 4). The inter- and intra-observer agreement for ABVS longest diameter response was 'excellent' with ICC 0.88 (0.73-0.95), 0.88 (0.73-0.95) and 0.85 (0.67-0.94) ($p<0.01$) respectively for observer 1 and 2 (Table 4). Agreements for MRI with ABVS in diameter response evaluation are graphically displayed by Bland-Altman plots (Fig. 3). It is shown that the differences for the two examinations fall mainly between the limits of agreement except for one measurement (Fig. 3). The tumour volume response showed a 'fair' correlation when comparing the 3-D MRI with 3-D ABVS (Table 5). Inter- and intra-observer agreement for ABVS tumour volume response evaluation was 'good' to 'excellent' (Table 5).

Table 3. First response according to RECIST (n=22).

		ABSV (1st observer)			
		Progressive disease	**Stable disease**	**Partial response**	**Complete response**
MRI (radiologist)	**Progressive disease**	0	0	0	0
	Stable disease	1	7^	1	0
	Partial response	0	3	8^	0
	Complete response	0	0	1	1^

MRI = Magnetic Resonance Imaging, ABVS = Automated Breast Volume Scanner
^Absolute concordance between MRI and ABVS RECIST response evaluation.

Table 4. ICC (95% confidence interval) first diameter response (n=20).

	MRI (radiologist)	ABVS (observer 1)	ABVS (observer 2)
MRI (radiologist)	NA		
ABVS (observer 1)	0.73 (0.43-0.88)*	0.88 (0.73-0.95)*§	
ABVS (observer 2)	0.71 (0.41-0.88)*	0.88 (0.73-0.95)*	0.85 (0.67-0.94)*§

MRI = Magnetic Resonance Imaging, ABVS = Automated Breast Volume Scanner.
§inter-observer agreement, *p-value <0.01.

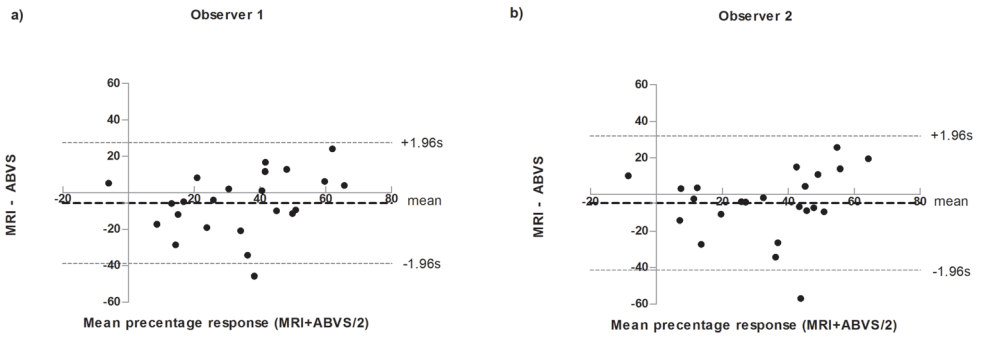

Figure 3. Bland-Altman plots of differences longest diameter (mid-NAC) MRI versus ABVS in observer 1 (Fig. 3a) and 2 (Fig. 3b).
Bland-Altman plots with representation of the mean difference (mean) and the limits of agreement (LOA), from -1.96s to +1.96s [a. LOA -38.8 to 27.5; b. LOA -41.3 to 32.0].

Table 5. ICC (95% Confidence Interval) first volume response (n=20).

	3-D MRI (observer 1)	3-D MRI (observer 2)	3-D ABVS (observer 1)	3-D ABVS (observer 2)
3-D MRI (observer 2)	1.00 (0.99-1.00)*			
3-D ABVS (observer 1)	0.52 (0.12-0.78)*	0.53 (0.13-0.78)*	0.95 (0.88-0.98)*§	
3-D ABVS (observer 2)	0.48 (0.05-0.75)	0.49 (0.07-0.76)	0.93 (0.84-0.97)*	0.68 (0.35-0.86)*§

MRI = Magnetic Resonance Imaging, ABVS = Automated Breast Volume Scanner, 3-D = three-dimensional.
§inter-observer agreement, *p-value <0.01.

Post-NAC response evaluation

MRI and ABVS (observer 1) showed an absolute concordance in 5/8 (62.5%) patients according to RECIST response (Supplementary Table S2). Three patients showed a complete radiological response and were excluded for a diameter and volume response comparison. ICC showed non-significant correlations between longest diameter response on MRI and ABVS (Supplementary Table S3). Agreements for MRI with ABVS in diameter response evaluation are graphically displayed by Bland-Altman plots (Supplementary Fig. 2). It is shown that the differences for the two examinations fall mainly between the limits of agreement. Inter- and intra-observer agreement

for ABVS longest diameter response was 'excellent' with ICC 0.99 (0.92-1.00)/1.00 (0.85-1.00), and 0.99 (0.87-1.00) respectively (p<0.01). In the five patients eligible for post-NAC evaluation longest diameter measured on both MRI and ABVS was compared with histopathological longest diameter. Concordance was seen in 4/5 (80%) patients. One patient showed pathological partial response (pPR) with <10% residual tumour (data not shown). The other, not concordant, patient showed pathological complete response (pCR), with absence of invasive cancer. Both breast MRI and ABVS however showed detectable surrounding cysts. Furthermore carcinoma in situ was found in histopathology (data not shown).

Tumour volume response showed significant and 'excellent' correlation between MRI and ABVS, ICC 0.98 (0.85-1.00) and 1.00 (0.96-1.00) (p<0.01) respectively for MRI observer 1 and ABVS observer 1 and 2 (Supplementary Table S4).

Patient satisfaction

Patients ranked ABVS as more acceptable than the breast MRI, 93% versus 12% respectively (Table 6). None of the patients reported the ABVS as 'not acceptable', in contrast to breast MRI (Table 6). Patients reported ABVS less invasive and time-consuming when compared to breast MRI (data not shown).

Table 6. Patient satisfaction regarding breast MRI and ABVS in 27 patients, n (%).

Acceptability MRI	
Very acceptable	3 (12.0)
Acceptable	12 (46.0)
Neutral	6 (22.0)
Moderately acceptable	4 (15.0)
Not acceptable	2 (8.0)
Acceptability US	
Very acceptable	25 (93.0)
Acceptable	1 (4.0)
Neutral	1 (4.0)
Moderately acceptable	.0
Not acceptable	.0

DISCUSSION

This is the first study showing the accuracy of (3-D) ABVS compared to (3-D) breast MRI in measuring tumour response during and after NAC in breast cancer patients.

In the 20 patients eligible for mid-NAC diameter evaluation we observed 'good' correlation for both observers using ABVS compared to MRI. Comparable 'good' results were found in the post-NAC

evaluation in five patients. Agreement with the RECIST response criteria was also high with an absolute concordance in 73% and 62.5%, mid- and post-NAC evaluation respectively. Bland Altman plots, comparing MRI to ABVS, showed most measurements within the limits of agreement, which are relatively wide because of the small patient number. For both measurements, the line of equality was within the interval, meaning that there is no significant systematic error between breast MRI and ABVS according to the percentage response observed.

A strength of our study is that three-dimensional volume measurements were done in addition to diameter measurements, where other studies did not[13 18]. Studies assessing the feasibility of 3-D US for volume calculation of solid breast lesions in patients suggest that 3-D US is a reliable method for the volumetric assessment[19 20]. A previous evaluation within our institute evaluating patients undergoing primary surgery showed a higher association for 3-D ABVS than 3-D MRI [ICC 0.78 (95% CI 0.55-0.91) versus ICC 0.73 (0.44-0.88) respectively][14]. These results in combination with operator-independency of the 3-D ABVS[20] suggest 3-D ABVS to be a reliable and promising method for tumour volume measurements.

Patients ranked ABVS much more acceptable as compared to breast MRI, which is an advantage of the ABVS. Patients found ABVS less invasive (less time-consuming, more comfortable, with avoidance of contrast agents) and appreciated the fact they could directly view the ultrasonography images during the examination.

Another strength of the present study is the evaluation by two observers and therefore inter- and intra-observer agreement evaluation of ABVS, with 'good' to 'excellent' correlations for longest diameter response as well for the tumour volume response. Both observers were trained in analysing ABVS data but had no previous experience in interpreting ABVS data, suggesting a short learning curve.

We did not evaluate the inter- and intra-observer agreement of the breast MRI measurements, which is a limitation of our study. Another weakness of the present study is the small patient number especially in the post-NAC response evaluation. This is a consequence of the pilot-design. The ABVS could not be used for response evaluation in 3 patients as the tumour was not clearly visible on ultrasonography. In these patients the boundaries of the tumour could not be properly defined using ABVS. All had additional DCIS with a large diameter that, as expected[29 30], enlarged the discrepancy since it is better (only) detected by MRI than by US. Presence of surrounding DCIS is a limitation of ABVS in the breast cancer tumour response evaluation. An additional limitation was that in 2 patients showing a complete radiological response at first MRI evaluation no ABVS was performed.

Differences in response evaluation can be possibly explained by different tumour visualization between ABVS and breast MRI. Ultrasound measurements are based on structural changes in breast tissue. Breast MRI on the other hand is contrast-enhanced. Malignant tumours are classified by the

kinetics of their contrast enrichment based on tumour angiogenesis[31]. Therapy causes an effect on neo-vascularisation presenting a decrease in contrast-intensity especially in the tumour periphery on MRI-images. Therefore, effect on response measurements are assumed larger with MRI than with ultrasonography. This hypothesis is supported by the 'excellent' correlation between 3-D MRI and 3-D ABVS in the volume response evaluation post-NAC. Since less decrease in contrast enhancement is seen and therefore differences between MRI and ABVS are smaller. Interestingly, ABVS showed larger lesions as compared to breast MRI post-NAC (23.5 mm and 17.0 mm respectively). A marker placed in the target lesion prior to NAC may contribute to this longer diameter by the acoustic shadowing caused by the marker generating a signal void on the ultrasonography images. This cannot always be precisely differentiated from residual tumour. This can explain that three patients with complete response on MRI were scored as having partial response on ABVS post-NAC (data not shown). Histopathological specimen showed a complete pathological response (n=2) or a micro-invasion (n=1) component. Due to a limited patient numbers, no conclusions can be drawn regarding the concordance with final histopathological evaluation.

A pathological complete response (pCR; i.e. the absence of in situ and invasive residual tumour at histopathological specimen evaluation following the course of NAC) is an important predictor for long-term disease-free and overall survival [2 32 33]. Over the years pCR-rates have increased, questioning the necessity to also perform breast surgery within these patients. Multiple studies are now undertaken to evaluate this necessity in patients showing pCR (for example NTR6120). In these studies patients are selected based on a *radiological* complete response diagnosed during or following the course of NAC. To increase the (future) applicability of the (3-D) ABVS for response evaluation not only the diameter or volume response, but also the accuracy for a prediction of a pCR during or following NAC should be investigated.

Following this pilot study inclusion is continued in a larger prospective study; RESPONDER II (NTR6799). Based on the variance found for the mid-NAC evaluation using (3-D) ABVS compared to the (3-D) MRI a power analysis was conducted to estimate the number of patients needed to evaluate the accuracy of ABVS for response evaluation in breast cancer patients during NAC. Post-NAC (3-D) ABVS scans are being performed in all patients to evaluate the accuracy of ABVS in the post-NAC response and the concordance with histopathological response.

CONCLUSIONS

ABVS showed 'good' correlation with MRI tumour response evaluation in breast cancer patients during NAC with 'excellent' inter- and intra-observer agreement. ABVS has patients' preference over breast MRI and could be considered as alternative to breast MRI. Results of an ongoing prospective trial haves to be awaited.

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SUPPLEMENTARY FILES CHAPTER 2

Supplementary Table S1. RECIST Tumour response criteria

Complete response (CR)	Disappearance of all target lesions.
Partial response (PR)	At least a *30% decrease* in the sum of diameters
Stable disease (SD)	Neither sufficient shrinkage to qualify PR nor sufficient increase to qualify for PD
Progressive disease (PD)	At least a *20% increase* in the sum of diameters of target lesions. [In addition the sum must also demonstrate an absolute increase of at least 5 mm. (Note; the appearance of one of more new lesions is also considered progressive disease)]

Supplementary Table S2. Second response according to RECIST (n=8)

		ABVS (1st observer)			
		Progressive disease	**Stable disease**	**Partial response**	**Complete response**
MRI (radiologist)	**Progressive disease**	1^	0	0	0
	Stable disease	0	1^	0	0
	Partial response	0	0	3^	0
	Complete response	0	0	3	0

MRI = Magnetic Resonance Imaging, ABVS = Automated Breast Volume Scanner.

Supplementary Table S3. ICC (95% confidence interval) second diameter response (n=5)

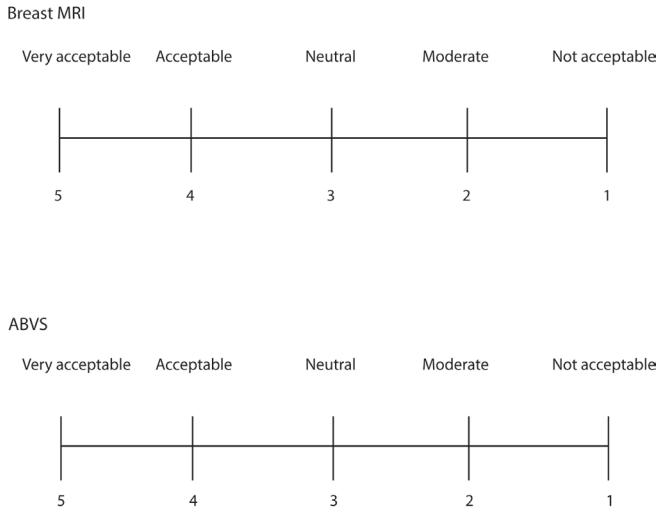
	MRI (radiologist)	**ABVS (observer 1)**	**ABVS (observer 2)**
MRI (radiologist)	NA		
ABVS (observer 1)	0.76 (-0.14-0.97)	0.99 (0.92-1.00)*§	
ABVS (observer 2)	0.69 (-0.27-0.96)	0.99 (0.87-1.00)*	1.00 (0.85-1.00)*§

MRI = Magnetic Resonance Imaging, ABVS = Automated Breast Volume Scanner.
§inter-observer agreement, *p-value <0.01.

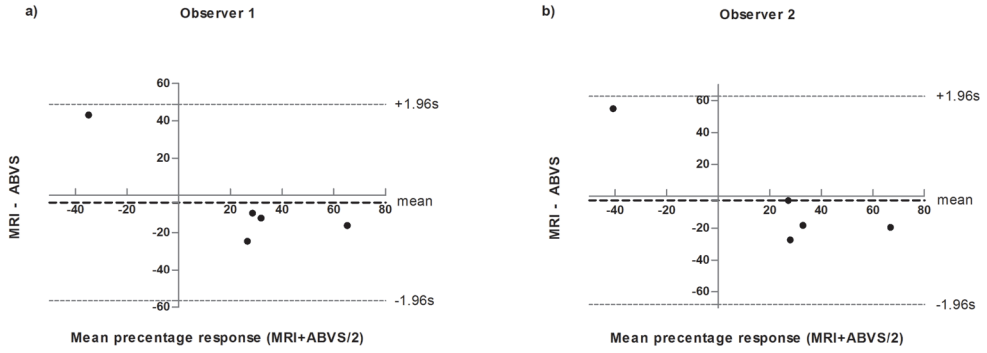
Supplementary Table S4. ICC (95% confidence interval) second volume response (n=5)

	3-D MRI (observer 1)	**3-D MRI (observer 2)**	**3-D ABVS (observer 1)**	**3-D ABVS (observer 2)**
3-D MRI (observer 2)	0.98 (0.85-1.00)*			
3-D ABVS (observer 1)	0.98 (0.79-1.00)*	0.94 (0.56-0.99)*	1.00 (0.98-1.00)§*	
3-D ABVS (observer 2)	1.00 (0.96-1.00)*	0.97 (0.74-1.00)*	0.99 (0.92-1.00)*	1.00 (0.98-1.00)§*

MRI = Magnetic Resonance Imaging, ABVS = Automated Breast Volume Scanner, 3-D = three-dimensional.
§inter-observer agreement, *p-value <0.01.



Supplementary Figure S1. Ranking score acceptability breast MRI and ABVS



Supplementary Figure S2. Bland-Altman plots of difference longest diameter (post-NAC) MRI versus ABVS in observer 1 (Fig S2a) and 2 (Fig S2b)

Bland Altman plots with representation of the mean difference (mean) and the limits of agreement (LOA), from -1.96s to +1.96s [a. LOA -56.6 to 48-9; b. LOA -68.0 to 62.7].

Part II

Perioperative

Chapter 3

Patient-reported outcome measures
in breast cancer patients

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ABSTRACT

Introduction

In the International Consortium for Health Outcome Measures (ICHOM) breast cancer outcome set Patient Reported Outcome Measurements (PROMs) form an important but rather innovative part. Few data exist on scores per type of breast surgery and how to use scores in surgical practice. We evaluated PROM scores as well as satisfaction with and expectations of the use of PROMs in breast cancer patients using the national and local patient advocate society.

Methods

Through an online survey patients were asked to report age, type of breast cancer surgery (whether breast-conserving therapy (BCT), mastectomy, autologous or implant breast reconstruction) and time since surgery. PROMs (EORTC-QLQ-C30/BR23 and BREAST-Q postoperative modules) were compared for the different surgeries. Additional comparison was made with literature normative and reference scores. Three questions evaluated satisfaction with PROMs and expectations

Results

496 patients completed all PROMs and 487 the satisfaction/expectation-questionnaire. Significantly reduced physical functioning was reported following BCT as compared to other surgeries and literature reference values. Satisfaction scores were higher following autologous reconstruction and lower following implant reconstruction as compared to BCT. PRO scores were comparable to normative scores and references scores except for the 'physical functioning' (BREAST-Q) scores that reported lower in the present study. Ninety-four percent of the participants was (highly) satisfied with future PROM use.

Conclusions

Statistical significant differences were found for PROMs following different types of breast surgery. The significance of these results should become clearer trough collection of future data. The great majority of participants considered PROMs as (highly) acceptable and reacted positively on their proposed future use.

INTRODUCTION

Health outcomes embody the results of the healthcare delivered. Value in health care is defined as the health outcome per total cost[1]. Traditionally health outcome is reported by healthcare providers and consist for example of survival, recurrence or complication rates. Multiple outcomes are often used per medical condition in order to define and compare results of healthcare[1]. In value-based healthcare (VBHC) the value is defined based on outcomes important to the patient and therefore additionally consist of patient-reported outcome measures (PROMs). The International Consortium for Health Outcomes Measurement (ICHOM) in collaboration with health care professionals of different international institutions developed standard sets of health outcome measures for specific medical conditions[2]. Breast cancer was among the first conditions covered by ICHOM[3]. It is expected that by reporting and comparing this ICHOM breast cancer set among patients and between institutions, the value of the care delivered can be improved[1 3].

Especially for breast cancer patients in whom high survival rates are reached, patient-reported outcomes (PROs) are of great importance. Furthermore at least equal survival and recurrence rates are described in early-stage breast cancer patients when comparing breast-conserving therapy [(BCT) – breast-conserving surgery with additional radiation therapy of the breast] and mastectomy (with/without breast reconstruction)[4-6]. Surgical treatment decisions should therefore be focused on (long-term) health related quality of life. Especially the understanding of PROMs is expected to greatly improve this complex shared treatment decision-making by giving insight in quality of life and daily functioning after certain treatment decisions. Although these PROMs comprise around 75% of the ICHOM breast cancer outcome set, not much data is available on 'reference scores' or expected scores per surgical treatment.

This study aimed to add knowledge on PROMs within a Dutch breast cancer population sample. Three breast cancer PROMs, as proposed in the ICHOM outcome set, were evaluated and compared to normative scores (obtained in non-breast cancer patients) and reference scores (obtained in breast cancer patients) available in literature. Patients were additionally asked to give satisfaction and expectation scores on the use of PROMS within clinical practice.

METHODS

Study population

Participants were recruited via an online survey available from February 12th to March 13th 2017. The survey was available on the website of the Dutch breast cancer association[7] and the social media page of our institute[8]. The Dutch breast cancer association has a strong national online forum of approximately 2,000 breast cancer patients [9]. To evaluate the PROMs following surgery or active breast cancer treatment breast cancer patients that had not undergone surgery (yet) or that had undergone surgery <6 months were excluded.

PROMs

All participants were asked to complete the PROMs as proposed in the international ICHOM breast cancer outcome set. The generic PROM EORTC-QLQ-C30 version 3, the disease specific-PROM EORTC-QLQ-BR23 version 1 and the BREAST-Q postoperative modules were used. Scores of the EORTC-QLQ-C30/BR23 range from 0-100. For the functional scales: 'Global Health status'/ 'Role functioning'/ 'Physical functioning'/ 'Emotional functioning'/ 'Social functioning' (EORTC-QLQ-C30) and the 'Body Image'/ 'Sexual functioning' (EORTC-QLQ-BR23) higher scores represent a higher quality of life. Higher scores at the symptoms scales: 'Pain'/ 'Fatigue' (EORTC-QLQ-C30) and 'Breast symptoms'/ 'Arm symptoms' represent less functioning or more symptoms experienced by participants.

The modules in the BREAST-Q were dependent on type of surgery performed; the breast-conserving therapy module, mastectomy module or the reconstructive module. For all modules scores range from 0 to 100 in which higher scores represent higher functioning/quality of life. Differences as compared to the ICHOM breast cancer set were the use of the 'Psychosocial, Physical and Sexual wellbeing' modules of the postoperative BREAST-Q (i.e. not only 'the satisfaction with breast' module). PROM scores were calculated according to the questionnaires' scoring protocol. Modules were judged as incomplete according to the questionnaires' protocol[10]. Normative scores (i.e. scores obtained in the general population/non-breast cancer patients) or reference scores (i.e. scores obtained in breast cancer patients) were used to compare the PROM scores of the current survey. For the BREAST-Q normative scores reported by Mundy and colleagues were used[11], who evaluated scores obtained using the preoperative modules in 1,201 participants. Normative scores of the EORTC-QLQ-C30 were based on an evaluation of 7,802 healthy participants[12]. Since no normative scores are available for the EORTC-QLQ-BR23 references scores (obtained in breast cancer patients) were used[12]. The reference scores available for the EORTC-QLQ-C30 were additionally compared to the current cohort by graphically displaying the means and standard deviations of the different populations.

Procedure

Participants recruited by the Dutch breast cancer association were redirected to the survey after completion of 6 questions introducing the VBHC-initiative (data shown in online forum B-force)[9]. Participants were asked to report their age, time since surgery and the type of surgery performed. The survey was ended if participants had not undergone breast cancer surgery (yet). All other participants were directed to the PROMs. Following the completion of the PROMs participants were asked to answer three additional (self-made) questions on their satisfaction with and expectations of the routine use of PROMs (optional). The first questions asked if participants thought that PROMs used in the context of VBHC could aid in the care for future breast cancer patients (yes/no). Second, participants were asked if they experienced the PROMs as helpful to gain insight in their current functioning (yes/no). Acceptability of the PROMs was scored as; 'Very acceptable'/

'Acceptable'/ 'Average'/ 'Not acceptable' or 'Other'. Surveys were considered as complete when the questions regarding the respondents characteristics were completed and all 4 PROMs were activated.

Statistics

All data were analysed with SPSS version 21 (IBM). To compare the different surgeries (i.e. BCT, mastectomy alone, mastectomy followed by implant reconstruction and mastectomy followed by autologous reconstruction) with non-parametric continuous variables (age, duration questionnaire) the Kruskal-Wallis test was used. Surgical groups and categorical variables (time since surgery, 'satisfaction and expectations'-questionnaire) were compared using the Chi-square test. The one-way ANOVA was used to compare parametric continuous variables (PROMs) between surgical groups. Post hoc analyses were performed with the two-sided Dunnett t-test using breast-conserving therapy as a control group. The correlation between PROMs was calculated using the Pearson correlation coefficient. A correlation coefficient (r) of <0.4 was rated as a 'weak' correlation, 0.4-0.59 as 'moderate' and ≥0.60 as a 'strong' correlation[13]. A p-value <0.05 was considered statistical significant. Additionally, the R^2 statistic was calculated to evaluate the proportion of variance explained by the correlation between PROMs evaluated. True correspondence was evaluated for scores present in the 4th (upper) quartile of the EORTC-QLQ-C30/BR23 and the BREAST-Q (number of participants/total participants per questionnaire with scores in the 4th quartile for both questionnaires).

RESULTS

A total of 624 patients activated the online survey of which 72.6% and 27.4% respectively from the national and local patients advocate society (Fig. 1). Twenty-four (3.8%) questionnaires contained no data and were excluded. Additional exclusions were based on 21 (3.4%) participants that had not undergone breast cancer surgery (yet), 30 (4.8%) that had undergone breast surgery <6 months and 53 (8.5%) that did not activate all 4 PROMs. Of the included participants 9 (1.8%) did not complete the 'satisfaction and expectations with PROM'-questionnaire (Fig. 1). Median age of the participants was 54.0 years [Interquartile range (IQR) 49.0-61.0], median time since surgery was 5.0 years [IQR 3.0-7.0] (Table 1). The reported duration to complete all questionnaires was 10 [IQR 9.0-15.0] minutes (Table 1). All baseline characteristics were comparable between the different surgical groups except for the time since surgery, see Supplementary Table S1.

PROM scores after different surgeries

Differences between the surgical groups were present in the EORTC-QLQ-BR23 (breast and arm symptoms) and the BREAST-Q (all modules except the Sexual functioning), see Table 2.

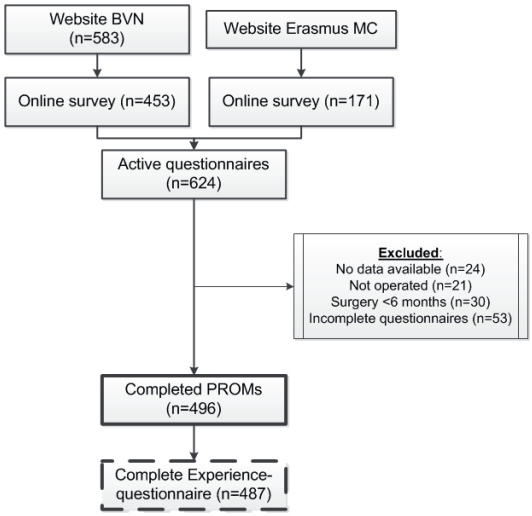

Figure 1. Flow diagram participant inclusion.
BVN = Dutch abbreviation for Dutch breast cancer patients' advocates society

Of the 5 significantly different PROM scores 3 concerned symptom scales. Significantly less 'Breast symptoms' (EORTC-QLQ-BR23) were reported following a mastectomy, autologous and/ or implant reconstruction as compared to BCT: -7.5 (p=0.001), -8.7 (p=0.034), -8.0 (p=0.007) (Table 2 and supplementary Table S2). Mastectomy patients rated their 'Arm symptoms' 7.0 points worse than BCT patients (p=0.005). The mean 'Physical functioning' (BREAST-Q) was significantly better following a mastectomy, autologous and/ implant reconstruction than following BCT: +22.2 (p<0.001), +25.0 (p<0.001) and +21.3 (p<0.001) respectively. The mean 'Satisfaction with breast' (BREAST-Q) showed favourable scores +9.6 (p=0.014) following an autologous reconstruction and unfavourable scores -8.5 (p=0.004) following an implant reconstruction as compared to BCT. 'Psychosocial functioning' (BREAST-Q) was significantly lower in mastectomy patients compared to BCT patients, -5.6 (p=0.009). PROM scores gained did not differ from normative nor from reference scores of the EORTC-QLQ-C30 (Fig. 2) and from reference scores of the EORTC-QLQ-BR23 (Fig. 3). PROMs were comparable to normative scores of the BREAST-Q except for the 'Physical functioning' scale which showed lower scores in the current cohort (Fig. 4). Overall 'moderate' to 'weak' correlations were seen between the EORTC-QLQ-C30/BR23 and BREAST-Q (Supplementary Table S3). True correspondence for ratings within the 4th quartile showed absolute percentages of: 13.6% ['Body Image'(EORTC-QLQ-BR23) versus 'Q-satisfaction'], 12.2%, 11.2%, 13.9% ['Role, Emotional and Social functioning' (EORTC-QLQ-C30) versus 'Q-psychosocial'], 6.6% ['Physical functioning (EORTC-QLQ-C30) versus 'Q-physical'] and 3.8% ['Sexual functioning (EORTC-QLQ-BR23) versus 'Q-sexual'] (data not shown).

Table 1. Baseline characteristics (n=496).

Median age [years (IQR)]	55.0 (49.0-60.8)
Median time since surgery [years (IQR)]	5.0 (3.0-7.0)
Type of breast cancer surgery [n (%)]	
Breast-conserving therapy	223 (45.0)
Mastectomy	162 (32.7)
Mastectomy with autologous reconstruction	38 (7.7)
Mastectomy with implant reconstruction	73 (14.7)
VBHC experiences (n=487)	
Median duration PROM completion [minutes (IQR)]	10.0 (9.0-15.0)
Improvement breast cancer care [n (%)]	
Yes	434 (89.1)
No	53 (10.9)
Tool for self-reflection [n (%)]	
Yes	398 (81.7)
No	89 (18.3)
Acceptability PROMs [n (%)]	
Very acceptable	222 (45.6)
Acceptable	240 (49.3)
Average	17 (3.5)
Not acceptable	1 (0.2)
Other	7 (1.4)

IQR = interquartile range, VBHC = value-based healthcare.

Patients' experience and satisfaction with PROMs

A total of 222 (45.6%) participants scored the PROMs as 'very acceptable', 240 (49.3%) as 'acceptable', 17 (3.5%) as 'average', 1 (0.2%) as 'not acceptable' and 7 (1.4%) as 'other' (Table 1). A total of respectively 434 (89.1%) and 398 (81.7%) of the participants responded positive when asked if 1) they thought a structural use of the PROMs could improve the quality of care and 2) they thought the PROMs could be used as a 'guidance tool for themselves' in their individual care (Table 1). Participants' experiences did not differ within the surgical groups (Supplementary Table S1).

DISCUSSION

Early-stage breast cancer patients are faced with difficult treatment decisions following their diagnosis. Overall high[15] and comparable survival and recurrence rates are reported in early-stage breast cancer patients following either BCT or a mastectomy[4-6]. Both strengthen the necessity to base treatment decisions on other outcomes than oncological outcomes alone focused on survivorship. The VBHC-initiative is expected to pave the way for shared-decision-making in surgical treatment decisions. The ICHOM breast cancer outcome set consists for 75% of PROMs[3].

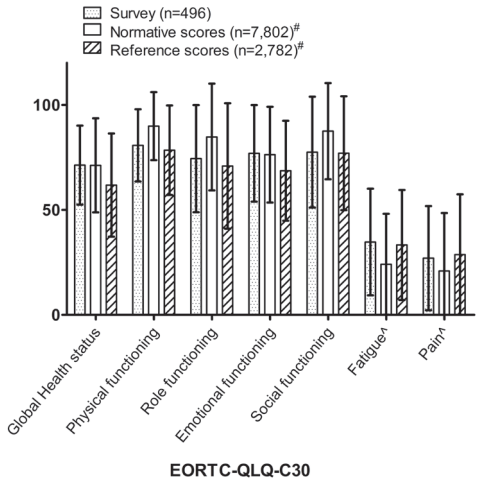

Figure 2. EORTC-QLQ-C30 Survey scores versus normative and reference scores [12].

Mean scores with standard deviations (error bars) for EORTC scores. Higher scores represent better functioning. ^Higher scores represent higher pain scores or more fatigue. #Reference and normative scores as based on 7,802 participants of the general population and 2,782 breast cancer patients respectively [12].

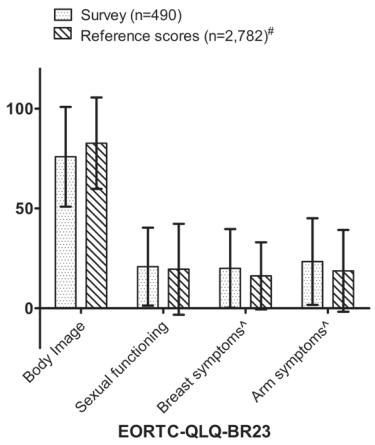

Figure 3. EORTC-QLQ-BR23 Survey scores versus reference scores.

Mean scores with standard deviations (error bars) for EORTC scores. Higher scores represent better functioning. ^Higher scores represent more symptoms. #Reference scores as based on 2,782 breast cancer patients [12].

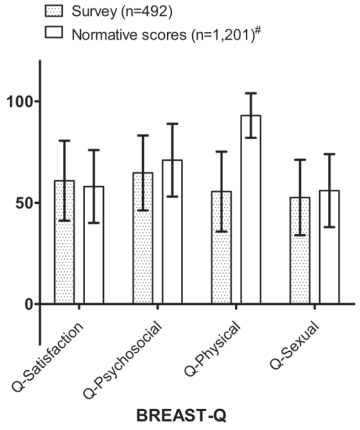

Figure 4. BREAST-Q Survey scores versus normative reconstructive scores.

Mean scores with standard deviations (error bars) for Q-scores. Higher scores represent better functioning. #Normative scores as calculated on 1,201 [14].

Table 2. Mean PROM scores (SD) for all participants and per type of surgery performed.

	All	BCT	MAS	REC A	REC I	*p*-value[§]
EORTC-QLQ-C30	*(n=496)*	*(n=223)*	*(n=162)*	*(n=38)*	*(n=73)*	
Global health status	71.3 (18.8)	71.0 (19.3)	71.7 (18.2)	71.5 (17.0)	71.3 (19.6)	0.98
Role Functioning	74.4 (25.5)	76.5 (25.2)	71.5 (26.5)	72.8 (24.9)	74.9 (24.1)	0.28
Physical Functioning	80.7 (17.2)	81.4 (16.7)	78.9 (18.4)	81.1 (14.3)	82.6 (17.0)	0.38
Emotional Functioning	76.9 (23.0)	77.3 (22.3)	76.3 (24.2)	77.4 (20.7)	77.1 (24.2)	0.98
Social Functioning	77.5 (26.4)	78.1 (27.9)	77.6 (24.8)	76.3 (22.8)	76.3 (27.1)	0.95
Pain^	27.0 (24.8)	26.6 (25.0)	27.6 (24.3)	31.1 (28.8)	24.9 (23.4)	0.63
Fatigue^	34.7 (25.4)	34.9 (25.7)	34.6 (25.4)	41.8 (25.5)	30.3 (24.1)	0.16
EORTC-QLQ-BR23	*(n=490)*	*(n=221)*	*(n=159)*	*(n=37)*	*(n=73)*	
Body image	75.9 (25.0)	78.9 (22.4)	73.2 (25.7)	76.3 (28.3)	72.4 (28.5)	0.09
Sexual Functioning	20.9 (19.6)	21.6 (19.5)	18.5 (19.6)	21.2 (18.3)	23.4 (20.3)	0.28
Breast symptoms^	20.0 (19.7)	24.2 (21.8)	16.8 (26.8)	15.5 (20.1)	16.2 (16.3)	<0.001
Arm symptoms^	23.4 (21.7)	20.8 (20.5)	27.8 (22.8)	26.7 (23.6)	19.8 (20.0)	0.005
BREAST-Q	*(n=492)*	*(n=222)*	*(n=160)*	*(n=38)*	*(n=72)*	
Satisfaction with breast	60.9 (19.7)	62.3 (21.8)	59.5 (17.3)	71.9 (16.4)	53.8 (16.4)	<0.001
Psychosocial functioning	64.7 (18.5)	66.5 (19.3)	60.9 (15.8)	72.7 (19.1)	63.5 (19.5)	0.001
Physical functioning	55.50 (19.7)	43.1 (16.5)	65.3 (15.5)	68.1 (16.6)	64.4 (17.3)	<0.001
Sexual functioning	52.59 (18.6)	52.6 (17.1)	50.5 (19.3)	60.2 (19.8)	52.6 (19.4)	0.046

SD = standard deviation, BCT = breast-conserving therapy, REC A = Autologous reconstruction, REC I = Implant reconstruction, [§]ANOVA.
Overall higher scores represent higher quality of life. ^Higher scores represent lower quality of life.

Using an online survey the current study evaluated the PROMs (as proposed in the ICHOM set) within a Dutch breast cancer population sample and evaluated the participants' satisfaction with and expectations of PROMs. We found statistical significant different results for PROMs following different types of breast surgery, which are important for future clinical decision-making. Most participants reacted positively on future use of PROMs in clinical practice.

Post hoc analyses showed more 'Arm symptoms' (EORTC-QLQ-BR23) following a mastectomy compared to BCT. BCT patients showed more 'Breast symptoms' (EORTC-QLQ-BR23) and lower 'Physical functioning' (BREAST-Q) as compared to other surgeries. Higher 'Satisfaction with breast' (BREAST-Q) was reported following autologous reconstruction and lower scores following implant reconstruction as compared to BCT. Results for the 'Satisfaction with breast' scale are in line with previous studies showing favourable outcomes following autologous reconstruction[14 16]. Comparable satisfaction for BCT and autologous reconstruction are however also reported[17]. Using the BREAST-Q, Howes and colleagues also reported a reduced physical functioning following BCT[18].

Three out of 5 PROM modules differed significantly based on a reduced physical functioning/ more symptoms experienced following BCT. This was also present when comparing the results to normative scores showing a significantly decreased 'Physical functioning' (BREAST-Q) within our cohort. The significance of these possible differences in physical functioning or symptoms experienced following BCT should be explored in additional cohorts. The possible effect of radiation therapy (administered to all BCT participants) on physical function should be taken in consideration when evaluation future cohorts. It is however known that the high score (mean 91) found in the normative scores obtained by Mundy and colleagues can partly be explained by differences in the preoperative questionnaire (used to obtain the normative scores) and postoperative questionnaire (used to evaluate the current cohort) of the BREAST-Q[11 14 19]. Since PROMs are commonly used to evaluate an intervention, little data is available of non-interventional studies exploring PROMs following (surgical) breast cancer treatment. To adequately evaluate possible differences not only a statistical significance but also a clinical significance should be addressed. Clinically relevant differences for the EORTC-QLQ-C30/BR23 and BREAST-Q are not well defined but in some literature defined this as half a standard deviation (0.5SD) difference[14]. For future VBHC-initiatives and trials a clinically relevant difference is of great importance and should be calculated based on different international cohorts.

An important strength of the current study lies in the evaluation of PROMs as proposed in the ICHOM set. This enabled a comparison of outcome scores for the different PROMs and a first 'patients' satisfaction and expectations' evaluation of the proposed ICHOM set. The availability of different PROMs within the same patient furthermore enabled a comparison of the correlation between the different PROMs in which the yes/no necessity for the different PROMs could be evaluated. When significant, all correlation present between the BREAST-Q and EORTC-QLQ-C30/BR23 were 'moderate' to 'weak' suggesting that overall the PROMs are different and can generate different perspectives on the patients' functioning. The relationship between the EORTC-QLQ-C30/BR23 and the BREAST-Q only explained 0.1% minimum to maximum 65.7% of the variety. Absolute concordances for scores given in the upper (4^{th}) quartile of comparable modules of the BREAST-Q and EORTC-QLQ-C30/BR23 was low, varying from 3.8% to 13.9%.

Limitations of the study were primarily a result of the study population analysed. PROM scores are dependent on the type of cohort evaluated and could be biased within this study. Patients within both patients' advocates societies form a strong community that is actively involved in their personal care and that of other (future) breast cancer patients possibly influencing the experiences regarding the VBHC-initiative or influencing the PROM scores. Furthermore, a small absolute number of patients had undergone breast reconstruction (n=38 and n=73 respectively for autologous and implant reconstruction), limiting the statistical power to conclude specifically within this group. Data on the number of breast surgeries performed or bilateral breast cancer operations were unavailable and all data on breast operations were self-reported. PROM data were analysed as parametric data. A graphical inspection of the PROMs (all ranging from 0-100) showed that a normal distribution was present in most PROM modules. Skewed scores were however present

in some modules of the EORTC-QLQ-C30/BR23 that are in line with the skewed results found in the normative/ reference scores. Importantly, when analysing the PROM scores as non-parametric data no differences in the (non-)significance were seen (data not shown).

The significant differences detected by the BREAST-Q can be explained by the surgery-specific questions[20]. In the development of the BREAST-Q newer psychometric methods were used possibly improving the clinical utility as compared to the EORTC-QLQ-C30/BR23[20]. Furthermore, the BREAST-Q scores did show a parametric spread for all the outcome modules. The authors believe that all the modules of the BREAST-Q need to be used when evaluating breast cancer patients in future VBHC-initiatives and/or clinical trials. Although this is not proposed in the ICHOM breast cancer set this could increase the clinical utility and therefore facility of more adequate monitoring of patients. The overall 'weak' to 'moderate' correlations between the BREAST-Q and the EORTC-QLQ-C30/BR23 are an additional argument to include the BREAST-Q.

A majority of the patients, 81.7% and 89.1% agreed that the PROMs could serve as a tool for self-reflection in time and expected the PROMs to lead to an improvement of the breast cancer care if used as a tool to guide treatment and discuss quality and functioning throughout care by physicians and nurses. The overall positive experiences (94.4% of participants rated the PROMs as (highly) acceptable) are supported by a recent evaluation in which PROMs are preferred over clinical outcomes or symptoms[21 22]. Positive results regarding VBHC and use of PROMs in clinical practice are also reported by randomized trials evaluating the use of PROMs as a tool to guide the individual care for breast cancer patients[23] or cancer patients in general[24 25]. Kotronoulas and colleagues reviewed the use of PROMs within different studies and reported that overall positive effects were seen following the prospective and continues use of PROMs during cancer treatment or follow-up[26]. It is expected, however, that the success of the VBHC-initiative is partly dependent on the availability of reference scores for the different PROMs. A comparison of PROM scores with representative reference values enables an adequate evaluation of the care delivered or an intervention where needed which can then be evaluated. The comparison of our PROM data with normative scores for the EORTC-QLQ-C30[12] and BREAST-Q[14] but also reference scores for the EORTC-QLQ-C30/BR23[12] forms an example of an initial evaluation of PROMs within a specific cohort. To properly access clinical significance ongoing future cohorts should focus on prospectively collected PROMs that enable an evaluation through time.

CONCLUSIONS

This is a first Dutch initiative to evaluate PROM scores of the ICHOM breast cancer set. Differences were found according to the type of surgery performed. Future studies should focus on obtaining reference values based on large patient cohorts in time aiming to improve the interpretation of the scores. Importantly the overall positive experiences reported by participants regarding these PROMs have further substantiated the value of the rising VBHC initiative.

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SUPPLEMENTARY FILES CHAPTER 3

Supplementary Table S1. Patients' experiences PROMs per type surgery performed [n(%)].

	BCT (n=223)	**Mastectomy (n=162)**	**REC-A (n=38)**	**REC-I (n=73)**	**P-value^^**
Median age [years (IQR)]	54 (48.0-61.0)	55.0 (49.0-61.0)	55.0 (50.0-60.0)	55 (46.5-60.0)	0.90
Median time since surgery [years (IQR)]	5.0 (3.0-7.0)	6.0 (4.0-7.0)	6.0 (4.0-7.0)	5.0. (3.0-7.0)	0.002
VBHC experiences (n=487)	**BCT (n=220)**	**Mastectomy (n=157)**	**REC A (n=37)**	**REC I (n=73)**	**P-value¶**
Duration questionnaire (minutes)	10.0 (8-15)	10.0 (8-15)	10.0 (7.5-15)	10.0 (10.0-15.0)	0.028^^
Improvement breast cancer care					0.16
Yes	199 (90.5)	140 (89.2)	32 (94.6)	60 (82.2)	
No	21 (9.5)	17 (10.8)	2 (5.4)	13 (17.8)	
Tool for self-reflection					0.09
Yes	188 (85.5)	119 (758)	29 (78.4)	62 (84.9)	
No	32 (14.5)	38 (24.2)	8 (21.6)	11 (15.1)	
Acceptability PROMs					0.90
Very acceptable	102 (46.4)	66 (42.0)	15 (40.5)	39 (53.4)	
Acceptable	107 (48.6)	82 (52.2)	20 (54.1)	31 (42.5)	
Average	8 (3.6)	5 (3.2)	2 (5.4)	2 (2.7)	
Not acceptable	0 (.0)	1 (0.6)	0 (.0)	0 (.0)	
Other	3 (1.4)	3 (1.9)	0 (.0)	1 (1.4)	

BCT = breast-conserving therapy. ^^Kruskall-wallis test ¶Chi-square. REC A = Autologous reconstruction, REC I = Implant reconstruction

Supplementary Table S2. Post hoc comparison significantly different PROM scores for surgical type.

	Surgery vs BCT (reference)	Mean difference	P-value[#]	95% CI
EORTC-QLQ-BR23				
*Breast symptoms^*	Mastectomy	-7.47	0.001	-12.28; -2.66
	Autologous reconstruction	-8.71	0.034	-16.9; -0.48
	Prosthesis reconstruction	-8.04	0.007	-14.28; -1.79
*Arm symptoms^*	Mastectomy	7.00	0.005	1.67; 12.32
	Autologous reconstruction	*5.90*	0.31	-3.19; 15.01
	Prosthesis reconstruction	-1.00	0.97	-7.94; 5.89
BREAST-Q				
Satisfaction with breast	Mastectomy	-2.81	0.39	-7.58; 1.96
	Autologous reconstruction	9.60	0.014	1.52; 17.67
	Prosthesis reconstruction	-8.51	0.004	-14.74; -2.27
Psychosocial functioning	Mastectomy	-5.63	0.009	-10.13; -1.13
	Autologous reconstruction	6.20	0.15	-1.44; 13.84
	Prosthesis reconstruction	-3.00	0.51	-8.88; 2.87
Physical functioning	Mastectomy	22.21	<0.001	18.17; 26.24
	Autologous reconstruction	25.04	<0.001	18.20; 31.87
	Prosthesis reconstruction	21.31	<0.001	16.06; 26.58
Sexual functioning	Mastectomy	-2.06	0.66	-6.96; 2.83
	Autologous reconstruction	7.61	0.06	-0.31; 15.52
	Prosthesis reconstruction	0.01	1.0	-6.22; 6.24

CI = confidence interval. [#]Post hoc test Dunnett T (2-sided), the Dunnett T-test treat one group as a control and compares all other groups against it, the BCT group serves as a control group.
Overall represent higher scores a higher quality of life. ^Higher scores represent lower quality of life.

Supplementary Table S3. Pearson correlation coefficient (r) and r^2 for the different EORTC-QLQ-C30/ BR23 compared to the BREAST-Q.

	BREAST-Q							
	Q-satisfaction with breast		Q-Physical		Q-psychosocial		Q-sexual	
	r	r^2	r	r^2	r	r^2	r	r^2
EORTC-QLQ-C30								
Global health status	0,292*	0.085	0,054	0.003	0,403*	0.162	0,243*	0.059
Physical functioning	0,256*	0.066	0,038	0.001	0,311*	0.097	0,126*	0.016
Role functioning	0,263*	0.069	0,032	0.001	0,328*	0.108	0,148*	0.022
Emotional functioning	0,237*	0.056	0,038	0.001	0,457*	0.209	0,308*	0.095
Social functioning	0,222*	0.049	0,047	0.002	0,372*	0.138	0,218*	0.047
Fatigue	-0,200*	0.040	-0,060	0.004	-0,316*	0.100	-0,200*	0.040
Pain	-0,262*	0.069	-0,031	0.001	-0,293*	0.086	-0,186*	0.035
EORTC-QLQ-BR23								
Body Image	0,516*	0.267	0,004	0.000	0,657*	0.431	0,566*	0.320
Arm symptoms	-0,242*	0.059	-0,013	0.000	-0,315*	0.099	-0,127*	0.016
Breast symptoms	-0,272*	0.070	-0,089	0.008	-0,311*	0.097	-0,228*	0.052
Sexual functioning	0,132*	0.017	0,014	0.000	0,143*	0.021	0,344*	0.118

*Correlation is significant at the 0.01 level (2-tailed)

Chapter 4

Patient-reported outcome measures may add value in breast cancer surgery

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ABSTRACT

Purpose

Considering the comparable prognosis in early-stage breast cancer for breast-conserving therapy (BCT) and mastectomy, quality of life should be a focus in treatment decision(s). We retrospectively collected PROs and analysed differences per type of surgery delivered. We aimed to obtain reference values helpful in shared decision-making.

Methods

pTis-T3N0-3M0 patients operated between January 2005 and September 2016 were eligible if: 1) no chemotherapy was administered <6 months prior to enrolment, and 2) identical surgeries were performed in case of bilateral surgery. After consent, EQ-5D-5L, EORTC-QLQ-C30/BR23, and BREAST-Q were administered. PROs were evaluated per baseline characteristics using multivariable linear regression models. Outcomes were compared for different surgeries as well as for primary (PBC) and second primary or recurrent (SBC) breast cancer patients using analyses of variance (ANOVAs).

Results

Response rate was 68%. PROs in 612 PBC patients were comparable to those in 152 SBC patients. Multivariable analyses showed increasing age to be associated with lower 'Physical functioning' [β -0.259, p<0.001] and 'Sexual functioning' [β -0.427, p<0.001] and increasing time since surgery with less 'Fatique' [β -1.083, p<0.001]. Mastectomy [β -13.596, p=0.003] and implant reconstruction [β -13.040, p=0.007] were associated with lower 'Satisfaction with breast' scores than BCT. Radiation therapy was associated with lower satisfaction scores than absence of radiotherapy.

Discussion

PRO scores were associated with age, time since surgery, type of surgery and radiation therapy in breast cancer patients. The scores serve as a reference value for different types of surgery in the study population and enable prospective use of PROs in shared decision-making.

INTRODUCTION

Breast cancer is the most frequently diagnosed cancer in women[1]. In the Netherlands, 1 in 7 women are diagnosed with breast cancer[2]. Favourable high survival rates are reported eminently in early stages[3]. Survivorship as well as physical, sexual and psychosocial consequences of breast cancer therapies should therefore be accounted for in treatment decision-making. In early-stage breast cancer high survival rates are achieved irrespective of type of surgery whether breast-conserving therapy (BCT; breast-conserving surgery with breast radiation therapy) or mastectomy (with/without reconstruction)[4-6]. Consequently, anticipation of outcomes reflecting physical, sexual and psychosocial functioning is very important in treatment decision-making in these patients.

Value in healthcare is defined as the health outcome per total costs. Multiple health outcomes are often used for one medical condition to define this value[7]. In value-based healthcare (VBHC), the defined outcomes are patient orientated and therefore form a combination of more traditional clinical outcomes (for example, oncological outcome or complication rates) and patient-reported outcomes (PROs). Collaborations of the International Consortium for Health Outcomes Measurement (ICHOM) with several other healthcare institutions worldwide resulted in the development of a standard breast cancer outcome set[8]. The incorporation of this set is expected to pave the way towards value-based breast cancer care with an impulse in shared decision-making as well as follow-up.

Patient-reported outcome measures (PROMs) are pivotal in the ICHOM breast cancer outcome set, accounting for approximately 75% of outcomes, the other 25% being related to clinical outcomes. Little is known about PROM scores following different surgeries in relation to differences in patient, tumour and systemic or radiation treatment characteristics. Our institute implemented a breast cancer outcome set embedded in the institutional VBHC initiative in October 2015. At predetermined time points breast cancer patients received digitalized PRO questionnaires prior to their routine visit at the outpatient clinic. PROs were evaluated with the patient at the outpatient clinic and used to improve individual care[9]. Consequently, there was an urgent need to propose valid and meaningful reference scores. It was hypothesized that PROs differ between surgical treatments. The aim of this study was to assess the correlation between PROs and patient, tumour and treatment characteristics and to provide PRO reference values for different breast cancer surgeries. We therefore collected PROs amongst breast cancer patients operated in the last 10 years within our institute.

METHODS

Study population

Ethical approval was granted by the Institutional Review Board of the Erasmus Medical Centre (Erasmus MC), Rotterdam, the Netherlands (MEC-2015-669). Patients who had undergone breast cancer surgery between January 2005 and September 2016 were identified from the electronical patient files using operation codes. Women aged >18 years with pTis-3N0-3M0 breast cancer were deemed eligible. Patients were excluded if they had been treated with chemotherapy within 6 months prior to the PRO assessment or had bilateral breast surgery with different types of surgery performed per side.

Procedures

This cross-sectional study retrospectively reviewed medical records to compile the following data: age, date and type of breast surgery, tumour morphology, Tumour, Node and Metastasis (TNM) staging according to TNM classification system (7th edition)[10], hormonal receptor status, human epidermal growth factor receptor (HER2) status, *BRCA1/2* status, local recurrence, second primary breast cancer, and details regarding chemotherapy and/or immunotherapy and endocrine therapy. Time since surgery was defined as time between first surgery and questionnaire completion. The respondents were categorized in 'primary breast cancer' (PBC) and 'second primary or recurrent breast cancer' (SBC). PBC patients represented women with primary unilateral or bilateral breast cancer, while SBC patients represented women with local recurrence or second primary breast cancer. In case of breast cancer recurrence or a second primary breast cancer, data regarding patient age, tumour morphology and TNM stage of the primary diagnosis was used.

Operation types defined were: breast-conserving therapy (BCT), mastectomy alone (MAS), mastectomy followed by immediate or delayed implant reconstruction (REC-I) and mastectomy followed by immediate or delayed autologous reconstruction (REC-A). Nodal stage at primary diagnosis was categorized as N0, N+ (N1-3), or unknown. Adjuvant systemic therapy was categorized as: 1) no systemic therapy, 2) chemotherapy and/or immunotherapy (CTx), 3) endocrine therapy (ETx), 4) chemotherapy/immunotherapy & endocrine therapy (CTx & ETx) or 5) unknown. Radiotherapy was categorized as: 1) radiation therapy following breast-conserving surgery, 2) no radiation therapy, or 3) thoracic wall radiotherapy in case of mastectomy and/or locoregional radiotherapy in case of mastectomy or BCT.

Eligible women were contacted by telephone to request their participation. Upon oral informed consent, details on adjuvant therapy and last breast surgery were verified. Patients who did not answer were called up to six times, after which participation was no longer pursued.

Following consent four questionnaires were administered; Euro-QoL 5D-5 L (EQ-5D-5 L version 2.0)[11], The European Organization of Research and Treatment of Cancer quality of life question-

naires (EORTC-QLQ-C30 version 3.0[12] *and* EORTC-QLQ-BR23 version 1.0[13]) and BREAST-Q (postoperative version 1.0)[14]. The questionnaires are proposed in the ICHOM breast cancer outcome set to evaluate breast cancer patients undergoing locoregional treatment(s)[8]. The EORTC-QLQ-C30 is a generic oncologic questionnaire containing 30 questions with 6 single-items scores, 9 multiple-item scales, 3 symptom scales, and an additional global health status/quality of life (QoL) scale[15]. The EORTC-QLQ-BR23 is a breast cancer specific questionnaire of the EORTC QLG that contains 23 questions made up of 8 multiple-item scales and is considered an addition to the EORTC-QLQ-C30 specifically for breast cancer patients. The BREAST-Q is a surgery-specific questionnaire proposed in the ICHOM set to measure 'Satisfaction with breast' following breast cancer surgery. Multiple-item domains are, however, also available to evaluate 'Satisfaction with overall outcome', 'Psychosocial wellbeing', 'Sexual wellbeing', 'Physical wellbeing', and 'Satisfaction with care'[14]. In the current study, all modules of the BREAST-Q except 'Satisfactions with overall outcome' were used.

Patients were given the choice for internet-based questionnaires sent by email or paper-based questionnaires sent by mail (with postage-paid return envelope). If the questionnaires remained uncompleted, a weekly reminder up to 3 weeks was sent by email (internet-based). After 4 weeks of no response, patients were contacted by telephone and requested to complete questionnaires (internet-based and paper-based). Thereafter, response was no longer actively pursued. PRO scores were calculated according to questionnaire scoring manual. PROs were evaluated for patients who completed at least the EORTC-QLQ-C30 questionnaire.

Study outcomes

The primary outcome was to obtain reference values for PROs following different surgical strategies in relation to patient, tumour, and treatment characteristics of PBC patients. Additionally, PROs of SBC patients were evaluated and compared to PROs of PBC patients.

Statistical analysis

All analyses were performed in SPSS Statistics for Windows (version 21.0). Baseline characteristics were compared for responders versus nonresponders and PBC versus SBC patients. The different surgical groups were compared within both PBC and SBC using a one-way ANOVA. Post hoc analyses were performed to detect differences between specific groups. To evaluate the effect of patient, tumour and treatment on PROs, a multivariate linear regression was used in PBC patients. Factors evaluated were age, time since surgery, uni/bilateral breast cancer, *BRCA* mutation status, tumour stage, nodal stage, systemic therapy status and radiotherapy status. Beta coefficients (β) with corresponding *p*-values were calculated for the index value (EQ-5D-5L), 'Global Health status'/ 'Physical functioning'/ 'Role functioning' (EORTC-QLQ-C30), 'Body image'/ 'Sexual functioning' (EORTC-QLQ-BR23) and 'Q-Satisfaction with breast'/ 'Q-physical'/ 'Q-psychosocial' and 'Q-sexual' (BREAST-Q). *P*-values ≤0.01 were considered statistically significant.

RESULTS

Out of 1,850 patients identified, 1,230 (66.5%) had pTis-T3N0-3M0 breast cancer at primary diagnosis. A total of 1,116 (90.7%) was eligible for participation (Fig. 1). Out of eligible patients, 764 (68.5%) responded. Of 352 non-responders, 114 (40.9%) could not be reached, 162 (46%) declined participation, and 46 (13.1%) did not complete the EORTC-QLQ-C30.

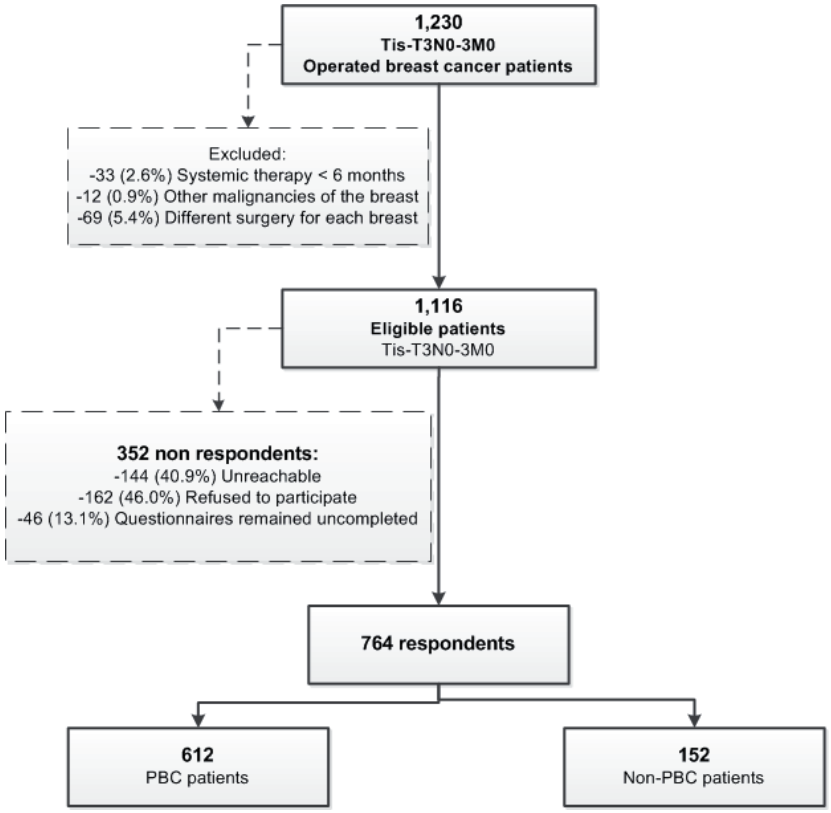

Figure 1. Flow chart study selection process.
T = tumour stage, N = nodal stage, PBC = primary breast cancer, SBC = second primary or recurrent breast cancer.

Study population

Responders versus nonresponders

Responders were significantly younger compared to non-responders (50.5 vs. 52.4 years, p = 0.04). Significant differences were additionally found for type of surgery performed, T- stadium, systemic and radiation therapy (Supplementary Table S1).

Responders: baseline characteristics and treatment

A total of 612 (80.1%) responders had PBC (Table 1) and 152 (19.9%) women had SBC (Supplementary Table S2). Of PBC patients, 257 (41.9%) underwent BCT, 162 (26.6%) mastectomy, 110 (17.9%) implant reconstruction and 83 (13.5%) autologous reconstruction (Table 1). PBC patients showed significant differences between the surgical groups for age, time since surgery, unilateral/bilateral surgery, T-stage, N-stage, systemic therapy, radiation therapy and *BRCA* mutation status (Table 1).

Table 1. Baseline characteristics of 612 primary breast cancer patients per type of surgery, n (%).

	All n = 612	**BCT n = 257**	**MAS n = 162**	**REC-I n = 110**	**REC-A n = 83**	**p-value[§]**
Median age, years (IQR)	51.0 (43.0 – 60.0)	54.0 (48.0 – 62.0)	55.0 (47.0 – 63.0)	42.5 (36.0 – 51.0)	45.0 (37.0 – 52.0)	< 0.001[¥]
Median time since surgery, years (IQR)	6.3 (3.3 – 9.4)	5.3 (2.8 – 8.1)	7.1 (3.7 – 9.8)	7.0 (3.7 – 10.4)	7.2 (4.7 – 9.5)	< 0.001[¥]
Surgery						< 0.001
Unilateral	475 (77.6)	251 (97.7)	133 (82.1)	51 (46.4)	40 (48.2)	
Bilateral	137 (22.4)	6 (2.3)	29 (17.9)	59 (53.6)	43 (51.8)	
Unknown	.0	.0	.0	.0	.0	
T stage						< 0.001
T1	354 (57.8)	173 (67.3)	86 (53.1)	58 (52.7)	39 (47.0)	
T2	128 (20.9)	42 (16.3)	51 (31.5)	14 (12.7)	21 (25.3)	
T3	18 (2.9)	.0	8 (4.9)	4 (3.6)	6 (7.2)	
CIS	108 (18.0)	42 (16.3)	17 (10.5)	33 (30.0)	16 (19.3)	
Unknown	2 (0.3)	.0	.0	1 (0.9)	1 (1.2)	
N stage						< 0.001
N0	442 (72.2)	211(82.1)	91 (56.2)	90 (81.8)	50 (60.2)	
N+	170 (27.8)	46 (17.9)	71 (43.8)	20 (18.2)	33 (39.8)	
Unknown	.0	.0	.0	.0	.0	
Systemic therapy						< 0.001
None	256 (41.8)	130 (50.6)	46 (28.4)	53 (48.2)	27 (32.5)	
CTx	88 (14.4)	26 (10.1)	20 (12.3)	16 (14.5)	25 (30.1)	
ETx	95 (15.5)	49 (19.1)	34 (21.0)	10 (9.1)	2 (2.4)	
CTx & ETx	173 (28.3)	52 (20.2)	62 (38.3)	31 (28.2)	29 (34.9)	
Unknown	.0	.0	.0	.0	.0	
Radiation therapy						< 0.001
RTx following BCS	233 (38.1)	233 (90.7)	.0	.0	.0	
No RTx	293 (47.9)	14 (5.4)	120 (74.1)	94 (85.5)	65 (78.3)	
Thoracic-wall and/or locoregional RTx	85 (13.9)	9 (3.5)	42 (25.9)	16 (14.5)	18 (21.7)	
Unknown	1 (0.2)	1 (0.4)	.0	.0	.0	

Table 1. Baseline characteristics of 612 primary breast cancer patients per type of surgery, n (%). (continued)

	All n = 612	BCT n = 257	MAS n = 162	REC-I n = 110	REC-A n = 83	p-value[§]
BRCA						< 0.001
BRCA1/2 negative	399 (65.2)	179 (69.6)	113 (69.8)	58 (52.7)	49 (59.0)	
BRCA1/2 positive	90 (14.7)	13 (5.1)	15 (9.3)	36 (32.7)	26 (31.3)	
Unknown	123 (20.1)	65 (25.3)	34 (20.9)	16 (14.6)	8 (9.6)	
Histological type						0.003
IDC	415 (67.8)	185 (72.0)	113 (69.8)	58 (52.7)	59 (71.1)	
ILC	44 (7.2)	16 (6.2)	16 (9.9)	7 (6.4)	4 (4.8)	
CIS	111 (18.2)	41 (16.0)	19 (11.7)	35 (31.8)	16 (19.3)	
Other	35 (5.7)	15 (5.8)	12 (7.4)	7 (6.4)	2 (2.4)	
Unknown	7 (1.1)	.0	2 (1.2)	3 (2.7)	2 (2.4)	
Differentiation grade^						<0.001
Grade 1	100 (16.3)	61 (23.7)	21 (13.0)	11 (10.0)	7 (8.4)	
Grade 2	216 (35.3)	100 (38.9)	63 (38.9)	31 (28.2)	20 (24.1)	
Grade 3	160 (26.1)	49 (19.1)	55 (34.0)	24 (21.8)	32 (38.6)	
NA	113 (18.5)	44 (17.1)	19 (11.7)	35 (31.8)	16 (19.3)	
Unknown	23 (3.8)	3 (1.2)	4 (2.5)	9 (8.2)	8 (9.6)	

BCT = breast-conserving therapy, MAS = mastectomy, REC-I = mastectomy followed by (in-) direct implant reconstruction, REC-A = mastectomy followed by (in-)direct autologous reconstruction, CTx = chemotherapy and/or immunotherapy, ETx = endocrine therapy, RTx = radiation therapy.
[§]Chi square test. [¥]Kruskall Wallis test.

Patient-reported outcomes

Completion rates for the individual PRO modules in respondents ranged between 88% and 100%, with the exception of the Q-sexual module, which showed lower response rates (Table 2). Statistically significant differences between surgical treatments were found in the PBC group in 'Physical functioning', 'Sexual functioning' and all Q-scores on univariate analyses (Table 2). Post hoc analyses showed that mastectomy patients overall reported significantly lower mean scores on 'Physical functioning' (80.1) compared to BCT (86.4, p=0.001), compared to implant (92.6, p<0.001) and compared to autologous reconstruction (87.5, p=0.006). 'Body image' was lower following mastectomy (75.7) compared to BCT (83.9, p=0.005). Significantly lower 'Sexual functioning' scores (EORTC-QLQ-BR23) were reported by BCT patients (24.2) compared to implant (36.6, p<0.001) and autologous reconstruction (33.6, p=0.001) patients. Lower mean 'Sexual functioning' scores were also reported by mastectomy patients (20.6) compared to both implant and autologous reconstruction patients, p<0.001 and p=0.001 respectively. 'Q-psychosocial' was lower following mastectomy (65.8) compared to implant (74.1, p=0.004) and autologous reconstruction (75.7, p<0.001). Mean 'Q-satisfaction with breast' reported by mastectomy patients (61.7) was significantly lower compared to BCT (65.7, p=0.006) and autologous reconstruction

Table 2. Mean PRO scores per type of surgery (SD), n (%)

	PBC	SBC		PBC				
	All (n = 612)	**All (n = 152)**	**p-value[§]**	**BCT (n = 257)**	**MAS (n = 162)**	**REC-I (n = 110)**	**REC-A (n = 83)**	**p-value[¥]**
EQ-5D-5L								
Index value°	0.83 (0.15) [*96*]	0.82 (0.16) [*97*]	0.25	0.83 (0.14) [*93*]	0.81 (0.16) [*96*]	0.86 (0.15) [*98*]	0.85 (0.14)	0.036
EORTC-QLQ-C30								
Global health status°	79.5 (18.3)	79.2 (17.5)	0.86	79.7 (17.5)	76.2 (19.5)	82.6 (18.6)	81.3 (17.5)	0.026
Physical function°	86.0 (15.8)	83.9 (15.6)	0.16	86.4 (14.4)	80.1 (19.6)	92.6 (9.8)	87.5 (14.6)	<0.001*
Role function°	83.1 (23.4)	79.8 (22.7)	0.11	85.0 (21.3)	78.0 (26.0)	86.2 (22.7)	83.7 (24.0)	0.01
Fatigue±	25.4 (24.5)	24.0 (22.1)	0.51	25.6 (25.0)	28.7 (24.1)	21.0 (23.0)	24.4 (25.3)	0.09
Pain±	17.0 (22.6)	18.9 (21.1)	0.37	16.6 (21.0)	20.9 (26.6)	13.2 (19.2)	16.1 (22.3)	0.042
EORTC-QLQ-BR23								
Body Image°	80.3 (23.6) [*97*]	76.0 (27.0) [*96*]	0.07	83.9 (21.3) [*99*]	75.7 (26.0) [*97*]	77.3 (25.1) [*90*]	81.9 (21.0) [*95*]	0.003*
Sexual function°	26.7 (23.0) [*92*]	24.1 (25.3) [*84*]	0.29	24.2 (20.8) [*95*]	20.6 (22.3) [*91*]	36.6 (24.0) [*89*]	33.6 (24.1) [*90*]	<0.001*
BREAST-Q								
Physical wellbeing°	74.2 (17.4) [*96*]	74.6 (16.8) [*96*]	0.86	71.2 (18.9) [*96*]	75.1 (19.2) [*98*]	76.8 (10.9) [*96*]	78.3 (13.8) [*98*]	0.002*
Psychosocial wellbeing°	70.5 (20.2) [*96*]	69.3 (19.9) [*96*]	0.52	70.1 (21.4) [*96*]	65.8 (18.8) [*98*]	74.1 (20.1) [*96*]	75.7 (17.5) [*98*]	0.001*
Satisfaction with breasts°	64.5 (20.0) [*96*]	63.7 (20.0) [*95*]	0.65	65.7 (22.4) [*95*]	61.8 (17.7) [*96*]	61.2 (15.7) [*96*]	70.5 (20.2) [*98*]	0.003*
Sexual wellbeing°	58.0 (20.0) [*76*]	58.0 (19.8) [*72*]	0.99	57.5 (20.3) [*73*]	54.7 (19.2) [*67*]	59.3 (19.9) [*85*]	62.4 (20.3) [*90*]	0.07

PBC = primary breast cancer patients, SBC = second primary or recurrent breast cancer.
EQ-5D-5L index-value: scale from -0.28 - 1.0. EORTC-QLQ-C30/BR23 and BREAST-Q scale 0 - 100. °Higher scores represent higher quality, ±Higher scores represent lower quality. [ ] percentages complete modules if not 100%. [§]Unpaired T-test. [¥]ANOVA. *Statistical significant differences.

patients (70.5, p=0.004). No significant differences in outcome were found between the different surgeries in the SBC group (data not shown).

When evaluating PROs in multivariate analyses, increasing age was related to lower scores on 'Physical functioning' (β -0.259, p<0.001) and 'Sexual functioning' (β -0.427, p<0.001) (Table 3). Longer time since surgery was associated with less 'fatigue' (β -1.083, p<0.001) (Table 3). 'Q-Satisfaction with breast' was significantly lower for patients following mastectomy (β -13.596, p=0.003) and implant reconstruction (β -13.040, p=0.007) compared to BCT (Table 3). If patients had not undergone radiation therapy, 'Q-satisfaction with breast' was significantly better than following BCT (with consequent radiation therapy) (β 11.956, p<0.009) (Table 3).

Table 3. Multivariate linear regression analyses in 612 primary breast cancer patients.

	EORTC-QLQ-C30		EORTC-QLQ-BR23				BREAST-Q					
	Physical functioning°		Body Image°		Sexual Functioning°		Q-Physical°		Q-psychosocial°		Q-satisfaction with breast°	
	β	p-value	β	p-value	β	p-value	β	p-value	β	p-value	β	p-value
Operation type												
BCT	*ref*	na	*ref*	na	*ref*	na	*ref*	na	*ref*	Na	*ref*	na
MAS	-3.781	0.27	-7.757	0.15	-8.185	0.10	-0.253	0.95	-2.620	0.57	-13.596	0.003*
REC-I	5.223	0.15	-4.033	0.48	2.544	0.64	2.579	0.53	6.365	0.18	-13.040	0.007*
REC-A	0.523	0.89	1.084	0.85	-0.881	0.87	4.712	0.26	9.434	0.05	-2.651	0.59
Age	-0.259	<0.001*	0.209	0.02	-0.427	<0.001*	0.095	0.13	0.090	0.22	0.097	0.19
Time since surgery	0.252	0.14	0.572	0.03	-0.473	0.06	0.446	0.02	0.299	0.19	-0.059	0.79
Surgery												
Unilateral	*ref*	na	*ref*	na	*ref*	na	*ref*	na	*ref*	Na	*ref*	na
Bilateral	-3.560	0.08	1.729	0.59	2.349	0.44	-3.732	0.11	2.888	0.28	-0.327	0.90
T stage												
T1	*ref*	na	*ref*	na	*ref*	na	*ref*	na	*ref*	Na	*ref*	na
T2	1.481	0.36	-1.757	0.51	-2.595	0.31	0.1997	0.92	-2.343	0.30	-2.122	0.33
T3	-2.700	0.48	-1.324	0.82	-2908	0.60	-0.761	0.86	-1.267	0.80	1.765	0.73
CIS	2.026	0.28	0.836	0.27	4.363	0.03	2.930	0.17	2.007	0.42	0.657	0.79
Unknown	5.721	0.59	na	na	-8.785	0.12	-0.833	0.95	-7.227	0.61	-1.205	0.93
N stage												
N0	*ref*	na	*ref*	na	*ref*	na	*ref*	na	*ref*	Na	*ref*	na
N+	1.096	0.52	-0.949	0.73	6.281	0.02	2.179	0.26	2.036	0.37	-4.348	0.06

Table 3. Multivariate linear regression analyses in 612 primary breast cancer patients. (continued)

	EORTC-QLQ-C30		EORTC-QLQ-BR23				BREAST-Q					
	Physical functioning°		Body Image°		Sexual Functioning°		Q-Physical°		Q-psychosocial°		Q-satisfaction with breast°	
	β	p-value	β	p-value	β	p-value	β	p-value	β	p-value	β	p-value
Systemic therapy												
None	*ref*	na	*ref*	na	*ref*	na	*ref*	na	*ref*	Na	*ref*	Na
CTx	-2.658	0.25	-2.189	0.55	3.586	0.31	-1.953	0.47	-4.660	0.14	1.281	0.68
ETx	-4.394	0.03	1.402	0.66	-2.850	0.36	0.201	0.93	4.366	0.11	2.341	0.39
CTx & ETx	-0.246	0.90	1.433	0.65	2.442	0.42	0.053	0.98	3.199	0.23	2.638	0.32
Radiation therapy												
RTx following BCS	*ref*	na	*ref*	na	*ref*	na	*ref*	na	*ref*	Na	*ref*	na
No RTx	-1.693	0.62	-1.144	0.83	4.617	0.36	5.290	0.17	-3.956	0.38	11.956	0.009*
Thoracic wall and/or locoregional RTx	-5.323	0.13	-2.702	0.63	2.890	0.58	-3.017	0.46	-4.903	0.30	8.860	0.07
BRCA												
BRCA1/2 negative	ref	na	ref	na	ref	na	ref	na	ref	Na	ref	Na
BRCA1/2 positive	4.602	0.04	-5.429	0.13	-1.371	0.69	1.454	0.58	-3.997	0.19	-5.242	0.09
Unknown	-0.437	0.78	-2.408	0.34	1.653	0.49	-2.311	0.20	-4.516	0.03	-0.969	0.65

The multivariable linear regression model was composed of all baseline characteristics present in the left column of the table. BCT = breast-conserving therapy; MAS = mastectomy, REC-I = mastectomy followed by (in) direct implant reconstruction, REC-A = mastectomy followed by (in-) direct autologous reconstruction, CTx = chemotherapy and/or immunotherapy, ETx = endocrine therapy.RTx = radiation therapy. *Significant beta coefficient. °Higher scores represent higher quality.

DISCUSSION

Breast cancer patients are faced with complex treatment decision(s) shortly after breast cancer diagnosis. Insights in not only prognosis but also quality of life or daily functioning resulting from these decisions could improve the shared decision-making process and ultimately the care delivered. Knowledge on QoL related to different surgical treatments is urgently needed. The aim of this study is to obtain and evaluate PROs in breast cancer patients according to the surgery performed. Collected PROs indeed showed statistically significant differences for the various surgeries performed. The collected PROs can serve as reference and ultimately pave the way for implementation of VBHC among future breast cancer patients at the outpatient clinic.

In primary breast cancer patients PRO scores in mastectomy patients were lower compared with BCT or breast reconstruction patients except for the 'Q-physical' and 'Q-satisfaction with breast'. Both mastectomy patients and patients with an implant reconstruction reported significantly lower 'Satisfaction with breast' scores compared to BCT or autologous reconstruction patients. These results corroborate previous studies which showed lower satisfaction and impaired sexual functioning, psychosocial and physical functioning following mastectomy compared to BCT or breast reconstruction[16 17]. After adjustment for patient, tumour and treatment characteristics a significant effect of surgical treatment on 'Q-Satisfaction with breast' scores persisted. Compared to BCT, statistically significant lower 'Q-Satisfaction with breast' was reported by mastectomy and implant reconstruction patients. No statistically significant differences were found in PROs between autologous reconstruction and BCT when adjusting for patient, tumour and treatment characteristics. Contradictory results are found in literature, reporting comparable PRO scores[18] or scores in favour of autologous reconstruction techniques[16]. 'No radiation therapy' was associated with statistically significant higher 'Q-Satisfaction with breast' scores as compared to BCT patients. Thoracic wall radiation therapy (25.9%, 14.5% and 21.7% of mastectomy, REC-I and REC-A patients respectively) and locoregional radiotherapy in 3.5% of the BCT patients was associated with lower Q-satisfaction scores compared to patients that had not undergone radiation therapy. Radiation therapy is therefore an important independent factor for 'Q-satisfaction with breast' scores in addition to the type of surgery performed.

Strengths of the current study include the size of the study population and the response rate of 68%. This enabled evaluation of 4 different PROMs, generating a detailed reflection of quality of life. To the best of the authors' knowledge, this is the largest study to evaluate the complete set of PROs proposed in the ICHOM breast cancer set per type of surgery with adjustment for potential confounders. This is a pivotal step forward in the extensive use of PROMs in clinical research and practice for the implementation of VBHC. It furthermore enables a future international comparison. When both PROs and baseline characteristics are available, case-mix corrected comparison between centres can be performed to benchmark.

Limitations form the single-centre and retrospective design. Moreover, not all variables that possibly affect PROs were available for the current cohort such as socioeconomic status[16]. Large

multicentre initiatives are needed to obtain narrow reference scores as well as the possibility for benchmarking. Evaluation of PROs obtained in retrospect does however generate the necessary insights into factors possibly related to PRO scores. These data could be used to build models to perform case-mix analyses which could be validated in other cohorts.

The response rate for sexual functioning (EORTC-QLQ-BR23) was lower compared to other PROs except for patients with breast reconstruction. Therefore, scores for sexual functioning might have been biased. Previous studies on sexual health in breast cancer patients showed that 50-90% of women experience sexual dysfunction[19 20] and that breast cancer surgery has a negative impact[21]. The VBHC initiative, with questions regarding sexual functioning, could possibly open the conversation and future consultation on sexuality in breast cancer patients at the outpatient clinic. Data on sexual functioning are hampered by the lower response rate and the lack of longitudinal data, limiting the clinical applicability of these scores.

There were no statistically significant differences in PROs between PBC and SBC patients. This conclusion is hampered concerning the BREAST-Q questionnaire. In the SBC group, in which patients are more often operated on both breasts, the applicability of the BREAST-Q is lower, since it does not account for two operated breast or different types of breast surgery.

Measuring PROs during treatment has the potential to monitor and detect changes in physical or psychosocial problems at the outpatient clinic. Consequently, targeted supportive care concerning health-related QoL may be provided and possibly improve the care delivered[9 22]. This evaluation enables a first insight in PRO scores according to patient, tumour and treatment characteristics. Reference scores for the different PROs are pivotal when PROs are being used at the outpatient clinic to tailor and improve the care delivered. Knowledge on differences in satisfaction scores per type of breast cancer surgery performed can be used for shared decision-making[16]. However, it should be stressed that we cannot determine a causal relation between the different treatments and outcome yet. Effects of treatments in observational data are potentially biased by confounding by indication and selection should be interpreted with caution. Prospective and repeated evaluations of PROs throughout care form the cornerstone of VBHC and potentially enable more patient-centred breast cancer care with the possibility of improved shared treatment decision-making in breast cancer patients.

CONCLUSIONS

PROs were evaluated in 764 historical patients according to patient, tumour and treatment characteristics in a single centre. ‘Satisfaction with breasts’ differed between type of surgery delivered. This knowledge as well as the collection of reference values could add value in shared decision-making concerning breast cancer surgery.

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SUPPLEMENTARY FILES CHAPTER 4

Supplementary Table S1. Baseline characteristics respondents versus non-respondents, n (%).

	PBC			SBC		
	Respondents n = 612	**Non-respondents n = 264**	**p-value[$]**	**Respondents n = 152**	**Non-respondents n = 88**	**p-value[$]**
Median age, years (IQR)	51.0 (43.0 – 60.0)	50.0 (43.0 - 64.0)	0.45[¥]	48 (40.0 – 54.8)	49 (39.0 – 63.0)	0.11[¥]
Surgery			0.001			0.08
BCT unilateral	251 (41.0)	77 (23.2)		2 (1.3)	2 (2.3)	
BCT bilateral	6 (1.0)	1 (0.4)		22 (14.5)	6 (6.8)	
MAS unilateral	133 (21.7)	92 (34.8)		28 (18.4)	15 (17.0)	
MAS bilateral	29 (4.7)	7 (2.7)		50 (32.9)	44 (50.0)	
REC-I unilateral	51 (8.3)	27 (10.2)		2 (1.3)	3 (3.4)	
REC-I bilateral	59 (9.6)	32 (12.1)		26 (17.1)	10 (11.4)	
REC-A unilateral	40 (6.5)	13 (4.9)		3 (2.0)	3 (3.4)	
REC-A bilateral	43 (7.0)	15 (5.7)		19 (12.5)	5 (5.7)	
T stage			<0.001			0.06
T1	354 (57.8)	98 (37.1)		75 (49.3)	51 (58.0)	
T2	128 (20.9)	85 (32.2)		31 (20.4)	24 (27.3)	
T3	18 (2.9)	15 (5.7)		4 (2.6)	2 (2.3)	
CIS	110 (18.0)	61 (23.1)		37 (24.3)	8 (9.1)	
Unknown	2 (0.3)	5 (1.9)		5 (3.3)	3 (3.4)	
N stage			0.98			0.81
N0	442 (72.2)	189 (71.6)		121 (79.6)	70 (79.5)	
N+	170 (27.8)	73 (27.7)		30 (19.7)	16 (18.2)	
Unknown	.0	2 (0.8)		1 (0.7)	2 (2.3)	
Systemic therapy			0.31			0.02
No	256 (41.8)	107 (40.5)		52 (34.2)	38 (43.2)	
CTx	88 (14.4)	49 (18.6)		30 (19.7)	17 (19.3)	
ETx	95 (15.5)	44 (16.7)		22 (14.5)	20 (22.7)	
CTx & ETx	173 (28.3)	63 (23.9)		48 (31.6)	12 (13.6)	
Unknown	.0	1 (0.4)		.0	1 (1.1)	

Supplementary Table S1. Baseline characteristics respondents versus non-respondents, n (%). (continued)

	PBC			SBC		
	Respondents n = 612	Non-respondents n = 264	p-value[§]	Respondents n = 152	Non-respondents n = 88	p-value[§]
Radiation therapy			0.001			0.43
RTx by BCT	233 (38.1)	66 (25.0)		22 (14.5)	8 (9.1)	
No RTx	293 (47.9)	152 (57.6)		58 (38.2)	42 (47.7)	
Thoracic wall and/or locoregional RTx	85 (13.9)	46 (17.4)		72 (47.4)	37 (42.0)	
Unknown	1 (0.2)	.0		.0	1 (1.1)	
BRCA			0.20			0.30
BRCA1/2 negative	399 (65.2)	158 (59.8)		106 (69.7)	59 (67.0)	
BRCA1/2 positive	90 (14.7)	39 (14.8)		33 (21.7)	16 (18.2)	
Unknown	123 (20.1)	67 (25.4)		13 (8.6)	13 (14.8)	
Histological type			0.16			0.10
IDC	415 (67.8)	161 (61.0)		88 (57.9)	57 (64.8)	
ILC	44 (7.2)	15 (5.7)		10 (6.6)	6 (6.8)	
CIS	111 (18.2)	61 (23.0)		36 (23.7)	8 (9.1)	
Other	35 (5.7)	20 (7.6)		11 (7.2)	11 (12.5)	
Unknown	7 (1.1)	7 (2.7)		7 (4.6)	6 (6.8)	
Differentiation grade^			0.02			0.02
Grade 1	100 (16.3)	27 (10.2)		16 (10.5)	9 (10.2)	
Grade 2	216 (35.3)	77 (29.2)		28 (18.4)	24 (27.3)	
Grade 3	160 (26.1)	83 (31.4)		32 (21.1)	11 (12.5)	
NA	113 (18.5)	65 (24.6)		38 (25.0)	10 (11.4)	
Unknown	23 (3.8)	12 (4.5)		38 (25.0)	34 (38.6)	

PBC = primary breast cancer patients, SBC = second primary or recurrent breast cancer. BCT = breast-conserving therapy, MAS = mastectomy, REC-I = mastectomy followed by (in-) direct implant reconstruction, REC-A= mastectomy followed by (in-) direct autologous reconstruction, CTx = chemotherapy and/or immunotherapy, ETx = endocrine therapy.

[§]Pearson's Chi square test. [¥]Mann-Whitney U test. ^Bloom Richardson differentiation grade.

Supplementary Table S2. Baseline characteristics 152 second primary or recurrent breast cancer patients, n (%).

	All (n = 152)	BCT (n = 24)	MAS (n = 79)	REC-I (n = 27)	REC-A (n = 22)	p-value[§]
Median age, years (IQR)	48.0 (40.0 – 54.8)	54.0 (48.5 – 61.3)	49.0 (42.0 – 55.0)	44.0 (35.0 – 50.0)	40.5 (35.0 – 47.3)	< 0.001[¥]
Median time since surgery, years (IQR)	13.0 (6.8 – 20.2)	10.3 (6.3 – 14.9)	14.0 (8.0 – 23.0)	10.0 (4.0 – 21.0)	15.0 (7.3 – 19.0)	0.027[¥]
Surgery						0.002
Unilateral	35 (23.0)	2 (8.3)	28 (35.4)	2 (7.4)	3 (13.6)	
Bilateral	117 (77.0)	22 (91.7)	51 (64.6)	25 (92.6)	19 (86.4)	
Unknown	.0	.0	.0	.0	.0	
T -stage						0.35
T1	75 (49.3)	14 (58.3)	39 (49.4)	14 (51.9)	8 (36.4)	
T2	31 (20.4)	3 (12.5)	14 (17.7)	6 (22.2)	8 (36.4)	
T3	4 (2.6)	0 (0.0)	4 (5.1)	0 (0.0)	.0	
CIS	37 (24.3)	7 (29.2)	19 (24.1)	7 (25.9)	4 (18.2)	
Unknown	5 (3.3)	.0	3 (3.8)	0 (0.0)	2 (9.1)	
N-stage						0.48
N0	121 (79.6)	20 (83.3)	59 (74.7)	24 (88.9)	18 (81.8)	
N+	30 (19.7)	4 (16.7)	19 (24.1)	3 (11.1)	4 (18.2)	
Unknown	1 (0.7)	.0	1 (1.2)	0 (0.0)	0 (0.0)	
Systemic therapy						0.06
None	52 (34.2)	9 (37.5)	21 (26.6	13 (48.1)	9 (40.9)	
CTx	30 (19.7)	2 (8.3)	15 (19.0)	8 (29.6)	5 (22.7)	
ETx	22 (14.5)	7 (29.2)	13 (16.5)	1 (3.7)	1 (4.5)	
CTx & ETx	48 (31.6)	6 (25.0)	30 (38.0)	5 (18.5)	7 (31.8)	
Unknown	.0	.0	.0	.0	.0	
Radiation therapy						<0.001
RTx by BCT	22 (14.5)	22 (91.7)	.0	.0	.0	
No RTx	58 (38.2)	1 (4.2)	35 (44.3)	13 (48.1)	9 (40.9)	
Thoracic wall and/or locoregional RTx	72 (47.4)	1 (4.2)	44 (55.7)	14 (51.9)	13 (59.1)	
Unknown	.0	.0	.0	.0	.0	
BRCA						0.07
BRCA1/2 negative	106 (69.7)	20 (83.4)	55 (69.6)	17 (63.0)	14 (63.6)	
BRCA1/2 positive	33 (21.7)	2 (8.3)	14 (17.7)	9 (33.3)	8 (36.4)	
Unknown	13 (8.6)	2 (8.3)	10 (12.7)	1 (3.7)	.0	

Supplementary Table S2. Baseline characteristics 152 second primary or recurrent breast cancer patients, n (%). (continued)

	All (n = 152)	BCT (n = 24)	MAS (n = 79)	REC-I (n = 27)	REC-A (n = 22)	p-value[§]
Histological type						0.58
IDL	88 (57.9)	14 (58.3)	43 (54.4)	15 (55.6)	16 (18.2)	
ILC	10 (6.6)	0 (0.0)	8 (10.1)	1 (3.7)	1 (4..5)	
CIS	36 (23.7)	7 (29.2)	18 (22.8)	7 (25.9)	4 (18.2)	
Other	11 (7.2)	3 (12.5)	7 (8.9)	1 (3.7)	.0	
Unknown	7 (4.6)	0 (0.0)	3 (3.8)	3 (11.1)	1 (4.5)	
Differentiation grade^						0.017
Grade 1	16 (10.5)	5 (20.8)	7 (8.9)	4 (14.8)	.0	
Grade 2	28 (18.4)	8 (33.3)	11 (13.9)	5 (18.5)	4 (18.2)	
Grade 3	32 (21.1)	3 (12.5)	14 (17.7)	5 (18.5)	10 (45.5)	
NA	38 (25.0)	8 (33.3)	20 (25.3)	7 (25.9)	4 (18.2)	
Unknown	38 (25.0)	0 (0.0)	27 (34.2)	6 (22.2)	4 (18.2)	

BCT = breast-conserving therapy, *MAS* = mastectomy, *REC-I* = mastectomy followed by (in-) direct implant reconstruction, *REC-A* = mastectomy followed by (in-)direct autologous reconstruction, *CTx* = chemotherapy and/or immunotherapy, *ETx* = endocrine therapy, RTx = radiation therapy. [§]Chi square test. [¥]Kruskall Wallis test

Supplementary Table S3. Multivariate Linear regression analyses in 612 primary breast cancer patients.

	EQ-5D-5L		EORTC-QLQ-CC30								BREAST-Q	
	Index value°		Global health status°		Role functioning°		Fatigue±		Pain±		Q-Sexual°	
	β	p-value	β	p-value	β	p-value	β	p-value	β	p-value	β	p-value
Operation type												
BCT	*ref*	na	*ref*	na	*ref*	na	*ref*	na	*ref*	na	*ref*	na
MAS	-0.063	0.07	-3.765	0.37	-2.266	0.67	6.462	0.25	6.376	0.22	-2.090	0.69
REC-I	-0.015	0.68	3.360	0.45	5.327	0.34	-1.759	0.76	-1.398	0.80	4.342	0.43
REC-A	-0.026	0.48	1.951	0.66	3.483	0.54	1.990	0.74	1.151	0.84	7.306	0.18
Age	<0.001	0.15	0.079	0.25	-0.717	0.41	-0.027	0.76	0.003	0.97	0.155	0.12
Time since surgery	0.004	0.02	0.289	0.16	0.647	0.01	-1.083	<0.001*	-0.456	0.07	-0.226	0.38
Surgery												
Unilateral	*ref*	na	*ref*	na	*ref*	na	*ref*	na	*ref*	na	*ref*	na
Bilateral	-0.008	0.71	-2.313	0.35	-5.319	0.10	5.049	0.12	7.594	0.01	-0.772	0.80
T-stage												
T1	*ref*	na	*ref*	na	*ref*	na	*ref*	na	*ref*	na	*ref*	na
T2	0.019	0.27	-3.574	0.08	-2.526	0.33	-1.558	0.57	0.517	0.84	0.940	0.72
T3	0.020	0.62	-6.283	0.18	-2.925	0.62	8.944	0.15	-0.198	0.97	2.661	0.61
CIS	0.046	0.02	2.416	0.29	1.435	0.62	-5.381	0.08	-3.904	0.16	3.090	0.28
Unknown	0.093	0.39	0.766	0.95	5.450	0.74	-7.299	0.67	-6.400	0.69	13.998	0.33
N-stage												
N0	*ref*	na	*ref*	na	*ref*	na	*ref*	na	*ref*	na	*ref*	na
N+	0.004	0.02	4.159	0.05	1.033	0.70	-4.946	0.07	2.775	0.28	4.264	0.11

Supplementary Table S3. Multivariate Linear regression analyses in 612 primary breast cancer patients. (continued)

	EQ-5D-5L		EORTC-QLQ-CC30								BREAST-Q	
	Index value°		Global health status°		Role functioning°		Fatigue±		Pain±		Q-Sexual°	
	β	p-value	β	p-value	β	p-value	β	p-value	β	p-value	β	p-value
Systemic therapy												
None	*ref*	na	*ref*	na	*ref*	na	*ref*	na	*ref*	na	*ref*	na
CTx	-0.007	0.78	-0.979	0.73	-2.073	0.56	1.911	0.61	-1.360	0.69	-2.134	0.55
ETx	0.010	0.65	-2.326	0.35	-2.768	0.38	3.613	0.27	-1.069	0.73	0.532	0.87
CTx & ETx	0.014	0.50	0.610	0.80	0.757	0.81	1.716	0.59	-4.320	0.15	0.570	0.85
Radiation therapy												
RTx by BCS	*ref*	na	*ref*	na	*ref*	na	*ref*	na	*ref*	na	*ref*	na
Thoracic wall and/or locoregional RTx	0.044	0.20	0.236	0.96	-4.014	0.45	-2.693	0.62	-3.310	0.52	-1.513	0.77
Additional RTx	0.013	0.72	-1.679	0.70	-8.272	0.14	-0.133	0.98	-0.780	0.88	-2.516	0.64
BRCA												
BRCA1/2 negative	ref	na	ref	na	ref	na	ref	na	ref	na	ref	na
BRCA1/2 positive	0.009	0.71	1.641	0.55	1.525	0.67	-3.388	0.35	-3.574	0.29	-1.731	0.61
Unknown	-0.014	0.40	-2.097	0.28	0.027	0.99	3.334	0.19	6.565	0.01	-3.825	0.13

BCT = breast-conserving therapy; *MAS* = mastectomy, *REC-I* = mastectomy followed by (in)direct implant reconstruction, *REC-A* = mastectomy followed by (in-)direct autologous reconstruction, *CTx* = chemotherapy and/or immunotherapy, *ETx* = endocrine therapy. RTx = radiation therapy. *Significant beta coefficient.

Chapter 5

Implementation of value-based breast cancer care

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ABSTRACT

Purpose

Adding value of care to patients is crucial for all stakeholders. The use of both provider and patient reported outcome data was implemented in a single academic breast cancer centre. We describe the development of the outcomes set, data integration within electronical health records (EHR) and clinical use.

Methods

An Integrated Practice Unit (IPU) was constructed providing the full care cycle for breast cancer patients. Provider reported outcomes and patient reported outcomes (PROs) were defined, reflecting the entire cycle of care and long-term sustainability of quality of life. Multidisciplinary provider and patient perspectives were obtained via focus groups and surveys. Patient pathways were redesigned in order to identify suitable opportunities for data collection during the entire care cycle.

Results

A Standard Set for Breast Cancer Outcomes together with case-mix variables and timelines was agreed upon within the IPU. A secure electronic platform, directly linked to the EHR, was designed to measure PROs during the outpatient phase. First year evaluation showed a decrease of response rates over time, from 83.3% at baseline to 45.2% at 12 months after surgery. Patients reacted positively to the use of PROMs in daily clinical cancer care.

Conclusion

Assessment of patient reported as well as provider reported outcomes was implemented within our standard of breast cancer care. For this, dedicated resources, change of culture and practice, and improved knowledge and awareness about Value-based healthcare (VBHC) were essential. Our proposed framework aims to serve as a blueprint for implementation of VBHC in daily care.

INTRODUCTION

Value-based healthcare (VBHC) aims to improve the quality of care delivered by measuring and improving outcomes that reflect value instead of volume[1,2]. Value of care is defined as health outcome per total costs[1]. Since value in healthcare depends on results, not inputs, value is measured by the outcomes achieved and not the volume of services delivered[1]. Ideally, these outcomes reflect patient-orientated results instead of structure or process measures that do not always reflect the results obtained[1]. Multiple health outcomes are often used to evaluate the care for a single medical condition. In a VBHC-design outcomes are both provider reported (i.e. breast cancer survival rates, complications, hospitalization rates) and patient reported (PROs)[1]. Inherently, these outcomes are disease specific and multidimensional to reflect the total cycle of care and quality of life (QoL) and disease burden in the long run[1,3].

Specifically in the care for (early-stage) breast cancer patients the importance of value is increasingly being recognized. High survival rates are achieved in early-stage breast cancer patients[4,5] irrespective of the type of surgery performed[6-8]. Considering these excellent and comparable oncological outcomes and the multiple locoregional strategies available in this setting (i.e. breast-conserving therapy (BCT), mastectomy, whether or not followed by breast reconstructive surgery; all with differences in outcomes and costs), there is an increasing need for outcome measurements that accurately differentiate between treatment strategies. In the era of increasing healthcare costs and stringent measures to lower costs, these outcomes could increase breast cancer care efficacy (by improving outcomes against equal or lower costs). In addition, adequate outcome assessment could also add in future treatment decision-making and/or follow-up regimens.

The Erasmus MC, a major academic healthcare institute within the Netherlands, initiated a VBHC-strategy. With commitment from both the institution and different multidisciplinary disease teams, multiple outcome sets were defined and a data collection tool was developed to capture these outcomes. Following a pilot phase the concept was gradually rolled out and is now used in daily practice for 10 medical conditions amongst which breast cancer. The International Consortium for Health Outcome Measurements (ICHOM) has initiated efforts to develop standard sets of patient-centred outcome measurements for various medical conditions amongst others breast cancer. As part of the ICHOM Working Groups, clinicians from the Erasmus MC have contributed to the development or implementation of multiple outcome sets on an international level[9-13].

Value-based breast cancer care was designed in 2014 and initiated in October 2015 by the dedicated multidisciplinary breast cancer team of the Erasmus MC Academic Breast Cancer Centre. A standardized outcomes set was created that encompassed both provider reported outcomes and PROs. Striving to implement value-based breast cancer care on a broader (inter)national scale, this article gives a step by step overview of the framework deployed for implementation of this outcome set and discusses the challenges within the implementation process. The description of our data collection tool that was linked to the electronic health records (EHRs) and the research performed during this implementation phase, is additionally aimed to serve as a guide for future implementations. Lastly, future steps are discussed needed to transform current breast cancer care towards a value-based breast cancer care.

METHODS

Within the institute a breast cancer specific-strategy was developed to transform the current breast cancer care to value-based breast cancer care (Fig. 1)[2 3]. This step by step overview functions as a blueprint in the implementation process.

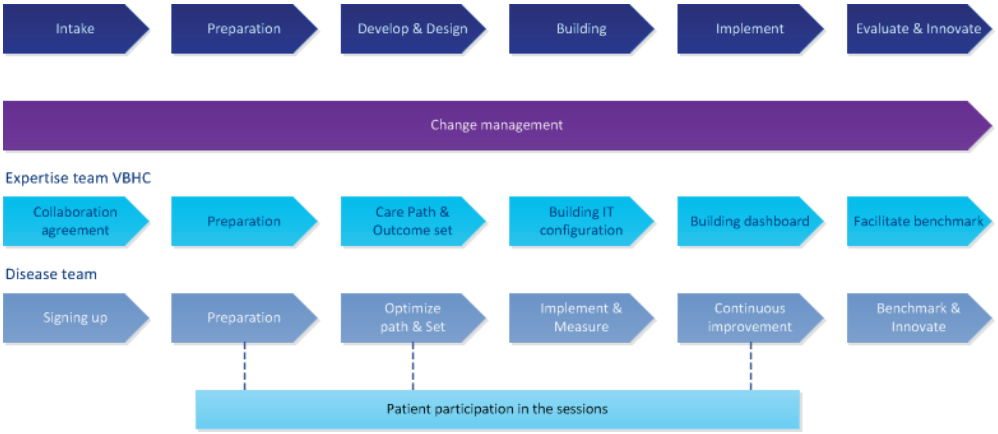

Figure 1. Erasmus MC's blueprint, facilitate the teams on their journey towards VBHC.
VBHC, Value-based healthcare; IT, Information Technology

Institutional dedication

Recently, the executive board of the Erasmus MC initiated a 5- year VBHC-strategy to transform the institute into a true value innovator. This institutional dedication is pivotal to enable a transformation of the current healthcare systems towards a VBHC-system. This institutional leadership ensures sufficient resources needed for this transformation[14]. We consulted the Institutional Review Board, who concluded that informed consent was not needed since the VBHC-strategy is considered standard of care in Erasmus MC.

Dedicated multidisciplinary team

An integrated, and thus multidisciplinary breast cancer practice unit was already operative within our institute. The team is composed of oncological (breast)surgeons, medical oncologists, radiation oncologist, radiologists, plastic & reconstructive surgeons, pathologists, specialist breast cancer nurses (all present at multidisciplinary board meetings), clinical geneticists, psychologists, gynaecologists, and thoracic surgeons (consulted upon indication). Within breast cancer care patient-reported outcome measures (PROMs) had already gained interest and participation in the institutional pilot phase was therefore seen as a unique opportunity.

Care pathway

Realigning services with patient needs is fundamental to deliver more efficient care[2]. For breast cancer, a 'complex' care pathway (involving many different disciplines), was first redesigned to serve as a starting-point for the design of other care-pathways: young women with (potentially hereditary) breast cancer who need neoadjuvant systemic treatment and afterwards undergo mastectomy with immediate (autologous) breast reconstruction. Within this redesign the time points when to visit several different physicians and when to evaluate different outcomes were determined (Supplementary Fig. S1).

Breast cancer outcomes set

Defining an outcomes set is an essential step within any VBHC-initiative which should occur before actual implementation. A first version of the outcomes set was composed by the multidisciplinary team after five 3-h work sessions. To ensure patients' input in the outcomes selection, interviews and surveys were performed within breast cancer patients in different treatment phases. Validated questionnaires were searched capturing the intended outcomes. PROMs incorporated in the set were the EORTC-QLQ-Core (C30)[15], EORTC-QLQ Breast Cancer (B23)[16], BREAST-Q (both pre-operative and postoperative modules)[17], EQ-5D-5L[18], Distress Thermometer[19], the Reproductive Concerns Scale (RCS-NL)[20], and the CarerQoL-7D[21]. All questionnaires were available in validated Dutch versions (Fig. 2).

Outcomes such as patient, tumour and treatment characteristics, survival rates and treatment-related complications were defined by physicians considering patient input. These outcomes serve as either an outcome on its own (for example survival rates) or as a variable in multivariable or case-mix analyses used to evaluate outcome scores (Supplementary Table S1).

The determined time points for data collection are equal to those in the, later developed, ICHOM set. Time points determined were: baseline (prior to treatment; T0), following the last course of neoadjuvant systemic therapy (T3), 6 months after surgery (T6) and annually thereafter (T12-60) (Fig. 2). To capture the period where patients might still be on endocrine therapy, follow-up was recommended up to 5-10 years in early breast cancer patients. Annual follow-up up to age 50 years was recommended for young breast cancer patients. Annual follow-up for 10 years was recommended for patients with advance disease.

Data collection tool

An in-house developed open source electronical data collection tool was used and configured, which allowed the construction of data collection-forms and automatic distribution of PROMs. Emails are sent to the patients in order to activate the distribution of PROMs. After the right treatment pathway is selected by the physician, all the following PROMs will be sent automatically by

the tool at the right time point. The tool was linked to the EHR enabling the review of the collected data for individual patients at the (outpatient) clinic. The secure platform is build up by two software programs, LimeSurvey[22] and GemsTracker[23]. The development team simultaneously developed a user-friendly interface to display the collected data. Since the selected BREAST-Q questionnaire is surgery-specific, multiple pathways for data collection had to be build (i.e. BCT, mastectomy alone and mastectomy with breast reconstruction, either with implants or autologous). Longitudinal PRO data and data from the caregivers is collected in these pathways (Fig. 2).

RESULTS

During the institutional pilot-phase, in which a VBHC-strategy was implemented for six medical conditions, multiple institutional and regional (breast cancer specific) symposia were organized to update and include both physicians within the hospital, primary care givers, patient advocacy groups and other stakeholders in the ongoing initiative. Currently a VBHC-strategy is being used in the daily care for 10 other medical conditions other than breast cancer[10-12].

Implementing value-based breast cancer care

An initial period of 3 months was used to test and evaluate the use of the different pathways. During this phase all emails (distributing the PROMs) were sent manually to patients by specialist nurses. This enabled proper insight in the functioning of

the pathways. The manual distribution consequently led to a reminder to discuss the initiative with patients or to follow-up on patients who had not responded. Currently, all postoperative modules are distributed automatically to patients (by the electronical data collection tool) 3 weeks before the scheduled consultation with 2 following weekly reminders. The preoperative surveys are distributed manually by specialist nurses considering their delicate timing of administration (directly following diagnosis and before surgery or start of neoadjuvant chemotherapy). An advantage of this continuous manual distribution is that it serves as a reminder to discuss the initiative with all patients (and caregivers) at the outpatient clinic. An additional change was made in the follow-up regimen, i.e. the PROs collection at the 6 month postoperative time point (T6) was considered mandatory instead of optional. The collected PROs at this time point were evaluated and discussed with the patient in the telephone consultation with the specialist nurse. A first consultation at the outpatient clinic was scheduled together with the (mammographic) follow-up visit. PRO scores were than evaluated and discussed with the patient in the consultation room.

An average of 20 min per patient was needed to complete the PROMs of the outcome set at one specific time point[24].

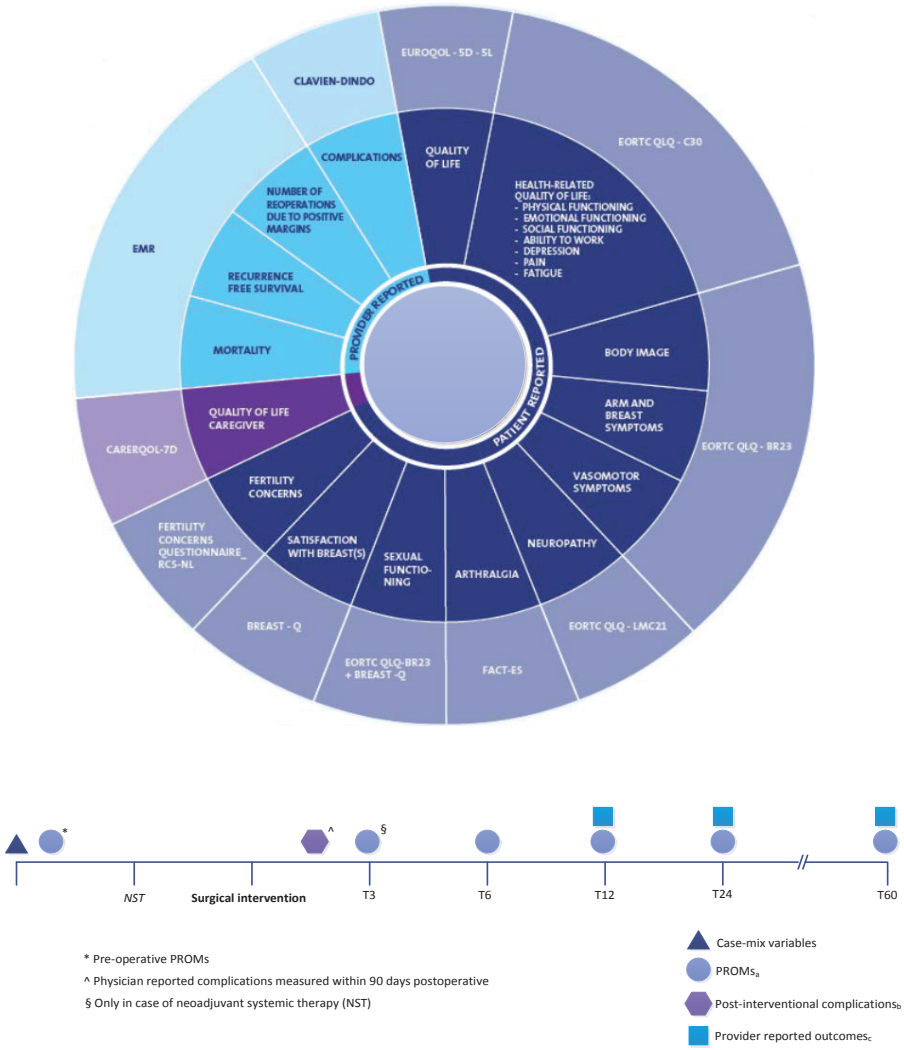

Figure 2. Erasmus MC's standard set for breast cancer.

[a] All PROMs are collected at baseline (T0), 6 months (T6) after treatment, and then annually (T12-T60), except for the BREAST-Q-satisfaction with breast module, which is only collected at baseline (T0), 1 year (T12) and 2 years (T24) after treatment.

[b] Collection of acute complications is recommended while the patient is undergoing treatment or within 90 days of treatment completion, except for complications of hormonal therapy, which are collected up to one year (T12).

[c] Survival and disease control.

NST = neoadjuvant systemic therapy; PROMs = patient reported outcome measurements.

First evaluation

We evaluated the first two years of our VBHC-initiative. Ethical approval for this evaluation was granted by the Institutional Review Board of the Erasmus MC (MEC-2018-1015). A total of 239 breast cancer patients, surgically treated at our institute, were enrolled between October 2015 and December 2017. A response rate of 83.3% (199/239 patients) was seen at baseline (T0), which decreased over time to 65.7% (157/239 patients) at 6 months postoperatively (T6) and 55.1% (108/196 patients) at 12 months postoperatively (T12). Looking at the different questionnaires it was found that not all questionnaires were completed at the several time points (T0, T6, and T12). For example, only the EORTC-QLQ-C30 and -B23 were completed and the BREAST-Q not, or otherwise (Fig. 3). Moreover, some time points were completely missed leaving all PROMs at that specific time point empty.

The specialist nurse monitored whether patients completed the PROMs and asked patients about their reason not completing the questionnaire (if applicable). When no responses were received patients mostly stated that they had forgotten about the surveys (preoperatively) or had not understood that they would be administered repeatedly (postoperatively).

Ongoing efforts resulted in a user-friendly interface that directly displays the outcomes collected in a dashboard so they can be evaluated by both patients and physicians. Concerning feedback, PROs are filled in prior to outpatient clinic visits and discussed by the healthcare provider. If not filled in, the patient is asked to do so and a phone call is planned. Essential for the success of this VBHC-initiative is the (direct) feedback of the PRO scores and/or the changes in the scores according to baseline values. An adequate interpretation of these (changes in) scores enables an appropriate change in care strategy or intervention. Reference scores are additionally needed to evaluate PROs scores in a broader perspective. In order to obtain useful reference scores applicable to our patient population, we evaluated PRO scores which were retrospectively assessed within our institute (all breast cancer patients treated over the last 10 years)[25] and through the regional and national patient advocacy groups[24]. In addition, we evaluated the median PROs for the different PROM modules over time during the first year. As expected PRO scores decreased between baseline (T0) and 6 months postoperatively (T6), but higher scores were seen at one year postoperatively (T12) compared to T6, Fig. 4. Graphical visualization of the trend of PRO scores over time, during treatment and/or follow-up, facilitate a quick overview of a patient's current state of health in the physiological, social, and physical areas and turn this information into a diagnostic tool.

To evaluate whether patients were satisfied with our initiative, an experience survey was composed, asking patients (n ¼ 30) how satisfied they were with the number of PROMs, the content of the PROMs and the feedback of the PRO scores during hospital visits. Patients reported that PROMs were aligned with their treatment (86.3%), and they felt themselves more heard at T6 (64.3%) and at T12 (100%). The majority of the patients even reported that that completing the PROMs helped them to become more aware of their everyday functioning (60.0%), and contributed positively to their breast cancer treatment (80%) (Fig. 5).

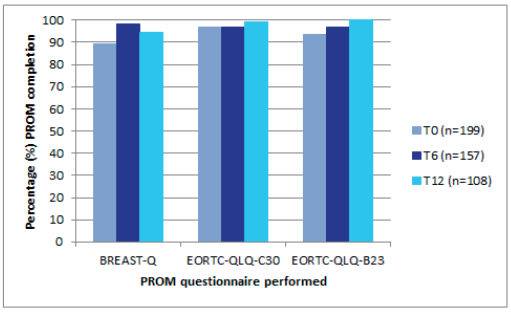

Figure 3. Percentage of breast cancer patients filled in the PROM questionnaires (n%) per time point during the first year.
Vertical axis shows the percentage (%) of patients who completed the PROM per time point.
T0= baseline (prior to treatment), T6= six months after surgery, T12= twelve months after surgery

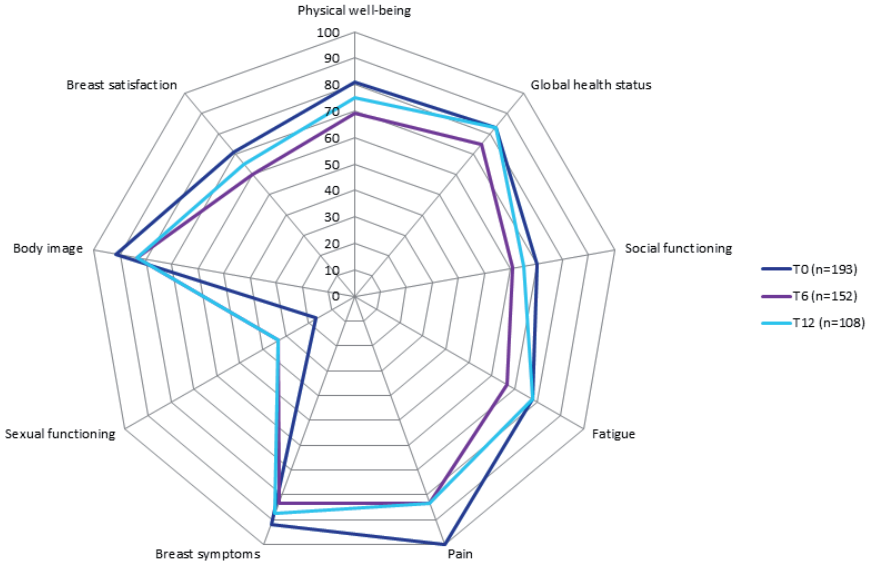

Figure 4. Spider plot representing the different PROM scores per time point (n=239).
T0= baseline (prior to treatment), T6= six months after surgery, T12= twelve months after surgery

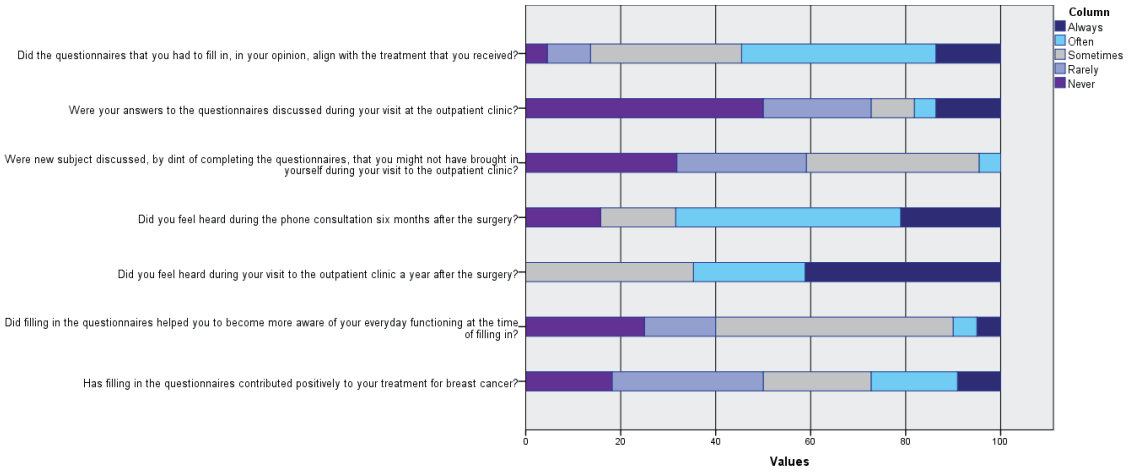

Figure 5. Experience survey (n=30)

DISCUSSION

Value-based breast cancer care was implemented within our institution over a time-period of three years. First, standardized care pathways were developed by the dedicated multidisciplinary team. Second, a breast cancer outcomes set was developed in collaboration with breast cancer patients and regional patient advocacy groups. Third, the outcomes set was integrated in clinical practice by using a newly developed data collection tool which was linked to the electronic health records. Patients within our institute now receive PROs at baseline and at predetermined time points throughout their care cycle to discuss these outcomes with their healthcare providers and tailor their supportive therapies were necessary.

The compliance during the first year was lower than expected. Possible explanations are patients' unawareness or misunderstanding about the repeated administration of the PROMs. False or changing e-mail addresses was another issue which explains the lower compliance rate over time. In order to tackle these difficulties, a brochure to explain the VBHC-initiative and the different time point of survey-assessment was therefore created.

Patients who have participated with the collection tool receiving and completing the PROMs have provided positive feedback about the initiative thus far. They stated that the use of PROMs helps them to prepare for the upcoming appointment, which makes it more tailored to their needs. Care providers at our institute reported similar benefits, additionally stating that with the use of PROMs a more complete view about the provided care can be obtained. Studies evaluating the use of a similar tool reported comparable positive feedback of both patients and care providers and identified several strengths[26-28]. The ability to prioritize topics for discussion at outpatient visits, symptom monitoring and management were well documented, as well as improved patient-

provider communication leading to more shared decision-making. Clinicians found PRO data useful and not disruptive to their practice[29-31]. Several tools are available nowadays and successful implementations of outcomes sets by IT-systems integrated in the EHRs have been reported [28 32-34]. Also, when enquiring about the expectations of breast cancer patients through the regional and national patient advocacy groups, positive answers were collected [24]. Recently, a collaboration with eight hospitals in the Southwest region of the Netherlands aiming at the same outcomes set was started to expand the local value-based breast cancer-initiative. In this way transparency between hospitals can be driven in order to improve quality of regional breast cancer care by benchmarking outcomes. Comparing outcomes for quality monitoring requires implementation of identical outcomes sets. Regional and national, or even international, efforts to adapt an identical set creates the possibility for benchmarking and comparative effectiveness research.

Both authors LK and MM were part of the ICHOM working group that established a consensus on the breast cancer outcome set[13]. The ICHOM breast cancer set was compared to the institutional outcomes set and changes were made to obtain the highest resemblance. In addition to the ICHOM set the Erasmus MC outcomes set also includes the EQ-5D-5L-questionnaire and all modules of the BREAST-Q (i.e. not only the 'satisfaction with breast'- module). This general health questionnaire was added mid-2016 within all VBHC-initiatives at the Erasmus MC in order to evaluate the health status of all patients referred to our centre[35]. The BREAST-Q is a surgery specific questionnaire developed in 2009 with the use of modern psychometric methods[17]. It is expected to accurately differentiate satisfaction with cosmetic outcome per type of surgery performed[36 37]. An important advantage of early adaption to a value-based breast cancer care-initiative is that it generates the possibility to gain insights in the validity and applicability of PROMs used.

Internationally, current payment systems are mostly based on the volume of services (fee-for-service-model). Bundled-payment is a value-based model in which the basis for reimbursement is bundled care and value (results rather than services). Wang et al.[38], examined the correlation of outcomes and medical expenditures by comparing a bundled-payment system to a fee for services-system in 17,940 breast cancer patients. With a range of 5-year follow-up, the medical payments of the bundled-payment group remained stable, whether the fee-for-service payments steadily increased. This suggests that bundled-payment systems may lead to better adherence to quality indicators, better outcomes, and more-effective cost-control over time[38]. Healthcare systems that already have a bundle-payment system could take advantage of the transformation made by breast cancer multidisciplinary teams towards a value-based breast cancer system. Although a VBHC-initiative is hard to translate to a fee-for-service model, it is expected that all stakeholders will benefit from such a transition to longer term bundles[3]. Not only in a fee-for-service system but also in a bundled payment system sufficient research to gain insight in PROs validity and applicability is needed before PROs can be used to guide payments.

Limitations seen within the implementation process should be rephrased into key lessons. Dedicated resources (human and financial) need to be established to make outcome measurement

core business. Changing culture as well as practice is a key part of the process and must be acknowledged in the attempted changes. Healthcare providers therefore need to make active efforts to secure support for VBHC in daily practice. The development of our data collection tool was a significant milestone in the implementation process. Due to IT functional problems implementation slowed down, but true progress could be made after the data collection tool was functioning well. This went hand in hand with improved knowledge and awareness about VBHC and the data collection tool. Running pilots and educating both providers and patients are therefore essential for high compliance rates with provider outcomes and PROs. Lastly, to ensure continuous adaptation and correction during the implementation process, small and incremental changes should be made instead of mass overhaul[12].

With breast cancer survival rates continuing to improve, the focus on survivorship issues and quality of life is increasingly becoming important. In the context of breast cancer care a value approach is expected to generate necessary insights in outcomes for the different surgical strategies and improve care efficiency (by improving outcomes and stabilizing or reducing costs). The VBHC-initiative is expected to pave the way[24]. Our initiative has now grown beyond its own centre to support other breast cancer centres to implement the same set of outcomes, seeding the potential for learning and improvement initiatives on a much broader scale. At the moment we analyse a large dataset in order to develop prediction models for quality of life concerning certain therapies.

CONCLUSION

A value-based breast cancer strategy including explicit and longitudinal PRO scores was successfully implemented within our institute. Measurement of PROs as well as provider reported outcomes was implemented within our standard care. Structured measurements will create opportunities for performance improvement, shared treatment decision-making and benchmarking between different providers and healthcare systems, both on a regional and international scale. For this, dedicated resources, change of culture and practice, and improved knowledge and awareness about VBHC were essential. The outline described of both the development and implementation of this initiative is meant as a guide for future implementations.

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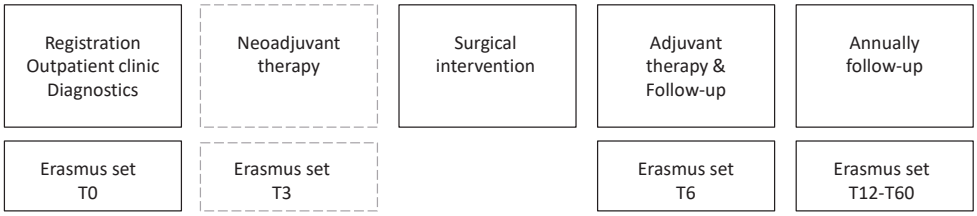
SUPPLEMENTARY FILES CHAPTER 5



Supplementary Figure S1. Recalibration of the current pathway for young woman with hereditary breast cancer.

The big squares show the previous pathway adapted to match the Erasmus MC standard set. The pathway involves multidisciplinary specialty interaction at different time points, with – in the smaller squares – approximations of data collection time points used where necessary. For breast cancer patients treated with neoadjuvant chemotherapy an additional data collection point was added (T3).

T0= baseline (prior to treatment), T3= following the last course of neoadjuvant chemotherapy or endocrine therapy, T6= six months after surgery T12= twelve months after surgery, and annually thereafter (T24-T60).

Supplementary Table S1. Case-mix and treatment variables, Erasmus MC's breast cancer standard set.

Patient population	Measure	Data Sources
Demographic factors		
All patients	Date of birth Ethnicity Education level Relationship status Social Economic Status Working status Smoking	Patient-reported
	Body mass index	Clinical
Baseline clinical factors		
All patients	Comorbidities	Patient-reported
	Laterality Second primary tumour	Clinical
Baseline tumour factors		
All patients	Date of histopathological diagnosis Mutation status predisposing breast cancer Tumour grade (invasive) Tumour grade (DCIS)	Clinical
Patients with NST	Clinical TNM status[§]	Clinical
Patients with surgery	Pathological TNM status[§] Size of invasive component of tumour (mm) Number of lymph nodes resected Number of lymph nodes involved Estrogen receptor status Progesterone receptor status Her-2-neu receptor status	Clinical
Treatment approaches	Type of surgery performed (neo)adjuvant chemotherapy (neo)adjuvant hormonal therapy (neo)adjuvant radiotherapy Target therapy No therapy	Clinical

DCIS = ductal carcinoma in situ, Her-2-neu = human epidermal growth factor receptor 2, NST = neoadjuvant systemic therapy, TNM= Classification of Malignant Tumours (Tumour Node Metastasis).
[^]Breast-conserving therapy, mastectomy, reconstructive surgery (implant/ autologous), [§]American Joint committee on Cancer (AJCC) 7th edition.

Chapter 6

Implementing patient-reported outcome measures in clinical breast cancer care: a systematic review

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ABSTRACT

Objective

Patient-reported outcome measures (PROMs) are increasingly being used to improve care delivery and are becoming part of routine clinical practice. This systematic review aims to give an overview of PROM administration methods and their facilitators and barriers in breast cancer clinical practice.

Study Design and Methods

A systematic literature search was conducted in Embase, MEDLINE, PsycINFO, Cochrane Central, CINAHL and Web of Science for potentially relevant articles from inception to November 2017. Reference lists of screened reviews were also checked. After inclusion of relevant articles, data was extracted and appraised by 2 investigators.

Results

A total of 2,311 articles were screened, of which 34 eligible articles were ultimately included. Method and frequency of PROM collection varied between studies. The majority of studies described a promising effect of PROM collection on patients (adherence, symptom distress, quality of life, acceptability and satisfaction), providers (willingness to comply, clinical decision-making, symptom management) and care process or system outcomes (referrals, patient-provider communication, hospital visits). A limited number of facilitators and barriers was identified, primarily of technical and behavioural nature.

Conclusion

Although interpreting the impact of PROM collection in breast cancer care is challenging owing to considerations of synergistic (multicomponent) interventions and generalizability issues, this review found that systematic PROM collection has a promising impact on patients, providers and care processes/systems. Further standardization and reporting on method and frequency of PROM collection might help increase the effectiveness of PROM intervention and is warranted to enhance their overall impact.

INTRODUCTION

Breast cancer is the most common cancer affecting women worldwide[1]. With survival rates continuing to improve, the focus on quality of life is becoming increasingly important. Because healthcare is shifting toward a more value-based framework for quality of care improvement, more attention is being paid to patient-reported outcome (PROs)[2]. PROs are defined as feedback on a patient's health condition (i.e. symptoms and quality of life) coming directly from the individual patient, thus without external interpretation[3].

PROMs are increasingly being collected and advocated in cancer care for aiding care management of the individual patient[4-7]. The use of PROMs has been associated with better patient satisfaction[8], perceptions of quality of care[9-11], health outcomes[12-14], and higher patient acceptability[12 15]. Routine collection of PROMs can also have a positive impact on patient-provider communication, (shared) decision-making, and symptom management[8 16 17]. Challenges in collecting, storing, analysing, and reporting PROM scores in real time can impede the routine use in clinical practice[5] making it important to identify these implementation issues. Howell et al.[17] published a review of the factors of PROM implementation and use in cancer clinical practice and concluded that PROMs have been tested most often in the breast cancer population. However, reviews focusing on methods of PROM administration, specifically in breast cancer care, have not been published.

This review sought to provide an overview of PROM collection methods in breast cancer care answering the following questions: 1) how have PROMs been administered in breast cancer care; 2) what is the impact of PROM administration on patients, care providers and healthcare services or processes; and 3) what are the facilitators and barriers that influence integration of PROM collection in routine breast cancer clinical practice?

METHODS

This systematic literature review was conducted according to the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) model[18] for reporting of systematic reviews.

Literature Search Strategy

Six electronic databases were searched – Embase, MEDLINE, PsycINFO, Cochrane Central, CINAHL and Web of Science – from study inception to November 3, 2017. No restrictions to language or country of publication were applied to either the search strategy or study selection. The comprehensive search strategy was devised jointly with an experienced librarian and included a combination of keywords for breast cancer, which was searched in free text and as exploded medical subject headings where possible. Additional related terms were used to maximize the sensitivity of the search. The full search strategy is provided in the appendix (Supplementary S1).

Study Selection

Figure 1 shows the PRISMA flow diagram of the study selection process. Two investigators (AO and LE) independently screened titles and abstracts and identified potentially relevant articles.

The reference lists of identified reviews were screened for other relevant publications. Studies were excluded if they: 1) did not include breast cancer patients, 2) had an irrelevant aim by focusing on PROMs as an evaluation method, endpoint or outcome for other interventions/ treatments, 3) had the following study design: case report, editorial, review, study protocol, 4) had an overlapping study population with another study (if relevant, the most recent article was included), and 5) were not published in full-text.

Remaining studies were reviewed in full-text by both authors using the same exclusion criteria. Disagreements on study eligibility were either resolved through discussion between both assessors, or ultimately, through consultation with the whole research team. Subsequently included full-text publications were listed in a taxonomy table that comprised of study descriptives (number of involved patients and healthcare providers, method and frequency of PROM collection, outcomes of PROM collection, and facilitators or barriers).

Data Extraction & Quality Assessment

Data that were extracted included information on study aim and design, sample characteristics (for intervention and control groups, if applicable), and method or frequency of PROM collection. Outcomes described in the included studies were divided into 3 categories during data extraction: 1) patient outcomes (i.e. adherence, symptoms, health outcomes, acceptability, and satisfaction), 2) care provider outcomes (i.e. adherence, impact on clinical decision-making, acceptability, and satisfaction), and 3) care process/system outcomes (i.e. impact on referral (rates), communication, hospital visits, and usability). Acceptability was defined as the extent to which PRO collection was found pleasant by study participants. Satisfaction was defined as the extent to which the study participants enjoyed completing the PRO instruments[19].

Finally, described facilitators and barriers of routine PROM use in breast cancer care were also extracted. The Critical Appraisal Skills Programme (CASP) tool was used by both reviewers (AO and LE) to evaluate the quality of included studies (Supplementary Table S2). Discrepancies were discussed between both reviewers and supervisors until consensus was reached. There was no meta-analysis performed due to the heterogeneity among the included studies.

RESULTS

After the initial screening of titles and abstracts (n = 2,311), 58 remaining potentially relevant articles were retrieved (Fig. 1). These remaining manuscripts were checked for eligibility based on full-text assessment. Thirty-four studies met the inclusion criteria (Table 1).

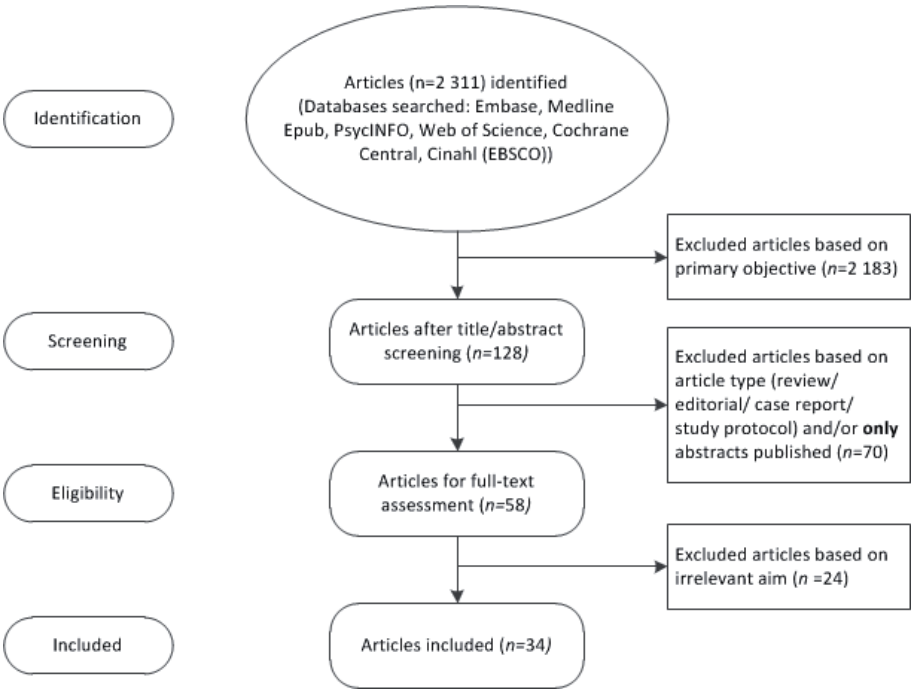

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram of relevant article selection.

Total Study Population

The total sum of patients across all selected studies was 14,083 of which 11,191 (79.5%) were breast cancer patients (range 13 – 8,359 patients). Sixteen of the 34 included articles exclusively involved breast cancer patients. In the remaining 18 studies, breast cancer patients were a subgroup of study populations with various cancer types (prostate, lung, colon, gynaecologic, and genitourinary cancer, among others). Mean age was 54.68 years (± standard deviation [SD] 5.01).

Implementation

The patient-reported outcome version of the Common Terminology Criteria of Adverse Events (PRO-CTCAE)[19-24] was used most often, followed by the European Organization for research and Treatment of Cancer Quality of life Questionnaire (EORTC) modules QLQ-C30 and QLQ-B23[25-34], M.D. Anderson Symptom Inventory (MDASI), EuroQol-5D questionnaire[24 27 35 36], the Functional

Assessment of Cancer Therapy questionnaires (FACT-B, -F, -G)[31 33 37 38], and the Hospital Anxiety & Depression Scale (HADS)[26 30 39] respectively.

PROMs were most often collected electronically (n=17). Web-based assessments were the primary method of data collection (n=7), both in and outside the clinic, followed by the use of a tablet (n=6), an (e-Health) application (n=2), email (n=1), and a software system (n=1) (Table 1). Four studies[22 31 33 40] used both electronic and paper-based interventions to collect PROMs. A telephone-based intervention was used in 9 studies, with 4 studies involving interactive voice response[32 41-43], 3 studies involving mobile applications[20 44 45], and 2 studies involving semi-structured (computer-assisted) telephone interviews or structured prompts of PRO domains[26 28]. One study used only a paper-based intervention[27]. Two qualitative studies involving patient focus groups did not include a PROM intervention[46 47]. One study[48] did not specify the way PRO scores were collected.

The frequency of PROM administration varied from once to daily during study time (Table 1). The duration of PROM interventions ranged from 1.5 months[20] to 24 months[48]. Most interventions (n=14) provided PROMs only in the clinic, while 8 studies required patients to complete PROMs at home (all electronic- or telephone-based interventions), and in 3 studies either at home or in the clinic. PROMs were collected during treatment (n=22), during follow-up (n=3), or during both treatment and follow-up (n=9). One third of PROM interventions restricted assessments to only monitor a specific phase of breast cancer treatment, most commonly during chemotherapy. The most common reminder method was by e-mail or phone.

In 4 studies[11 21 29 43], the electronic PRO systems were directly integrated into the electronic health record (EHR). Some PROM interventions also provided patient education (n=9); one of these[35] was administered through a module. Of 10 studies[11 19 22 23 25 26 28 29 46 47] describing healthcare provider involvement (i.e. focus group, interviews, satisfaction or usability questionnaires), only 2 studies[19 22] described providers actually being part of the PROM intervention. Within the PROM intervention, patients' providers could edit automatically generated care plans (based on PROM responses) to further tailor referrals and treatment recommendations. Once approved by providers, care plans were mailed to patients[19 22]. Outcomes were discussed by the treating clinician (n=9), nurse (practitioner) or physician assistant (n=5), or by a combination of these (n=7) (Table 1). Nearly one third of PROM interventions included alerts being sent to clinicians or patients. Alerts were typically sent by email or text message. In 18 studies, summary reports of PRO data were sent to prespecified providers.

Impact of PROMs on Patient Outcomes

Adherence. Among studies reporting on adherence (n=14), completion rates varied between 71%[32] and 100%[48] (Table 1). The extent of adherence variation over time was rarely reported: Dean and Crittenden[48] reported a decrease in compliance rate from 100% to 87.7% in 12 months, and Min et al.[36] observed a decline from 100% to 13.3 % at 90 days. Other noteworthy observations were that noncompliers were slightly older[43], that unemployed women had a higher compliance rate[36], and that

higher rates were seen for monthly rather than for weekly adherence[35]. Snyder et al.[11] reported that the proportion of missing PROM items was lower when PROMs were completed at home versus the clinic.

Symptoms. Three randomized controlled trials (RCTs) evaluated the effect of PRO collection on symptom (severity) over time. All reported significantly decreasing symptom prevalence or symptom distress over time in the intervention arm versus controls[32 39 49]. Other studies[26 41 43 45] also reported a reduction of symptoms postintervention when compared to baseline. More reporting of new or changing symptoms was observed when a PRO collection tool was used[34]. In addition, a (3-arm) RCT by Egbring et al.[20] found that when PROs were administered through an application instead of paper-based questionnaires, there was a higher frequency of symptom reporting. There was also a higher tendency to report overall symptoms when patients were not supervised by care providers[20].

Health outcomes. Eleven studies evaluated the impact of PROM administration on patient wellbeing (Table 1). Reduction of psychosocial distress was reported[30], as was reduction of symptom distress or burden[42 43], anxiety and depressive feelings[26 41], and pain[27 33]. Furthermore, improved physical functioning and improved emotional and sexual wellbeing were found[26 33 46 48]. A substantial effect on health-related quality of life (HRQoL) over time between PROM intervention and control group was reported in 1 RCT (n=776), in addition to the significantly higher overall and quality-adjusted survival in the intervention group[24]. Two other RCTs[26 30] also reported improved HRQoL scores, albeit not significantly improved. A qualitative study[46], in which focus groups and one-on-one interviews were conducted, found that for women postmastectomy, PROMs focusing on emotional wellbeing, education, communication, and process of care (e.g. scheduling appointments and transition of care) were of greatest importance.

Acceptability. Fifteen studies evaluated patients' acceptability of PRO collection (Table 1). Patients were generally positive, reporting that the interventions were helpful. Four studies used a tablet computer to collect PROMs, and over 90% of their study populations found tablets (very) easy to use[22 31 33 37]. Similar results were reported for the use of applications[45 50] and telephone-based interventions[11 41 42]. An online web-tool was used in 4 studies[19 29 31 35], all of which reported an overall high acceptability. The majority of patients reported that the length and number of PROM questionnaires was acceptable[19 22 37 43], the questionnaires were helpful in discussing health issues with their care providers during visits[11 23 29 41 47 50], they were willing to answer additional questions[23], and they liked being able to complete the questionnaires at home[23 29 35 47].

Satisfaction. Twelve studies reported the effect of PRO collection on patient satisfaction. A cohort study of 66 breast cancer patients that evaluated the use of a tablet computer for PROM collection found that 75% of patients were satisfied at baseline, and that percentage rose to 88% over time[31]. Of these patients, 84% to 94% were willing to recommend the PROM collection tool to other patients. In studies with a telephone-based PROM collection tool (n=4), patients reported a high satisfaction rate as well[11 28 41 42]. Comparable results were found for web-based collection tools with patients reporting them as helpful and enjoyable[19 22]. In 1 study, patients preferred the tablet computer over an online web-tool[23].

Impact of PROMs on Provider Outcomes

Compliance. Knoerl et al.[19] examined providers' willingness to review PROMs: All providers (5 nurse practitioners and 1 physician assistant) created an account to a web-based platform (Carevive) for PROM collection and ultimately reviewed and finalized 81.3% of generated personalized care plans. However, only 20% of providers who completed all outcome assessments (n=5) reported that they consistently reviewed care plans with their patients[19].

Clinical decision-making. Care providers' opinions were divided on whether PROM scores would influence their clinical decision-making. One study reported that none of the participating providers felt the PROM collection tool had led to different therapy decisions[25], whereas another study reported one third of providers reporting that their clinical decisions were influenced by symptom alerts[32]. Providers' email responses to symptom alerts were to maintain treatment strategies (46%), reassess the patient at the following clinic visit (33%), or alter the treatment (8%)[32].

Acceptability. Five studies evaluated if PROMs were helpful to providers in identifying and controlling patient symptoms and other areas of need[11 22 23 25 42]. A prospective cohort study[11] reported that 58% of providers were most likely to agree that a PROM intervention helped them to identify areas of concern. Stover et al.[23], who implemented a web-based PRO screening system with 21 items assessing symptoms and functional status, reported that providers found PRO summary reports most useful for reviewing symptoms (92%), and (very) helpful in changing the treatment plan (80%). Most providers (92%) also reported that discussing PRO results with patients during clinical visits did not lengthen the consultation time. Albert et al.[25] evaluated an electronic PRO collection tool (QoL Profiles) and reported that providers (n=14) found the system understandable (100%), felt it provided more information (63%), helped them notice patients' issues (25%), and found that the system corresponded to their own patient assessment (94%). Knoerl et al.[19] also observed that care providers reported PROM collection being helpful in identifying appropriate areas of concern or need.

Impact of PROMs on Care Process/ System Outcomes

Referrals. There was limited evidence concerning the effects of monitoring or tracking PROMs on referral rates. Girgis et al.[26] found a significant ($p<0.0001$) difference in the number of referral recommendations, as a response to PROM results, between nurses and clinicians with more referrals being recommended by nurses for unmet psychological, daily living, health service or information, and physical needs. Basch et al.[24] demonstrated that 8% of severe symptom email alerts resulted in referrals, whereas the majority (77%) of email alerts prompted telephone counselling by nurses for symptom management.

Hospital visits. Only 2 studies looked specifically at the effect of PRO collection and screening on the rate of emergency room (ER) visits[24 40]. Basch et al.[24] reported a significant 7% decrease ($p=0.02$) in ER visits between patients whose symptoms were electronically tracked and patients

who received usual care during active chemotherapy. Barbera et al.[40] reported comparable results, with the number of ER visits being 43% lower in breast cancer patients who received routine PRO assessments prior to clinic visits during active chemotherapy as opposed to patients who did not. Effects of PROM interventions on hospitalizations were not significant: Basch et al.[24] found a 4% decrease in hospitalizations (p=0.08) in patients whose PROMs were monitored compared to patients with usual cancer care; Wheelock et al.[34] did not find a difference between patients whose PROMs were electronically captured during breast cancer follow-up care compared to patients who did not receive the PROM intervention.

Communication. Regardless of study design, patients and providers were generally positive about the impact of systematic PROM collection on patient-provider communication[20 25 26 31]. Patients felt more encouraged after PRO assessment to discuss symptoms and issues with their providers that they otherwise would not have discussed[31] and also felt more focused and taken seriously during the consultation[20]. Although evidence was scarce, providers reported that reviewing PROMS encouraged clinical interactions between them and their patients[19] and that this review also led to more specific questioning during the clinic visit[25].

Facilitators and Barriers

Facilitators. Technical facilitators of PROM implementation in routine breast cancer care were the most frequently described (Fig. 2). One article pointed out that technological methods of PROM

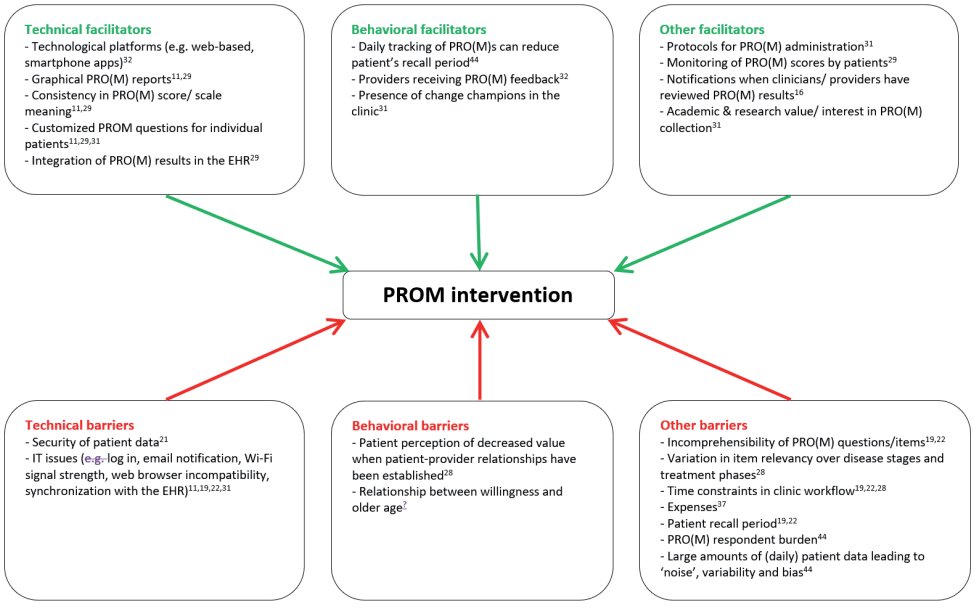

Figure 2. Description of facilitators and barriers
PRO(M), Patient-Reported Outcome (Measurements); EHR, Electronic Health Record

collection (e.g. web-based, smartphone applications, tablet computer) might be more acceptable[32]. Providers seem to prefer graphic presentations of PRO results above table reports, but they also valued addition of free-text comments by patients. Patient feedback included the recommendation of tailoring questions (through an interface) for individual patients and providing more information on PRO score results, which might enhance PRO collection and interpretation[11 29]. Email reminders to review PRO results could possibly increase care providers' awareness of patient symptoms and problems and thus encourage symptom management[32]. Some patients expressed a preference to be notified when providers reviewed PRO reports[29]. One study found that the presence of a "change champion" was essential to facilitating PROM implementation by not only encouraging patients' acceptance of the collection method (e.g. tablet computers), but also by guiding care providers through PRO reports and ensuring that appropriate actions are taken in response to significant patient issues[31].

Barriers. The clarity of PROM questions, including stating the (symptom) recall period, can be a hurdle for patients' acceptability of the PROM intervention[19 22]. Providers also indicated that the lack of integration and synchronization of the PRO data system with the EHR was a significant barrier in routine PRO review, because it required logging into additional systems (with additional passwords) and compatible Internet browsers[11 19 22 29]. Some articles reported that patients found it confusing if the meaning of PRO summary scores were inconsistent, with higher scores alternatively indicating better or worse outcomes[11 29]. Conflicting providers' opinions were reported regarding the timing of PROM review: Some providers indicated that most symptom alerts were received outside the hospital, thus impeding swift patient contact, whereas others reported that reviewing PROMs right before clinic appointments might disrupt the clinical practice flow owing to time constraints[19 22 29 32]. Another feasibility aspect was the burden to patients and staff: Not only can multiple PROMs become burdensome for patients over time, but reviewing and interpreting enormous amounts of patient data can also take its toll on providers [28 31 44].

DISCUSSION

This review studied implementation methods, impact, and facilitator and barriers of PROM collection in breast cancer clinical practice. The PROM interventions were generally developed to improve symptom management, to identify psychosocial problems, to facilitate patient-centred care and treatment-specific monitoring during treatment phases, and to improve patient-provider communication. Electronic PRO collection systems were most often used, which can allow patients to efficiently complete standardized assessments, can increase usability with a lower response burden, can lead to fewer missing data (when compared to paper-based PROMs), and can lead to higher satisfaction[31 51 52]. Electronic PROM collection can also provide a certain flexibility in assessment location (clinic vs home) and frequency, and can bridge treatment-specific and long-term PRO follow-up[6].

An essential point is that some selected studies described the effects of a combined intervention, which included not only a PROM collection component but also additional actions, such as enhanced care with patient education and coaching, proactive review of PROMs, and follow-up by providers. This makes it difficult, from a practical standpoint, to determine to which extent the observed impact of these multicomponent interventions can be attributed specifically to PROM collection and review. Then again, it might be unnecessary to separate the components, considering that complex interventions can lead to synergistic results and thus an accumulated impact. It might be more important to determine to what degree to which the individual parts of multicomponent strategies are implemented properly and according to the original proposed theory of the intervention[53].

Apart from differences in PROM collection methods across selected studies, there was also notable variety in the frequency ("intensity") of the assessments: PRO assessments ranged from daily to once (for screening purposes). PRO collection tools were used to monitor specific treatment phases (e.g. adverse effects during chemotherapy or radiotherapy) or entire breast cancer care trajectories (from diagnosis to the end of follow-up). Successful implementation of routine PRO assessment should integrate both options and should combine them with the appropriate PROM to ensure optimal patient engagement and management of care.

The heterogeneous study populations should be taken into account; more than half of the selected studies did not have a study population consisting entirely of breast cancer patients. In the studies included in our review, the percentage of breast cancer patients varied from 17.9% to 80%, with breast cancer patients being the majority in only 9 studies. Ruland et al.[50] described the differences between breast and prostate cancer patients in their use of WebChoice, an interactive e-Health application designed to support cancer patients in illness management. Breast cancer patients used the application twice as often and asked significantly more often for help than prostate cancer patients. The gender-specific nature of different cancer types makes it difficult to identify attributes that could explain usage discrepancies. Nevertheless, the findings are consistent with previous research, which indicates that women seek more health-related information online than men do. In addition, the breast cancer patient population in the selected studies was overall younger than other cancer populations, and it is well known that younger people seek information online more often than older people do[54 55].

Another striking observation is the limited diversity in study populations across the selected articles. Most of the included study participants were overwhelmingly Caucasian[11 19 22 23 28 29 31 33-35 38 41-43 46 56]. There were only 2 studies in which PROM interventions were targeted at predominantly minority populations[32 37]. Limited diversity also applied to education levels of study participants across most included studies, with the majority of patients having a college degree or higher. As most of the interventions across the included studies required patients to be able to speak English, it became obvious that routine PROM collection was primarily executed in a select patient population. Another important point is that most patients, across included articles were recruited in clinic

waiting rooms by being asked if they were willing to participate. This could have introduced some selection bias if willingness itself has associations with better adherence to other care components. Naturally, this selectiveness in patient characteristics can affect the outcome results of PROM interventions. By striving to avoid "preselection" of patients to participate in PROM intervention studies, generalizability issues can also be (partially) circumvented in future research.

Numerous selected studies in this systematic review mentioned facilitators and barriers of the PROM interventions. It must be noted that nearly all selected studies did not identify these facilitators and barriers after a thorough analysis because that was not the primary aim of the selected articles. The facilitators and barriers were mostly identified by observing the effects of PROM implementation in practice. Antunes et al.[57] reported that substantial leadership is necessary to boost motivation in patients and care providers and educating them on the use, interpretation and advantages of routine PROM collection could increase adherence. Further research involving facilitator and barrier analysis should be conducted in order to provide more guidance during the design of PROM interventions.

Among 2,311 initially screened articles, 8 reviews were excluded based on irrelevant aims (see Methods). Their references, however, were also screened by title and abstract to ensure thoroughness of the literature search. Fourteen references[12 15 58-69] were identified as potentially relevant but were not among the initial 2,311 articles. The apparent reason was that these articles were not indexed with breast cancer-related keywords or medical subject headings (e.g. "breast cancer", "breast tumour", "breast neoplasm"), probably because their study populations only contained a minimal proportion of breast cancer patients. So, it must be noted, for transparency reasons, that there could be some relevant articles that were not included because of their improper/incomplete indexing. These 14 articles did not provide any novel insights.

CONCLUSION

PROMs can be collected in a variety of methods, locations and frequencies. Although interpreting the impact of PROM interventions is challenging due to considerations of synergistic (multicomponent) interventions and generalizability issues, this review found that the systematic PROM collection in routine breast cancer care has a promising impact on patients, providers and care processes/systems.

RECOMMENDATIONS

A major challenge in the implementation of value-based healthcare is standardizing PROMs that are meaningful to patients across different cultural and geographical settings[70]. Although there seems to be scepticism around the feasibility and effectiveness of standardized PROM collection as a part of breast cancer care, a number of PROMs (BREAST-Q, EORTC-QLQ-C30 and -B23, EQ-5D-5L, and the FACT-ES) have been validated within the breast cancer population[71].

A breast cancer outcome set (including some of the aforementioned PROMs) was developed by the International Consortium for Health Outcomes Measurement (ICHOM), which recommended a timeline for PRO assessments in order to evaluate certain events (baseline, after neoadjuvant chemotherapy, surgery and follow-up) in breast cancer care[71]. If routine PROM collection is to be implemented in clinical practice, we recommend a standardized PROM set because it is one of the requirements for benchmarking treatments and healthcare providers. It could also ultimately allow comparisons of breast cancer outcomes across countries. By doing so, a major step will have been taken towards value-based healthcare.

Table 1. PROMs scored and their impact on patient-, clinician- and process/system-level outcomes.

Selected article	Study objective	Study design	Breast cancer study population	PROM intervention, method, setting and frequency of administration	Administered PROM
Abernethy et al. (31), 2009	To determine feasibility and acceptability of tablet computers for administering standard assessment questionnaires, and for collecting patient-reported symptom and QoL data	Prospective cohort study	66 breast cancer patients Characteristics: - Mean age 54 years (± SD 12) - Female 100% - Caucasian 77% - Metastatic 61% - College degree or higher 86%	"eTablet", a tablet computer for PRO data collection - Paper & electronic (tablet computer) - Clinic waiting room - 4 times in 6 months	1. FACT-G 2. FACT-B 3. MDASI 4. FACIT-F 5. FACIT-Self-Efficacy Scale 6. PCM, an 86-item survey for common cancer- and treatment-related symptoms 7. Satisfaction & Acceptability survey
Albert et al. (25), 2002	To implement individual QoL profile measurements in follow-up cancer care	Prospective cohort study	24 breast cancer patients Characteristics: - Median age 57 years (range 45-75) - Female 100%	Individualized graphic QoL Profiles based on PROMs - Electronic (software) - Clinic waiting room or doctor's office - At each follow-up visit	1. EORTC-QLQ-C30 2. EORTC-QLQ-BR23

(Medical) professional providing feedback to PRO	Intervention duration (months)	Patient outcomes	Provider outcome	Care process/system outcomes
- 4 clinicians reviewed a printed PRO summary report - 1 (research) nurse included PRO reports to patient files after marking alarming items	6	*Acceptability:* 60/64 (94%) patients found "eTablets" very easy to use, 98% found it easy to respond to survey questions on eTablets, 94% found it easy to navigate, 77% found the eTablet's weight very comfortable. *Satisfaction*: 48/64 (75%) patients were satisfied with the eTablet for PRO collection at baseline, which increased to 88% at the 4th visit; 84% of patients would recommend it to others at 1st visit, which increased to 94% by the 4th visit. *Other*: 42/57 (74%) patients felt the PCM helped them recall experienced symptoms, which remained in 29/40 (73%) patients.	-	*Communication*: 16/50 (32%) of patients, at the 1st visit, felt encouraged to address symptoms with clinicians that they otherwise wouldn't have discussed, which increased to 48% (16/33) patients) by the 4th visit
14 clinicians during follow-up care received mailed QoL profiles with discharge and most recent QoL scores	-	-	*Compliance:* 9/14 (64%) clinicians actively participated by completing most (67% response rate) routine surveys about usefulness of QoL profiles *Clinical decision-making:* None of the clinicians felt that the QoL profiles led to different therapy decisions *Acceptability:* - 16/16 (100%) found the QoL profiles understandable, 63% felt that they provided more information, 25% felt they helped notice patient issues - 94% felt that the profiles corresponded to their own patient assessment	*Communication:* 7/16 (44%) clinicians felt the QoL profiles had an effect on the patient-provider namely that more specific questions were being asked

Table 1. PROMs scored and their impact on patient-, clinician- and process/system-level outcomes. (continued)

Selected article	Study objective	Study design	Breast cancer study population	PROM intervention, method, setting and frequency of administration	Administered PROM
Anderson et al. (32), 2015	To determine the feasibility and efficacy of an automated telephone-based intervention on pain and symptom improvement in minority patients	RCT	60 low-income breast cancer patients Characteristics per group: *1) Intervention (n=31)*: - Mean age 49.6 years (± 9.9) - Female 100% - Latina 58% - Metastatic 35% - Years of education 10.6 years (± 4.1) *2) Control* (n=29): - Mean age 50.5 years (± 11) - Female 100% - Latina 59% - Metastatic 41% - Years of education 10 years (± 2.9)	*Intervention:* "Automated IVR" intervention for symptom reporting using dial-tone keypad for intensity rating - Telephone - Home - 2 times per week *Control:* Paper-based assessments at baseline and 2 follow-up points, without review by clinicians. Patients received usual symptom management, if indicated.	1. IVR-related pain and symptom list 2. MDASI 3. BQ-II 4. ECOG Performance Scale 5. PMI PROMs (#2 - #5) were administered during clinic visits at two time points (4-6 weeks and 8-10 weeks after enrolment).
Barbera et al. (40), 2015	To determine the impact of screening with ESAS on unplanned ER visit rates of breast cancer patients	Retrospective cohort study	8359 breast cancer (stage I-III) patients receiving adjuvant chemotherapy within 6 months of diagnosis Characteristics per group: *1) With ESAS screening (n=2541):* -Mean age 53.22 years (± SD 10.44) *2) Without ESAS screening (n=5818):* -Mean age 53.87 years (± SD 10.57)	Screening with ESAS instrument - Electronic (web-based) and paper-based - Clinic waiting room - Each follow-up visit at cancer centre	1. ESAS

(Medical) professional providing feedback to PRO	Intervention duration (months)	Patient outcomes	Provider outcome	Care process/system outcomes
Clinicians received IVR system-generated email-alerts, when symptoms were moderate-severe (pain score ≥ 5 on a 0-10 scale)	2	*Adherence:* 71% of IVR assessments were completed successfully. *Symptoms:* - Proportion of patients with moderate to severe pain decreased from 86% to 43% (p=0.004). No significant decrease in control group (from 80% to 56%). - Proportion of patients in the intervention group with moderate to severe symptoms (distress from 57% to 19%, sadness from 52% to 19%, drowsiness from 65% to 30%) decreased significantly (p=0.008, p=0.04, p=0.04, respectively) over follow-up. Conversely, no significant changes were observed in the control group. - No significant difference in proportion moderate-severe symptoms between intervention and control groups over time	*Clinical decision-making:* - 33.3% of clinicians disclosed that their clinical decisions were influenced by symptom alerts. - Clinicians' email response to symptom alerts were to maintain treatment course (46%), to assess the patient at the following clinic appointment (33%) or a new symptom treatment prescription (8%)	*Other:* - 100% of symptom alerts were detected; 161/221 (73%) symptom alerts were acknowledged by clinicians through an email response to the research staff. - No significant difference between groups in proportion of patients receiving adequate analgesics (33% vs. 28%), as determined by the PMI
Clinical team received summary reports on symptom scores to facilitate patient-provider communication about relevant symptoms	-	*Adherence:* Median number of ESAS assessments was 3 (IQR 1-5) for the 2541 patients that received at least one ESAS screening	-	*Hospital visits:* - ER visits were 43% lower in patients previously screened with ESAS compared to patients who were not. For each additional prior ESAS screening, there was a 17% decline in ER visits - Association of screening with ESAS on ER visits remained preventative even after adjusting for other types of visits

Table 1. PROMs scored and their impact on patient-, clinician- and process/system-level outcomes. (continued)

Selected article	Study objective	Study design	Breast cancer study population	PROM intervention, method, setting and frequency of administration	Administered PROM
Basch et al. (24), 2016	To determine the effect of routine web-based collection of PROMs on HRQoL and clinical outcomes in patients receiving adjuvant chemotherapy	RCT	143/776 (18.4%) breast cancer patients receiving outpatient chemotherapy Characteristics per group: *1) Intervention*: 89/441 (20%) breast cancer patients - 25% computer-experienced – 11% computer-inexperienced *2) Control*: 54/325 (17%) breast cancer patients - 19% computer-experienced. - 10% computer-inexperienced	*Intervention:* "STAR", a web-based interface for symptom reporting - Electronic (web-based; tablet computer) - Clinic and home (between-visit report) - Weekly email prompts to report symptoms *Control*: Usual care	1. CTCAE (adapted version) 2. EQ-5D
Berry et al. (49), 2014	To determine the effect of a web-based PRO assessment and educational intervention on symptom distress during cancer treatment	RCT	206/752 (27.4%) breast cancer patients Characteristics per group: *1) Intervention*: 109/374 (30%) breast cancer patients *2) Control*: 97/378 (26%) breast cancer patients	*Intervention:* Combination of patient education, communication coaching and a PRO assessment - Electronic (web-based) - Home and clinic waiting room - At least 4 times (study time points) and voluntary between visits *Control*: Enhanced usual care with 4 PRO assessments with clinicians receiving a summary report	ESRA-C, an electronic patient-report application containing 3 PROMs: 1. SDS-15 2. PHQ-9 3. EORTC-QLQ-C30

(Medical) professional providing feedback to PRO	Intervention duration (months)	Patient outcomes	Provider outcome	Care process/system outcomes
- Nurses received email alerts when symptoms progressed (by ≥ 2 points or absolute score ≥ 3 on a 0-5 scale) and responded directly - Clinicians received a printed report of symptoms tracked at each clinic visit	Median 3.7 (0.25-49)	*Adherence:* 73% of patients in the STAR arm completed a self-report at any given clinic visit *Health outcomes:* - HRQoL scores at 6 months improved in significantly more patients in the STAR group compared to control patients (34% vs. 18%, p<0.001) - EQ-5D subdomains mobility, self-care and anxiety/depression were significantly better in the STAR group compared to usual care (p=0.02, p=0.01 and p=0.01, respectively); significance was not reached for subdomains pain/ discomfort and usual activities - Overall survival at 12 months was higher in the STAR arm compared to the control arm (75% vs. 69%, p=0.05). Mean 12-month quality-adjusted survival was also significantly higher in the STAR arm (8.7 vs. 8 months, p=0.004)	*Clinical decision-making:* - 77% of alerts led to telephone counselling by nurses about symptom management, 12% of alerts led to start/change of supportive medication, 2% led to adjustment of chemotherapy dose	*Referrals:* 8% of alerts resulted in an ER/ hospital referral *Hospital visits:* Proportion of patients visiting the ER was significantly less in the STAR arm compared to usual care (34% vs. 41%, p=0.02) at 12 months A similar trend was observed for hospitalizations (45% vs. 49%, p=0.08) *Other:* - Patients in the STAR arm received significantly longer chemotherapy compared to the usual care group (8.2 vs. 6.3 months, p=0.002) - No significant difference in the amount of nursing calls was observed between the STAR arm and usual care (mean 12.8 vs. 12.9, p=0.93)
Clinicians could be called immediately if symptom levels were severe between clinic visits and they received summary reports at each visit	-	*Adherence:* No significant difference in rates of outcome completion were observed between the intervention arm and usual care group (77.3% vs. 77.2%) *Symptoms:* - Symptom distress was significantly lower in the intervention arm vs. controls (mean change SDS-15 score -0.04 ± 5.8 vs. 1.27 ± 6.7) - A statistically significant reduction (average 1.93 score change in SDS-15, p=0.002) was observed in patients ≥ 50 years within the intervention arm compared to usual care. No significant intervention effect was observed in patients <50 years.	-	-

Table 1. PROMs scored and their impact on patient-, clinician- and process/system-level outcomes. (continued)

Selected article	Study objective	Study design	Breast cancer study population	PROM intervention, method, setting and frequency of administration	Administered PROM
Bock et al. (56), 2012	To determine the effect of an online health survey on symptom reporting, symptom documentation & management by clinicians	Cross-sectional study	106 breast cancer patients Characteristics: - Mean age 56.9 years (32-85) - Female 100% - Caucasian 87% - Metastatic 0%	Online questionnaire on symptoms (frequency, severity and associated distress) & health behavior - Electronic (web-based with/without tablet computer) - Home or clinic waiting room	Unspecified PROM (symptoms and health history)
Børøsund et al. (39), 2014	To determine the effects of an online illness management system, IPPC service, and usual care on symptom distress, anxiety, depression and self-efficacy	RCT (3-arm)	167 breast cancer patients who underwent surgery or receiving other treatments (radiation, chemotherapy, hormone therapy or combinations) within 12 months post-surgery Characteristics per group: 1) *WebChoice intervention (n=64):* - Mean age 51 years (37-79) - Female 100% - College degree or higher 63% 2) *IPPC intervention: (n=45):* - Mean age 50 years (31-66) - Female 100% - College degree or higher 51% 3) *Usual care (n=58):* - Mean age 53 years (36-69) - Female 100% - College degree or higher 46%	*Intervention 1:* "WebChoice", an online illness management system *Intervention 2:* IPPC, a nurse-administered communication service - Electronic (web-based) - Home - Voluntary frequency *Control:* Usual care	1. Symptom list 2. MSAS 3. HADS 4. CBI

(Medical) professional providing feedback to PRO	Intervention duration (months)	Patient outcomes	Provider outcome	Care process/system outcomes
- 7 clinicians received patient-reported symptom reports attached to the medical record prior to clinic visit - 3 nurse practitio-ners	6	*Symptoms:* Number of patient-reported symptoms (mean 3.8, range 0-13) was significantly ($p<0.001$) higher than number of clinician-reported (mean 1.8, range 0-7)	-	*Other:* - More than half of symptoms mentioned by both patients and clinicians are addressed, regardless of number of symptoms - Considerable discordance between patient and clinician documentation of exercise behavior (100% vs. 28%) and alcohol use (100% vs. 70%)
- 6 clinicians - 11 nurses - 3 social workers IPPC messages were answered primarily by nurses through secure e-messages	6	*Adherence:* 49/64 (77%) WebChoice users logged on at least once in 6 months. Of those who logged on at least twice, median was 7 times (range 2-41). *Symptoms:* - Anxiety (mean difference -0.79, $p=0.03$) and depression (mean difference -0.79, $p=0.03$) were significantly lower in the WebChoice group vs. usual care group. - Symptom distress was significantly lower for patients in the WebChoice arm versus the usual care arm (mean difference -0.16, $p=0.001$). No difference was observed in symptom distress between IPPC and usual care. - WebChoice participants had higher self-efficacy scores over time (mean difference 8.81, $p=0.08$) than the usual care group	Adherence: 33/153 (22%) IPPC messages were answered by clinicians	-

Table 1. PROMs scored and their impact on patient-, clinician- and process/system-level outcomes. (continued)

Selected article	Study objective	Study design	Breast cancer study population	PROM intervention, method, setting and frequency of administration	Administered PROM
Braeken et al. (30), 2013	To evaluate the short- and long-term effects of using a psychosocial screening instrument on psychological distress and HRQoL	Cluster RCT	284/568 (50%) breast cancer patients receiving radiotherapy Groups: 1) Intervention: 145/268 (54.1%) 2) Control: 139/300 (46.4%) (no patient characteristics described)	*Intervention:* Psychosocial screening instrument - Mailed - Home - 2 times (at 3 and 12 months follow-up) *Control:* Usual care	1. SIPP 2. HADS 3. GHQ-12 4. EORTC-QLQ-C30 5. VAS
Dean et al. (48), 2016	To determine the utility of the BREAST-Q as PROM in routine cancer care	Prospective cohort study	343 breast cancer patients Characteristics: - Median age 52 years (24-82)	Routine assessment with BREAST-Q instrument - Unspecified administration method - Clinic waiting room - Ideally 5 times	1. BREAST-Q

(Medical) professional providing feedback to PRO	Intervention duration (months)	Patient outcomes	Provider outcome	Care process/system outcomes
7 clinicians reviewed the questionnaire scores to get an overview of psychosocial issues and patient needs/ preference for psychosocial care	12	Results for entire study population (n=568): *Adherence:* >85% of patients completed the study. No difference in loss-to-follow rates between intervention and control arms. *Health outcomes:* - No significant intervention effects on prevalence and extent of psychological distress were observed on short and long terms - No significant intervention effects on HRQoL were observed on short and long terms.	-	*Other*: Significant interactions between trial arm, 3-month follow-up, and referral rate were found: anxiety symptoms (β =2.16 and p = 0.03), emotional functioning (β = 15.16 and p = 0.02), appetite loss (β =15.67 and p = 0.04) and financial problems (β =11.39 and p=0.01). These interactions imply that early referral might affect short-term HRQoL.
- Nurses who scored the questionnaire and transferred the scores to the database - Clinic clerks entered questionnaire data	24 (range 1-58)	*Adherence:* - 219/219 (100%) patients completed preoperative PROM prior to their first reconstructive procedure - 79/219 (36.1%) patients completed the PROM after undergoing all reconstructive procedures - 68/106 (64.2%) patients completed the minimum of three BREAST-Q assessments (preoperative, postoperative ≤ 3 months and post-completion) *Health outcomes:* At baseline (screening), patients with intact breasts had significantly (p<0.001) higher scores across all BREAST-Q domains than those with mastectomy defects. *Other:* Completion of BREAST-Q by patient took approximately 10 minutes	-	*Other:* - Data entry by clinic clerks of questionnaires took 3 minutes - Nurse needed 5 minutes per questionnaire to score and transfer scores to a database

Table 1. PROMs scored and their impact on patient-, clinician- and process/system-level outcomes. (continued)

Selected article	Study objective	Study design	Breast cancer study population	PROM intervention, method, setting and frequency of administration	Administered PROM
Decker et al. (41), 2009	To develop and test an automated voice response system for monitoring oral chemotherapy adherence and symptoms	Cohort study	24/30 (80%) breast cancer patients receiving oral chemotherapy Characteristics per group: *1) Adherence group (n=23, 77%):* - Breast cancer patients 74% - Age >71 years: 30.4% / <70 years: 69.6% - Female 91.3% - Caucasian 95.7% - College degree or higher 34.8% *2) Non-adherence group (n=7, 23%):* - Breast cancer patients 100% -Age <70 years: 100% - Female 100% - Caucasian 71.4% - College degree or higher 42.3%	AVR system and self-help guide plus nursing intervention (for symptom management strategy) to monitor symptoms and oral chemotherapy adherence - Telephone (automated system) - Home - 8 times (weekly)	1. Symptom Experience Inventory 2. CESD-20 3. SF-12 4. Unspecified patient satisfaction questionnaire

(Medical) professional providing feedback to PRO	Intervention duration (months)	Patient outcomes	Provider outcome	Care process/system outcomes
Nurses would call patients when the AVR system indicated non-adherence and/ or symptom severity (≥ 4) for 3 consecutive weeks.	2.5	*Symptoms:* Difference in average sum of symptom severity before and after AVR intervention was a non-significant decrease of 4.35 (p=0.21). *Health outcomes:* - No significant differences in SF-12 items were observed between adherent and non-adherent groups. - Patients in the adherent group had a lower CESD-20 scores than patients in the non-adherent groups (8.67 vs. 11) *Acceptability:* 60% of patients felt the intervention was helpful, 30% felt that it was both burdensome and helpful and in 10% not helpful. *Satisfaction:* 17/17 (100%) patients that completed the questionnaire were either very satisfied or satisfied with the AVR system for monitoring symptoms. *Other:* 7/30 (23%) patients had confirmed nonadherence of chemotherapy	*Other:* Nurse interventions were especially indicated for fatigue and pain, the most commonly occurring symptoms with severity ≥4 for 3 consecutive weeks	*Hospital visits:* 4/30 (13%) patients had were admitted once to the hospital. 8/30 (27%) patients had primary care visits *Other*: out-of-pocket expenses for oral chemotherapy agents was not significantly different between the adherent and the non-adherent group.

Table 1. PROMs scored and their impact on patient-, clinician- and process/system-level outcomes. (continued)

Selected article	Study objective	Study design	Breast cancer study population	PROM intervention, method, setting and frequency of administration	Administered PROM
Egbring et al. (20), 2016	To determine the impact of a mobile app on patient-reported daily functional activity between supervised and unsupervised breast cancer patients	RCT (3-arm)	139 breast cancer patients receiving chemotherapy Characteristics per group: 1) *App use without physician review (unsupervised) (n=46):* - Mean age 50 years (± SD 10) - Female 100% - Metastatic 0% 2) *App use with physician review (supervised) (n=49):* - Mean age 53 years (± SD 12) - Female 100% - Metastatic 0% 3) *Control group (n=44):* - Mean age 56 years (± SD 15) - Female 100% - Metastatic 0%	*Intervention 1:* Mobile app for symptom reporting without clinician review (unsupervised) *Intervention 2:* Mobile app for symptom reporting with clinician review (supervised) - Electronic (mobile app and web-based) and paper-based - Home - Daily *Control:* Usual clinician support	1. ECOG Performance Status 2. CTCAE symptom list
Fu et al. (45), 2016	To describe the development and testing of TOLF health IT system, a web-based educational and behavioural intervention	Pilot cross-sectional study	30 breast cancer patients Characteristics: - Mean age 58.6 years (± SD 11.4) - Caucasian 73.3% - College degree or higher 86.6%	"TOLF" health IT system, an educational and behavioral self-care intervention including PROMs and symptom management - Electronic (mobile and web-based)	1. BCLE-SEI 2. Perceived Ease of Use and Usefulness Questionnaire 3. Post Study System Usability Questionnaire

(Medical) professional providing feedback to PRO	Intervention duration (months)	Patient outcomes	Provider outcome	Care process/system outcomes
Clinicians reviewed reported symptom data and patient charts of only supervised patients	1.5	*Symptoms:* - Both intervention groups reported more symptoms on the mobile app than the paper-based questionnaire (supervised: 1033 vs. 656 symptoms; unsupervised 852 vs. 823 symptoms) More overall symptoms were reported by unsupervised patients vs. supervised patients (4808 vs. 4463 symptoms) *Health outcomes:* - Initially, all groups had a decline in functional activity scores from the 1st to the 2nd visit. Only supervised patients reported improvement of functional activity from the 2nd to 3rd visit. - Overall, supervised patients had a stable functional activity over from the 1st to the 2nd (median 90.85 to median 84.76, p=0.72) *Satisfaction*: All supervised patients over time were satisfied with medical care	-	*Communication:* Less patients in the supervised group had concentration problems during clinic visits than the other groups, all supervised patients felt they were taken seriously
-	3	*Acceptability:* 27/30 (90%) patients didn't have major usability problems with TOLF *Symptoms:* Patients reported significantly (p=0.022) less pain, tenderness, aching, soreness, and lymphedema at 12 weeks post-intervention compared to baseline	-	-

Table 1. PROMs scored and their impact on patient-, clinician- and process/system-level outcomes. (continued)

Selected article	Study objective	Study design	Breast cancer study population	PROM intervention, method, setting and frequency of administration	Administered PROM
Girgis et al.(26), 2009	To evaluate the effect of supportive care models on anxiety, depression, physical/ emotional functioning and unmet care needs	RCT	174/356 (49%) breast cancer patients Characteristics per group: *1) CATI with an oncologist/ general practitioner intervention:* - Breast cancer patients 33% - Mean age 58.3 years (37-75) - Female 72.3 % - College degree or higher 39.5% *2) CATI with telephone caseworker:* - Breast cancer patients 34% - Mean age 57.8 years (33-75) - Female 72.5 % - College degree or higher 31.7% *3) Controls* - Breast cancer patients 33% - Mean age 57.4 years (28-75) - Female 71.8% - College degree or higher 37.6%	"Supportive care model" including CATI with a telephone caseworker (intervention #1) or an oncologist/ general practitioner (intervention #2) - Telephone - Home - 3 times (baseline, at 3- and 6-month intervals) *Control*: Usual care	1. HADS-14 2. EORTC-QLQ-C30 3. SCNS-SF 4. Needs Assessment for Advanced Cancer Patient Questionnaire

(Medical) professional providing feedback to PRO	Intervention duration (months)	Patient outcomes	Provider outcome	Care process/system outcomes
- Clinicians received feedback reports from CATI's for discussion at following clinic visits - Nurses as telephone caseworkers	6	*Symptoms:* - No significant differences in prevalence of severe anxiety and depression between intervention and control groups. - No overall intervention effect over time on anxiety and depression was observed between groups. Within the telephone caseworker group, there was a significant (p=0.01) decrease in elevated depression prevalence over time. *Health outcomes:* - Physical functioning was significantly (p=0.01) improved for patients in the telephone caseworker group. - No significant differences in QoL were observed between groups. QoL scores improved over time within groups, but there was no significant (p=0.88) overall intervention effect on QoL over time. - No significant differences were observed between groups in emotional, cognitive, or social functioning *Other:* - A trend towards decreased unmet supportive care needs was observed in the telephone caseworker group at 6 months (p=0.07). - No significant differences were seen in unmet needs between groups.	*Compliance:* Response to CATI feedback reports was significantly higher in the telephone caseworker group vs. oncologist/ general practitioner group (99.7% vs. 47.7%, p<0.0001)	*Referrals:* Referrals were significantly (p<0.0001) higher in the telephone caseworker group than the oncologist/ general practitioner group *Communication:* Patients who did CATI's with telephone caseworkers were significantly (p=0.0005) more inclined to strongly agree that study participation improved patient-doctor communication

Table 1. PROMs scored and their impact on patient-, clinician- and process/system-level outcomes. (continued)

Selected article	Study objective	Study design	Breast cancer study population	PROM intervention, method, setting and frequency of administration	Administered PROM
Graf et al. (27), 2016	To identify variables that influence willingness of breast cancer patients to use electronic PROMs	Cross-sectional study	96 breast cancer patients Characteristics (n=96): - Median age 56.68 years (± SD 12.38) - Metastatic 68%	Three-part survey concerning SES, HRQoL, and attitude towards electronic PROMs - Paper-based - Once	1. EORTC-C30 2. EQ-5D-5L/ EQ-VAS 3. Validated partial questionnaires including modules of KPF-BK
Hahn et al. (37), 2004	To describe the use and testing of a multimedia program for QoL assessment in cancer patients withlow and high levels of literacy	Intervention study	50/126 (39.7%) breast cancer patients Characteristics (n=126): - Mean age 50.9 years (± SD 13.7) - Female 69.8% - Caucasian 29.4% - College degree or higher 60.3%	"Talking Touchscreen", a multimedia program - Electronic (tablet) - Once	1. FACT-G 2. SF-36 3. SGUQ
Holch et al. (21), 2017	To describe the development of eRAPID, a system for patient-report and online adverse event management during cancer treatment	Qualitative study	2/13 (15.4%) breast cancer patients Characteristics (n=13): - Mean age 53 years (35-69) - College degree or higher 84.6% 9 patient advocates from PRO group	"eRAPID", a system with an integrated web application interface and an online questionnaire builder (QTool) - Electronic (web-based)	1. PRAE, with responses being allocated to scores corresponding with the CTCAE severity grade and UKONS

(Medical) professional providing feedback to PRO	Intervention duration (months)	Patient outcomes	Provider outcome	Care process/system outcomes
-	-	*Health outcomes:* Median EQ-VAS 64.67 (± SD 18.15), median EORTC-C30 56.16 (± SD 23.56), overall QoL 58 (± SD 23.50). *Acceptability:* - 54% of patients welcomed electronic PROs - 47% of patients thought it would have a positive impact on care. *Other:* Scores in computer skills differed; 35% had advanced computer skills, 34% used tablets	-	-
-	-	*Adherence:* Individual item response was nearly 100%; *Acceptability:* - 95.2% reported that the touch-screen was easy-very easy to use, > 80% found the assessment not too long - 64.4% preferred using the touchscreen rather than having an interviewer ask the question (P=0.172) - 14.1% of patients would not be willing to do the survey each time when visiting the doctor	-	*Other:* Average PROM completion time differed significantly for low and high literacy patients (33 vs. 28 minutes, p=0.041)
19 clinicians receive email alerts when severe symptoms are reported, and can respond to alerts by viewing reports in the EHR.	-	*Adherence:* Patient compliance is monitored by tracking website visits and questionnaire completions. Adherence was encouraged by the system through weekly generated reminders (email/ text message) *Other:* Patients can securely report AEs online from home	-	*Other:* - Automated tailored AE management advice for patients was generated by the system (from clinical algorithms)

Table 1. PROMs scored and their impact on patient-, clinician- and process/system-level outcomes. (continued)

Selected article	Study objective	Study design	Breast cancer study population	PROM intervention, method, setting and frequency of administration	Administered PROM
Javid et al. (46), 2016	To assess breast cancer patients' and clinicians' perspective on measurement tools, timing and method of capturing PRO data	Qualitative study	15 postmastectomy patients participated in focus groups or one-on-one interviews Characteristics: - Caucasian 85% - College degree or higher 69% 25 surgeons completed the prioritization questionnaire and participated in a web conference A Stakeholder Advisory Panel (12 clinicians and 5 patients) reviewed input from patients and clinicians about breast surgery PRO collection.	Intervention: - - Other (focus groups) - Consenting patients received mailed prioritization questionnaires and surgeons received online surveys about PRO domains	1. Prioritization questionnaires about PRO domains across key time periods 2. Focus groups and 1-on-1 interviews, or web conference
Judson et al. (35), 2013	To determine long-term patient adherence rate with self-reporting of common symptomatic chemotherapy-related toxicities	Feasibility study within larger (3-arm) RCT	72/286 (25%) breast cancer patients receiving chemotherapy Characteristics (n=286): - Mean age 58 years (30-85) - Female 64% - Caucasian 88% - College degree or higher 85%	"STAR", a web-based interface for symptomatic toxicity reporting - Electronic (web-based) - Home	1. CTCAE 3. EQ-5D-5L 4. Performance status
Kelleher et al. (33), 2016	To determine how PROs of self-efficacy for selected symptoms were associated with symptom severity, and to examine differences in PROM administration	Observational study	65/178 (36.5%) breast cancer patients Characteristics (n=65): - Mean age 54.6 years - Caucasian 78% - Metastasis 60%	Multiple PROMs - Electronic (tablet) and paper-based - Clinic waiting room - Once	1. Arthritis Self-Efficacy Scale (modified version) 2. Chronic Pain Self-Efficacy Scale 3. MDASI ("pain" item) 4. FACT-G 5. Electronic PRO-Satisfaction

(Medical) professional providing feedback to PRO	Intervention duration (months)	Patient outcomes	Provider outcome	Care process/system outcomes
-	12	*Health outcomes:* - HRQoL (including concerns about treatment, treatment complications, treatment decision satisfaction, impact on family/friends) was consistently ranked the highest domain, while sexual function was the lowest. - Treatment-decision-making and physical function were ranked highly preoperative and short-term postoperative. - Emotional wellbeing subdomains (fear of recurrence and impact on family and career) was prioritized highly in long-term postoperative period.	*Other:* - HRQoL domain (concerns about treatment, complications and decision satisfaction/regret) was prioritized highly in the preoperative and short-term postoperative period on family and friends, fear of recurrences was deemed most important in the long-term postoperative period. - In the late-term postoperative phase, providers also deemed emotional wellbeing (coping issues, distress feelings, personal relationships, support groups) a priority.	*Communication:* Communication was prioritized highly during the preoperative and short-term postoperative period *Other*: Care process themes that came up during discussions were scheduling clinic appointments, team-based care, transition of care, nurse navigation, and continuity of care.
- Clinician received printed patients' STAR reports to review at each clinic visit - Nurse received triggered automated email alerts in case of high grade or worsening symptoms	8.5 months (median)	*Adherence:* - In total, patients logged into STAR 8690 times, of which 71% from home (between visits) and 29% at the clinic - Average monthly compliance 83%, while average weekly compliance was 62% - Self-reported reasons for non-adherence were: 73% of patients said they forgot, were too busy, or did not feel like it, 11% experienced technical and illness-related barriers - Older age at baseline, Caucasian and higher education level were significantly associated with higher adherence	-	-
-	-	*Health outcomes:* Self-efficacy for functioning, pain and other symptoms was associated with their reported outcomes of pain, FACT-G sub-scales and MDASI scales. *Acceptability*: Patients felt the tablet computer was easy to read, to use, to navigate, and comfortable to use *Satisfaction*: Mean satisfaction score was 19.9 (± SD 1.55), out of a possible score of 20	-	*Other:* No differences in patients' responses were found between methods of PROM administration (electronic vs. paper-based)

Table 1. PROMs scored and their impact on patient-, clinician- and process/system-level outcomes. (continued)

Selected article	Study objective	Study design	Breast cancer study population	PROM intervention, method, setting and frequency of administration	Administered PROM
Kim et al. (44), 2016	To determine if a mobile mental-health tracker can potentially indicate depression, and to examine adherence on accuracy in depression screening	Cohort study	78 breast cancer patients Characteristics: - Mean age 44.35 years (± SD 7.01) - College degree or higher 52.6%	"Pit-a-Pat", a smartphone app for collecting PROs -Telephone (mobile app) - Daily (mental health) and biweekly (PHQ-9)	1. Mental health items: anxiety, mood and sleep satisfaction 2. PHQ-9
Knoerl et al. (19), 2017	To pilot test and determine the feasibility, acceptability, usability and satisfaction of the "Carevive Planning System" among breast cancer patients and clinicians	Single arm, pre-/post-test prospective cohort study	25 breast cancer patients planned for or receiving neurotoxic chemotherapy Characteristics (n=25): - Female 100% - Caucasian 80% - Metastatic 36% - College degree 88%	"CPS", a web-based platform for collecting patient-reported CIPN symptoms to generate a customized symptom care plan - Electronic (web-based platform) for symptoms - Clinic waiting room - 3 times (before clinic visit)	1. PRO-CTCAE 2. EORTC-QLQ-CIPN20 3. System Usability Scale 4. Adapted Acceptability E-scale

(Medical) professional providing feedback to PRO	Intervention duration (months)	Patient outcomes	Provider outcome	Care process/system outcomes
-	11	*Adherence:* - Lower adherence (n=58) group reported 208/497 (42%) observations, while the higher adherence (n=20) group reported 289/497 (58%) observations (p<0.001) - Self-report adherence was associated with an increase in the accuracy of depression screening, with all AUC's of the higher adherence group being statistically higher (p<0.01) than those of the lower adherence group *Symptoms:* Depression screening performance of mobile mental-health trackers is comparable to the traditional method, administration of a PHQ-9 test, in the clinical setting	-	Other: Screening accuracy with all three approaches (ratio, average, and frequency measurement of daily mental-health ratings) was statistically higher (p<0.05) for patients in the higher adherence group than the lower adherence group
Providers (n=6) - 5 nurse practitioner - 1 physician assistant Characteristics: - Female 100% - College degree or higher 100% Providers reviewed generated personalized care plans based on patients' response to PROMs and could edit them to further tailor treatment options and referrals	Unspecified; 3 clinic visits	*Adherence:* -25/25 (100%) patients created a CPS account - All patients completed 74/75 (98.6%) questionnaires over 3 clinic visits *Acceptability:* - Easy to use 4.90 (± SD 0.29) (range 4-5) - Helpfulness of CPS 4.08 (± SD 0.93) (range 2-5) - Understandability of questions 4.75 (± SD 0.53) (range 3-5) - Acceptability of time required for PROM completion 4.58 (± SD 0.58) (range 3-5) - Overall acceptability ranged from 4.08 (± SD 0.93) to 4.90 (± SD 0.29) (range 1-5) (n=24) *Satisfaction*: - Enjoyment of CPS 4.19 (± SD 0.73) (range 3-5) - Overall satisfaction 4.56 (± SD 0.65) (range 3-5) *Other:* - Usability score 85.00 (± SD 11.54) (range 62-100)	*Adherence:* - 6/6 (100%) providers created a CPS account - 61/75 (81.3%) patient care plans were reviewed - 20% of providers reviewed care plans consistently with patients *Acceptability:* - Ability of CPS to identify appropriate issues of concern 3.20 (± SD 0.84) (range 2-4) - Ability to identify symptoms or areas of need 2.40 (± SD 1.14) (range 1-4) - Overall acceptability ranged from 1.60 (± SD 0.89) to 3.20 (± SD 0.84) (range 1-5) (n=5) *Other:* - Usability score 33.50 (± SD 17.19) (range 12.50-57.50) - 100% of CIPN care plan recommendations were accepted by providers - 35% of tasks associated with treatment recommendations were accepted at visit 1 and 53% of tasks were accepted at visit 3	*Communication:* - Helpfulness of CPS in guiding clinical conversations with patients 1.80 ± SD 1.10 (1-3) - Helpfulness in patient-provider communication improvement 1.60 ± SD 0.89 (1-3)

Table 1. PROMs scored and their impact on patient-, clinician- and process/system-level outcomes. (continued)

Selected article	Study objective	Study design	Breast cancer study population	PROM intervention, method, setting and frequency of administration	Administered PROM
Knoerl et al. (22), 2017	To determine if CPS can encourage patient activation in breast cancer patients for symptomatic polyneuropathy management	Single arm, pre-/post-test prospective cohort study	75 breast cancer patients planned for or receiving neurotoxic chemotherapy Characteristics: - Mean age 51.93 years (25-82) - Female 100% - Caucasian 88% - Metastatic 13.3%	"CPS", a web-based platform for collecting patient-reported CIPN symptoms to generate a customized care plan - Electronic (tablet computer) and paper-based (only PAM) - Clinic waiting room - 3 clinic visits NB. also a pencil/paper version of the PAM at the first and third visit	1. PRO-CTCAE (visit 1-3) 2. QLQ-CIPN20 (visit 1-3) 3. PAM (visit 1 and 3) 4. System Usability Scale (visit 3) 5. Adapted Acceptability E-scale (visit 3)

(Medical) professional providing feedback to PRO	Intervention duration (months)	Patient outcomes	Provider outcome	Care process/system outcomes
Providers (n=6) - 5 nurse practitioners - 1 physician assistant Characteristics: - Female 100% - College degree or higher 100%	Unspecified; 3 clinic visits	*Symptoms:* - Mean QLQ-CIPN20 sensory and motor severity scores remained low across 3 study visits, ranging from 6.28 to 17.68 (scale 0–100) - Mean PRO-CTCAE numbness and tingling severity and interference scores also remained low, ranging from 0.32 to 1.07 (range 0–4) *Acceptability*: - Easy to use 4.49 (± SD 0.94) (range 1-5) *Other*: - 85% of patients possessed high (level III-IV) patient activation at baseline. PAM scores improved significantly (p=0.02) from baseline to final clinic visit from 67.15 (± SD 13.5) to 69.29 (SD ± 16.18) - Helpfulness of CPS 3.75 (± SD 1.10) (range 1-5) - Understandability of questions 4.27 (± SD 1.0) (range 1-5) - Acceptability of time required for PROM completion 4.03 (± SD 1.14) (range 1-5) - Overall acceptability ranged from 3.63 (± SD 1.18) to 4.49 (± SD 0.94) (range 1-5) *Satisfaction:* -Enjoyment of CPS 3.63 (± SD 1.18) (range1-5) - Overall satisfaction 4.11 (± SD 1.04) (range 1-5) *Other:* - Usability was highly rated with a mean score of 76.18 (± SD 21.93) (range 0-100)	*Acceptability*: Providers reported several barriers to reviewing the care plans with the patients: - lack of time to review - not finding CIPN management recommendations useful - difficulty logging into Carevive website due to password and/or software operational errors	*Other:* 60/67 (89.6%) patients received at least 1 care plan, while only 37/67 (55.2%) patients received all 3 care plans during the study period

Table 1. PROMs scored and their impact on patient-, clinician- and process/system-level outcomes. (continued)

Selected article	Study objective	Study design	Breast cancer study population	PROM intervention, method, setting and frequency of administration	Administered PROM
Kuijpers et al. (47), 2015	To assess cancer survivors' and care providers' expectations of potential attributes of an interactive portal including PROs with feedback	Qualitative study	21/34 (61.8%) breast cancer survivors Characteristics: *Breast cancer survivors (n=21):* - Mean age 52.9 years (range 27-76) - Female 100% - College degree or higher 33% *Health professionals (n=31):* - Mean age 45.5 years (range 24-62) - Medical n=7 - Paramedical n=10 - Psychosocial n=14	Interactive portal including PROs with feedback, among others. - Other (focus groups) - Once	Focus group discussion on expectations' concerning an interactive portal
Leung et al. (38), 2016	To assess the feasibility of PROMIS CAT for fatigue and sleep-disturbance items	Cohort study	60/336 (17.9%) breast cancer patients Characteristics (n=336): - Mean age 57.44 years (± SD 15.71) - Female 54.8% - Caucasian 74.6% - Metastatic 30%	PROMIS CAT of cancer-related fatigue and other sleep-disturbance items - Electronic (tablet) - During clinic visits	1. PROMIS CAT 3 domain item banks 2. FACIT-F 3. ISI 4. Acceptability survey
Min et al. (36), 2014	To determine the feasibility of a sleep-disturbance data collection app	Cohort study	38 Korean breast cancer patients receiving neoadjuvant chemotherapy 30 patients completed the study Characteristics (n=30): - Mean age 45 years (36-65) - Lymph node metastasis 77% - College degree or higher 47%	"Pit-a-Pat", a smartphone app for collecting PROs - Electronic (mobile app) - 30-minute interview at admission - Daily	30-minute interview (app use) + 1. EQ5D-3L 2. BDI 3. Sleep disturbance symptoms 4. Acute symptomatic chemotherapy-related toxicity 5. Medication 'diary'

(Medical) professional providing feedback to PRO	Intervention duration (months)	Patient outcomes	Provider outcome	Care process/system outcomes
-	-	*Other:* - Patients indicated that the information from completing PROMs could increase the knowledge about their health status - Patients had doubts about care providers' incentives to review PROs due to time constraints	*Other:* - Care providers expected an increase in knowledge of patients' health status - Care providers had their doubts about who the responsibility, for PRO review and feedback, would fall onto	*Communication:* - Both patients and care providers expected that the patient-provider communication would improve through PRO feedback by providers (and thus better preparedness for appointment)
-	-	*Acceptability:* - >98% indicated that symptom screening was not burdensome - 65% were willing to complete survey at every visit *Other:* - 67% thought PRO results were useful for clinicians	-	*Other*: - Average number of items completed of ISI was 5.36 (±SD 2.16) for sleep-disturbance, and 4.51 (± SD 1.59) for FACIT-F (score range 0-52) for fatigue - Overall time 15-20 minutes per patient to complete all measures
Clinicians could review the data in the EHR as the database was integrated in it.	3	*Adherence:* - Overall compliance rate 45% - Longitudinal compliance curve decreased from 100% (day 1) to 50% (day 34) to 13.3% (day 90) - Cumulative compliance rate decreased steadily from 50% (day 70) to 45% (day 90) - Unemployed women were associated with a higher rate of compliance (p=.03) - Rate of self-reporting in the jobless subgroup was significantly higher compared to employed patients (55% ± SD 25.7 vs. 30.7% ± 19.2, p=.006) *Acceptability:* Reasons that patients gave for not self-reporting were that the app did not work (38% of patients), forgetting to (29%), finding the app not useful (21%), feeling too sick to self-report (8%), not feeling like it (4%)	-	The rate self-reporting was higher in the subgroup with a 1-day lag time (self-report immediately after enrollment) than in patients that had a lag-time of ≥ 2 days (51.6% ± SD 24 vs. 29.6% ± 25.3, p=0.03)

Table 1. PROMs scored and their impact on patient-, clinician- and process/system-level outcomes. (continued)

Selected article	Study objective	Study design	Breast cancer study population	PROM intervention, method, setting and frequency of administration	Administered PROM
Mooney et al. (42), 2014	To determine whether timely emailed alert reports would encourage patient-provider communication, enhance unrelieved symptom treatment, and thus lead to better symptom outcomes	RCT	99/250 (39.6%) breast cancer patients receiving chemotherapy Characteristics per group: *1) Intervention (n=129):* - Breast cancer patients n=63 (48.8%) - Mean age 55.2 years (21-86) - Female 82.2% - Caucasian 89.6% *2) Control (n=121):* - Breast cancer patients n=36 (29.8%) - Mean age 55.8 years (19-81) - Female 69.4% - Caucasian 93.2%	*Intervention:* Automated IT-based chemotherapy-related symptom reporting system, with symptom alerts (if moderate-to-severe levels) being sent to care providers - Telephone - Home - Daily *Control:* Equivalent contact duration with automated IT-system without generated symptom alerts	10 symptoms (pain, fatigue, nausea/ vomiting, fever, insomnia, anxiety, depression, mouth sores, diarrhea, and constipation)

(Medical) professional providing feedback to PRO	Intervention duration (months)	Patient outcomes	Provider outcome	Care process/system outcomes
An oncology physician and nurse received automated alerts of unrelieved symptoms	1.5	*Adherence:* - Overall daily call adherence was 65% of expected days - No difference in average days called between intervention and control groups (28.72 ± 15.62 days vs. 29.69 ± 16.78 days, p=0.66) *Symptoms:* - Most frequent moderate-severe symptoms in both groups were fatigue (89.2% of patients), trouble sleeping (74.9%) and pain (70.4%). - Severe levels were significantly (p<0.001) more common in the treatment group - Less talking about symptoms at patient-initiated contacts in intervention group (62 % vs. 73%, P=0.19) *Health outcomes:* - No significant difference between symptom severity or distress scores between arms (mean difference=0.06, p=0.58) *Acceptability:* - 94% quiet or very easy to use - 91% call length acceptable - 61% very much or quite helpful in keep track of their symptoms - 52% system helped them feel like participating in their care - 79% quiet or very confident the system notified their oncology providers of their symptoms - 25% agreed the system helped their doctor/nurse decrease their symptoms *Satisfaction*: - 77% quite or very satisfied with using the system	*Acceptability:* - 100% found the alert reports to be timely - 89% found the system easy to interpret - 82% found it useful - 0% reported technical difficulties *Satisfaction:* - 11/13 (85%) providers were somewhat to very satisfied with the system	*Hospital visits:* - No difference between intervention and control group in number of times an alert was generated (p=0.80) - No difference in frequency of patient- and/or provider-initiated unscheduled contacts (p=0.73) - No difference in patient- vs. provider-initiated unscheduled contacts (p=0.14) - More provider-initiated contacts in intervention group than the control group (18 vs. 10 contacts)

Table 1. PROMs scored and their impact on patient-, clinician- and process/system-level outcomes. (continued)

Selected article	Study objective	Study design	Breast cancer study population	PROM intervention, method, setting and frequency of administration	Administered PROM
Mooney et al. (43), 2017	To determine the efficacy of an automated symptom management system in reducing chemotherapy side-effects as vs. enhanced usual care	RCT	156/358 (43.6%) breast cancer patients, starting chemotherapy with at least 3 planned cycles Characteristics per group (n=358) *1) Intervention (n=180):* - Mean age 54.77 years (±12.17) - Female 75% - Caucasian 80% - College degree or higher 69% *2) Controls (n=178):* - Mean age 56.79 years (± 10.54) - Female 76% - Caucasian 86% - College degree or higher 69%	*Intervention:* "Symptom Care at Home" system, a combined intervention with daily symptom reporting, self-management coaching and nurse-practitioner follow-up - Telephone - Home - Daily *Control:* Enhanced usual care with daily symptom reporting without review by care providers	11 symptoms (fatigue, insomnia, nausea/ vomiting, pain, numbness or tingling, depression, anxiety, distress over appearance, diarrhea, mouth sore, and trouble thinking/concentrating)

(Medical) professional providing feedback to PRO	Intervention duration (months)	Patient outcomes	Provider outcome	Care process/system outcomes
Nurse practitioners responded to alerts indicating symptom severity exceeding present thresholds by calling intervention patients to provide guideline-based symptom care	6 months or till chemo-therapy course completion, which ever came first	*Adherence*: - Daily call adherence was high and not significantly (p=0.80) different between intervention and control arms - 12% voluntary withdrawal was recorded but the difference between groups was not significant; non-compliant patients (SCH 25 patients; UC 27 patients) were slightly older (58.45 vs. 55.08 years, p=0.02) *Symptoms:* - Most prevalent symptoms with moderate-severe levels were fatigue (reported by 86% of patients), pain (80% of patients), sleep troubles (78% of patients) and nausea (60% of patients) - 10/11 reported symptoms were significantly lower for intervention patients (p<0.001 - 0.025) than control patients *Health outcomes:* - Post-baseline symptom burden reduction (treatment impact) for intervention patients was 3.59 severity points (p < 0.001), roughly 43% of the control group - Intervention patients had 3 times fewer (67% less) severe days (p<0.001) and 1.65 times fewer (39% less) moderate days (p=0.001) than control patients; intervention patients had 39% more mild days (p=0.016) and 25% more 'no symptom' days (p=0.006) than control patients *Other:* Intervention patients reported alerting symptoms only on 19% of calls, while control patients alerted on 37% of calls	-	-

Table 1. PROMs scored and their impact on patient-, clinician- and process/system-level outcomes. (continued)

Selected article	Study objective	Study design	Breast cancer study population	PROM intervention, method, setting and frequency of administration	Administered PROM
Ruland et al. (50), 2013	To report patients' use of WebChoice, a multi-component application for disease management in cancer patients	Cross-sectional study (sub-study of previously conducted RCT)	56/103 (54%) breast cancer patients, who had access to WebChoice (intervention) and had logged on at least 2 times Characteristics: - Mean age 51 years (± SD 7.1) - Metastatic 17.7% - College degree or higher 71%	"WebChoice", a multi-component interactive e-Health application including self-monitoring symptoms/health problems, individualized information/advice for disease management, email communication with nurses, and a patient discussion forum. -Electronic (web-based)	1. 3 sections of WebChoice: self-management intervention, discussion forum, and personal email messages to a nurse. 2. Diary (personal notes) 2. Usefulness questionnaire (scale 1-9 points)

(Medical) professional providing feedback to PRO	Intervention duration (months)	Patient outcomes	Provider outcome	Care process/system outcomes
Nurses monitored the accuracy of posts in the patient discussion forum, and also posted helpful advice	6	*Adherence:* - System was used 4153 times (median=13.5 times, range 2-892 log-ons) - 216 personal messages to nurse (median=1 time) - Discussion forum most used of WebChoice with 374 posts by breast cancer patients, which was significantly (p=0.01) higher compared to 132 posts by prostate cancer patients - 291 vs. 209 (p=0.54) self-assessments were made by breast cancer and prostate cancer patients, respectively. - 93/103 (90%) of usefulness questionnaires were returned *Acceptability:* - Most useful section of WebChoice, considered by patients, was receiving an answer from the nurse (score 7.6, range 3-9) - Most common reasons for using each section were: “get help with a problem” (75% of breast cancer patients), “get information about a problem”(77%), compare experiences with other patients (81%) and “prepare communication with health personnel” (29%)	-	-

Table 1. PROMs scored and their impact on patient-, clinician- and process/system-level outcomes. (continued)

Selected article	Study objective	Study design	Breast cancer study population	PROM intervention, method, setting and frequency of administration	Administered PROM
Snyder et al. (28), 2010	To identify the topics that patients and clinicians report as being relevant in a PROM for use in clinical practice	Cross-sectional study	21/41 (51.2%) breast cancer patients Characteristics (n=41): - Mean age 63.8 years (± SD 12.56) - Female 51.12% - Caucasian 68.3% - College degree or higher 65.9%	Semi-structured interviews with patients and clinicians regarding prioritizing issues/ domains for discussion during appointments - Telephone - Home - Once	-

(Medical) professional providing feedback to PRO	Intervention duration (months)	Patient outcomes	Provider outcome	Care process/system outcomes
6/15 (40%) breast cancer clinicians (medical and radiation oncologists)	-	*Acceptability:* - 67% of breast cancer patients preferred questions about whether it is an issue they want to have addressed - Slight preference for a categorical assessment and reporting of results *Other:* - 2 domains discussed by >70% of breast cancer patients were pain and information needs - 7 domains discussed by <50% of all patients (n=41): cognitive function, social function, sexual function, nausea/vomiting, constipation, emotional function, and dyspnea - >70% of breast cancer patients reported physical function, role function, pain, fatigue and information needs, to be relevant for inclusion in a PROM	*Acceptability:* - 83% of breast cancer clinicians (n=6) preferred questions about how bothered the patient is *Other:* - 9 domains discussed by >70% of clinicians (n=15): physical function, nausea/ vomiting, role function, diarrhea, information needs, pain, fatigue, constipation, and sexual function. - 3 domains discussed by <50% of clinicians: cognitive function, social function, and sleep problems. - >70% of clinicians reported 6 domains (information needs, cognitive function, emotional function, role function, sexual function, fatigue, fatigue) to be relevant for inclusion in a questionnaire	-

Table 1. PROMs scored and their impact on patient-, clinician- and process/system-level outcomes. (continued)

Selected article	Study objective	Study design	Breast cancer study population	PROM intervention, method, setting and frequency of administration	Administered PROM
Snyder et al. (11), 2013	To evaluate PatientViewpoint's use, usefulness, & acceptability to patients and clinicians	Prospective cohort study	34/47 (72%) breast cancer patients undergoing treatment (47/52 patients completed the study) Characteristics (n=37): - Mean age 57 years (range 28-80) - Caucasian 79% - Metastatic 52% - College degree or higher 73%	"PatientViewpoint", a webtool for administering PRO surveys at intervals and to generate those in graphical score reports - Electronic (web-based; integrated in EHR) - Home or clinic - Every 2 weeks (regardless of visit frequency)	1. 6 PROMIS short forms (physical function, pain interference, satisfaction with social roles, fatigue, anxiety, & depression) 2. EORTC-QLQ-BR23 3. 15-item feedback form on PatientViewPoint

(Medical) professional providing feedback to PRO	Intervention duration (months)	Patient outcomes	Provider outcome	Care process/system outcomes
Clinicians could choose how to review PROM results: in paper report, on the website, in the EHR, or not at all.	-	*Adherence:* - 87% of questionnaires was completed offsite - 3/47 (60%) patients only completed PROMs in the clinic; 28/47 (60%) patients completed PROMs only at offset - 84% no missing items on PROMIS questionnaires when completed at home vs. 67% at the clinic *Symptoms:* Among breast cancer patients, most prevalent domains were systemic therapy including symptoms and/or side effects (53%), and sexual function (50%) *Acceptability:* - Patients were generally positive with >90% indicating "strong" usability - 46% reported clinicians used the reported information - 39% reported care quality improved *Satisfaction:* - Patients reported the webtool to be well organized and laid-out, and that it allowed opportunities to discuss issues that would otherwise have not been - Patients also mentioned that they questioned whether their care providers reviewed the PROM results	*Clinical decision-making:* - Most likely to discuss systematic therapy (89%), pain interference (80%), fatigue (80%), and sexual function (6%) - Most common actions taken in response to identified issues were providing information and/or advice *Acceptability:* - PROM results of 24/47 (51%) patients were reviewed by clinicians in the HER, while in 17% of patients the results were reviewed on the paper report. Results of 15/47 (32%) patients were reviewed in PatientViewpoint or not at all - On 10/47 (21%) feedback forms, clinicians reported not using the PRO information. Clinicians reported the following reasons for questionnaire use: it provided additional information (51%), it confirmed knowledge of patients' problems (49%), it provided an overall assessment (43%), it identified issues for discussion (38%), it contributed to patient management (30%) - On 27/47 (58%) feedback forms, clinicians reported that the questionnaire assisted them in identifying areas of concern, and that it improved quality of care (54%) *Acceptability:* - Clinicians strongly preferred graphical PROM results in PatientViewPoint but preferred plain-text score reports in the HER - More explanation about PRO item content and score meaning was desired	*Other:* - PROMIS completion: median 6 minutes (2-12) - EORTC-QLQ-BR23 completion: median 3 minutes (1-11)

Table 1. PROMs scored and their impact on patient-, clinician- and process/system-level outcomes. (continued)

Selected article	Study objective	Study design	Breast cancer study population	PROM intervention, method, setting and frequency of administration	Administered PROM
Stover et al. (23), 2015	To develop a web-based PRO screening system through cognitive interviews with cancer patients, and to assess patients' and clinicians' acceptability and value of PRO review and feedback	2-phase qualitative study Phase 1: Cognitive interviews (9 breast cancer patients) Phase 2: Usability assessment in the clinic (10 breast cancer patients)	19/74 breast cancer patients (26%) receiving chemotherapy Characteristics (n=74): - Age ≥ 60 43% - Female 50% - Caucasian 66% - College degree or higher 38%	"Patient-Reported Symptom Monitoring" system - Electronic (web-based/ tablet) - Clinic waiting room	1. PRO-CTCAE 2. PROMIS- Global Health scale 3. 2 items written by the authors ("agenda setting" & "other unlisted symptoms")
Wheelock et al. (34), 2015	To integrate and determine the use of SIS.NET, a multi-component intervention, in the follow-up of breast cancer survivors	RCT	100 breast cancer patients (TNM stages I-III), who completed and recovered from acute treatment (surgery, chemo- and/ or radiotherapy, or experimental therapy) Characteristics per group: *1) Intervention (n=59):* - Mean age 54.78 years (± SD 8.66) - Caucasian 69.5% *2) Control (n=41)*: - Mean age 53.32 years (± SD 10.79) - Caucasian 78.1%	*Intervention:* "SIS.NET", a combined intervention with routine online health surveys, generated summary reports with highlighted concerning symptoms, review by nurse practitioners, and tailored automated referrals, and additional patient requests for interim health surveys and appointments - Electronic (web-based) - Before clinic visit - 4 times (3-month intervals) *Control:* Standard care with similar online question-naires with generated summary reports for clinician review during appointment	1. SF-36 2. PHQ-8 3. MSAS

(Medical) professional providing feedback to PRO	Intervention duration (months)	Patient outcomes	Provider outcome	Care process/system outcomes
A summarized report of most severe to least severe symptoms, was generated and given to both patients and clinicians prior to the appointment.	-	*Acceptability*: - 92% of patients found it helpful in discussing health issues - 82% wanted to review PRO results with clinicians during future appointments - 87% would recommend the system to other patients - 64% reported screening questions were helpful in discussing medical issues with provider that might have been missed otherwise - 80% chose to make an agenda for discussion during the visit - 92% were willing to answer additional questions - 82% were willing to do the survey at home *Satisfaction:* - High satisfaction with the web-based screening tool and summarized PRO report . - Patients recommended the use of the tablet computer.	*Acceptability:* - 83% of clinicians found summarized PRO report easy to interpret - 67% found it helpful for communicating with patients - 92% would recommend it to future patients - 92% found the PRO summarized report most useful for reviewing symptoms - 80% (4/5) felt that the PRO summary was (very) helpful in changing the treatment plan - 92% reported that discussing the summarized PRO report with their patient during the clinic appointment did not change the duration of the consultation	-
Nurse practitioners received notifications from SIS.NET to review available completed questionnaires	18	*Adherence:* No significant difference in proportion of questionnaires completed between intervention (average 50%) and control arms (average 62.5%) *Symptoms:* Significant difference in the number of changed or new symptoms between SIS.NET and control arm (mean 7.36 vs. mean 3.2, p=0.00445)	-	*Hospital visits:* No significant differences between intervention and control arms in number of appointments with clinicians (10.8 ± SD 8.2 vs. 9.6 ± SD 7.3, p=0.45) or number of breast cancer visits (4.2 ± SD 2.3 vs. 4.1 ± SD 1.8, p=0.78) *Other:* No significant difference in number of medical tests between SIS.NET and control arm (average 3.5 ± SD 2.2 vs. 3.8 ± SD 2.4, p=0.51)

Table 1. PROMs scored and their impact on patient-, clinician- and process/system-level outcomes. (continued)

Selected article	Study objective	Study design	Breast cancer study population	PROM intervention, method, setting and frequency of administration	Administered PROM
Wu et al. (29), 2016	To assess patients' and clinicians' perspectives on the usability of PatientViewpoint, a webtool to incorporate PROMs in clinical oncology practice	2-round quality improvement sub-study	17/42 (40.5%) breast cancer patients Characteristics (n=42): - Mean age 65 years (32-83) - Metastatic 30% - Caucasian 81% - College degree or higher 69%	"PatientViewpoint", a webtool that allows clinicians to assign PROMs to patients, that collects PROM data, links it to the EHR, and displays it in graphical reports - Electronic (web-based) - Clinic or home or elsewhere - Every 2 weeks (regardless of visit frequency)	1.EORTC-QLQ- C30 2. SCNS-SF 3. PROMIS short forms

Table 1 Legend: PRO(M) = Patient Reported Outcome (Measure); SD = Standard Deviation; QoL = Quality of Life; FACT-G = Functional Assessment of Cancer Therapy – General; FACT-B = Functional Assessment of Cancer Therapy – Breast Cancer; MDASI = MD Anderson Symptom Inventory; FACIT-F = Functional Assessment of Chronic Illness Therapy – Fatigue Scale; FACIT-Self-Efficacy Scale = Functional Assessment of Chronic Illness Therapy – Self Efficacy Scale; PCM = Patient Care Monitor; EORTC-QLQ-C30 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire of Cancer patients, 30-item; EORTC-QLQ-BR23 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire of Breast, 23-items; RCT = Randomized Controlled Trial; IVR = Interactive Voice Response; BQ-II = Barriers Questionnaire-II; ECOG = Eastern Cooperative Oncology Group, PMI = Pain Management Index; ESAS = Edmonton Symptom Assessment Scale; ER = Emergency Room; IQR = Inter-Quartile Range; HRQoL = Health-Related Quality of Life; STAR = Symptom Tracking and Reporting; CTCAE = Common Terminology Criteria for Adverse Events; EQ-5D = EuroQol 5-Dimension; ESRA-C = Electronic Self-Report Assessment-Cancer, SDS-15 = Symptom Distress Scale-15, PHQ-9 = Patient Health Questionnaire, 9-items; IPPC = Internet-based Patient-Provider Communication Service; MSAS = Memorial Symptom Assessment Scale, HADS = Hospital Anxiety and Depression Scale, CBI = Cancer Behavioral Inventory, SIPP = Dutch Screening Inventory of Psychosocial Problems, GHQ-12 = Goldberg's General Health Questionnaire-12, VAS = Visual Analogue Scale, BREAST-Q = Breast-Questionnaire, AVR = Automated Voice Response, CESD-20 = Centre for Epidemiologic Studies Depression Scale-20; SF-12 = Short Form-12; TOLF = The-Optimal-Lymph-Flow health IT system; BCLE-SEI = Breast Cancer and Lymphedema - Symptom Experience Index; CATI = Computer-Assisted Telephone Interviews; SCNS-SF = Supportive Care Needs Survey; SES = Socio-Economic Status; EQ-VAS = EuroQol-Visual Analogue Scale; KPF-BK = Kölner Patientenfragebogen für Brustkrebs; SF-36 = Short Form-36; SGUQ = Standard Gamble Utility Questionnaire; eRAPID = electronic patient self-Reporting of Adverse-events: Patient Information and aDvice; PRAE = Patient-Reported AE adaptation of the gold standard CTCAE; UKONS = United Kingdom Oncology Nursing Society; HER = Electronic Health Record; CPS = Carevive Planning System; CIPN-20 = Chemotherapy-Induced Polyneuropathy Questionnaire-20 item; PAM = Patient Activation Measure; PROMIS = Patient-Reported Outcomes Measurement Information System; CAT = Computerized Adaptive Testing; FACIT-F = Functional Assessment of Chronic Illness Therapy; ISI = Insomnia Severity Index; BDI = Beck Depression Inventory; SCH = Symptom Care at Home; UC = Usual Care; SIS.NET = System for Individualized Survivorship Care; TNM = Tumour Node Metastasis

(Medical) professional providing feedback to PRO	Intervention duration (months)	Patient outcomes	Provider outcome	Care process/system outcomes
Clinicians could review in the EHR an automatically generated graphical report of PROM data with poor or worsening outcomes highlighted	-	*Acceptability:* Strengths of the webtool: - Notifications/ reminders to complete questionnaires - Possibility of filling out questionnaires at home - Discussing issues with clinicians that they otherwise would not have - Free-text comments for additional details - Possibility of tracking scores over time Recommendations: - Sufficient reminders about survey - Tailoring questions - Additional information on PRO results including consistent score meanings - Clinicians' responsibility to review scores, discuss abnormal results, and act on them	*Acceptability:* All clinicians reported that it could be helpful Concerns: - Limited time to review PRO results if they were filled in just before the appointment - Rather face-to-face interaction than looking at graphical reports in EHR Wanted: - Email reminders - Graphical presentation is preferred above tables - Clearer and consistent score meanings for interpretation - Full integration into her - No additional login to access system	-

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SUPPLEMENTARY FILES CHAPTER 6

Supplementary S1: Search Strategy: Literature Search Terms for Embase
('breast tumour'/exp OR 'mastectomy'/exp OR (((breast* OR mamma*) NEAR/3 (cancer* OR tumour* OR tumour* OR carcino* OR neoplas* OR oncolog* OR malignan* OR resection* OR amputat*)) OR mammacarcinom* OR mastectom* OR mammectom* OR postmastectom*):ab,ti) AND ('patient-reported outcome'/de OR 'patient reported outcome measure'/de OR (('self report'/de) AND ('outcome assessment'/de OR 'quality of life'/exp OR 'quality of life assessment'/exp OR 'complication'/de OR 'symptom'/de OR 'wellbeing'/de OR 'psychological well-being'/de OR 'health status'/de)) OR (((patient* OR self) NEAR/3 (report* OR based OR centreed OR centred OR rate OR rating OR rated OR questionnaire* OR assess* OR survey* OR index OR indices OR instrument*) NEAR/6 (outcome* OR measur* OR quality-of-life OR qol OR hrqol OR hrql OR ql OR symptom* OR complication* OR psychosocial OR 'well-being' OR wellbeing OR functioning OR disabil* OR 'health status')) OR ((patientreport* OR selfreport* OR patientcent*) NEXT/2 (outcome* OR factor* OR measur*)) OR PROM OR PROMs):ab,ti) AND ('health care quality'/de OR 'quality of care'/de OR 'clinical effectiveness'/de OR 'clinical practice'/de OR 'health care'/de OR 'nursing care'/exp OR (care OR ((clinical OR nursing) NEXT/2 (effectiveness* OR practice*))):ab,ti)

Supplementary Table S2. Critical Appraisal Skills Programme (CASP) quality scoring according to the study design performed.

Author	Study design	1	2	3	4	5	6	7	8	9	10	11	12
Abernethy et al.(31), 2009	Cohort	Yes	Yes	Yes	Yes	Yes	Yes	eTablets: - 94% easy to read - 99% easy to navigate - 90% comfortable - 89% easy to respond - 75% was satisfied with PCM reporting - 88% would recommend PCM - 74% felt PCM helped to report symptoms	Can't tell	Yes	Yes	Yes	N/A
Albert et al.(25), 2002	Cohort	Yes	Yes	Yes	Yes	Yes	Yes	100% found QoL profile a usefull diagnostic tool, giving added value to both patients and doctors	Can't tell	Yes	Yes	Yes	N/A
Anderson et al.(32), 2015	RCT	Yes	Yes	Yes	No	Yes	Yes	- Pain severity: 0.6 vs 2.3 at timepoint 1, 1.2 vs 3.5 at timepoint 2. - Symptom severity: sign descrease between timepoint 1 and 2. - Symptom threshold: significant differences in ORs	P<0.01	No	Can't tell	Yes	N/A
Barbera et al.(40), 2015	Cohort	Yes	Yes	Yes	Yes	Yes	Yes	Rate was 43% lower when screening with ESAS; for each additional ESAS assessment there was a 17% decrease rate of ED visits	Can't tell	Yes	Yes	Yes	N/A
Basch et al.(24), 2016	RCT	Yes	Yes	Yes	No	Yes	Yes	Effect size of 0.37 at 6 months	P<0.001	No	Can't tell	Yes	N/A
Berry et al.(49), 2014	RCT	Yes	Yes	Yes	No	Yes	Yes	SDS-15 score: -1.21	95% CI 0.2-2.20	Yes	Can't tell	Yes	N/A
Bock et al., 2012	Cross-sectional	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes

Supplementary Table S2. Critical Appraisal Skills Programme (CASP) quality scoring according to the study design performed. (continued)

Author	Study design	1	2	3	4	5	6	7	8	9	10	11	12
Børøsund et al.(39), 2014	RCT	Yes	Yes	Yes	No	Yes	Yes	Mean difference: - Symptom distress: 0.16 - Anxiety: 0.79 - Depression: 0.79	95% CI 0.06-0.25 95%CI 0.09-1.49 95%CI 0.09-1.49	No	Yes	Yes	N/A
Braeken et al.(30), 2013	RCT	Yes	Yes	Yes	No	Yes	Yes	Primary outcomes at 12 months: - Anxiety: 0.18 - Depression: 0.01 - Psychological distress: 0.46	P>0.05	Yes	Yes	Yes	N/A
Dean et al.(48), 2016	Cohort	Yes	Yes	Yes	Yes	Yes	Yes	Breast reconstruction following mastectomy: - Satisfaction with breast: 64.92 - Psychosocial wellbeing: 71.47 - Physical wellbeing 74.78 - Sexual wellbeing: 54.17	(61.92-67.92) (68.09-74.85) (77.43-77.13) (50.55-57.78)	Yes	Yes	Yes	N/A
Decker et al.(41), 2009	Cohort	Yes	Yes	Yes	Yes	Yes	Yes	The average sum of symptoms severity decreased by 4.35 in the intervention group	P= 0.21	Yes	Can't tell	Yes	N/A
Egbring et al.(20), 2016	RCT	Yes	Yes	Yes	Physicians (single-blinded)	Yes	Yes	Functional activity scores: from 90.385 (IQR 30.67) to 84.76 (IQR 18.29) (supervised group)	P=0.72	Yes	Can't tell	Yes	N/A
Fu et al.(45), 2016	Cross-sectional	Yes	Yes	Yes	Can't tell	Yes	Can't tell	Yes	Yes	Yes	Yes	Yes	Yes
Girgis et al.(26), 2009	RCT	Yes	Yes	Yes	No	Yes	Yes	Improves outcomes in the intervention group.	P<0.001 – P=0.01	Yes	Yes	Yes	N/A
Graf et al.(27), 2016	Cross-sectional	Yes	Yes	Yes	No	Yes	No	No	Yes	Yes	No	Can't tell	Yes

Supplementary Table S2. Critical Appraisal Skills Programme (CASP) quality scoring according to the study design performed. (continued)

Author	Study design	1	2	3	4	5	6	7	8	9	10	11	12
Hahn et al.(37), 2004	Cohort	Yes	Yes	Yes	Yes	Can't tell	Yes	An electronical intervention with touch screen is useful in outcome measurement	Can't tell	Yes	Yes	Yes	N/A
Holch et al.(21), 2017	Qualitative	Yes	Yes	Yes	Can't tell	Yes	Can't tell	Can't tell	Can't tell	Yes	Valuable	N/A	N/A
Javid et al.(46), 2016	Qualitative	No	Yes	Yes	Yes	Can't tell	Can't tell	Can't tell	No	Yes	Valuable	N/A	N/A
Judson et al.(35), 2013	RCT	Yes	Yes	Yes	No	N/A	Yes	Can't tell	Can't tell	Yes	Can't tell	Yes	N/A
Kelleher et al.(33), 2016	Observational	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Can't tell	Yes	Valuable	N/A	N/A
Kim et al.(44), 2016	Cohort	Yes	Yes	Yes	Yes	Can't tell	Yes	- Lower adherence (n=58) group reported 208/497 observations, while the higher adherence (n=20) group reported 289/497 observations - Self-report adherence was associated with an increase in the accuracy of depression screening	Precise	Yes	Yes	Can't tell	N/A
Knoerl et al.(22), 2017	Cohort	Yes	Yes	Yes	Yes	Yes	Yes	Scores improves significantly due to the intervention	P=0.02	Yes	Yes	Yes	N/A
Knoerl et al.(19), 2017	Cohort	Yes	Yes	Yes	Yes	Yes	Yes	The intervention was feasible, with high usability, satisfaction and acceptability scores.	Precise	Yes	Yes	Yes	N/A
Kuijpers et al.(47), 2015	Qualitative	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Can't tell	Yes	Valuable	N/A	N/A
Leung et al.(38), 2016	Cohort	Yes	Yes	Yes	Yes	Can't tell	Yes	CAT scores were significantly correlated with the scores of both PROM questionnaires.	P<0.0001	Yes	Can't tell	Yes	N/A

Supplementary Table S2. Critical Appraisal Skills Programme (CASP) quality scoring according to the study design performed. (continued)

Author	Study design	1	2	3	4	5	6	7	8	9	10	11	12
Min et al.(36), 2014	Cohort	Yes	Yes	Yes	Yes	Can't tell	Yes	- Overall compliance rate 45% - Longitudinal compliance curve decreased from 100% (day 1) to 13.3% (day 90) - Unemployed women had a higher rate of compliance	Precise	Yes	Yes	Can't tell	N/A
Mooney et al.(42), 2014	RCT	Yes	Yes	Yes	No	Yes	Yes	No significant difference in change of symptom severity between both groups (mean = 0.06)	P=0.58	Yes	Yes	Yes	N/A
Mooney et al.(43), 2017	RCT	Yes	Yes	Yes	No	Yes	Yes	Significantly less symptom severity in intervention group.	P<0.001	Yes	Yes	Yes	N/A
Ruland et al.(50), 2013	RCT	Yes	Yes	Yes	No	Yes	Yes	Can't tell	Can't tell	Yes	Can't tell	Yes	N/A
Snyder et al.(28), 2010	Cross-sectional	Yes	Yes	Yes	Yes	Yes	No	No	Yes	No	No	Can't tell	Yes
Snyder et al.(11), 2013	Qualitative	Yes	Yes	Yes	Yes	Yes	Can't tell	Yes	No	Yes	Valuable	N/A	N/A
Wheelock et al.(34), 2015	RCT	Yes	Yes	Yes	No	Yes	Yes	More or new reported symptoms in intervention group (7.36 vs 3.2)	P=0.0045	Yes	Can't tell	Yes	N/A
Wu et al.(29), 2016	Qualitative	Yes	Yes	Yes	Yes	Yes	Can't tell	Yes	No	Yes	Valuable	N/A	N/A

Qualitative study:

1) Was there a clear statement of the aims of the research?
2) Is a qualitative/ quantitative methodology appropriate?
3) Was the research design appropriate to address the aims of the search?
4) Was the recruitment strategy appropriate to the aims of the research?
5) Was the data collected in a way that addressed the research issue?
6) Has the relationship between researcher and participants adequately considered?
7) Have ethical issues been taken into consideration?
8) Was the data analysis sufficiently rigorous?
9) Is there a clear statement of findings?
10) How valuable is the research?

Randomized controlled trail (RCT):

1) Did the trial address a clearly focused issue?
2) Was the assignment of patients to treatments randomized?
3) Were all of the patients who entered the trial properly accounted for at its conclusion?
4) Were patients, health workers and study personnel 'blind' to treatment?
5) Were the groups similar at the start of the trial?
6) Aside from the experimental intervention, were the groups treated equally?
7) How large was the treatment effect?
8) How precise was the estimate of the treatment effect?
9) Can the results be applied to the local population, or in your context?
10) Were all clinically important outcomes considered?
11) Are the benefits worth the harms and costs?

Cohort study:

1) Did the study address a clearly focused issue?
2) Was the cohort recruited in an acceptable way?
3) Was the exposure accurately measured to minimize bias?
4) Was the outcome accurately measured to minimize bias?
5) A. Have the authors identified all important confounding factors? B. Have they taken account of the confounding factors in the design and/or analysis?
6) A. Was the follow up of subjects complete enough? B. Was the follow-up of subjects long enough?
7) What are the results of this study?
8) How precise are the results?
9) Do you believe the results?
10) Can the results be applied to the local population?
11) Do the results of this study fit with other available evidence?
12) What are the implications of this study for practice?

Cross-sectional study:

1) Did the study address a clearly focused question / issue?
2) Is the research method (study design) appropriate for answering the research question?
3) Is the method of selection of the subjects (employees, teams, divisions, organizations) clearly described?
4) Could the way the sample was obtained introduce (selection)bias?
5) Was the sample of subjects representative with regard to the population to which the findings will be referred?
6) Was the sample size based on pre-study considerations of statistical power?
7) Was a satisfactory response rate achieved?
8) Are the measurements (questionnaires) likely to be valid and reliable?
9) Was the statistical significance assessed?
10) Are confidence intervals given for the main results?
11) Could there be confounding factors that haven't been accounted for?
12) Can the results be applied to your organization?

Chapter 7

Machine learning with PROs in breast cancer surgery;
Caution: collecting PROs at baseline is crucial

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ABSTRACT

As high breast cancer survival rates are achieved nowadays, irrespective of type of surgery performed, prediction of long-term physical, sexual, and psychosocial outcomes is very important in treatment decision-making. Patient-reported outcomes (PROs) can help facilitate this shared decision-making. Given the significance of more personalized medicine and the growing trend on the application of machine learning techniques, we are striving to develop an algorithm using machine learning techniques to predict PROs in breast cancer patients treated with breast surgery. This short communication describes the bottlenecks in our attempt to predict PROs.

SHORT COMMUNICATION

Improvement in early detection and treatment of breast cancer has resulted in increased long-term breast cancer survivors[1]. The cornerstone of breast cancer management still is surgery. In breast cancer surgery, equal survival rates are achieved, irrespective of type of surgery performed[2-4]. However, breast cancer surgery can adversely affect women's psychological health and health-related quality of life (HRQoL). Prediction of long-term physical, sexual, and psychosocial outcomes is therefore very important in treatment decision-making.

Patient reported outcomes (PROs) come directly from the patient without interpretation by a healthcare provider and reflect aspects of health, quality of life, and related constructs[5]. The routine collection of PROs has been implemented in many health institutions[6-10], and it is clear that PROs have an important role in today's clinical practice. Collaboration of the International Consortium for Health Outcomes Measurement (ICHOM) with several other healthcare institutions worldwide has resulted in the development of a Standard Set for breast cancer outcomes[10]. Within this outcome set, patient-reported outcome measures (PROMs) are pivotal and accounting for 75% of the outcomes evaluated[10].

PROs can help facilitate in shared decision-making through informing treatment decisions and settings expectations. The ability for patients to understand what other patients with breast cancer experienced after surgery is thereby vital.

Predictive modelling is not new to medicine. In clinical medicine, a multivariable prediction model combines information from multiple predictors to predict the probability of or risk for a specific disease or outcome[11]. Predictive modelling has the purpose of informing patients and guiding clinicians in decision-making on treatment decisions. The majority contains prediction of patient outcomes focused on cancer survival and risk of cancer recurrence or local control[12-14], but little has been done to predict PROs into the future. Moreover, to our knowledge, there are no tools available focusing on predicting HRQoL outcomes after breast surgery into the future. Given the significance of more personalized medicine and the growing trend on the application of machine learning techniques, our breast cancer team is striving to develop an algorithm using machine learning techniques to predict PROs in breast cancer patients treated with breast surgery.

We aimed to develop and validate a simple prediction model for improvement of HRQoL after breast cancer surgery using data from 3 PRO questionnaires as proposed in the ICHOM Standard Set for Breast Cancer, namely the EORTC QLQ-C30 and EORTC QLQ-B23, and the BREAST-Q (postoperative modules). To this end, a retrospective cohort collected and described previously[6] was used. This cohort contained 764 female patients with breast cancer (pTis-3N0-3M0) who underwent breast cancer surgery between January 2005 and September 2016 at Erasmus MC Academic Breast Cancer Centre, Rotterdam, the Netherlands. Data on patient characteristics, age, date and type of surgery, tumour morphology, TNM staging (7th edition[15]), hormonal status, HER2 status, *BRCA* 1/2 gene mutation status, local recurrence, second primary breast cancer, details regarding chemotherapy and/or immunotherapy and endocrine therapy, radiotherapy and follow-up were available. Machine learning (i.e. General Linear Model regression (GLM), Support Vector Machines (SVM), single-layer Artificial Neural Networks (ANN), and Deep Learning (DL))[16], was used to jointly study presurgical prognostic variables relating to age, medical status, tumour characteristics, and possible (neo)adjuvant treatment indications/treatment characteristics. Unfortunately, a lack of relationship was found between outcome variables and their predictors, meaning that the accuracy reflected just the population prevalence of the outcomes. Machine learning models have an immense number of parameters that must be either learned using data or set manually by the researcher[17]. By combining variables in a reduced number of dimensions, we tried to help the analysis, but this did not yield substantial changes and required days of computational time.

During the process some crucial obstacles were identified, which stagnated the development of a machine learning model in this data set. This included the cross-sectional design, the lack of baseline PROs and the relative small sample size. Given the increase in the use of machine learning techniques in medical research and the, worldwide, desire to predict and influence PROs after breast surgery, we believe it is important to draw attention to our findings.

Machine learning describes the use of computer algorithms that learn nonlinear associations retrospectively from the data to estimate risk of a specific outcome. Even though machine learning is increasingly used in medical research[18-20], success is not always guaranteed. As with any method, a good understanding of the problem and an appreciation of the limitations of the dataset is important. Also crucial is an understanding of the assumptions and limitations of the algorithms being applied. If a machine learning experiment is properly designed, with correctly implementation and validated results, there usually is a good chance of success.

Although we used patient and treatment characteristics, and outcomes of interest to both patients and clinician (i.e. validated PROMs as proposed in the ICHOM Standard Set for Breast Cancer) there were some important limitations in using the existing dataset[6]. With 764 breast cancer patients, the study was relatively large, although for machine learning techniques probably not large enough. The size of the dataset is one of the most common limitations noted in studies reporting machine learning techniques[14]. The dataset needs to be sufficiently large, which allows sufficient

partitioning into training and testing sets, leading to reasonable validation of the estimators[14] in order to enhance the generalizability of the predictive model.

The most important limitation however is the cross-sectional design of the dataset, meaning the absence of baseline PROs. Traditional methods for evaluating PROMs look at the change over time, using the baseline compared to the endpoint. Enabling comparison with preoperative PROs is expected to reflect the influence of different treatments on HRQoL outcomes better than a single score obtained following treatment. One explanation probably is the fact that not every individual patient will score their breasts to the highest possible level at baseline. Although preoperative PROs were not available, all known other potential predictors were assessed, except for socioeconomic status (which cannot be easily obtained in the Netherlands for privacy reasons). The next step toward further validation of this approach to prediction would be to work with a more complete dataset, including baseline PROs and lifestyle measures. The research team has secured a prospective data set over a longer time frame, but this dataset currently consists of a small number of patients. Since PROM collection is considered standard of care at our institute nowadays[9], in combination with a regional and international collaboration, this cohort will be progressively enlarged over time. There are plans in place to develop and test the performance of the machine learning techniques in this dataset in the near future. However, the above-described study was a valuable first step towards modelling PROMs data for use in breast cancer surgery. Once developed, the model could have potential for use outside breast surgery because similar sets are used in other diseases. But, as also suggested by Beam et al.[17], the challenges and obstacles to reproducibility of machine learning techniques must be carefully considered to ensure the validation, safety and effectivity of these new class of prediction tools.

In conclusion, using machine learning methods, we endeavoured to develop a clinical prediction model for PROs after breast surgery. Clinicians could use information on the level of patient HRQoL outcome improvement, when counselling patients about the (prognostic) outcomes of breast cancer surgery, allowing patients to be more involved in their treatment decision. To actually realize an effective clinical prediction model, information regarding patients starting position is crucial. This emphasize the urgent need of collecting PROMs at baseline, leading to the opportunity of predictive modelling on PROMs in breast cancer surgery in the future.

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Chapter 8

Patient-reported outcome measures may optimize shared decision-making for cancer risk management in BRCA mutation carriers

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ABSTRACT

Purpose

The aim of this study was to compare patient-reported outcomes (PROs) of *BRCA1/2* mutation carriers, either after bilateral prophylactic mastectomy (BPM) or during breast surveillance, to improve shared decision-making in their cancer risk management.

Methods

Unaffected *BRCA1/2* mutation carriers at least one year after BPM followed by immediate breast reconstruction (BPM-IBR) or one year under surveillance were eligible. After informed consent, the Hospital Anxiety and Depression Scale (HADS) and BREAST-Q were administered and compared between the different strategies. PROs were also compared to available normative data.

Results

Ninety-six participants were analysed in this study and showed significant differences between strategies in age, age at genetic testing, and time since BPM or starting breast surveillance. All HADS scores were below 8 suggesting no signs of anxiety or depression in both groups. Higher mean 'Q-physical wellbeing' scores were reported by the surveillance group (81.78 [CI 76.99 – 86.57]) than the BPM group (76.96 [CI 73.16 – 80.75]; p= 0.011). Overall, for both questionnaires better scores were seen when compared to age-matched normative data.

Conclusions

No signs of anxiety or depression were seen in the surveillance or BPM-IBR group. Slightly better mean BREAST-Q scores were seen for the surveillance group in comparison to BPM-IBR, except for 'Q-psychological wellbeing'. The difference in 'Q-physical wellbeing' was significantly worse for BPM-IBR. Approaches to obtain longitudinal PROs and reference values should be explored in the future, which could add value to shared-decision-making in regards to breast cancer risk management in this specific patient population.

INTRODUCTION

A woman's lifetime risk of developing breast cancer is greatly increased when she inherits a *BRCA1* or *BRCA2* gene mutation. While the general population has a lifetime risk of 12%[1], *BRCA1* and *BRCA2* mutation carriers have a cumulative breast cancer risk of, respectively, 72% and 69%[2] till 80 years of age.

Breast cancer risk management for *BRCA1/2* mutation carriers encompass the possibility of intensive breast surveillance aimed at early detection, or bilateral prophylactic mastectomy (BPM). BPM has shown a risk reduction up to 95%[3-7] and is associated with decreased general and cancer-related distress[8 9]. As BPM is a major, elective and irreversible procedure, however, it is also associated with a negative impact on health-related quality of life (HRQoL) outcomes such as body image, psychosocial-, psychosexual-, and physical wellbeing[8 10 11].

The alternative is intensive breast surveillance, consisting of annually alternating mammography and breast MRI, and semi-annual clinical breast examination commencing at 25 years of age[12]. Carriers who choose surveillance might have fewer problems with body image in the psychosocial- and psychosexual area, but will be confronted with difficulties concerning cancer-related distress and the risk of breast cancer[13].

Since BPM, either followed by immediate breast reconstruction (BPM-IBR) or not, and surveillance are both validated options with high survival rates[14], the choice between them is dependent on the individual woman's preferences. To facilitate decision-making, it is important to fully explain the pros and cons of both options, especially when considering preference-based care for which there exists more than one clinically appropriate treatment option[15]. Therefore, women considering BPM(-IBR) should be informed about the impact of prophylactic surgery on not only survival and the risk of cancer but on the expected HRQoL outcomes as well[8 15-18].

According to value-based healthcare principles, these HRQoL outcomes can be both provider-reported as well as patient-reported outcomes (PROs). Since PROs are direct assessments from patients, typically collected through validated questionnaires (i.e. PROMs = patient-reported outcome measurements), they reflect patients' quality of life or functional status. PRO data is incredibly valuable to get insight into long-term HRQoL and can be used as a guide for *BRCA1/2* mutation carriers in their decision-making process in regard to their breast cancer risk management. However, little is known about PROs following the choice for either BPM or surveillance in *BRCA1/2* mutation carriers.

It was hypothesized that PROs differ between women choosing BPM(-IBR) and women opting for breast surveillance. This study aimed to compare PROs between *BRCA1/2* mutation carriers following their choice for either BPM-IBR or breast surveillance.

METHODS

Study population

A total of 96 unaffected *BRCA1/2* mutation carriers, diagnosed at the Academic Breast Cancer Centre of the Erasmus MC between 2014 and 2017, were included. Female *BRCA1/2* mutation carriers, aged over 18 years and with an adequate understanding of the Dutch language, were deemed eligible. Mutation carriers who were at least 1 year post-BPM-IBR (autologous or implants) were identified from the electronic health records using operation and diagnosis codes. Mutation carriers scheduled for at least 1 year of breast surveillance were approached at the surgical oncology outpatient clinic. Mutation carriers were asked to participate until at least 50 participants were enrolled in each group. Women with a past history of (in situ) breast cancer were excluded. Ethical approval was granted by the Institutional Review Board of the Erasmus Medical Centre, Rotterdam, The Netherlands (MEC-2018-1601).

Procedures

In this cross-sectional study, medical records were retrospectively reviewed to collect the following data: *BRCA1/2* mutation status and date of genetic testing, age at genetic testing, family history of breast cancer, comorbidities, smoking status, family status, time since start breast surveillance, or time since surgery, and – if applicable – type of surgery performed. Missing data was handled by contacting the participant via telephone. For the BPM-IBR group, eligible women were recruited by telephone or mail. Women in the surveillance group were asked to participate at the outpatient clinic. Following informed consent, two PROM questionnaires were administered: the Hospital Anxiety and Depression Scale (HADS)[19] and the BREAST-Q version 1.0 (pre-mastectomy module for the surveillance group and the post-reconstruction module for BPM-IBR)[20]. Both PROMs were web-based questionnaires and administered through the software program "GemsTracker"[21], an online system for distributing and collecting surveys. If the questionnaires remained uncompleted, a weekly reminder was sent by the system. If patients had not responded in 4 weeks, participants were contacted by telephone and asked to complete the questionnaires. PROM scores were calculated according to the questionnaires' scoring manuals.

Statistical analysis

All analyses were performed using Statistical Package for Social Sciences (SPSS), Version 24.0 (IBM Corporation, Armonk, NY, USA). Baseline characteristics were compared between women who underwent BPM-IBR versus those who chose breast surveillance. Comparisons across both groups were made using the Mann-Whitney U test for continuous variables, and Fisher's exact test or the Chi-squared test, as appropriate, for categorical variables. Two-sided p value <0.05 was considered statistically significant. In addition, PROM scores were compared to normative scores[22-24].

RESULTS

Study population

Between October 2018 and May 2019, 168 women were contacted via telephone, mail or at the outpatient clinic (Fig. 1). Of the eligible participants, 143 (85%) women responded. Eight (5.6%) responders declined participation. Of the surveillance group, 22 (25.3%) responders did not reply despite verbal consent being obtained at the outpatient clinic. After informed consent, 55 (63.2%) women participated in the surveillance group and 53 (67%) in the BPM-IBR group. Three women were excluded from the BPM-IBR group: one woman underwent a delayed breast reconstruction and the other two due to the absence of a *BRCA1/2* gene mutation.

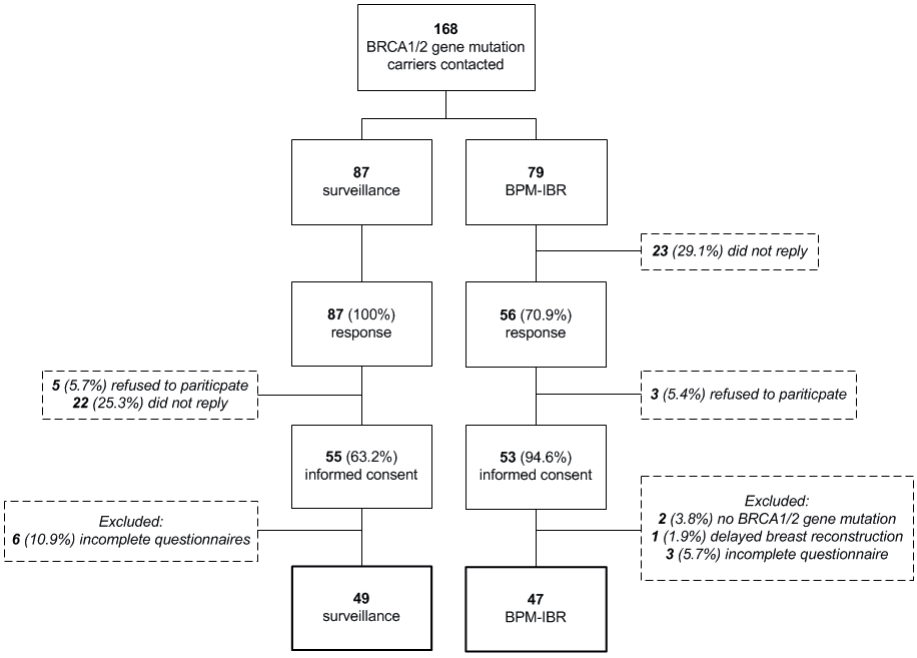

Figure 1. Flowchart of study selection process.
BPM-IBR, bilateral prophylactic mastectomy followed by immediate breast reconstruction

Characteristics

A total of 96 participants were included for analysis: 47 BPM-IBR and 49 breast surveillance participants (Table 1). Statistically significant differences were seen between both groups in age at study enrolment, age at genetic testing, and time since surveillance start or since BPM-IBR. Overall, the study population was relatively young: 43% of the surveillance group and 45% of the BPM-IBR group were aged below 35 years. Approximately 60% of both groups had a positive family history for breast cancer in two or more relatives. Risk-reducing bilateral salpingo-oophorectomy (RRSO) or prophylactic tubectomy were performed in, respectively, 45% and 11% of the study population.

Table 1. Characteristics of 96 *BRCA1/2* mutation carriers per type of cancer risk management, n (%)

	All (n=96)	Surveillance (n=49)	BPM-IBR (n=47)	p value
Mean (SD) age (years)[§]	42.4 (10.7)	44.5 (12.0)	40.2 (8.8)	0.046
Mean (SD) age (years) at genetic testing[§]	36.6 (10.3)	38.7 (10.6)	34.3 (9.6)	0.039
Mutation type[¥]				0.969
BRCA1	57 (59)	29 (59)	28 (60)	
BRCA2	39 (41)	20 (41)	19 (40)	
Mean (SD) age (years) at start cancer risk management[§]	37.9 (9.8)	38.7 (10.7)	37.1 (8.7)	0.447
Mean (SD) time (years) since start of cancer risk management[§]	4.7 (3.7)	6.1 (4.7)	3.1 (1.2)	0.002
Family history[¥]				0.723
0	13 (14)	7 (14)	6 (13)	
1	24 (25)	10 (20)	14 (30)	
≥2	57 (59)	30 (61)	29 (62)	
Unknown	2 (2)	2 (4)	.0	
First degree family history[¥]				0.176
0	66 (69)	30 (61)	36 (77)	
1	28 (29)	17 (35)	11 (23)	
≥2	.0	.0	.0	
Unknown	2 (2)	2 (4)	.0	
Second degree family history[¥]				0.229
0	63 (66)	32 (65)	31 (66)	
1	28 (29)	15 (31)	13 (28)	
≥2	.0	.0	3 (6)	
Unknown	2 (2)	2 (4)	.0	
Third degree family history[¥]				0.617
0	32 (33)	16 (33)	16 (34)	
1	31 (32)	14 (29)	17 (36)	
>2	31 (32)	17 (35)	14 (30)	
Unknown	2 (2)	2 (4)	.0	
Marital status[¥]				0.079
Single	8 (8)	1 (2)	7 (15)	
Relationship	21 (22)	11 (22)	10 (21)	
Married	58 (60)	30 (61)	28 (60)	
Unknown	9 (9)	7 (14)	2 (4)	
Parity, mean (SD)[§]	1.4 (1.0)	1.4 (0.9)	1.5 (1.07)	0.461
Ovarian status[¥]				0.147
In situ	31 (32)	16 (33)	15 (32)	
RRSO	45 (47)	27 (55)	18 (38)	
Tubectomy	11 (11)	3 (6)	8 (17)	
Unknown	9 (9)	3 (6)	6 (13)	
Smoking status[¥]				0.910
Yes	9 (9)	4 (8)	5 (11)	
No	73 (76)	31 (63)	42 (89)	
Unknown	14 (15)	14 (29)	.0	

BPM-IBR, bilateral prophylactic mastectomy followed by immediate breast reconstruction; *RRSO*, risk-reducing bilateral salpingo-oophorectomy;
[¥] Chi squared test. [§] Mann-Whitney U test.

PROMs

Table 2 gives an overview of the PROM scores. For both groups, all individual HADS scores were below 8, which was defined as the upper limit of normal[22]. Slightly better mean BREAST-Q scores were seen in the surveillance group as compared to the BPM-IBR group, except for the domain 'Q-psychological wellbeing'. In contrast, only the difference in 'Q-physical wellbeing' was significantly higher in the surveillance group (81.78; CI 76.99 – 86.57) than the BPM-IBR group (76.96; CI 73.16 – 80.75; $p = 0.011$).

Obtained HADS scores were compared to normative data[22], demonstrating lower scores on both the anxiety and the depression scale in both groups (Fig. 2a). As the mean age of our cohort was 42.4 years, normative data of the female age category 40 – 44 years was used for comparison. The normative data of the preoperative reconstruction module was used for the comparison with BREAST-Q scores of both groups in our cohort[23,24]. PROMs were comparable to normative scores of the BREAST-Q except for the 'Q-physical wellbeing' scale, which showed lower scores in the current cohort (Fig. 2b).

Table 2. PROM scores of 96 *BRCA1/2* mutation carriers per type of cancer risk management, mean (95% CI)

		All (n=96)	Surveillance (n=49)	BPM-IBR (n=47)	
		Mean (95% CI)	**Mean (95% CI)**	**Mean (95% CI)**	**p value¥**
HADS°	Anxiety scale	5.36 (4.62 – 6.09)	5.47 (4.30 -6.63)	5.26 (4.30 – 6.21)	0.691
	Depression scale	2.40 (1.80 – 3.00)	2.51 (1.66 – 3.36)	2.30 (1.42 – 3.18)	0.591
BREAST-Q§	Satisfaction with breasts	68.96 (65.09 – 72.82)	71.51 (65.56 – 77.47)	66.51 (61.42 – 71.60)	0.304
	Psychosocial wellbeing	74.08 (70.14 – 78.01)	70.78 (65.17 – 76.38)	77.23 (71.67 – 82.80)	0.143
	Physical wellbeing chest	79.32 (76.29 -82.34)	81.78 (76.99 – 86.57)	76.96 (73.16 – 80.75)	0.011
	Sexual wellbeing	61.53 (57.87 – 65.20)	62.82 (57.24 – 68.41)	60.30 (55.33 – 65.27)	0.644

BPM-IBR, bilateral prophylactic mastectomy followed by immediate breast reconstruction; *HADS*, Hospital Anxiety and Depression Scale HADS index value: scale from 0-21; BREAST-Q scale from 0 to 100.
° Higher scores represent lower quality. § Higher scores represent higher quality.
¥ Mann-Whitney U test

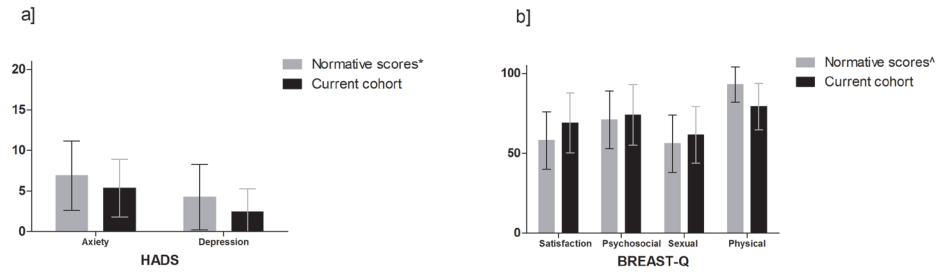

Figure 2: Comparison of PROM scores with normative scores.

2a] HADS survey scores versus normative scores[22]. Mean scores with standard deviations (error bars) for HADS-scores.
HADS index value: scale from 0-21. Higher scores represent lower quality.
*Normative scores as based on 486 patients (anxiety subscale) and 489 patients (depression subscale)[22], presented by gender and age (i.e. female and 5-year age group 40-44 years).

2b] BREAST-Q survey scores versus normative reconstructive scores[23]. Mean scores with standard deviations (error bars) for Q-scores.
BREAST-Q scale from 0 to 100. Higher scores represent better functioning.
^Normative scores as based on 1201 participants of the general population[23].

DISCUSSION

BRCA1/2 mutation carriers are faced with complex decisions within breast (and ovary) cancer risk management. Insights into not only cancer risk but also into HRQoL or daily functioning as a result of these decisions could improve the shared decision-making process and ultimately the care delivered. Therefore, this study aimed to obtain and evaluate PROs in *BRCA1/2* mutation carriers according to their choice of breast cancer risk management (BPM-IBR versus breast surveillance).

The PROMs in this study have succeeded in providing valuable insights into HRQoL in *BRCA1/2* mutation carriers, in both the BPM-IBR and the breast surveillance group. The interpretation of these data was done both separately and in comparison to available normative data[22-24].

HADS demonstrated no scores outside normal cut-off values on the two scales. Moreover, mean scores observed for both groups were quite similar and all reported scores were below the upper limit. These observations indicate that none of the mutation carriers in the present study reported anxiety or depression that reached clinically relevant levels. In addition, no significant differences in anxiety or depression outcomes were observed between women in the surveillance group and the BPM-IBR group.

Overall, slightly better BREAST-Q scores were seen for the surveillance group compared to BPM-IBR. The surveillance group scored lower on 'Q-psychological wellbeing', albeit not statistically significant. This difference was expected since previous studies have already shown elevated levels of psychological distress in women at increased risk of developing breast cancer[8 13]. Only the difference in 'Q-physical wellbeing' was statistically significant, which can be explained by the

surgical procedure these women have undergone. However, it has been acknowledged that not only the statistical significance of the differences in QoL questionnaires is important but the clinical relevance of them as well[25]. Although there is no consensus yet on clinically relevant BREAST-Q scores, it is generally accepted that a difference of 5 points should be considered as a small clinical difference, 10 points as moderate, and 20 points as a very clinically important difference[26]. There was a difference of 5 – 10 points for all BREAST-Q modules except for 'Q-sexual wellbeing', which suggests a small clinical difference between both groups. PROs should be collected longitudinally in order to evaluate the clinical differences in PROM scores over time within both groups.

Of all BREAST-Q subscales, the lowest scores were reported for 'Q-sexual wellbeing' by both BPM-IBR and breast surveillance women. Previous studies have shown that breast cancer surgery may have a negative impact on sexual health[27 28]. The low 'Q-sexual wellbeing' scores might also be explained by the high proportion of women with a risk-reducing ovarian cancer intervention (RRSO or tubectomy). Since RRSO substantially decreases the levels of oestrogen and testosterone, it has an effect on quality of life and sexual functioning, among other domains, at an early age[29 30]. However, we also compared mean 'Q-sexual wellbeing' scores between women with and without RRSO/tubectomy and found slightly higher mean scores in the RRSO/tubectomy group (i.e. 65.04 [60.01 – 70.07] and 55.90 [49.43 – 62.38], respectively). This emphasizes our rationale of the impact that breast surgery can have on a woman's sexual health, which is in line with our previous publication also showing low 'Q-sexual wellbeing'-scores in surgical treated breast cancer patients (without a BRCA1/2 mutation)[31]. Also noteworthy is that only 33.9% of the women were treated with hormone replacement therapy (n=8 in the BMP-IBR and n=11 in the surveillance group) (data not shown).

Available normative data for the HADS were derived from the Epidemiology of Functional Disorders (EpiFunD) Study[22] and normative data for the BREAST-Q from the Army of Women community[23]. When comparing the PROM scores of our cohort with the normative data, one must take into account that the normative data were obtained in the United Kingdom (HADS) and the United States (BREAST-Q). Due to cultural differences between these countries and the Netherlands, this data does not entirely reflect normative scores for Dutch women. However, similar Q-scores were seen when comparing the current cohort with Dutch cohorts[27 32]; i.e. overall better scores except for 'Q-psychical wellbeing'. HADS scores were not available within these cohorts.

Significant differences in patient characteristics existed between both groups, suggesting a possible treatment indication bias. Available data on the impact of patient characteristics on a woman's decision to undergo BPM vary. Most studies show that age at genetic testing does not significantly affect the choice for BPM[8 13 15 33], which is in opposition to our findings. On the other hand, no significant differences in family history, ovarian status, marital status and parity existed between both groups, in contrast to other studies showing that these factors *do* have a significant impact on the choice for BPM[10 13 33-35]. However, due to the retrospective design of this pilot study, baseline (anxiety) scores could not be obtained. Women may experience physical- and psycho-

logical trauma associated with being diagnosed with a *BRCA1/2* mutation, which will affect their HRQoL. Thus, changes in PROs before and after diagnosis are to be expected, which emphasizes the necessity of PRO collection at baseline.

The significant differences in age at study enrolment, age at genetic testing, and the time since BPM-IBR or starting breast surveillance could be explained by the manner in which women were selected. Eligible participants for the BPM-IBR group were found through a search in the electronic health record. The search was thereby limited by year of surgery, namely between 2014 and 2017. Gene mutation carriers scheduled for breast surveillance were asked to participate at the outpatient clinic. No limitations on patient inclusion was set for this group and could, therefore, be completed before 2014. Although the duration of the inclusion period was over 6 months and all *BRCA1/2* mutation carriers were scheduled for follow-up every 6 months during their surveillance, a potential selection bias could have been introduced. Moreover, the time since the start of cancer risk management significantly differed between both groups (6.1 years for surveillance versus 3.1 years for BPM-IBR, p=0.002), and time since BMP-IBR was relatively short. Previous studies have shown that psychological outcomes as well as coping strategies change over time[8 13 13]. Coping strategies represent cognitive and behavioural efforts to deal with stressful encounters[36]. Effects of coping can differ depending on the duration and controllability of the stress factor. As women in our cohort did not have a history of breast cancer (consistently favourable results during their surveillance), long-term breast cancer-related distress might decrease as a consequence of 'underestimating' their breast cancer risk[13]. This observation may be a possible explanation for the low distress and anxiety levels in our cohort. Another possible explanation for the low scores is potential selection bias, as the women who experienced increased levels of depression might have been less likely to participate.

We did not find that women in the BMP-IBR group were more likely to have a first-degree relative with a history of breast cancer (35% surveillance versus 23% BPM-IBR, p=0.176), which is in contrast to what others have reported[33 37].

Intuitively, it would seem that women with a *BRCA1* mutation would most likely be the ones to consider BPM as they have a higher breast cancer risk than *BRCA2* mutations[2]. Moreover, a previous study with 5,889 Dutch *BRCA1*/2 mutation carriers showed that, compared to breast surveillance, BPM was associated with lower mortality for *BRCA1* mutation carriers, whereas for *BRCA2* mutation carriers breast cancer-specific survival rates were similar between BPM and breast surveillance[38]. In our cohort, however, there were no differences in the percentage of *BRCA1* carriers in the BPM-IBR group compared to the surveillance group. The observations that BPM was associated with lower mortality rates than surveillance for *BRCA1* and similar breast cancer-specific survival for *BRCA2*, underscore the importance of counselling *BRCA1/2* mutation carriers on their choice between breast surveillance and BPM. Knowledge of patient-reported HRQoL outcomes can be valuable in facilitating this choice.

Limitations include the relatively small sample size and the retrospective study design. The power was limited due to the small study population. Longitudinal PRO collection and comparison with baseline

PROM scores are needed when striving to showcase the influence of different risk management strategies[13 15]. However, the retrospective evaluation of PROs does provide the necessary insight into (case-mix) factors possibly associated to PROs, and their inclusion for predictive modelling.

Multiple PROM instruments are available nowadays. Only two questionnaires were selected in this study. HADS was chosen since it is a short questionnaire and the most extensively validated scale for screening emotional distress in cancer patients[39], while BREAST-Q was chosen since it is a validated breast-specific instrument that is used worldwide. Razdan et al.[15] evaluated PROs after BPM and concluded that generic instruments were not sensitive enough to measure physical and mental changes related to specifically BPM, either followed by (immediate) breast reconstruction or not. The use of a breast-specific instrument (e.g. BREAST-Q) was recommended. We support this recommendation combined with the standardization of PROMs, since this will provide results that are comparable with other similar studies.

Several initiatives of longitudinal PRO collection in breast cancer patients have proven to be helpful in daily practice and are appreciated by both patients and providers[40 41]. The present study provides a first insight into PROs in *BRCA1/2* mutation carriers following their choice for either breast surveillance or BPM-IBR. Collected PROs can serve to pave the way for the implementation of a value-based healthcare strategy among future *BRCA1/2* mutation carriers at the outpatient clinic. Interpretability of the important differences in PRO(M)s is the cornerstone to its successful use in individual clinical care, comparative effectiveness research, and regulatory efforts. Knowledge about differences in HRQoL outcomes between BPM and surveillance can be used to facilitate shared decision-making. Informing *BRCA1/2* mutation carriers about both positive and negative consequences of either BPM-IBR or breast surveillance is of great importance for building up realistic expectations[9]. Measuring PROs in *BRCA1/2* mutation carriers from gene mutation diagnosis to the subsequent trajectory has the potential to monitor and detect changes in psychosocial or physical problems over time. Reference PROM scores for the different strategies are then essential for the use of PROs at the outpatient clinic to personalize and improve the care delivered. Large multicentre initiatives and prospective PRO collections are, therefore, needed to obtain (and narrow down) these reference scores. Such an initiative is currently pending at our institution.

CONCLUSION

Patient-reported HRQoL outcomes were evaluated in unaffected *BRCA1/2* mutation carriers who underwent either breast surveillance or BPM-IBR. No signs of anxiety or depression were seen in both groups. Slightly better mean BREAST-Q scores were seen for the surveillance group in comparison to BPM-IBR except for 'Q-psychological wellbeing'; the difference in 'Q-physical wellbeing' was significantly worse for BPM-IBR. A first step was made towards value-based healthcare for *BRCA1/2* mutation carriers. Future possibilities should be explored to obtain reference PROM values, which could add value to the shared decision-making process in regard to cancer risk management in this specific population.

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Part III

Postoperative

Chapter 9

Opportunities for personalised follow-up care among patients with breast cancer: a scoping review to identify preference sensitive decisions

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ABSTRACT

Introduction

Current follow-up arrangements for breast cancer do not optimally meet the needs of individual patients. We therefore reviewed the evidence on preferences and patient involvement in decisions about breast cancer follow-up to explore the potential for personalised care.

Methods

Studies published between 2008 and 2017 were extracted from MEDLINE, PsycINFO, and EMBASE. We then identified decision categories related to content and form of follow-up. Criteria for preference sensitiveness and patient involvement were compiled and applied to determine the extent to which decisions were sensitive to patient preferences and patients were involved.

Results

Forty-one studies were included in the full-text analysis. Four decision categories were identified: 'surveillance for recurrent/secondary breast cancer; consultations for physical and psychosocial effects; recurrence-risk reduction by anti-hormonal treatment, and improving quality of life after breast cancer'. There was little evidence that physicians treated decisions about anti-hormonal treatment, menopausal symptoms, and follow-up consultations as sensitive to patient preferences. Decisions about breast reconstruction were considered as very sensitive to patient preferences, and patients were usually involved.

Conclusion

Patients are currently not involved in all decisions that affect them during follow-up, indicating a need for improvements. Personalised follow-up care could improve resource allocation and the value of care for patients.

BACKGROUND

Breast cancer is the most common form of cancer among women worldwide[1]. The five-year relative survival for early-stage breast cancer is high, with rates exceeding 96% for stage I and 86% for stage II disease[2 3]. International guidelines state that the goals of breast cancer follow-up care are to detect recurrent disease or new malignancies at an early stage, and to inform and counsel patients about the physical and psychosocial (late) effects of therapy[4-7]. Schemes for detecting recurrences often comprise annual physical and mammographic examinations for at least five years, depending on the patient's age, genetic predisposition, and/or tumour characteristics. Consultations that seek to detect physical and psychosocial effects are often linked to the visits for recurrence detection, and are most frequently planned during the first year of follow-up[4 6].

At present, arrangements for follow-up suboptimally meet the needs of patients with breast cancer, and there is concurrently a growing demand for personalised care planning within cancer follow-up care[8-11]. Such personalised follow-up care could be based on the patient's individual risk of recurrence for the length and/or frequency of surveillance[12 13], or on the type of treatment, and therefore, the management of treatment-induced (late) effects and complaints[4 6]. Moreover, cancer survivors might experience very different psychosocial consequences after the disease and treatment, including fear of recurrence, sleeping difficulties, cognitive issues, fatigue, and sexual issues[14]. Each of these effects require a personalized follow-up strategy. Patient-preferences about the preferred form and content of the follow-up care have been reported in previous studies[15 16].

Since the advent of value-based healthcare, there have been ongoing efforts to improve care quality by adding value throughout an individual patient's journey from diagnosis, through treatment, and to follow-up care[17]. A way to meet this goal of personalised care is to include patients and their preferences in the decision-making process. For example, in the shared decision-making (SDM) process, decisions are based on both the best available (medical) evidence and the patients' needs and values. Preference sensitive care involves making treatment decisions with significant trade-offs that should reflect a patient's personal values and preferences. Besides, only when patients have enough information to make an informed choice, a decision can be made[18]. This means that the quality of this SDM process might affect the eventual effect on the value of care, in terms of outcomes, costs, and organizational effort[19].

In the present study, we hypothesised that decisions about breast cancer follow-up are sensitive to patient preferences, and that it is an option to include SDM in the follow-up care of these patients. Thus, we aimed to discover the potential for personalising follow-up care among patients with breast cancer by exploring the evidence on preferences for, and patient involvement in, decisions about breast cancer follow-up care.

METHODS

The review was registered in PROSPERO (reference No.: CRD42018082501)[20].

Search strategy

Three research questions were posed: (1) 'what decisions are made during follow-up about content or form of follow-up care for breast cancer survivors?'; (2) 'to what extent are these decisions sensitive to patient preferences?', and (3) 'to what extent and how are patients with breast cancer involved in making these decisions?'. The literature was searched separately for each question, between 18th July and 25th September 2017, in the MEDLINE (accessed through PubMed), PsycINFO (accessed through Ovid), and EMBASE databases (Table 1). We included any study that discussed decisions made or interventions applied during follow-up for breast cancer, provided it was written in English and published in the last 10 years (2008-2017). The time restriction was set because breast cancer care and treatment have changed significantly over previous decades. The follow-up period was defined as the time period after surgery for breast cancer.

After removing duplicates, study titles and abstracts were screened by two independent screeners (KdL and LvE). Studies were excluded if they did not include patients with breast cancer, did not discuss follow-up, did not describe actual decision-making, or did not describe the patients' roles in decision-making. Studies were also excluded if they included patients receiving palliative treatment. Full texts were retrieved for the remaining studies. Those without full text articles were excluded after attempt to contact the corresponding authors to access the text. EndNote[21] was used to manage all search results.

Quality assessment

The quality of the included studies was assessed by the Critical Appraisal Skills Programme checklist, comprising criteria for qualitative studies, randomised controlled trails, cohort studies, and systematic reviews. Criteria could be scored with a positive or negative response; when criteria were not applicable or unknown/unable to be assessed, this was recorded as well [22]. First, we determined the study design for each included study, provided this was not already described in the study's method section. Studies were deemed of sufficient quality when half or more of the criteria could be scored positive, provided there was a clear aim or research question.

Analyses

First, we identified the decisions were made or could be made about content or form of follow-up care delivered to breast cancer patients. Second, criteria were compiled to determine whether decisions were sensitive to patient preferences and whether patients were involved in making the decisions. Third, these criteria, in turn, were used to assess the degree to which decisions were sensitive to patient preferences and the extent to which patients were involved in making these decisions.

Criteria for preference sensitiveness (PS0-5) were based on the definition by Van der Weijden et al. [23]. Decisions were considered preference-sensitive if the following criteria were met:

0. There were multiple options available (PS0); *and*
1. Options had potential favourable and unfavourable outcomes, leading to an individual trade-off (PS1); *or*
2. Options did not differ in terms of favourability of the outcomes, or (un)favourable outcomes were equally (un)desirable (PS2); *or*
3. There was insufficient evidence about favourable or unfavourable outcomes to determine the best option (PS3); *or*
4. The potential risks of an option were high, regardless the potential benefits of this option (PS4); *or*
5. The outcomes were highly dependent on patient cooperation, or the actions required for the preferred option had high impact on the patient's lifestyle (PS5).

Criteria for the extent of patient-involvement (SDM1-7) were based on the conditions set by Légaré et al. [18] and the components described by Coulter and Collins. [24]:

1. The decision was preference sensitive (SDM1); *and*
2. There was sufficient time to make a decision (SDM2); *and/or*
3. The patient was capable and sufficiently informed to make a decision (SDM3); *and/or*
4. There was a belief that SDM would lead to better patient outcomes (SDM4); and/or
5. The physician was motivated for SDM and clarified the options and preferences (SDM5); *and/or*
6. There was a belief that SDM will lead to better clinical outcomes (SDM6); *and/or*
7. There was a system for recording, communicating, and implementing the patient's preferences (SDM7).

RESULTS

Figure 1 summarises the selection process according to the PRISMA scheme. In total, 3,077 records were screened after removing duplicates (n = 2,539, 28, 1,058 per research question). After screening titles, abstracts, and full-texts, we finally included 41 studies.

Within the screened records, '*follow-up*' often referred to the study design rather than the post-treatment period, and '*preference-sensitive*' was used little or infrequently, only appearing as a key word in 21 records. Studies also generally described gaps in patient involvement rather than care that was already well-organized. Moreover, we excluded many studies (n=2871) that could not be related to the SDM criteria because they did not describe decision-making about the content or form of follow-up care. Another 11 studies were excluded because the full texts were not available. These were mainly studies published as conference abstracts, dissertations, or books. Contact details were available for only five of the corresponding authors of these abstracts, and only one responded.

All included studies (n=41) were rated as valuable in the quality assessment (Supplementary Table 2). Most studies employed a design with surveys (n=11) or interviews (n=16; comprising focus groups, needs assessments, and semi-structured/directed/open-ended interviews. The survey-based studies included larger samples (n=5-41), whereas the interview-based studies included smaller groups (n=5–41). Less common methods included studies of electronic health records (n=1) and internet fora (n=1). Randomised Controlled Trials (RCT) designs were used for studies about life style interventions (n=2) and SDM-related tools about breast reconstruction (n=3).

Table 2 summarizes the preference-sensitive aspects (criterion PS) and aspects of patient involvement (criterion SDM) for each decision about the content or form of follow-up care. Decisions were classified into those concerning (1) 'surveillance for recurrent or secondary breast cancer'; (2) 'consultations for physical and psychosocial (late) effects'; (3) 'recurrence-risk reduction by anti-hormonal treatment'; and (4) 'improving quality of life after breast cancer'. Results are described in more detail below. Supplementary Table S1 summarizes the included studies.

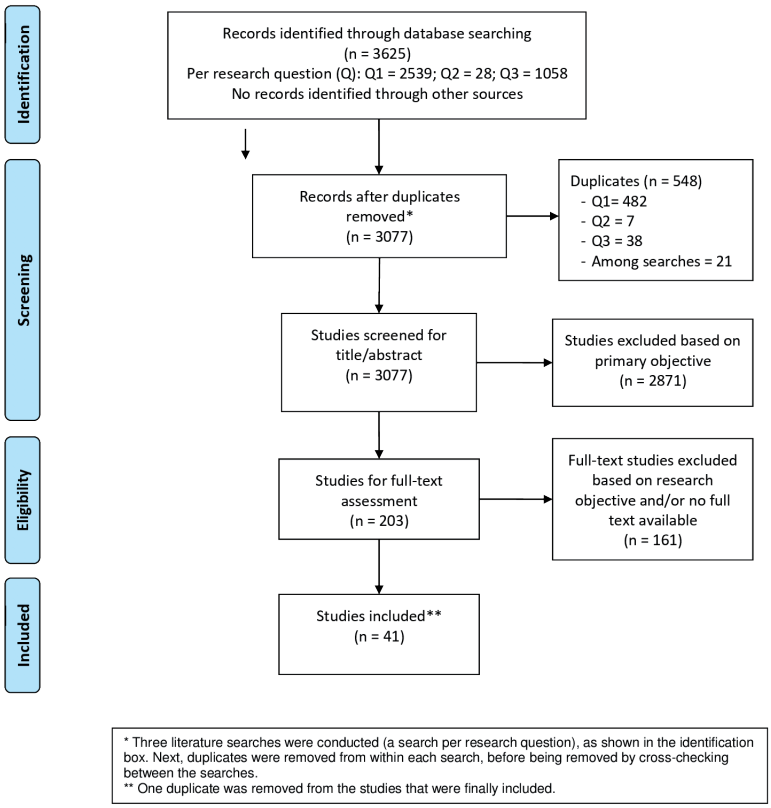

Figure 1. PRISMA flow chart of study inclusion

(1) Surveillance for recurrent or secondary breast cancer

Follow-up aims to detect recurrent disease or new associated malignancies at an early-stage through surveillance imaging (mammography and/or MRI) and physical examination[4-7]. Two included studies discussed decisions about the *form* and *frequency of surveillance imaging* (PS0)[25 26]. Klaassen et al.[25] assessed the needs of Dutch patients and physicians with regard to an aftercare decision-aid. Brandzel et al.[26] then described the experiences and preferences for breast imaging among breast cancer survivors in the United States. The main *form* of surveillance tended to be mammography, though some also received MRI; however, the authors did not specify who received what type of surveillance imaging or the reasons for the differences. If their breast cancer initially was missed on mammography, patients sometimes lost trust in this method, and preferred other imaging modalities. Furthermore, many patients received surveillance mammography more often than the recommended annual frequency without clinical indication[26]. Patients preferred this higher *frequency* because it reassured them about the absence of recurrences[25 26]. However, breast imaging also caused anxiety and was considered uncomfortable for many patients[26], suggesting scope for a trade-off between burdens and benefits of surveillance imaging (PS1). Surveillance preferences were also affected by financial costs and insurance coverage[26], and therefore, the patient's willingness to bear these costs (PS5).

Little evidence was found for patient involvement in surveillance-related decisions. Brandzel et al.[26] found that physicians typically determined the imaging type and frequency of surveillance (SDM5), despite the opposing preferences and trade-offs expressed by patients. The patient's understanding of the goal of surveillance could be improved here: patients felt confused about the options for the type of surveillance imaging and frequency of surveillance imaging, and expressed a need for information about the transition from treatment to surveillance care (SDM3). The aftercare decision-aid produced by Klaassen et al.[25] provides an overview of follow-up options (SDM7), and could reduce information needs before initiating follow-up. Surveillance *length* was not discussed in the literature.

Hereditary testing is most often performed during breast cancer diagnosis and may be less relevant during follow-up[4]. However, Rini et al.[27] described hereditary testing in women with a history of breast cancer. Hereditary testing leads to information about the risk of secondary breast cancer, and/or risk of breast cancer or ovarian cancer in family members. This can affect surveillance schemes or preventative options, such as contralateral prophylactic mastectomy (PS0).

(2) Consultations for physical and psychosocial (late) effects

A second goal of follow-up is informing and counselling patients about the physical and psychosocial (late) effects of treatment[4-7]. Two studies described decision-making regarding the *form, frequency, and length of follow-up consultations* within follow-up care (PS0). Patients preferred more personal attention from their physician and a higher *frequency* of oncology-led aftercare than was offered (current situation not defined), which gave them more security about their health[25]. Regarding the *length* of follow-up consultation, all USA-based participants in a study by Hudson

et al. had received follow-up care from a cancer specialist within the previous year, even though the time since their last active cancer treatment ranged from three to seventeen years; however, decisions about length were not discussed further[28]. Regarding the *form* of consultations, patients preferred consultations by a breast cancer specialist, possibly alternated with nurse consultations (PS1)[25]. Regardless of these preferences, patients were rarely offered options about the frequency, form, or length of consultations, indicating low patient-involvement.

By contrast, most physicians stated that SDM was common practice in their healthcare facilities and in their own work, and reported that using SDM made the patients feel positively involved in decisions related to follow-up (SDM5)[25]. Referral to other medical specialists or care providers during follow-up was not specifically described. However, 24% of patients sought care from multiple providers, including a primary care provider, general internist, or gynaecologist[28].

(3) Recurrence risk reduction by anti-hormonal treatment

Seven studies described *treatment decisions about anti-hormonal therapy*[29-35]. This consisted of tamoxifen or aromatase-inhibitor use to increase locoregional tumour control and survival, given for a minimum of five consecutive years, and continuing during follow-up[4]. Respectively, there were two and five studies on decisions regarding *therapy initiation*[30 35] and *therapy adherence*[29-32 34]. Within the literature, therapy initiation was rarely regarded as a preference sensitive decision: one study described that 96% of patients were steered towards anti-hormonal therapy, irrespective of the expected benefit[33]; in another study, patients felt obliged to take the therapy (PS0)[30]. However, the decision about *anti-hormonal therapy* is not an one-off decision: four studies described that the decision to adhere to anti-hormonal therapy leads to patients making an ongoing risk-versus-benefit trade-off between the risk-reducing effect of treatment and the severity of treatment-induced side-effects (PS4)[29-32 34]. Nonadherent patients in two studies felt unable to cope with side-effects that severely affected their lives (PS5)[30 31]. Three studies reported that professional guidance or support from physicians for managing these side effects could be improved[29 31 32]. Such guidance is important, because patients can better persevere with side effects if they have a high belief in their ability to manage and control their medication and side effects (PS1)[32]. However, four studies reported gaps in providing information about expected side effects[29 30 33] or their management (SDM3)[30 31].

Frequently reported effects of anti-hormonal therapy were menopausal symptoms and joint pain, with cognitive decline and cardiac distress also occurring, but less frequently[30]. Two studies specifically discussed the identification and treatment of *treatment-induced menopausal symptoms* (PS0)[36 37], such as hot flashes, weight gain, loss of sexuality, and increased osteoporosis. Symptom treatment was considered a preference sensitive decision because hormone replacement therapy is the customary and most effective option, even though it increases the risk of recurrence and should be avoided in patients with breast cancer (PS4)[36 37]. However, there are few alternatives (PS2), with these limited to various lifestyle changes, pharmaceutical options, and complementary treatments (e.g. mind-body therapies and natural health products)[36]. As both studies reported, a lack of reliable and unambiguous information about these options makes it difficult to select the

best option (PS3). Concerning this dilemma, patients were frustrated by the lack of conclusive information, particularly about complementary therapies, and by an inability to differentiate between credible and non-credible information sources (SDM3). Balneaves et al.[36] suggested using an SDM-tool that could summarise credible information about accepted options and thus facilitate decision-making (SDM7). Two-third of patients in this study still used complementary therapy to manage symptoms, despite the lack of information[36].

(4) Improving quality of life after breast cancer treatment

This topic was subdivided into three subtopics. Sixteen studies focused on *delayed breast reconstruction*, two on *lifestyle changes*, and four on *getting pregnant after breast cancer*.

Breast reconstruction yields positive psychosocial effects[38-41] and may contribute to the patients wellbeing after breast cancer. Although some, if not most decisions about breast reconstruction are made before surgical treatment, resulting in immediate breast reconstruction, some patients and/or clinicians delay the decision about breast reconstruction until after treatment. Patients must then first decide whether to undergo delayed breast reconstruction, and when they do, decide which reconstruction technique should be used (PS0). Decisions about delayed breast reconstruction can remain relevant years after tumour surgery[42 43] and have been recognised as highly preference sensitive in three studies[38 44 45]. Furthermore, seven studies indicated that breast reconstruction yields positive psychosocial effects[38-41] and that it is an important option for patients who have undergone mastectomy[42 46 47]. In three studies, common reasons for opting to delay breast reconstruction rather than undergoing breast reconstruction were reported, and it was concluded that either patients wanted to focus on other treatment modalities first[39 42], or that the desired technique was not available at their facility[45]. Patients generally refused breast reconstruction if they felt it was not important, urgent[42], or necessary, or feared undergoing further surgery[39]. Thus, apart from medical contra-indications, decisions about undergoing breast reconstruction were affected by its timing and individual decisions about trade-offs (PS1). Regardless of the potential for positive psychosocial effects[38-41], risks of breast reconstruction can be high (PS4). Indeed, it is a major and invasive surgery[38 39 42 47 48], and patients have reported concerns about surgical complications, and interference with cancer surveillance[42], or postmastectomy radiotherapy[39]. There are also multiple options, such as autologous or implant-based breast reconstruction (PS0), with each associated with to different outcomes (PS1)[38 40 43 49].

Current patient involvement in decisions about breast reconstruction appeared to be high: fifteen studies described elements of patient-involvement or SDM[38-48 50-52], and patients in two studies specifically reported feeling involved in decision-making (SDM5)[51 52]. SDM about breast reconstruction led to less conflict around decisions and to more satisfaction with the information provided (SDM4)[43]. By contrast, four studies reported that patients experienced decision-making uncertainty[41-43 47] and eight studies recommended further improvement of information provision (SDM3)[38 40 42 45 47 48 50 52]. This could be addressed by using one of four decision aids that have been developed (SDM7)[38 43 49 50].

In younger patients, breast cancer treatment can interfere with the desire to have a family. Four studies described the decision to *get pregnant after treatment for breast cancer* [29 53-55]. Although this decision may feel like a risk, there is consensus that pregnancy following breast cancer is safe[53]. Nevertheless, both patients and physicians have expressed concerns about the potential for pregnancy to increase recurrence risk in patients with hormone-sensitive breast cancer (PS4)[53-55]. Patients not only felt under informed (SDM3)[53], but also, patients worried whether breast cancer and its treatment would negatively affect the health of a future child (PS4)[53 55]. In general, there was a wide variety in the level of concern about fertility and getting pregnant. The importance of family building depended on personal circumstances, values, and expectations[53-55]. In a study of Chinese breast cancer survivors, social and cultural perceptions about having children were important motives (PS1)[55]. Although all three included studies described patient involvement in decisions about fertility management, it was also noted that the information provided could be improved (SDM3).

Anti-hormonal therapy may cause infertility in premenopausal patients. Those on anti-hormonal therapy may therefore have to wait to the end of the treatment period (i.e. five years), while may be accompanied by an age-related decline in fertility (PS1). In some patients, oncologists were willing to discuss the option of a reduced duration of anti-hormonal treatment[53]. Another study recognised the need to counsel patients about family-building periodically during anti-hormonal treatment[29]. Indeed, fertility counselling may remain important throughout follow-up because treatment-affected fertility may have negative psychosocial consequences[54 55].

Chemotherapy treatment can also lead to reduced fertility. Therefore, patients should have the option to choose from a range of artificial reproductive techniques, including ovarian stimulation, and oocyte or embryo cryopreservation, before treatment (PS0)[53]. These decisions will also affect decision-making during follow up, for instance, patients who have opted for artificial reproductive techniques before treatment will have to decide on what to do with their preserved oocytes or embryos after treatment (PS0). All patients in a study by Corney and Swinglehurst[53] indicated that they would not use the embryos or oocytes if they were able to conceive naturally, leading to moral decision about what to do with the oocytes or embryos.

Quality of life improvements after cancer may be found by implementing *lifestyle changes.* Two RCTs described a lifestyle intervention and the reasons why patients did and did not participate (PS0)[56 57]. Shtaynberger and Krebs[57] described how decisions about physical activities and fruit and vegetable intake were based on an individual weighing the pros and cons of making a change (the so-called decisional balance) (PS1). Carter et al.[56] described the reasons for cancer patients to participate in either of two physical activity programmes (walking or 'dragon boat' rowing') offered in their RCT. They reported that decisions were based on physical (health benefits), social (meeting new people, learning new skills), and practical (time investment, scheduling) considerations, but did not state whether the decision was discussed with a physician.

Table 1. search strategy per research question* for MEDLINE (accessed through PubMed), PsycINFO (accessed through Ovid), and EMBASE

	Databases			Research question*		
Search words	**MEDLINE (PubMed)**	**PsychINFO (Ovid)**	**EMBASE**	**1**	**2**	**3**
Breast cancer	(("breast"[MeSH Terms] OR "breast"[All Fields]) AND ("neoplasms"[MeSH Terms] OR "neoplasms"[All Fields] OR "cancer"[All Fields])) OR ("neoplasms"[MeSH Terms] OR "neoplasms"[All Fields] OR "malignancy"[All Fields]) OR ("tumour"[All Fields] OR "neoplasms"[MeSH Terms] OR "neoplasms"[All Fields] OR "tumour"[All Fields]) OR ("carcinoma"[MeSH Terms] OR "carcinoma"[All Fields]) OR "neoplasms"[MeSH Terms] OR "neoplasms"[All Fields] OR "neoplasm"[All Fields] OR "mass"[All Fields] OR Nodule[All Fields] OR ("cysts"[MeSH Terms] OR "cysts"[All Fields] OR "cyst"[All Fields])	exp BREAST NEOPLASMS/ OR (exp BREAST/ AND exp NEOPLASMS/) OR breast cancer. mp OR ((breast.mp OR exp BREAST/) AND (cancer.mp OR neoplasm*.mp OR carcin*.mp OR tumour*.mp OR tumour*.mp OR metasta*.mp OR malig*.mp))	breast cancer'/exp OR (breast:ti,ab AND carcinoma*:ti,ab) OR (breast:ti,ab AND cancer*:ti,ab) OR (breast:ti,ab AND neoplasm*:ti,ab) OR (breast:ti,ab AND tumour*:ti,ab) OR (breast:ti,ab AND tumour*:ti,ab) OR (breast:ti,ab AND metasta*:ti,ab) OR (breast:ti,ab AND malig*:ti,ab) OR ('breast'/exp AND (neoplas*:ti,ab OR cancer*:ti,ab OR carcin*:ti,ab OR tumour*:ti,ab OR tumour*:ti,ab OR metasta*:ti,ab OR malig*:ti,ab OR 'neoplasm'/exp))	x	x	x
Follow-up	follow-up[All Fields] OR ("aftercare"[MeSH Terms] OR "aftercare"[All Fields] OR ("after"[All Fields] AND "treatment"[All Fields]) OR "after treatment"[All Fields]) OR "survival"[MeSH Terms] OR "survival"[All Fields] OR "survivorship"[All Fields] OR (care[All Fields] AND plan[All Fields]) OR care[All Fields] OR surveillance [All Fields]	follow-up.mp. OR exp POSTTREATMENT FOLLOWUP/ OR followup.mp OR aftercare.mp OR after-care.mp OR exp Aftercare/ OR ((exp PATIENTS/ or patient.mp) AND (monitoring.mp. or exp MONITORING/)) OR after treatment.mp OR exp Survivors/ OR survival.mp OR survivorship. mp OR exp Treatment Planning/ OR care plan.mp OR surveillance.mp	follow up':ti,ab OR 'aftercare':ti,ab OR 'aftercare'/de OR (after NEAR/1 treatment):ti,ab OR 'survival':ti,ab OR 'survival'/de OR 'survivorship'/de OR 'survivorship':ti,ab OR (care NEAR/1 plan):ti,ab OR 'surveillance'/de OR 'surveillance'	x		x
Decision-making	("Decisions"[Journal] OR "decisions"[All Fields]) AND ("decision support techniques"[MeSH Terms] OR ("decision"[All Fields] AND "support"[All Fields] AND "techniques"[All Fields]) OR "decision support techniques"[All Fields] OR ("decision"[All Fields] AND "analysis"[All Fields]) OR "decision analysis"[All Fields])	decision-making.mp. or exp Decision-making/ OR ((support techniques.mp) AND (decision. mp)) OR ((support.mp) AND (techniques.mp)) OR decision support techniques.mp OR ((decision. mp) AND (analysis.mp)) OR decision analysis.mp	decision-making'/de OR 'decision-making':ti,ab OR ('decision'/de OR decision AND ('support'/de OR support) AND techniques) OR 'decision'/de OR decision AND ('analysis'/de OR analysis)	x		

Table 1. search strategy per research question* for MEDLINE (accessed through PubMed), PsycINFO (accessed through Ovid), and EMBASE (continued)

	Databases			Research question*		
Search words	**MEDLINE (PubMed)**	**PsychINFO (Ovid)**	**EMBASE**	**1**	**2**	**3**
Preference-sensitive decisions	preference[All Fields] AND sensitive[All Fields] AND ("Decisions"[Journal] OR "decisions"[All Fields])	preference-sensitive.mp	preference sensitive':ti,ab		x	
Shared decision-making	decision-making[MeSH Terms] OR ("decision"[All Fields] AND "making"[All Fields]) OR "decision-making"[All Fields] OR ("shared"[All Fields] AND "decision"[All Fields] AND "making"[All Fields]) OR "shared decision-making"[All Fields]	((shared.mp) AND (decision-making.mp or exp Decision-making/))	shared decision-making'/de OR 'shared decision-making'			x

* 1) What are the common complaints and issues that can occur for woman treated for breast cancer with curative intent for which decisions have to be made with regard to management within five years after curative treatment?; 2) To what extent are decisions with regard to the management of these complaints preference sensitive?; 3) To what extent and how are patients with breast cancer involved in making these follow-up-related decisions?

Table 2. Preference sensitiveness and patient involvement, based on the prespecified criteria for each decision about the content or form of follow-up

Decision	Degree in which decisions are preference-sensitive (criteria PS)	Conditions for shared-decision-making (criteria SDM)
Surveillance for recurrent or secondary breast cancer		
Form (Klaassen et al., 2017, Brandzel et al., 2017)	0) Women underwent various types of surveillance imaging (not specified), although almost all woman received mammographic examination. Some also received MRI (Brandzel et al., 2017). 1) Some women stated that they would prefer a false-positive result with follow-up procedures, other women wanted to avoid false-positive results and follow-up procedures because the additional tests caused too much worry, physical discomfort, and potential expense. 1) Some women whose breast cancer was not found with screening mammography had less trust in mammography. Other women were confident in mammography and did not feel the need for reassurance from additional imaging modalities (Brandzel et al., 2017). 5) Cost and insurance coverage was an important topic that sometimes affected participant preferences (Brandzel et al., 2017).	3) Patients reported a need for information about the transition to surveillance care (Brandzel et al., 2017). Women reported feeling confusion about the choices for surveillance imaging or about the frequency of imaging examinations (Brandzel et al., 2017). 3) A point of improvement was women's understanding of (the goal of) surveillance (Brandzel et al., 2017). 5) Women reported trust in their providers and relied on providers for imaging decision-making (Brandzel et al., 2017). Most participants reported that either their oncologist or surgeon recommended and made the referrals for their imaging type and frequency after treatment (Brandzel et al., 2017). 7) Although some patients received a detailed survivorship care plan, others reported that they did not receive clear information (Brandzel et al., 2017). 7) To promote SDM about form and frequency of follow-up, Klaassen et al (Klaassen et al., 2017) suggest a follow-up decision-aid.
Frequency (Klaassen et al., 2017, Brandzel et al., 2017)	0) Many patients received surveillance mammography more often than the recommended annual frequency. 1) Most women were satisfied with the frequency or wanted more frequent surveillance to reassure they did not have a recurrent breast cancer (Klaassen et al., 2017). However, women also reported that breast imaging caused anxiety and was an uncomfortable experience (Brandzel et al., 2017).	3) A point of improvement was women's understanding of (the goal of) surveillance (Brandzel et al., 2017). 3) Women reported feeling confusion about the choices for surveillance imaging or about the frequency of imaging examinations (Brandzel et al., 2017). 5) Most of the participating patients had not discussed their preferences with any of the HPs, as they were afraid to damage the relationship they had with their HP (Klaassen et al., 2017). Most participants reported that either their oncologist or surgeon recommended and made the referrals for their imaging type and frequency after treatment (Brandzel et al., 2017). 7) To promote SDM about form and frequency of follow-up, Klaassen et al (Klaassen et al., 2017) suggest a follow-up decision-aid.

Table 2. Preference sensitiveness and patient involvement, based on the prespecified criteria for each decision about the content or form of follow-up (continued)

Decision	Degree in which decisions are preference-sensitive (criteria PS)	Conditions for shared-decision-making (criteria SDM)
Length	No studies identified	No studies identified
Hereditary testing (Rini et al., 2009)	0) Hereditary testing leads to information about the risk of secondary breast cancer or breast cancer in family members, affecting surveillance schemes or decisions about preventative options, such as contralateral prophylactic mastectomy 3) Inconclusive evidence: hereditary tests cannot always rule out completely the presence of genetic mutations. Counsellors typically provide these women with a qualitative estimate of their residual risk of carrying a mutation and of developing a second cancer. These risk estimates, which are based on various characteristics of a woman's family pedigree, are highly heterogeneous and entail a great deal of uncertainty. It is not currently clear how receiving an uninformative BRCA1/2 test result influences the difficulty of women's risk management decisions (Rini et al., 2009).	3) Because of the inconclusiveness of the results, decisions about risk reduction options can be underinformed (Rini et al., 2009). 5) The findings suggest that a substantial number of these women may benefit from assistance with risk management decision-making. Genetic counsellors are one potential source of such assistance (Rini et al., 2009). 7) The development of a decision aid for women who receive uninformative BRCA1/2 test results may be warranted, particularly in light of the increasing availability and use of these tests (Rini et al., 2009).
Follow-up consultations for physical and psychosocial (late) effects		
Form (Hudson et al., 2012); (Klaassen et al., 2017)	1) Approximately, one quarter (24 %) of participants reported seeking care from multiple providers, including a primary care physician (PCP, i.e., family physician, general internist, or gynaecologist) (Hudson et al., 2012). 1) Patients preferred consultations by a breast cancer specialist, possibly alternated with consultations with a nurse (Klaassen et al., 2017).	3) Women in their study reported that most patients were not offered options regarding structure and frequency of the aftercare appointments (Klaassen et al., 2017), although the option of between-appointment calls with the nurse practitioner was provided to some patients (Klaassen et al., 2017). 5) Patients reported difficulty in expressing their need for options to their health professional (Klaassen et al., 2017). HPs felt that most patients want the same thing concerning aftercare (Klaassen et al., 2017). 7) To promote SDM about form and frequency of follow-up, Klaassen et al (Klaassen et al., 2017) suggest a follow-up decision-aid.

Table 2. Preference sensitiveness and patient involvement, based on the prespecified criteria for each decision about the content or form of follow-up (continued)

Decision	Degree in which decisions are preference-sensitive (criteria PS)	Conditions for shared-decision-making (criteria SDM)
Frequency (Hudson et al., 2012); (Klaassen et al., 2017)	1) In all focus groups, patients mentioned that they would like either more personal attention from the HP, a higher frequency of physical checks-ups to detect recurrences or more aftercare consultations in general (Klaassen et al., 2017).	3) Women in their study reported that most patients were not offered options regarding structure and frequency of the aftercare appointments (Klaassen et al., 2017), although the option of between-appointment calls with the nurse practitioner was provided to some patients (Klaassen et al., 2017). 5) Physicians said that SDM is common practice in their healthcare facilities and in their own work as well and believed SDM made the patients feel positively involved in follow-up related decisions. 5) Patients reported difficulty in expressing their need for options to their health professional (Klaassen et al., 2017). HPs felt that most patients want the same thing concerning aftercare (Klaassen et al., 2017). 7) To promote SDM about form and frequency of follow-up, Klaassen et al (Klaassen et al., 2017) suggest a follow-up decision-aid. 7) However, not every patient is sufficiently activated and skilled to retrieve the care they require [29].
Length (Hudson et al., 2012); (Klaassen et al., 2017)	0) All participants reported having received follow-up care from a cancer specialist (i.e., medical/surgical/radiation oncologist) within the past year (Hudson et al., 2012).	
Recurrence-risk reduction by anti-hormonal treatment		
Treatment with adjuvant anti-hormonal therapy: initiation (Bluethmann et al., 2017, Neugut et al., 2012).	0) Therapy initiation (Bluethmann et al., 2017, Neugut et al., 2012). 0) 96% of patients were steered towards undergoing anti-hormonal therapy, irrespective of expected benefits (Engelhardt EG et al., 2016). 1) Preliminary evidence suggests that prioritizing fertility, along with concerns about side effects, leads to ET non-initiation and early discontinuation (Benedict et al., 2017).	2) Patients might feel overwhelmed: decision is directly posed after surgery, while patients might still be processing this surgery (Engelhardt EG et al., 2016). 3) Educational materials about family building after cancer are still not consistently available or provided (Benedict et al., 2017). 5) Patients did not always get to make a decision or were steered towards the option favoured by the clinician (Engelhardt EG et al., 2016). 6) Non-initiation was less likely in those who found the quality of patient/physician communication to be higher (Neugut et al., 2012).

Table 2. Preference sensitiveness and patient involvement, based on the prespecified criteria for each decision about the content or form of follow-up (continued)

Decision	Degree in which decisions are preference-sensitive (criteria PS)	Conditions for shared-decision-making (criteria SDM)
Treatment with adjuvant anti-hormonal therapy: adherence (Benedict et al., 2017, Bluethmann et al., 2017, Brauer et al., 2016, Cahir et al., 2015, Hershman et al., 2016, Engelhardt EG et al., 2016).	0) Therapy adherence (Benedict et al., 2017, Bluethmann et al., 2017, Brauer et al., 2016, Cahir et al., 2015, Hershman et al., 2016, Engelhardt EG et al., 2016). 1) Key enablers for adherent/persistent women were identified within the domain beliefs about consequences (breast cancer recurrence), intentions and goals (high-priority), beliefs about capabilities (side effects) and behaviour regulation (managing medication)(Cahir et al., 2015). Quality of life and attitudes toward ET at baseline were associated with non-persistence (Hershman et al., 2016). Preliminary evidence suggests that prioritizing fertility, along with concerns about side effects, leads to ET non-initiation and early discontinuation (Benedict et al., 2017). 3) The adverse effects of AIs were difficult to disentangle from what women attributed to comorbid conditions or getting older. This challenge in attribution, coupled with less frequent contact with their oncology team, resulted in many women “winging it” or persisting with the AI despite significant struggles (Brauer et al., 2016). 4) Risk-versus-benefit trade-off (Bluethmann et al., 2017, Brauer et al., 2016, Engelhardt EG et al., 2016): anti-hormonal therapy is an established risk-reduction strategy for recurrences and contra-lateral breast cancer vs severity of side-effects (Benedict et al., 2017, Bluethmann et al., 2017, Brauer et al., 2016, Hershman et al., 2016). 5) Its effectivity is highly dependent of the patients cooperation (therapy adherence) (Cahir et al., 2015); highly affect the patient’s lifestyle by its side-effects (Bluethmann et al., 2017, Brauer et al., 2016).	3) Gaps in information provision (Bluethmann et al., 2017, Brauer et al., 2016, Cahir et al., 2015, Engelhardt EG et al., 2016), for instance about expected side effects or possible management strategies (Bluethmann et al., 2017). 5) Regarding persistence, many reported lack of professional guidance or support with respect to persisting with the AI, especially when adverse effects were present, and relied on a variety of self-management strategies to maintain treatment with the AI (Brauer et al., 2016).

Table 2. Preference sensitiveness and patient involvement, based on the prespecified criteria for each decision about the content or form of follow-up (continued)

Decision	Degree in which decisions are preference-sensitive (criteria PS)	Conditions for shared-decision-making (criteria SDM)
Menopausal symptoms following from breast cancer therapies (Balneaves et al., 2016, Sayakhot et al., 2012).	0) Identification and treatment of menopausal symptoms. 2) As there are limited other conventional treatment options available, patients reside in alternative treatments as mind-body therapies and natural health products (Balneaves et al., 2016). 3) There is a lack of reliable and unambiguous information about these options (Sayakhot et al., 2012). 4) The potential risks of hormone replacement therapy, which is the customary and most effective treatment option, could be high. This option is usually avoided for breast cancer patients as it increases recurrence risks (Balneaves et al., 2016, Sayakhot et al., 2012).	3) Although 80% of women were given breast cancer information, only 54% were given menopause information at diagnosis. Women were least satisfied (26%) with information regarding the long-term complications of menopause (Sayakhot et al., 2012). 3) A lack of reliable and unambiguous information about treatment options for menopausal symptoms was reported (Balneaves et al., 2016, Sayakhot et al., 2012). 3) Some women were not aware their symptoms were menopause, induced by their cancer treatment— and not a temporary, remediable effect. Although many of the women were informed that their menstrual cycles would end following treatment, they did not fully realize the implications and meaning of the associated physiological changes. The women were surprised by the sudden onset and intensity of their menopausal symptoms (Balneaves et al., 2016). 3) In addition to being inundated by the large volume of information, the women were frustrated by the lack of conclusive information, particularly regarding complementary therapies. The majority of women were also frustrated by their inability to differentiate between credible and non-credible information sources (Balneaves et al., 2016). 7) Balneaves et al (Balneaves et al., 2016), suggest a tool that summarizes evidence for each option of menopausal treatment.

Table 2. Preference sensitiveness and patient involvement, based on the prespecified criteria for each decision about the content or form of follow-up (continued)

Decision	Degree in which decisions are preference-sensitive (criteria PS)	Conditions for shared-decision-making (criteria SDM)
Improving quality of life		
Breast reconstruction (Alderman et al., 2011, Causarano N et al., 2015, Fu et al., 2017, Hamnett and Subramanian, 2016, Heller et al., 2008, Morrow et al., 2014, Ogrodnik et al., 2016, Potter et al., 2013, Sherman et al., 2016, Lee et al., 2010, Flitcroft et al., 2016, Zielinski et al., 2015, Fasse et al., 2017, Temple-Oberle et al., 2014)	0) Patients might decide to undergo breast reconstruction for years after surgery has taken place (Alderman et al., 2011, Sherman et al., 2016). 1) One-third of mastectomy-treated patients choose delayed reconstruction as they focussed on more on other treatment modalities (Alderman et al., 2011, Flitcroft et al., 2016). Two-thirds of patients without reconstruction said this procedure was of no importance to them (Alderman et al., 2011); other reasons were that it was were 'unnecessary' and 'being practical'(Flitcroft et al., 2016), poor timing (25 %), indecision (17 %), desired method of reconstruction not available at treating facility (10 %), persistent obesity (8.3 %), continued smoking (4 %), and reason not specified (35 %) (Ogrodnik et al., 2016), it is not essential for their mental state, or they fully accepted their appearance after mastectomy (Zielinski et al., 2015). Older patients (>60 years) were less likely to choose for breast reconstruction (Flitcroft et al., 2016). Patients spoke about breasts as a function of their roles as a wife or mother, eliminating the need for breasts when these roles were fulfilled (Fu et al., 2017). Many addressed the fear of multiple operations (Fu et al., 2017, Zielinski et al., 2015). 4) A breast reconstruction is a major and invasive surgery (Alderman et al., 2011, Causarano N et al., 2015, Flitcroft et al., 2016, Fu et al., 2017, Hamnett and Subramanian, 2016), regardless of the vast part of included studies that recognised the positive psychosocial effects that BR yields (Causarano N et al., 2015, Flitcroft et al., 2016, Potter et al., 2013, Zielinski et al., 2015) and the importance of breast reconstruction for mastectomy patients (Alderman et al., 2011, Fasse et al., 2017, Fu et al., 2017). Half of the respondents was concerned about surgical complications and interference with cancer surveillance (Alderman et al., 2011), or postmastectomy radiotherapy might interfere with reconstruction (Flitcroft et al., 2016).	1) Within several studies, the preference-sensitive nature of breast reconstruction decisions was literally appointed (Causarano N et al., 2015, Lee et al., 2010, Ogrodnik et al., 2016). 3) Information provision could be improved (Alderman et al., 2011, Causarano N et al., 2015, Fu et al., 2017, Hamnett and Subramanian, 2016, Heller et al., 2008, Morrow et al., 2014, Ogrodnik et al., 2016, Potter et al., 2013). The older patient is less likely to do research independently (Hamnett and Subramanian, 2016). 4) SDM about breast reconstruction yields positive effects as lower decisional conflict and higher satisfaction with information (Sherman et al., 2016). 5) Patients felt involved in the decision-making process (Kadmon et al., 2016, Morrow et al., 2014). 7) Already several decision aids were developed for breast reconstruction (Heller et al., 2008, Sherman et al., 2016, Temple-Oberle et al., 2014, Causarano N et al., 2015).
Breast reconstruction techniques (Causarano N et al., 2015, Potter et al., 2013, Sherman et al., 2016, Temple-Oberle et al., 2014).	0) In the decision to undergo a BR, there are multiple options of autologous or implant-based BR, each leading to its own outcomes (criterion PS1) (Causarano N et al., 2015, Potter et al., 2013, Sherman et al., 2016, Temple-Oberle et al., 2014). 1) Patients placed greater importance on avoiding use of a prosthesis (Lee et al., 2010).	

Table 2. Preference sensitiveness and patient involvement, based on the prespecified criteria for each decision about the content or form of follow-up (continued)

Decision	Degree in which decisions are preference-sensitive (criteria PS)	Conditions for shared-decision-making (criteria SDM)
Getting pregnant after breast cancer (Benedict et al., 2017, Corney and Swinglehurst, 2014, Gorman et al., 2011, Hsieh and Huang, 2017).	0) Getting pregnant after cancer treatment. 1) A wide variety in level of concern about fertility was noted, as this depends on personal circumstances, values and expectations (Gorman et al., 2011, Hsieh and Huang, 2017). Management of fertility issues was heavily influenced by social and cultural perceptions about having children (Hsieh and Huang, 2017). 3) More than half of the participants (n = 9, 56%) were concerned about passing cancer-positive genes to their child; they worried that cancer-related treatment could affect the child's health in the future. (Hsieh and Huang, 2017). 4) Women in the study proactively collected information about cancer, cancer treatment and pregnancy. They then weighed the personal risk–benefit between conceiving and contraception based on their assessment of their personal situation and condition. Patients worried whether breast cancer and the treatment had a negative effect on their child	3) Patients were not sufficiently informed about risks of getting pregnant (Corney and Swinglehurst, 2014). 3) All included studies stated that patient information about management of fertility could be improved (Corney and Swinglehurst, 2014, Gorman et al., 2011, Hsieh and Huang, 2017). 3) The study by Balneaves et al. (Benedict et al., 2017) about menopausal symptoms described that oncology providers stated that they felt ill-equipped to inform patient about fertility-issues management. 5) Participants reported having very good relationships with their oncologists, describing them as a trusted and valuable source of information when making critical treatment decisions. However, the relationship later became strained for some women who felt that their decisions about pregnancy were not supported (Gorman et al., 2011).
Pregnancy and anti-hormonal treatment (Benedict et al., 2017, Corney and Swinglehurst, 2014, Gorman et al., 2011, Hsieh and Huang, 2017).	1) An important cause of non-initiation of anti-hormonal therapy is the prioritising of family-building over the benefits of anti-hormonal therapy (Benedict et al., 2017). 1) The patients increasing age during anti-hormonal treatment administration may give a decline in fertility as well (Corney and Swinglehurst, 2014)	3) All included studies stated that patient information about management of fertility could be improved (Corney and Swinglehurst, 2014, Gorman et al., 2011, Hsieh and Huang, 2017). 3) The study by Balneaves et al. (Benedict et al., 2017) about menopausal symptoms described that oncology providers stated that they felt ill-equipped to inform patient about fertility-issues management. 3) Clinical efforts to improve adherence to endocrine therapy might need to consider patients' familybuilding goals during the course of treatment and to appropriately counsel patients according to their priorities and family-building intentions. Educational materials about family building after cancer are still not consistently available or provided (Benedict et al., 2017).
Pre-treatment artificial reproductive techniques (Corney and Swinglehurst, 2014, Zielinski et al., 2015)	0) Women choose from a range of options including ovarian stimulation, or oocyte or embryo cryopreservation (Corney and Swinglehurst, 2014). 1) Women without a partner that did not want to opt for the less successful oocyte preservation, had to find a donor to enable embryo cryopreservation (Zielinski et al., 2015). 1) All the women indicated that they would not use the embryos or oocytes if they were able to conceive naturally. However, this led to the moral dilemma on what they would do with the eggs or embryos (Corney and Swinglehurst, 2014).	2) Decisions had to be made quickly [37]; women felt they were informed too late about their options [38]. 5) No woman was offered supportive counselling to aid the decision pursuing artificial reproductive techniques (Corney and Swinglehurst, 2014).

Table 2. Preference sensitiveness and patient involvement, based on the prespecified criteria for each decision about the content or form of follow-up (continued)

Decision	Degree in which decisions are preference-sensitive (criteria PS)	Conditions for shared-decision-making (criteria SDM)
Lifestyle changes		
Lifestyle changes (Carter et al., 2010, Shtaynberger and Krebs, 2016)	1) The trade-off is aimed at weighing pros and cons of making a change, so-called decisional balance (Shtaynberger and Krebs, 2016). Participants' reasons for selecting a particular physical activity program are diverse. A variety of activity programmes might be necessary to fit the needs of cancer survivors (Carter et al., 2010). 5) The effect of lifestyle interventions is highly dependent of the patients cooperation.	
Alternative medicine		
Use of alternative and complementary medicine (Holmes et al., 2017)	3) Holmes et al. (Holmes et al., 2017) describe patients opting for complementary alternative medicine in general and whether and how they were supported in this decisions. information available on the internet plays a factor in the decision-making process to use CAM, as it may be seen as the only comprehensive way to get information on CAM.	3) Many participants expressed a need for information after their cancer diagnosis and viewed the internet as the only accessible way to get information. Due to the unrestricted nature of the internet, many had concerns about the legitimacy of website content. 5) Patients mainly used the internet to inform themselves about this topic, as they experienced a lack of approval from their social network and healthcare providers (Holmes et al., 2017).

Aspects of preference sensitive decisions (PS):
PS0) There were multiple options available
PS1) Options had potential favourable and unfavourable outcomes, leading to an individual trade-off
PS2) Options did not differ in terms of favourability of the outcomes, or (un)favourable outcomes were equally (un)desirable
PS3) There was insufficient evidence about favourable or unfavourable outcomes to determine the best option
PS4) The potential risks of an option were high, regardless the potential benefits of this option
PS5) The outcomes were highly dependent on patient cooperation, or the actions required for the preferred option had high impact on the patient's lifestyle

Conditions for shared decision-making (SDM):
SDM1) The decision was preference sensitive
SDM2) There was sufficient time to make a decision
SDM3) The patient was capable and sufficiently informed to make a decision
SDM4) There was a belief that SDM would lead to better patient outcomes
SDM5) The physician was motivated for SDM and clarified the options and preferences
SDM6) There was a belief that SDM will lead to better clinical outcomes
SDM7) There was a system for recording, communicating, and implementing the patient's preferences

Abbreviations:
AI: aromatase inhibitors; BR: breast reconstruction; CI: confidence interval; CAM: complementary alternative therapy; ET: endocrine therapy; HP: healthcare practitioner; IBR: immediate breast reconstruction; NBR: no breast reconstruction; RCT: randomised controlled trial

DISCUSSION

In this study, we aimed to assess the potential to personalise follow-up care for patients after breast cancer treatment, by exploring the evidence on patient preferences for, and patient involvement in decisions about follow-up care. We identified many decisions that needed to be made during follow-up, including those related to surveillance imaging, follow-up consultations, anti-hormonal treatment, treatment-induced menopausal symptoms, and lifestyle changes. Moreover, we identified decisions that were made during treatment, but that required additional decisions during follow-up, such as delayed breast reconstruction, hereditary testing, and pregnancy. The literature revealed that there was a large variety in the degree of preference sensitiveness and patient involvement with each decision during follow-up. Decisions about delayed breast reconstruction, for instance, were among those shown to be highly preference sensitive and for which many indications for patient-involvement existed. Equally, however, decisions were identified for which patients exhibited preferences, but for which they were not necessarily involved. Notably, this included decisions about the form, frequency, and length of surveillance imaging and follow-up consultations. Some decisions were not currently regarded as preference sensitive with a low recognition of the need for patient involvement, such as decisions about anti-hormonal therapy and the management of treatment-induced menopausal symptoms.

Notably, the data indicated that the patient's role and involvement should be improved for several decisions. First, regarding the form, frequency, and length of surveillance imaging, patients desired more frequent[25 26] and intensive[26] surveillance; continuity of care and more frequent or longer appointments were preferences expressed in other studies already[15 16]. Despite these strong preferences, patients were rarely involved in making decisions, with physicians typically setting the imaging type and frequency[26]. However, this is probably a legitimate approach because guidelines provide clear, evidence-based recommendations about surveillance schemes and imaging modalities[4-7]. We suspect that the identified preferences were primarily based on the patient's need for reassurance[25 26 58], and that they may be unaware that more intensive surveillance has no evidence base[59], or that increased exposure might even be harmful[60 61]. Efforts should be made to improve patient understanding of the goals of surveillance[62], specifically at the point of transition from treatment to follow-up[26 63]. Furthermore, the frequency and length of surveillance could be determined by recurrence risk stratification[61], based on data from nomograms or risk-calculators. Although Rabin et al.[64] reviewed 22 cancer prognostic tools, of which 8 focussed on breast cancer, patient-involvement with these tools was not discussed. The authors found only limited evidence reporting actual use of these in practice.

Issues also existed for follow-up consultations aimed at the physical and psychosocial effects of treatment. The available research indicated that patients preferred more frequent consultations than was recommended, that these should be led by specialised oncology-providers[25], and that these should be provided over a longer period of time[28]. As literature described unmet needs in information provision about follow-up, health promotion, late and long term-effects, or emotional and social needs[63 65-68], these preferences may be the result of these unmet needs. Moreover, 24%

of patients sought care from multiple other providers[28], suggesting that referral for personalised care may sometimes be more appropriate than providing general oncology-led follow-up. We expect that using patient-reported outcome measures (PROMs) would help to identify patients' needs regarding specific forms of care[69]. PROMs can include symptom-specific scales about, for instance, physical impairments, sexuality problems, psychosocial problems, and body image[70 71]. Patients and physicians would be able to discuss the results and subsequently ensure appropriate referrals to physiotherapists, sexologists, gynaecologists, medical social workers, psychologists, or plastic surgeons, as necessary.

Decisions about anti-hormonal treatment had little recognition as preference sensitive decisions among physicians, which is somewhat consistent with the 2015 European Society for Medical Oncology guideline. Although this guideline states that follow-up care should seek to motivate patients to continue anti-hormonal treatment[6], we should remember that patients must suffer many side-effects over a long period of time[29-32 34], and that this often occurs without proper counselling[29 31 32]. This leaves patients struggling to cope with difficult symptoms with minimal support [31]. Given that therapy-adherence depends on perseverance despite side-effects[30 31], the needs and preferences of patients require more personalised attention in the long-term. This may be challenging, particularly for patients confronted with menopausal symptoms, for whom safe and effective evidence-based options for symptom relief are scarce[36 37]. Finally, treatment-affected fertility in young premenopausal women may conflict with the desire to build a family, producing negative long term psychosocial effects[29 54 55]. These issues necessitate explicit information provision, counselling, and ongoing support to ensure treatment compliance and management of side effects[67 72 73].

Strengths and limitations

Several limitations should be kept in mind when interpreting the results of this study. In the interview and focus-group studies, the samples included in these studies were small, which may limit the generalizability of the data. However, all the included studies were rated as valuable in the quality assessment.

We considered that the effectiveness of patient involvement or SDM is a separate research topic. Shay and Lafaya[74] concluded that evidence about the association between empirical measures of SDM and patient behavioural and health outcomes is lacking. Given that SDM is not associated with improved outcomes, it should not be considered a goal in itself. However, because outcomes do tend to improve with personalised care, SDM may moderate some other factor[74].

Practice implications and recommendations

Currently, there is an international trend towards increased SDM in the diagnosis and treatment of all disease, based on the value-based healthcare initiative[17]. Further personalisation of follow-up

care may lead to care that is not only of greater value for the individual patient, but also to care that is more appropriate from a financial perspective, potentially leading to more responsible use of available healthcare services as well. The process used when deciding on breast reconstruction may be considered an example of best-practise for other decisions about follow-up. Eight studies recommended improvement in information provision[38 40 42 45 47 48 50 52], and four reported on decision aids to address these information gaps[38 43 49 50]. Although patient-involvement seemed to be more straightforward when making elective decisions about breast reconstruction, true involvement in the decision-making process requires that patients be given the best available evidence, including details of the risks and benefits[18]. When the evidence for a certain decision is low, such as when making decisions about relieving menopausal symptoms, this uncertainty should be outlined by physicians[75].

CONCLUSION

We identified a variety of decisions that can be made about the content or form of follow-up care for patients with breast cancer. We grouped these into four categories: surveillance for recurrent or secondary breast cancer, consultations for physical and psychosocial (late) effects, recurrence risk reduction by anti-hormonal treatment, and improving quality of life. More attention should be given to the patient's role and the involvement in decisions where their input is both relevant and possible. Further personalisation of follow-up care may lead to care of greater relevance and value to individual patients.

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SUPPLEMENTARY FILES CHAPTER 8

Supplementary Table S1: selected studies per research question*

		Study design					Answers the following research questions*		
Author	**Subject**	**Primary study goal**	**Study population**	**Study design**	**Outcome measures**	**Most important outcome**	**1**	**2**	**3**
Alderman, 2011	Breast reconstructive surgery	(1) To describe the proportion of mastectomy-treated patients who undergo delayed breast reconstruction; (2) To evaluate the underlying factors that contribute to the decision to receive immediate, delayed, or no breast reconstruction; and (3) To assess the association between receipt of immediate, delayed, or no breast reconstruction with patients' satisfaction with their surgical decision.	Population-based cohort of mastectomy-treated BC patients who were initially surveyed at time of diagnosis in 2002 and reported to the Los Angeles and Detroit SEER registries.	5-year follow-up survey	The receipt of immediate and delayed postmastectomy breast reconstruction, expressed in use of reconstruction, factors associated with reconstruction, decision satisfaction.	Of the 384 mastectomy-treated BC patients in the study, 138 (35.9%) received immediate reconstruction, 44 (11.5%) received delayed reconstruction, and 202 (52.6%) did not receive reconstruction. Factors associated with delayed reconstruction were primarily related to uncertainty about the procedure, concern about cancer surveillance, and low priority. Those without reconstruction demonstrated significant informational needs, which should be addressed with future research efforts.	x	x	x

Supplementary Table S1: selected studies per research question* (continued)

		Study design					Answers the following research questions*		
Author	**Subject**	**Primary study goal**	**Study population**	**Study design**	**Outcome measures**	**Most important outcome**	**1**	**2**	**3**
Balneaves, 2016	Treatment-induced (early) menopause	Identification of BC survivors' use of complementary therapy (CT) and general information and decision-making needs related to menopausal symptoms.	BC survivors (n=22) and healthcare professionals (n=5). The sample of women was diagnosed between 2008 and 2010, the majority with ER+ stage II BC. Healthcare practitioners included dietitians, pharmacists, nurses, general practitioners in oncology, and medical and radiation oncologists.	Needs assessment by interpretive descriptive methodology; Focus groups with survivors, interviews with conventional and CT. Thematic, inductive analysis as conducted on the data.	Use of complementary therapies, and general information and decision-making needs related to menopausal symptoms.	Menopausal symptoms have significant negative impact on BC survivors. Close to 70 % of the sample were currently using CTs, including mind-body therapies (45.5 %), natural health products (NHPs) and dietary therapies (31.8 %), and lifestyle interventions (36.4 %). However, BC survivors reported inadequate access to information on the safety and efficacy of CT-options. Survivors also struggled in their efforts to discuss CT with HCPs, who had limited time and information to support women in their CT decisions. Concise and credible information about CTs was required by BC survivors to support them in making informed and safe decisions about using CTs for menopausal symptom management.	x	x	x
Benedict, 2017	(Long term) adjuvant anti-hormonal therapy	Not clearly specified	Young BC survivors	Not clearly specified	Not clearly specified	Preliminary evidence suggests that prioritizing fertility, along with concerns about side effects, leads to ET noninitiation and early discontinuation. Clinical efforts to improve adherence might need to consider patients' family-building goals during the course of treatment and to appropriately counsel patients according to their priorities and family-building intentions. Educational materials about family building after cancer are still not consistently available or provided.	x	x	x

Supplementary Table S1: selected studies per research question* (continued)

		Study design					Answers the following research questions*		
Author	**Subject**	**Primary study goal**	**Study population**	**Study design**	**Outcome measures**	**Most important outcome**	**1**	**2**	**3**
Bluethmann, 2017	(Long term) adjuvant anti-hormonal therapy	The aims were to build on survey results to qualitatively explore survivors' experiences with prescribed AET to (a) describe appraisal and management of AET side effects and (b) deconstruct decisions to initiate, discontinue, or maintain AET.	452 survivors completed a survey, and 30 took part in telephone interviews. Most interview participants (N = 30) were Caucasian, married, and college educated, with a mean age of 57 years (range = 49–86 years).	Survey, telephone interviews. Mixed-methods explanatory sequence research design with a qualitative emphasis.	Appraisal and management of AET side effects; decisions about initiation, discontinuing, or maintaining AET.	Among adherent survivors, the themes of tolerance of side effects and perseverance were strong. Nonadherent survivors expressed more difficulty managing side effects and perceived fewer benefits when side effects were bothersome. The most common side effects mentioned by all survivors were menopausal symptoms and joint pain; less common side effects were cognitive decline and cardiac distress. Some sought advice from their oncology team. Nonadherent survivors appeared initially motivated to maintain AET but identified a tolerance limit for side effects after which a provider's recommendation was less influential in their decision to maintain or discontinue AET.	x	x	x

Supplementary Table S1: selected studies per research question* (continued)

		Study design					Answers the following research questions*		
Author	**Subject**	**Primary study goal**	**Study population**	**Study design**	**Outcome measures**	**Most important outcome**	**1**	**2**	**3**
Brandzel, 2017	Form, frequency, and length of follow up	Determining where gaps in care and knowledge could be filled regarding surveillance imaging.	41 women in California, North Carolina, and New Hampshire (USA). Participants were aged 38–75 years, had experienced stage 0–III BC within the previous 5 years, and had completed initial treatment, but could be still taking adjuvant hormone therapy. Women were selected from the BC Surveillance Consortium (BCSC) registries in the US.	Six focus groups followed by a combination of deductive and inductive thematic analysis	Key themes in experiences and preferences about BC surveillance imaging	Women reported various types and frequencies of surveillance imaging and a range of surveillance imaging experiences and preferences. The most commonly reported pattern of surveillance breast imaging after completing BC treatment was mammography every 3 or 6 months for 1 to 3 years after completion of treatment. Many women experienced discomfort during breast imaging and anxiety related to the examination, primarily because they feared subsequent cancer detection. Women reported trust in their providers and relied on providers for imaging decision-making. However, women wanted more information about the treatment surveillance transition to improve their care.	x	x	x

Supplementary Table S1: selected studies per research question* (continued)

		Study design					Answers the following research questions*		
Author	**Subject**	**Primary study goal**	**Study population**	**Study design**	**Outcome measures**	**Most important outcome**	**1**	**2**	**3**
Brauer, 2016	(Long term) adjuvant anti-hormonal therapy	To understand what factors are associated with persistence and how these medications fit into the broader life context of older BC survivors from the perspectives of the women themselves.	27 women age 65 years or older who were treated for locoregional BC and had started an AI 4 to 36 months before study enrolment. The women were diagnosed on average at 72 years of age and had diverse racial, ethnic, cultural, marital, and socioeconomic backgrounds.	Grounded theory methodology to conduct in-depth, semi-structured interviews	Decisions about persisting with aromatase inhibitors (AIs)	A total of 27 women were interviewed, and they reported that integrating the AI treatment into daily life posed many challenges. The adverse effects of AIs were difficult to disentangle from what women attributed to comorbid conditions or getting older. This challenge in attribution, coupled with less frequent contact with their oncology team, resulted in many women "winging it" or persisting with the AI despite significant struggles. In particular, participants expressed concerns about the impact of perceived adverse effects on quality of life and ability to carry out social roles. Many reported lack of professional guidance or support with respect to persisting with the AI, especially when adverse effects were present, and relied on a variety of self-management strategies to maintain treatment with the AI. The women often described circumstances, or potential tipping points, under which they might discontinue the AI prematurely.	x	x	

Supplementary Table S1: selected studies per research question* (continued)

		Study design					Answers the following research questions*		
Author	**Subject**	**Primary study goal**	**Study population**	**Study design**	**Outcome measures**	**Most important outcome**	**1**	**2**	**3**
Cahir, 2015	(Long term) adjuvant anti-hormonal therapy	The aim of this study was to use qualitative methods to investigate influences on adjuvant hormonal therapy Medication-taking behaviour (MTB) in women with stage I–III BC.	Participants were purposively sampled across two cancer centres in Ireland with strata defined by their hormonal therapy MTB. Eligible participants were identified from the cancer centres' oncology databases and were aged ≥18 years, English speaking, had stage I–III invasive BC at diagnosis and had been prescribed adjuvant hormonal therapy for ≥3 months at the time of study commencement. Thirty-one women participated in interviews (mean age 51 years, SD±10), 14 women were adherent and persistent, 7 women were non-adherent and persistent and 10 women were non-persistent.	This was a qualitative study using semi-structured face-to-face interviews. the Framework Method with the Theoretical Domains Framework (TDF) informing the analysis framework.	Modifiable influences on hormonal therapy MTB.	Three domains identified both barriers and enablers to hormonal therapy MTB across the three MTB strata: beliefs about consequences, intentions and goals and behaviour regulation, but their influence was different across the strata. Key enablers for adherent/persistent women were identified within the domain beliefs about consequences (BC recurrence), intentions and goals (high-priority), beliefs about capabilities (side effects) and behaviour regulation (managing medication). Barriers were identified within the domain behaviour regulation (no routine), memory, attention and decision processes (forgetting) and environmental context and resources (stressors) for non-adherent/persistent women and intentions and goals (quality of life), behaviour regulation (temporal self-regulation), reinforcement, beliefs about consequences (non-necessity) and social influences (clinical support) for non-persistent women.	x	x	

Supplementary Table S1: selected studies per research question* (continued)

		Study design					Answers the following research questions*		
Author	**Subject**	**Primary study goal**	**Study population**	**Study design**	**Outcome measures**	**Most important outcome**	**1**	**2**	**3**
Carter, 2010	Lifestyle changes	To determine factors associated with selecting between two group physical activity programs.	Participants (n=133) were male and female adult cancer survivors who resided in the Charleston, South Carolina metropolitan area. Inclusion criteria were (a) age 18 years or older, (b) diagnosis of cancer (excluding non-melanoma skin cancer) regardless of time since diagnosis, and (c) sufficient functional status to engage in an exercise program. In our study sample, participants had breast (56%), prostate (8%), female reproductive organ (7%), haematological (6%), colorectal (5%), head and neck (5%), and other cancer types (14%).	The present study is nested in a non-randomized trial. The parent study was a non-randomized intervention trial to compare the physical and quality-of-life effects of participation in an 8-week team-oriented dragon boat paddling program versus a group oriented walking program.	physical activity program chosen and demographic, clinical, physical and psychosocial characteristics.	Roughly equal proportions chose to participate in dragon boat paddling or walking (55% versus 45%). Of the many variables studied, few were associated with program selection. Compared to those who chose the walking program, those who chose the dragon boat paddling team were more likely to be Caucasians (p=.015) and younger (p=.027), and marginally significantly more like to have cancers other than BC (p=.056) and have greater lower-body strength (p=.062). To meet the needs of cancer survivors, a menu of physical activity program options may be optimal.	x		

Supplementary Table S1: selected studies per research question* (continued)

		Study design					Answers the following research questions*		
Author	**Subject**	**Primary study goal**	**Study population**	**Study design**	**Outcome measures**	**Most important outcome**	**1**	**2**	**3**
Causarano, 2015	Breast reconstructive surgery	To evaluate the feasibility and effect of a pre-consultation educational group intervention on the decision-making process for breast reconstruction.	Inclusion: adult women ≥18; mastectomy; referred to plastic surgeons for consultation of delayed postmastectomy breast reconstruction. Exclusion: active or atypical BC; not speak English; preferred breast revision or nipple reconstruction only; had a previous consultation with plastic surgeon; cognitive impairment or uncontrolled psychiatric diagnosis. 41 patients were enrolled resulting in a recruitment rate of 72 %.	Pilot study for RCT; Patients randomized to the intervention group participated in a pre-consultation educational group intervention in addition to receiving routine education.	Decisional conflict scale, the decision self-efficacy scale, two subscales from the Modified-Perceived Involvement in Care Scale (M-PICS), and one subscale from the BREAST-Q.	The Cohen's d effect size in reduction of decisional conflict was moderate to high for the intervention group compared to routine education (0.69, 95 % CI=0.02–1.42), while the effect sizes of increase in decision self-efficacy (0.05, 95 % CI=–0.60–0.71) and satisfaction with information (0.11, 95 % CI=–0.53–0.76) were small. A higher proportion of patients receiving routine education signed informed consent to undergo breast reconstruction (14/20 or 70 %) compared to the intervention group (8/21 or 38 %) P=0.06. A pre-consultation educational group intervention improves patients' shared decision-making quality compared to routine preoperative patient education.		x	x

Supplementary Table S1: selected studies per research question* (continued)

		Study design					Answers the following research questions*		
Author	**Subject**	**Primary study goal**	**Study population**	**Study design**	**Outcome measures**	**Most important outcome**	**1**	**2**	**3**
Corney, 2014	Fertility management	The aim of this qualitative study was to investigate in detail the fertility-related experiences of young childless women with BC, including the information they received, the fertility preservation options given, and the dilemmas they faced.	Women were eligible for interview provided that they had a first episode of BC six or more months ago, were aged under 45, and therefore considered of child-bearing age, and were currently childless but wanted children in the future. Interviews were conducted with 19 childless women aged below 45 with first episode BC diagnosed at least 6 months before. The women's ages at diagnosis ranged from 20 to 41 and at interview from 24 to 44. Timing of the interview from diagnosis varied from 6 months to 5 years ago. However, the majority had the diagnosis within the last 3 years.	A qualitative individual interview method; Transcripts were analysed using the thematic method developed by Braun and Clarke. A simple framework for categorization of within-case themes was used to order themes from the outset using the topic guide questions.	Themes for fertility decision-making; a set of within-case themes was developed for each participant.	The amount of information given to women from health professionals varied considerably. Only half were given the opportunity to pursue assisted reproductive techniques prior to chemotherapy. Most women were worried about what the future might hold, including their fertility, the impact of pregnancy on recurrence, and the health of the child. They were generally given little information or support on these issues.	x		

Supplementary Table S1: selected studies per research question* (continued)

		Study design					Answers the following research questions*		
Author	**Subject**	**Primary study goal**	**Study population**	**Study design**	**Outcome measures**	**Most important outcome**	**1**	**2**	**3**
Engelhardt, 2016	(Long term) adjuvant anti-hormonal therapy	To assess the frequency of use of implicit persuasion during consultations and whether the use of implicit persuasion was associated with expected treatment benefit and/or decision-making for decision between hormonal and endocrine therapy.	Stage I&II BC patients treated at oncology outpatient clinics of general teaching hospitals and university medical centres. Eighteen oncologists (56% male; mean age 51 years [range: 34-66]) included 105 patients. Patients were on average 59 years (range: 35-87), and 53% had stage I disease.	Observational study in consecutive consultations	(1) Unbalanced presentation of benefits and side-effects, (2) presenting treatment recommendations as authorised decisions, (3) creating the illusion of decisional control and (4) persuading patients using (clinical) experience.	A median of five (range: 2e10) implicitly persuasive behaviours were employed per consultation. The number of behaviours used did not differ by disease stage (P Z 0.07), but did differ by treatment option presented (P Z 0.002) and nodal status (P Z 0.01). About 50% of patients with stage I or node-negative disease were steered towards undergoing chemotherapy, whereas 96% of patients were steered towards undergoing endocrine therapy, irrespective of expected treatment benefit. Decisions were less often postponed if more implicit persuasion was used (P Z 0.03). Oncologists frequently use implicit persuasion, steering patients towards the treatment option that they think is in their patients' best interest. Expected treatment benefit does not always seem to be the driving force behind implicit persuasion.		x	x

Supplementary Table S1: selected studies per research question* (continued)

		Study design					Answers the following research questions*		
Author	**Subject**	**Primary study goal**	**Study population**	**Study design**	**Outcome measures**	**Most important outcome**	**1**	**2**	**3**
Fasse, 2017	Breast reconstructive surgery	This study aimed to gain a better understanding of the couples' decision-making process for BR in the cancer context and particularly to investigate the partners' involvement in this process.	Eighteen participants (nine women who underwent a mastectomy and their intimate partners) took part in this study. The time of the BC diagnosis varied between 2 and 8 years (M = 5; SD = 2.4). Inclusion criteria were as follows: at least 18 years old, speaking and reading French fluently, being married, and/or living together in a heterosexual long-term relationship at least since the BC diagnosis. For women with DBR, BR had to be finished for at least 6 months. The women of the sample were aged between 33 and 66 years (M = 54, SD = 7.5) and their partner between 40 and 76 years (M = 59, SD = 11.6).	Semi-directive interviews, and a general inductive approach was chosen to capture the representations of the couples.	Themes and sub-themes in the couples' decision-making process for BR in the cancer context. During the interviews, the following domains were explored: decision about BR and its potential evolution over time, motivations for decision, individual representations of BR/ no BR, and beliefs and expectations of the surgical procedure.	The analysis revealed 11 major themes. The two most salient ones were 'external influence' and 'implication of the partner'. The exploration of the subthemes revealed that the decision-making process is often reported as an interrelated experience by the couples and as a dyadic stressor. The partner's role is depicted as consultative and mostly supportive.	x	x	x
Flitcroft, 2016	Breast reconstructive surgery	To document the reasons women with high-risk BC choose IBR, DBR or no BR (NBR).	Fifty-one women from a metropolitan breast oncology practice, who were likely to require postmastectomy radiotherapy (PMRT), were recruited after making their decision about BR. The study took place in an oncoplastic breast surgical practice in metropolitan Sydney, Australia.	Single-site pilot sub-study, questionnaire	Factors that affect the decision about BR classified into eight issue-based domains (feeling normal, feeling good, being practical, influence of others, expectations, fear, timing and unnecessary).	Women over 60 were more likely to choose NBR ($p = 0.005$), while women living with a partner were more likely to choose IBR ($p = 0.032$). The most relevant domains for both IBR and DBR were 'feeling good' and 'feeling normal'; and for NBR were 'unnecessary' and 'being practical'. Although all women understood pre-operatively the potential aesthetic limitations of PMRT, 63% still chose IBR.	x	x	x

Supplementary Table S1: selected studies per research question* (continued)

		Study design					Answers the following research questions*		
Author	**Subject**	**Primary study goal**	**Study population**	**Study design**	**Outcome measures**	**Most important outcome**	**1**	**2**	**3**
Fu, 2017	Breast reconstructive surgery	To investigate cultural factors, values, and perceptions held by Asian women that might impact breast reconstruction rates.	Thirty-five immigrant East Asian women who underwent surgical treatment for BC. The average years lived in America was greater than 27.4, with a range of 3 to 40 years. The mean age of participants was 51 years, with a range from 33 to 72 years. Seventeen patients (48.6%) had undergone at least one mastectomy and reconstruction, 13 patients had undergone at least one mastectomy without reconstruction (37.1%), and five patients had undergone a lumpectomy (14.3%).	Semi-structured interviews with open-ended questions. Each interview session was audio-recorded and transcribed for analysis. Once transcribed, three study investigators trained in qualitative methods independently applied open coding in NVivo software	Recurring themes for cultural factors, values, and perceptions held by Asian women that might impact breast reconstruction rates.	Emerging themes include functionality, age, perceptions of plastic surgery, inconvenience, community/family, fear of implants, language, and information. Patients spoke about breasts as a function of their roles as a wife or mother, eliminating the need for breasts when these roles were fulfilled. Many addressed the fear of multiple operations. Quality and quantity of information, and communication with practitioners, impacted perceptions about treatment. Reconstructive surgery was often viewed as cosmetic. Community and family played a significant role in decision-making.	x	x	x

Supplementary Table S1: selected studies per research question* (continued)

		Study design					Answers the following research questions*		
Author	**Subject**	**Primary study goal**	**Study population**	**Study design**	**Outcome measures**	**Most important outcome**	**1**	**2**	**3**
Gorman, 2011	Fertility management	To gather information about how young women make cancer treatment decisions and to investigate the role of fertility in their decision-making process.	Participants were early-stage BC survivors (Stage I or II) diagnosed at age 40 or younger. Women were recruited from the Women's Healthy Eating and Living (WHEL) study, a multisite randomized, controlled trial to evaluate the effectiveness of a high-vegetable, low-fat diet to reduce recurrence and through a local affiliate of the Young Survival Coalition YSC). Twenty young BC survivors diagnosed with Stage I (30%) or Stage II (70%) BC between the ages of 26 and 38 years participated. Women were recruited from multiple geographic regions and diagnosed between 1 and 13 years prior to the interview.	Telephone interviews, 45 to 75 minutes in duration. We used a semi-structured interview guide so that each participant was asked a similar set of questions. Questions were open-ended to facilitate conversation on each topic and participants were encouraged to elaborate on their answers.	Themes and sub-themes for fertility decision-making; cross-case analysis was applied, where data from all participants were combined rather than analysed as individual cases.	The main themes were: 1) I was young, I wanted to do everything possible to move forward with my life and not to have the cancer come back, 2) Fertility concerns are different for every woman 3) My oncologist was great… a huge part of my survivorship, and 4) They didn't tell me about my options and I didn't think about fertility until it was too late. While fertility was important to many participants, treatment decisions were mainly motivated by survival concerns. Fertility concerns depended on life circumstances and the timing in relation to diagnosis varied. There is a need for improved information regarding the impact of treatment on fertility and fertility preservation options, even if concerns are not expressed at diagnosis.	x	x	x

Supplementary Table S1: selected studies per research question* (continued)

		Study design					Answers the following research questions*		
Author	**Subject**	**Primary study goal**	**Study population**	**Study design**	**Outcome measures**	**Most important outcome**	**1**	**2**	**3**
Hamnett, 2016	Breast reconstructive surgery	The primary aim is to use this evidence to improve the current decision-making process and produce an algorithm that would guide the patient, the surgeon and the breast care nurse throughout each stage of this decision-making process.	BC patients	Narrative literature review; A literature search was conducted using PubMed, Medline, evidence.nhs.uk and the Cochrane database.	Factors directing the patient and reconstructive surgeon	If reconstruction is oncological plausible and co-morbidities and frailty formally assessed, older women should be actively informed about breast reconstruction, receive support and engage in 'shared decision-making'. The older patient is less likely to do research independently. Amongst other factors, body image, cancer fears, employment and carer responsibilities play a part in the decision. With adequate preoperative and frailty assessment and early involvement of the geriatrician and anaesthetist, microsurgical reconstruction is safe.	x	x	x
Heller, 2008	Breast reconstructive surgery	To assess the effectiveness of an interactive digital education aid for breast reconstruction patients.	BC patients who were candidates for breast reconstruction were recruited and randomized into a control group and a study group. A total of 133 women participated, 66 in the control group and 67 in the study group.	Prospective randomized study	Knowledge, anxiety, and satisfaction before the initial plastic surgery consultation, immediately before surgery, and 1 month after surgery.	An interactive digital education aid is a beneficial educational adjunct for patients contemplating breast reconstruction. Patients who use an interactive digital education aid demonstrate greater factual knowledge, reduced anxiety, and increased postoperative satisfaction compared with patients given preoperative instructions using standard methods alone.			x

Supplementary Table S1: selected studies per research question* (continued)

		Study design					Answers the following research questions*		
Author	**Subject**	**Primary study goal**	**Study population**	**Study design**	**Outcome measures**	**Most important outcome**	**1**	**2**	**3**
Hershman, 2016	(Long term) adjuvant anti-hormonal therapy	To determine associations of demographic and clinical factors, psychosocial factors, quality of life, and patient treatment satisfaction with the risk of ET non-persistence among women who had initiated it.	Women with BC receiving care in an integrated healthcare system between 2006 and 2010. We identified 601 patients with HR-positive BC who met our initial inclusion criteria. Of these, 523 initiated therapy and had a baseline and subsequent interview. The cohort was primarily white (74.4 %), stage 1 (60.6 %), and on an aromatase inhibitor (68.1 %).	Serial interviews were conducted at baseline and every 6 months.	The Functional Assessment of Cancer Therapy (FACT), Medical Outcomes Survey, Treatment Satisfaction Questionnaire (TSQM), Impact of Events Scale (IES), Interpersonal Processes of Care measure, and Decision-making beliefs and concerns were measured.	Of the 523 women in our final cohort who initiated ET and had a subsequent evaluation, 94 (18 %) were non-persistent over a 2-year follow-up. At follow-up, the FACT, TSQM, and IES were associated with non-persistence (p\0.001). Most women continued ET. Women who reported a better attitude toward ET, better quality of life, and more treatment satisfaction, were less likely to be non-persistent and those who reported intrusive/avoidant thoughts were more likely to be non-persistent.	x	x	
Holmes, 2017	Alternative medicine	The objective was to explore BC survivors' use of the internet when making decisions about complementary and alternative medicine (CAM) use.	11 BC survivors, from a selection of BC survivors who were 18 years of age or older who had completed active cancer treatment (chemotherapy, radiotherapy and/or surgery) in the last five years, were internet users and had considered using some form of Complementary and Alternative Medicine.	Quantitative questionnaire and a qualitative telephone interview. A mixed-method design was used, combining a qualitative interview study with an embedded questionnaire study.	Participants' experiences of using the internet to make decisions about CAM and identify the barriers and facilitators to using the internet as a self-management resource.	All participants found information on CAM using the internet and used some form of CAM after their diagnosis. Themes from the interviews went beyond the standard definitions of the TPB areas. Despite the lack of approval from their social network and healthcare team, participants used the internet to find information on CAM. Further, participants' cancer diagnosis changed their needs, transforming how they perceived and experienced the internet.	x		x

Supplementary Table S1: selected studies per research question* (continued)

		Study design					Answers the following research questions*		
Author	**Subject**	**Primary study goal**	**Study population**	**Study design**	**Outcome measures**	**Most important outcome**	**1**	**2**	**3**
Hsieh, 2017	Fertility management	To understand the risk–benefit perception of choosing conception versus contraception among women who have completed BC treatment in Taiwan.	BC survivors who were diagnosed with breast carcinoma before 49 years of age, who finished cancer-related chemotherapy before 50 years of age, who admitted making the decision to conceive after treatment, and who could communicate in Chinese were included in the study. In all, 16 cancer survivors were recruited, with nine women trying to get pregnant and seven women taking contraceptive action. The mean age of all participants at cancer diagnosis was 36.8 years (range, 23–48 years). The average number of years after cancer treatment was 6.8 (range, 1–16 years).	In-depth interviews; grounded theory approach to analyse the data following the principles of constant comparison.	Risks and benefits of pregnancy after their cancer diagnosis and treatment process, how the decision to conceive or not was reached and whether patients finally tried to conceive	Seven dimensions of risk–benefit perception of pregnancy, including perceived health status, safety, expected gain, harm, loading, support and time were explored among women treated for BC. We found that women treated for BC applied risk–benefit perceptions to decide whether to become pregnant. Implementing contextual counselling could help to decrease perceived barriers to choose pregnancy and increase the quality of pregnancy care.	x	x	

Supplementary Table S1: selected studies per research question* (continued)

		Study design					Answers the following research questions*		
Author	**Subject**	**Primary study goal**	**Study population**	**Study design**	**Outcome measures**	**Most important outcome**	**1**	**2**	**3**
Hudson, 2012	Form, frequency, and length of follow up	To propose a research, policy, and practice agenda that advocates for multifaceted decision support to enhance cancer survivorship and follow-up care.	33 cancer survivors, recruited cancer were survivors in New Jersey who had received their cancer treatment from one of five community hospitals. purposive sample of ambulatory, early-stage (I or II) breast and prostate cancer survivors for whom the Institute of Medicine authors recommend longitudinal survivorship healthcare (i.e., defined as ≥2 years from completion of cancer therapy other than hormonal therapy). Patients with severe comorbid conditions that require extensive specialist care coordination (e.g., congestive heart failure, myocardial infarction, angina) were excluded.	An exploratory qualitative study by in-depth, individual interviews. qualitative analysis used a multistep immersion/ crystallization approach.	Survivor experiences	Three types of survivor experiences were identified from narratives of patients treated in community oncology and National Cancer Institute designated comprehensive cancer centres, ranging from nonactivated patients who need enhanced health care communication and decision support to navigate their care to highly activated patients adept at navigating complex healthcare settings.	x	x	x

Supplementary Table S1: selected studies per research question* (continued)

		Study design					Answers the following research questions*		
Author	**Subject**	**Primary study goal**	**Study population**	**Study design**	**Outcome measures**	**Most important outcome**	**1**	**2**	**3**
Kadmon, 2016	Breast reconstructive surgery	To address decision-making styles among BC survivors considering breast reconstruction.	70 women who had undergone breast reconstruction surgery in the past five years. The mean age of the participants was 52.7 years (SD = 10.2), with a median age of 52 years. Thirty-eight women had chosen a mastectomy and immediate reconstruction, and the rest had reconstructive surgery later. In 70% of cases, the mastectomy was unilateral; in the rest, it was bilateral.	Single-centre questionnaire	Level of involvement in decision-making, decision-making model between provider and patient, and decision-making styles	A statistically significant correlation was found between the level of involvement in decision-making and the decision-making style of the patient. Nurses should assess patient decision-making styles to ensure maximum patient involvement in the decision-making process based on personal desires regardless of age.	x		x
Klaassen, 2017	Form, frequency, and length of follow up	The aim of this study was to assess the needs of patients and health professionals with regard to an aftercare decision aid to systematically develop such a decision aid.	11 female patients who finished their curative BC treatment in one of two medical centres in the southern part of the Netherlands. The average age of the patients was 62 years (range 49–75).	Focus groups and individual interviews. A semi-structured question guide was used during the focus group interviews. A similar but adjusted semi-structured question guide was used to conduct the face-to face interviews.	Needs of patients and health professionals with regard to an aftercare decision aid	Although most patients felt few aftercare options were available to them, health professionals reported to provide various options on the patients' request. Patients reported difficulty in expressing their need for options to their health professional. Although most patients were unfamiliar with decision aids, the majority preferred a paper-based patient decision aid, while most health professionals preferred an online tool.	x		x

Supplementary Table S1: selected studies per research question* (continued)

		Study design					Answers the following research questions*		
Author	**Subject**	**Primary study goal**	**Study population**	**Study design**	**Outcome measures**	**Most important outcome**	**1**	**2**	**3**
Lee, 2010	Breast reconstructive surgery	To identify the most important facts and goals for decisions about breast reconstruction after mastectomy, and to compare patients' and providers' perspectives.	BC survivors and providers. Survivors (n=21): Those who were older than 21, with a history of early-stage BC diagnosed within 5 years prior to contact and treated with mastectomy, and who could speak and read English were eligible. The patient response rate was 79%. Providers (n=20): the provider response rate was 77% in the larger study.	Cross-sectional survey. The study was part of a larger study of patients' and providers' perspectives on reconstruction, surgery (lumpectomy vs. mastectomy), and systemic therapy (chemotherapy and hormone therapy).	Facts and goals/ concerns related to breast reconstruction after mastectomy.	Providers were more concerned about the impact of radiation on the success of the reconstruction than patients (60% vs. 24%, 95% CI of the difference: 64, 8). Thirty percent of providers placed the fact that women who do not have reconstruction are equally satisfied as women who have reconstruction in the top 3, whereas almost no patients did (30% vs. 5%, 95% CI: 47, 3). For all 3 of the facts about immediate versus delayed reconstruction, women placed a higher priority on these facts than providers did. Goals: Patients placed greater importance on avoiding use of a prosthesis (33% vs. 0%, 95% CI of the difference: 13, 54). There was a trend toward less patient concern about "looking natural without clothes" compared to providers (24% vs. 40%, 95% CI of the difference: 12, 44).	x	x	x

Supplementary Table S1: selected studies per research question* (continued)

		Study design					Answers the following research questions*		
Author	**Subject**	**Primary study goal**	**Study population**	**Study design**	**Outcome measures**	**Most important outcome**	**1**	**2**	**3**
Morrow, 2014	Breast reconstructive surgery	To examine correlates of breast reconstruction after mastectomy and to determine if a significant unmet need for reconstruction exists.	Women aged 20 to 79 years diagnosed as having ductal carcinoma in situ or stages I to III invasive BC. The analytic sample for this study consists of the 485 patients who reported undergoing mastectomy at the initial survey, completed the follow-up survey, and indicated that they did not have a recurrence of BC. The mean age was 55.8 years; 42.2% had no more than a high school ucation,and64.3%had stage I or II BC. Black and Latina women were oversampled to ensure adequate representation of racial/ethnic minorities.	Survey	Breast reconstruction at any time after mastectomy and patient satisfaction with different aspects of the reconstruction decision-making process.	Factors significantly associated with not undergoing reconstruction were black race (adjusted odds ratio [AOR], 2.16 [95%CI, 1.11-4.20]; P = .004), lower educational level (AOR, 4.49 [95%CI, 2.31-8.72]; P < .001), increased age (AOR in 10-year increments, 2.53 [95%CI, 1.77-3.61]; P < .001), major comorbidity (AOR, 2.27 [95% CI, 1.01-5.11]; P = .048), and chemotherapy (AOR, 1.82 [95%CI, 0.99-3.31]; P = .05). Only 13.3% of women were dissatisfied with the reconstruction decision-making process, but dissatisfaction was higher among non-white patients in the sample (AOR, 2.87 [95%CI, 1.27-6.51]; P = .03). The most common patient-reported reasons for not having reconstruction were the desire to avoid additional surgery (48.5%) and the belief that it was not important (33.8%), but 36.3%expressed fear of implants. Reasons for avoiding reconstruction and systems barriers to care varied by race; barriers were more common among non-white participants.	x	x	x

Supplementary Table S1: selected studies per research question* (continued)

		Study design					Answers the following research questions*		
Author	**Subject**	**Primary study goal**	**Study population**	**Study design**	**Outcome measures**	**Most important outcome**	**1**	**2**	**3**
Neugut, 2012	(Long term) adjuvant anti-hormonal therapy	To investigate factors related to non-initiation of hormonal therapy among women with newly diagnosed, non-metastatic Hr-positive BC recruited from three U.S. sites.	Women with newly diagnosed, non-metastatic Hr-positive BC recruited from three U.S. sites. Of 1,050 BC patients recruited, 725 (69 %) had HR-positive BC, of whom 87 (12.0 %) based on self-report and 122 (16.8 %) based on medical record/ pharmacy fill rates did not initiate hormonal therapy.	A prospective cohort design by interviews	Factors related to non-initiation of hormonal therapy	In a multivariable analysis, non-initiation of hormonal therapy, defined by medical record/ pharmacy, was associated with having greater negative beliefs about efficacy of treatment (OR 1.42, 95 % CI 1.18–1.70). Non-initiation was less likely in those who found the quality of patient/ physician communication to be higher (OR 0.96, 95 % CI 0.93–0.99), the hormonal therapy treatment decision an easy one to make (OR 0.45, 95 % CI 0.23–0.90) or neither easy nor difficult (OR 0.34, 95 % CI 0.20–0.58); and had more positive beliefs about hormonal therapy efficacy (OR 0.40, 95 % CI 0.34–0.62).	x	x	x

Supplementary Table S1: selected studies per research question* (continued)

		Study design					Answers the following research questions*		
Author	**Subject**	**Primary study goal**	**Study population**	**Study design**	**Outcome measures**	**Most important outcome**	**1**	**2**	**3**
Ogrodnik, 2016	Breast reconstructive surgery	To explore patterns in delayed reconstruction (DR), identify barriers to follow through, and to determine the adequacy of EHR documentation in providing information about decision-making for breast reconstruction.	From the year 2008 to 2012, a total of 367 women were identified undergoing total mastectomy for BC (Fig. 1). One hundred forty-eight women (40.33 %) had IR, either with tissue expanders or autologous tissue. Out of the remaining 219 women, 13 (5.9 %) completed DR.	Retrospective electronic health record review	The determinants impacting rates of delayed breast reconstruction, potential barriers to follow through with an initial decision to pursue delayed reconstruction, the adequacy of the electronic health record to provide information pertaining to the decision-making process for breast reconstruction.	Of 367 women who had undergone a total mastectomy, 219 did not receive immediate reconstruction. Of these, 24.6 % expressed no interest in DR, 21.9 % expressed interest but were still pending the procedure, and 5.9 % had completed DR. Of decision-making regarding breast reconstruction, 47.5 % lacked documentation. Median follow-up was 34 months. Reasons for not following through with DR included poor timing (25 %), indecision (17 %), desired method of reconstruction not available at treating facility (10 %), persistent obesity (8.3 %), continued smoking (4 %), and reason not specified (35 %). Many women do not receive breast reconstruction despite expressing an initial interest in the procedure. Reasons were multi-factorial and the extent of documentation was inconsistent. Further exploration of potential barriers to breast reconstruction as well as opportunities to enhance shared decision-making may serve to improve patient experience and satisfaction following mastectomy.	x	x	x

Supplementary Table S1: selected studies per research question* (continued)

		Study design					Answers the following research questions*		
Author	**Subject**	**Primary study goal**	**Study population**	**Study design**	**Outcome measures**	**Most important outcome**	**1**	**2**	**3**
Potter, 2013	Breast reconstructive surgery	To explore access to care and the provision of procedure choice to women seeking reconstructive surgery.	Sixty-two interviews were undertaken with 35 health professionals (including two interviews with pairs of CNS) and 31 patients. Interviews were undertaken with OPBS (n=11), plastic surgeons (n=11), CNSs (n=11) and clinical psychologists (n=2) providing specialist reconstructive services at 15 centres throughout the United Kingdom. Thirty-one women with a median age of 51 years (range 31–72 years) who had undergone a range of reconstructive procedures (expander–implant reconstruction n=11; latissimus dorsi (LD) flap reconstruction n=10; DIEP flap reconstruction n=11) were interviewed at a median of 14 months (range 2–37 months) following surgery. Twenty-eight women had undergone reconstruction at the time of mastectomy (IBR) and eight received delayed reconstructive procedures.	Semi-structured interviews; Interviews were transcribed verbatim and analysed using the constant comparative technique of grounded theory.	Provision of choice in reconstructive surgery, barriers to the provision of choice.	Both patients and professionals expressed concerns about the provision of adequate procedure choice and access to care. Lack of information and/or time, involvement in decision-making and issues relating to the evolution and organisation of reconstructive services, emerged as potential explanations for the inequalities seen. Interventions to improve cross-speciality collaboration were proposed to address these issues. Inequalities in the provision of choice in BR exist, which may be explained by a lack of integration between surgical specialities.	x	x	x

Supplementary Table S1: selected studies per research question* (continued)

		Study design					Answers the following research questions*		
Author	**Subject**	**Primary study goal**	**Study population**	**Study design**	**Outcome measures**	**Most important outcome**	**1**	**2**	**3**
Rini, 2009	hereditary testing and subsequent risk-behaviour	To investigate high-risk BC survivors' risk reduction decision-making and decisional conflict after an uninformative BRCA1/2 test.	Potential participants were adult, English-speaking women with a history of BC who were probands being tested for BRCA1/2 mutations at three centres between April, 2001 and July, 2004. Women in the sample were, on average, 52 years old (SD = 10 years). Most were married (72%), White (96%), had completed at least some college (96%), and had moderate to high annual household income (median > $75,000). They had been diagnosed with BC nearly six years earlier, on average (M = 5.96, SD = 7.80). Thirty-seven percent had undergone full BRCA1/2 sequencing and the rest had undergone Jewish panel testing. 182 women in the final sample.	Questionnaire, Prospective, longitudinal study of 182 probands undergoing BRCA1/2 testing, with assess-ments 1-, 6-, and 12-months post-disclosure.	Main outcomes included women's perception of whether they had made a final risk management decision (decision status) and decisional conflict related to this issue.	There were four patterns of decision-making, depending on how long it took women to make a final decision and the stability of their decision status across assessments. Late decision makers and non-decision makers reported the highest decisional conflict; however, substantial numbers of women—even early and intermediate decision makers—reported elevated decisional conflict. Analyses predicting decisional conflict 1- and 12-months post-disclosure found that, after accounting for controls and decision status, health beliefs and emotional factors predicted decisional conflict at different timepoints, with health beliefs more important one month after test disclosure and health beliefs more important one year later. Many of these women may benefit from decision-making assistance.	x	x	x

Supplementary Table S1: selected studies per research question* (continued)

		Study design					Answers the following research questions*		
Author	**Subject**	**Primary study goal**	**Study population**	**Study design**	**Outcome measures**	**Most important outcome**	**1**	**2**	**3**
Sayakhot, 2012	Treatment-induced (early) menopause	To investigate the perception and experience of menopause diagnosis and therapies, the information provided and health behaviours in younger women with BC.	The questionnaire study was completed by 114 women, aged 40 – 51 years, with non-metastatic BC. Women were recruited from outpatient clinics and the community.	Questionnaire	Information provision, experience of menopause diagnosis and treatment	Most women were satisfied with the manner in which they were informed of the BC (69%) and the menopause (59%) diagnoses. Although 80% of women were given BC information, only 54% were given menopause information at diagnosis. Women were least satisfied (26%) with information regarding the long-term complications of menopause. Women perceived exercise (68%) and improving lifestyle (61%) as most effective in alleviating symptoms of menopause. The majority of women reported that they did not understand the risks/benefits of ' bioidentical ' hormones (79%) and herbal therapies (78%), while 58% perceived hormone replacement therapies as associated with an increased risk of BC. Most women reported weight gain (68%) and osteoporosis (67%) as the most common problems/fears regarding menopause. However, regarding health behaviours, only 56% reported having relevant tests including a blood sugar test or a bone density test.	x	x	x

Supplementary Table S1: selected studies per research question* (continued)

		Study design					Answers the following research questions*		
Author	**Subject**	**Primary study goal**	**Study population**	**Study design**	**Outcome measures**	**Most important outcome**	**1**	**2**	**3**
Sherman, 2016	Breast reconstructive surgery	To assess the impact of an online decision aid [Breast RECONstruction Decision Aid (BRECONDA)] on breast reconstruction decision-making.	Women (n = 222) diagnosed with BC or ductal carcinoma in situ, and eligible for reconstruction following mastectomy, completed an online baseline questionnaire. They were then assigned randomly to receive either standard online information about breast reconstruction (control) or standard information plus access to BRECONDA (intervention). Forty-five women had undergone bilateral mastectomy for contralateral primary tumours (no women had undergone bilateral prophylactic mastectomy).	Randomized controlled trial	Decisional conflict	Linear mixed-model analyses revealed that 1-month decisional conflict was significantly lower in the intervention group (27.18) compared with the control group (35.5). This difference was also sustained at the 6-month follow-up. Intervention participants reported greater satisfaction with information at 1- and 6-month follow-up, and there was a non-significant trend for lower decisional regret in the intervention group at 6-month follow-up. Intervention participants' ratings for BRECONDA demonstrated high user acceptability and overall satisfaction. Women who accessed BRECONDA benefited by experiencing significantly less decisional conflict and being more satisfied with information regarding the reconstruction decisional process than women receiving standard care alone.			

Supplementary Table S1: selected studies per research question* (continued)

		Study design					Answers the following research questions*		
Author	**Subject**	**Primary study goal**	**Study population**	**Study design**	**Outcome measures**	**Most important outcome**	**1**	**2**	**3**
Shtaynberger, 2016	Lifestyle changes	To validate decisional balance measures for physical activity and fruit and vegetable (F/V) consumption among an adult survivorship population.	Participants were n=86 patients who completed primary treatment for breast or prostate cancer at least 5 years previously and were enrolled in an e-health intervention that aimed to improve physical activity and nutrition behaviours. Participants were pre dominantly non-Hispanic White (81.2%), and female (96.4%), with a mean age of 59.8 (SD=11.4).	Randomized pilot study	Decisional balance, stage of change, fruit/vegetable consumption, and physical activity.	Overall, findings provide validation for these decisional balance measures as indicators of health behaviours and support the value of using these measures in further research to aid understanding of behaviour change in this population.	x	x	

Supplementary Table S1: selected studies per research question* (continued)

		Study design					Answers the following research questions*		
Author	**Subject**	**Primary study goal**	**Study population**	**Study design**	**Outcome measures**	**Most important outcome**	**1**	**2**	**3**
Temple-Oberle, 2014	Breast reconstructive surgery	To present a heterogeneous group of women treated with the spectrum of breast reconstruction options, and report their satisfaction.	One hundred twenty three of 176 (70%) women completed the questionnaire (43% autologous, 47% alloplastic, and 10% LD/implant reconstructions). The LD/implant group had a low rate of immediate reconstruction (8.3%, P=0.04), and the highest rate of chemotherapy (91.7%, P=0.002) and radiation (100%, P=0.003).	Intervention assessment by questionnaire	Reconstruction satisfaction expressed by ten subscales of the BRECON-31	One hundred twenty three of 176 (70%) women completed the questionnaire (43% autologous, 47% alloplastic, and 10% LD/implant reconstructions). The LD/implant group had a low rate of immediate reconstruction (8.3%, P¼0.04), and the highest rate of chemotherapy (91.7%, P¼0.002) and radiation (100%, P¼0.003). The alloplastic group had a high rate of bilateral reconstruction (86.8%, P¼0.01). All groups scored well on the self-image, arm concerns, intimacy, satisfaction, and expectations subscales. All groups scored moderately on the self-consciousness, appearance, and nipple subscales. The autologous group scored the lowest on recovery (51 vs. 68 and 65, P<0.0001) and only moderately well on the abdomen subscale (67). Multiple regression analysis showed that satisfaction was not driven by type of reconstruction (P>0.05).			

Supplementary Table S1: selected studies per research question* (continued)

		Study design					Answers the following research questions*		
Author	**Subject**	**Primary study goal**	**Study population**	**Study design**	**Outcome measures**	**Most important outcome**	**1**	**2**	**3**
Wandrey, 2015	Breast reconstructive surgery	To explore lesbian BC survivors' attitudes toward breast reconstruction. This study represents the first published study to analyse data from a lesbian-specific BC forum to evaluate such attitudes.	Lesbian BC survivors; Two hundred fifty-five users posted to the lesbian-specific forum; 53 of these users discussed breast reconstruction and were included in the present analysis. We analysed a total of 168 posts.	Online support forum analysis	Lesbian BC survivors' attitudes toward breast reconstruction.	Our analysis revealed five important themes related to breast reconstruction attitudes as follows: (1) rejecting being defined by their body image, (2) privileging sensation over appearance, (3) believing that being breastless is protective, (4) perceiving their social context as supportive of non-reconstruction, and (5) feeling pressured by social norms to undergo reconstructive surgery.	x	x	

Supplementary Table S1: selected studies per research question* (continued)

		Study design					Answers the following research questions*		
Author	**Subject**	**Primary study goal**	**Study population**	**Study design**	**Outcome measures**	**Most important outcome**	**1**	**2**	**3**
Zielinski, 2015	Breast reconstructive surgery	To investigate the reasons why women after amputation of the breast due to cancer are not likely to undergo breast reconstructive surgery.	73 women from Silesian province aged 37-79 who undergone breast amputation due to malignant neoplasm in 1987-2013. The mean age of examined women was 58 years. The largest group were patients in their sixties (n=34).	Questionnaire	Reasons given by women for refraining from breast reconstruction	From all of the reasons given by women for refraining from breast reconstruction, the most frequently pointed was the fear of being subjected to further surgery (38.3%). 23 women (31.5%) admitted that they were also afraid of postoperative pain. Similarly, a common response (35.6%) was that it is not essential for their mental state, and 30% of respondents fully accepted their appearance after mastectomy. Concern about the effect of failed reconstruction was reported by 24.6% of the women, and the fear that the surgery could negatively affect the process of cancer treatment by 27.4% of respondents. Lack of information about the capabilities and knowledge of breast reconstruction methods was not an important factor in decision-making. Most of the surveyed women who abandon breast reconstruction surgery, make this decision on the basis of more than one reasons.	x	x	x

* 1) What are the common complaints and issues that can occur for woman treated for BC with curative intent for which decisions have to be made with regard to management within five years after curative treatment?; 2) to what extent are decisions with regard to the management of these complaints preference-sensitive?; 3) To what extent and how are BC patients involved in making these follow-up-related decisions?

Supplementary Table S2: Critical Appraisal Skills Programme (CASP) quality scoring according to the study design performed, for all included studies

		Quality scoring criteria, according to the study design*											
Author	**Study design**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
Alderman, 2011 [42]	Cohort	Y	Y	Y	Y	Y	Y	Woman who received IBR did differ from those who received DBR or NBR by several clinical factors	?	Y	Y	Y	Education, improved information provision and decision-making, and develop and deploy decision tools
Balneaves, 2016 [36]	Qualitative	Y	Y	Y	Y	Y	?	?	Y	Y	V	n/a	n/a
Benedict, 2017 [29]	Qualitative	N	?	?	?	Y	?	?	N	Y	V	n/a	n/a
Bluethmann, 2017 [30]	Qualitative, Quantitative	Y	Y	Y	Y	Y	?	Y	N	Y	V	n/a	n/a
Brandzel, 2017 [26]	Qualitative	Y	Y	Y	Y	Y	?	Y	N	Y	V	n/a	n/a
Brauer, 2016 [31]	Qualitative	Y	Y	Y	N	Y	?	Y	?	Y	V	n/a	n/a
Cahir, 2015 [32]	Qualitative	Y	Y	Y	Y	Y	?	Y	Y	Y	V	n/a	n/a
Carter, 2010 [56]	RCT	Y	N	Y	N	Y	Y	The combined average attendance was 74%, and on average paddlers had significantly better attendance than walkers (p = 0.0059)	?	?	Y	Y	n/a
Causarano, 2015 [38]	RCT	Y	Y	Y	N	Y	Y	The decrease in decisional conflict was greater In the intervention group compared to routine education (*d* 0.69)	95% CI = -0.60 to 0.71	Y	Y	Y	n/a
Corney, 2014 [53]	Qualitative	Y	Y	Y	Y	Y	?	?	Y	Y	V	n/a	n/a
Engelhardt, 2016 [33]	Qualitative	Y	Y	Y	Y	Y	?	Y	Y	Y	V	n/a	n/a
Fasse, 2017 [46]	Qualitative	Y	Y	Y	Y	Y	?	Y	Y	Y	V	n/a	n/a

Supplementary Table S2: Critical Appraisal Skills Programme (CASP) quality scoring according to the study design performed, for all included studies (continued)

		Quality scoring criteria, according to the study design*											
Author	**Study design**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
Flitcroft, 2016 [39]	Pilot, Cohort	Y	Y	Y	Y	Y	Y	The range of reasons why woman chose IBR, DBR, and NBR. Utility of domains	?	Y	?	Y	BR decision-making and to discuss all options fully with women
Fu, 2017 [47]	Qualitative	Y	Y	Y	Y	Y	?	Y	N	Y	V	n/a	n/a
Gorman, 2011 [54]	Qualitative	Y	Y	Y	Y	Y	Y	yes	N	Y	V	n/a	n/a
Hamnett, 2016 [48]	Review	Y	Y	?	N	n/a	Evidence-based recommendations for decision-making about BR in older women	?	Y	Y	Y	n/a	n/a
Heller, 2008 [50]	RCT	Y	Y	Y	N	Y	Y	Interactive digital education aid group showed a sign greater improvement in their knowledge level (p = 0.02) and were more satisfied (p = 0.03)	?	Y	Y	Y	n/a
Hershman, 2016 [34]	Qualitative	Y	Y	Y	Y	Y	?	Y	Y	Y	V	n/a	n/a
Holmes, 2017 [64]	Qualitative, Quantitative	Y	Y	Y	Y	Y	Y	Y	N	Y	V	n/a	n/a
Hseish, 2017 [55]	Qualitative	Y	Y	Y	Y	Y	?	Y	Y	Y	V	n/a	n/a
Hudson, 2012 [28]	Qualitative	Y	Y	Y	Y	Y	?	Y	Y	Y	V	n/a	n/a
Kadmon, 2016 [51]	Cohort	Y	Y	Y	Y	Y	Y	Patient age did not correlate with decision-making style or declared level of involvement in the decision-making process for BR	?	Y	N	Y	Understanding the decision-making process about BR and increasing knowledge on the subject
Klaassen 2017 [25]	Qualitative	Y	Y	Y	Y	Y	Y	Y	Y	Y	V	n/a	n/a

Supplementary Table S2: Critical Appraisal Skills Programme (CASP) quality scoring according to the study design performed, for all included studies (continued)

		Quality scoring criteria, according to the study design*											
Author	**Study design**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
Lee, 2010 [44]	Cohort	Y	Y	Y	Y	Y	Y	Substantial variability existed among patients and between patients and providers about the key facts for BR decisions	? (various 95% CIs)	Y	N	Y	Attention to the most important goals and concerns of women
Morrow, 2014 [52]	Qualitative	Y	Y	Y	Y	Y	Y	Y	Y	Y	V	n/a	n/a
Neugut, 2012 [35]	Cohort	Y	Y	Y	Y	?	?	Factors influencing non-initiation of adjuvant hormonal therapy are complex and influenced by patient belief about treatment efficacy and side effects	Precise (relatively small 95% CI)	Y	?	Y	Educational interventions may be used in the future to improve initiation and adherence
Ogrodnik, 2016 [45]	Cohort	Y	Y	Y	Y	Y	Y	Many women do not receive BR despite interest, but the reasons are both patient- and provider-related	?	Y	N	Y	Clinicians need to be more explicit about patient preference at every decision
Potter, 2013 [40]	Qualitative	Y	Y	Y	Y	Y	Y	Y	?	Y	V	n/a	n/a
Rini, 2009 [27]	Qualitative	Y	Y	Y	Y	Y	Y	Y	N	Y	V	n/a	n/a
Sayakhot, 2012 [37]	Qualitative	Y	Y	Y	Y	Y	Y	Y	N	Y	V	n/a	n/a
Sherman, 2016 [43]	RCT	Y	Y	Y	N	Y	Y	Use of the decision aid reduced conflict about decisions and improved satisfaction with information about BR choice	Precise	Y	Y	Y	n/a

Supplementary Table S2: Critical Appraisal Skills Programme (CASP) quality scoring according to the study design performed, for all included studies (continued)

		Quality scoring criteria, according to the study design*											
Author	**Study design**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
Shtaynberger, 2016 [57]	RCT	Y	Y	Y	N	N	Y	The estimated effect sizes were 1.94 (pros) and –1.43 (cons)	Precise	N	Y	Y	n/a
Temple-Oberle, 2014 [49]	Cohort	Y	Y	Y	Y	Y	?	Various (8.3% to 100%)	Precise	Y	Y	Y	n/a
Wandrey, 2015 [65]	Qualitative	Y	Y	Y	N	Y	?	Y	N	Y	V	n/a	n/a
Zielinski, 2015 [41]	Qualitative	Y	Y	Y	Y	Y	?	?	N	Y	V	n/a	n/a

Key:? = unable to tell; N = no; n/a = not applicable; P, Precise; V = Valuable; Y = yes.
Abbreviations: BR: breast reconstruction; CI: confidence interval; IBR: immediate breast reconstruction; NBR: no breast reconstruction; RCT: randomized controlled trial
*** Critical Appraisal Skills Programme criteria per study type:**

Qualitative study

11) Was there a clear statement of the aims of the research?
12) Is a qualitative/ quantitative methodology appropriate?
13) Was the research design appropriate to address the aims of the search?
14) Was the recruitment strategy appropriate to the aims of the research?
15) Was the data collected in a way that addressed the research issue?
16) Was the relationship between researcher and participants adequately considered?
17) Have ethical issues been taken into consideration?
18) Was the data analysis sufficiently rigorous?
19) Is there a clear statement of findings?
20) How valuable is the research?

RCT

12) Did the trial address a clearly focused issue?
13) Was the assignment of patients to treatments randomised?
14) Were all of the patients who entered the trial properly accounted for at its conclusion?
15) Were patients, health workers and study personnel 'blind' to treatment?
16) Were the groups similar at the start of the trial?
17) Aside from the experimental intervention, were the groups treated equally?
18) How large was the treatment effect?
19) How precise was the estimate of the treatment effect?
20) Can the results be applied to the local population, or in your context?
21) Were all clinically important outcomes considered?
22) Are the benefits worth the harms and costs?

Cohort

13) Did the study address a clearly focused issue?
14) Was the cohort recruited in an acceptable way?
15) Was the exposure accurately measured to minimise bias?
16) Was the outcome accurately measured to minimise bias?
17) A. Have the authors identified all important confounding factors?
    B. Have they taken account of the confounding factors in the design and/or analysis?
18) A. Was the follow-up of subjects complete enough?
    B. Was the follow-up of subjects long enough?
19) What are the results of this study?
20) How precise are the results?
21) Do you believe the results?
22) Can the results be applied to the local population?
23) Do the results of this study fit with other available evidence?
24) What are the implications of this study for practice?

Systematic review

1) Did the review address a clearly focused question?
2) Did the authors look for the right type of papers?
3) Do you think all the important, relevant studies were included?
4) Did the review's authors do enough to assess quality of the included studies?
5) If the results of the review have been combined, was it reasonable to do so?
6) What are the overall results of the review?
7) How precise are the results?
8) Can the results be applied to the local population?
9) Were all important outcomes considered?
10) Are the benefits worth the harms and costs?

Chapter 10

Current clinical practice and determinants of the use of delayed breast reconstruction in the Netherlands

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Submitted

SUMMARY

Delayed breast reconstruction (DBR) is a valid option for postmastectomy breast cancer patients who did not undergo immediate breast reconstruction (IBR). The objective of this study was to investigate the clinical practice and determinants of the use of DBR in the Netherlands. Stage I-III breast cancer patients diagnosed between January and March 2012 and treated with mastectomy were selected from the Netherlands Cancer Registry. Routinely collected patient, tumour, treatment and hospital characteristics were complemented with data about DBR up to 2018. Multivariable logistic regression analyses were performed to identify factors independently associated with postmastectomy DBR. Factors associated with time to DBR were identified through Cox regression analyses.

Of all patients who underwent mastectomy (N=1,415), 13.7% underwent IBR, 10.2% DBR, and 76.1% mastectomy alone. DBR patients more often received autologous reconstruction compared to IBR patients (37.5% vs 6.2%, $p<0.001$). Age below 50 years (OR 4.3) and neoadjuvant and adjuvant chemotherapy (OR 2.99 and OR 2.85, respectively) were significantly associated with DBR. Mean time to DBR was 2.4 years [range 1-6 years]. Time to DBR was significantly associated with radiotherapy (HR 0.61) and adjuvant chemotherapy (HR 0.53).

The use of DBR after mastectomy could not be fully explained by age below 50 years and chemotherapy. Treatment with radiotherapy and adjuvant chemotherapy increased time to DBR. More information about patient preferences is needed to understand the use and timing of reconstruction.

INTRODUCTION

In breast cancer treatment, decisions about surgery are part of a continuum of treatment decisions rather than stand-alone decisions. Although breast-conserving therapy (BCT, breast-conserving surgery followed by radiotherapy) has become the central component of surgical breast cancer treatment[1], many women still elect to undergo mastectomy[2], despite possible negative effects on body image and psychosocial wellbeing[3 4]. Postmastectomy breast reconstruction is considered an important treatment modality in breast cancer care, as it not only restores the breast contour but also provides psychological, psychosocial and functional improvement, including body image and sexuality[4-7]. Patients treated with mastectomy may opt for breast reconstruction, which is either performed during mastectomy as an immediate breast reconstruction (IBR) or as delayed breast reconstruction (DBR) at any given point in time following mastectomy[8].

Multiple factors may affect the timing of breast reconstruction, including both tumour and treatment characteristics as clinical cancer stage, tumour size and localization, comorbidity, smoking, as well as individual patient's and surgeon's preferences[8 9]. From a clinical perspective, DBR is considered a good option for patients with a high risk of postmastectomy radiotherapy, typically with stage II or III breast cancer. While IBR is not absolutely contraindicated in patients indicated for radiotherapy, the general clinical believe within the Netherlands is that patients who are scheduled for postmastectomy radiotherapy are better served by DBR. Reasons are that radiotherapy following IBR may not only increase the chance of implant loss, reconstruction failure, or poorer aesthetic outcomes[10 11], but that IBR may also negatively affect the quality of radiotherapy, specifically if tissue expanders with integrated valves are used[12-15]. Furthermore, in Dutch clinical practice, tumour resection is done by oncological surgeons, while breast reconstruction is typically performed by plastic surgeons. Presumably, differences exist between hospitals and regions in local 'in-house styles' and organization of care.

From a patient perspective, common reasons or preferences for choosing DBR over IBR range from a preference to focus on oncological treatment first[16 17] to the unavailability of the desired technique in the facility of breast cancer treatment[18]. Also, patients may feel it is unimportant, unnecessary, nor urgent[16], or they choose to undergo limited surgery as the first procedure[17]. Ultimately, decisions regarding DBR may be relevant from pre-treatment up to years after breast cancer surgery[19].

Trends in IBR have been evaluated extensively, both nationally[20 21] and internationally[2 22 23]. Compared to IBR, where data can be easily studied as IBR is linked to the mastectomy performed, proper collection of DBR-data is more challenging since DBR can be performed years after mastectomy. Consequently, reliable information regarding the current clinical practice of DBR from a national perspective is lacking. Therefore, the objective of the present study was to investigate the clinical practice of the use of DBR in stage I-III breast cancer patients in the Netherlands and the factors affecting its use.

METHODS

Study population

As DBR may remain relevant years after breast cancer surgery[19], we selected breast cancer patients diagnosed between January and March 2012 from the Netherlands Cancer Registry (NCR) for our nationwide population-based study. Patients with stage I-III disease, treated with a mastectomy, were included. The NCR records data for all newly diagnosed malignancies in the Netherlands since 1989 and incorporates data on patient, tumour and treatment characteristics. Data about breast reconstruction is only routinely collected for IBR, therefore, information regarding DBR was manually and retrospectively retrieved for our cohort. Patients' electronic health records were checked in 2018, leading to a follow-up period of about five years after diagnosis.

Tumour stage was classified according to the AJCC TNM Classification for Breast Cancer (7th Edition). Topography, morphology, and grade were coded according to the International Classification of Diseases for Oncology, using tumour, node, and metastasis classification system (ICD-O, 3rd edition). Data about recurrent disease was available up to five years after diagnosis.

This study was approved by the Privacy Review Board of the NCR.

Construction of variables

The primary study outcome was DBR, defined as any reconstruction performed at any other date after mastectomy; other treatment groups were patients treated with IBR (defined as any reconstruction on the same date as mastectomy) and patients treated with mastectomy only.

Hospitals were grouped according to hospital of oncologic surgery and hospital of reconstruction. The surgical volume of a hospital was defined as the annual number of breast cancer patients in 2012, divided into low-volume <175 (n=51), mid-range volume 175-245 (n=29), and high-volume >245 (n=19). Hospitals were categorized as either academic hospitals (including cancer centres, n=8), teaching hospitals (n=44) and general hospitals (n=51). Both academic and teaching hospitals provide medical training to surgical residents. Plastic surgery training is provided in a more limited number of specific hospitals.

Statistical analyses

Patient, tumour, treatment and hospital characteristics were summarized per treatment group and compared using Pearson Chi-square tests (two-sided). Multivariable logistic regression analyses were used to determine factors that were independently associated with use of DBR in contrast to mastectomy alone, controlled for patient, tumour, and treatment characteristics that had a significant relationship with DBR in univariable analyses (significance level $p<0.10$). To determine factors

influencing the time between mastectomy and DBR, a Cox regression analysis was performed controlled for patient, tumour, and treatment characteristics that had a significant relationship with DBR in univariable analyses (significance level $p<0.10$). Variables were selected based on literature[8 9] and included age at time of surgery, clinical tumour and nodal stage, morphology, differentiation grade, chemotherapy, radiotherapy, hospital type, and hospital volume. Conditions of proportionality were analyzed graphically. In multivariable analyses, P-values <0.05 were considered as statistically significant. All analysis was performed using STATA (version 14)[24].

Sample size

To enable regression analyses, Harris' rule of thumb (1985) prescribes a minimum of 10 participants per predictor variable in equations including six or more variables[25]. We expected to include 10-15 independent variables in our multivariable regression, requiring a minimum of 150 DBR patients. In a similar cohort study performed in Denmark, that has an identical nationwide cancer registry, 10.1% of women received DBR in the years following diagnosis (1999-2006, follow-up to 2009)[26]. By including 1500 patients treated with mastectomy, about a quarter of annually newly diagnosed breast cancer patients treated with mastectomy in the Netherlands, we expected to include enough DBR patients. In 2012, quarterly rates of mastectomy and IBR were constant, suggesting generalizability of DBR-rates over a similar period.

RESULTS

Patients characteristics

Of all patients diagnosed with stage I-III breast cancer between January and March 2012, 36% of patients (n=1,415) had been surgically treated with mastectomy (Table 1). Of these patients, 194 (13.7%) patients received IBR, 144 (10.2%) DBR, and 1,077 (76.1%) mastectomy without any reconstructive procedures in the years following resection. DBR patients had a significantly lower mean age than IBR patients (47.4 [range 25.1 – 74.9] years versus 51.1 [range 26.7 – 78.8] years, respectively, $p<0.001$). DBR patients were significantly more often diagnosed with higher clinical stage (stage III: 11.8%; T2-stage: 40.3% or T3-stage: 13.2%) and nodal involvement (57.6%; $p<0.05$) compared to IBR-patients. Statistically significant differences were found between all groups for treatment characteristics, including radiotherapy and chemotherapy ($p<0.001$), as well as for hospital type ($p<0.001$) and hospital volume ($p<0.006$, Table 1).

Figure 1 shows a flowchart of the treatment characteristics for all breast reconstruction patients following mastectomy. Most patients who had undergone breast reconstruction (either IBR or DBR) were not treated with adjuvant radiotherapy.

Table 1: Patient, tumour, treatment, and hospital characteristics for patients treated with mastectomy (n=1415), diagnosed between January and March 2012 (n,%).

		IBR (n=194)	%	DBR (n=144)	%	Mastectomy (n=1077)	%	p-value*
				Patient characteristics				
Age in years (at diagnosis)	<35	19	9.8%	22	15.3%	18	1.7%	<0.001
	35-49	73	37.6%	73	50.7%	169	15.7%	
	50-75	99	51.0%	49	34.0%	609	56.5%	
	75+	3	1.5%	0	0.0%	281	26.1%	
	Median (range)	51.1	26.7-78.8	47.4	25.1-74.9	64.5	26.3-96.5	n/a
Tumour characteristics								
Stage (clinical)	I	93	47.9%	43	29.9%	336	31.2%	<0.001
	II	81	41.8%	78	54.2%	585	54.3%	
	III	5	2.6%	17	11.8%	112	10.4%	
	Unknown	15	7.7%	6	4.2%	44	4.1%	
Clinical tumour size (cT)	0/IS	2	1.0%	0	0.0%	2	0.2%	<0.001
	cT1	99	51.0%	58	40.3%	401	37.2%	
	cT2	69	35.6%	58	40.3%	473	43.9%	
	cT3	10	5.2%	19	13.2%	98	9.1%	
	cT4	0	0.0%	2	1.4%	55	5.1%	
	Missing	14	7.2%	7	4.9%	48	4.5%	
Grade	Grade I	38	19.6%	15	10.4%	145	13.5%	0.090
	Grade II	79	40.7%	60	41.7%	446	41.4%	
	Grade III	46	23.7%	48	33.3%	345	32.0%	
	Unknown	31	16.0%	21	14.6%	141	13.1%	
HER2 status	Positive	146	80.2%	112	79.4%	877	82.4%	0.393
	Negative	3	1.6%	0	0.0%	16	1.5%	
	Unclear	33	18.1%	29	20.6%	171	16.1%	
Hormone receptor status	Positive	127	68.6%	99	68.8%	654	61.1%	0.053
	Mixed	28	15.1%	15	10.4%	201	18.8%	
	Negative	30	16.2%	30	20.8%	215	20.1%	
ER status[a]	Negative	31	16.8%	31	21.5%	221	20.7%	0.438
	Positive	154	83.2%	113	78.5%	849	79.3%	
PR status[a]	Negative	57	30.8%	44	30.6%	410	38.3%	0.043
	Positive	128	69.2%	100	69.4%	660	61.7%	
Multifocality	No	129	69.7%	91	63.2%	745	69.6%	0.447
	Yes	56	30.3%	52	36.1%	318	29.7%	
Lymph node status	N0	132	68.0%	61	42.4%	491	45.6%	<0.001
	>N1	58	29.9%	83	57.6%	552	51.3%	
	Not applicable	4	2.1%	0	0.0%	34	3.2%	

Table 1: Patient, tumour, treatment, and hospital characteristics for patients treated with mastectomy (n=1415), diagnosed between January and March 2012 (n,%). (continued)

		IBR (n=194)	%	DBR (n=144)	%	Mastectomy (n=1077)	%	p-value*
Follow-up characteristics								
Recurrent cancer (5 yeas follow-up)	Yes	10	5.4%	13	8.8%	221	8.0%	0.416
Mean time to recurrence (in days)	Mean (SD)	1012	466	1070	428	884	447	n/a
Type of recurrence	Local	4	2.2	4	2.7	40	1.5	n/a
	Regional	3	1.6	4	2.7	57	2.1	
	Metastasis	7	3.8	10	6.8	196	7.1	
Treatment characteristics								
Chemotherapy	Yes	120	61.9%	120	83.3%	522	48.5%	<0.001
	Neoadjuvant	89	74.2%	94	78.3%	390	74.7%	0.758
	Adjuvant	27	22.5%	23	19.2%	122	23.4%	
	Both	4	3.3%	3	2.5%	10	1.9%	
Endocrine therapy	Yes	121	62.4%	102	70.8%	707	65.6%	0.267
Radiotherapy	Yes	28	14.5%	52	36.1%	359	33.3%	<0.001
	Before BR	0	0.0%	48	92.0%	n/a	n/a	<0.001
	After BR	28	100.0%	4	8.0%	n/a	n/a	
Hospital characteristics								
Hospital type (hospital of oncologic treatment)[b]	General hospital	56	28.9%	60	41.7%	385	35.7%	<0.001
	Teaching hospital	111	57.2%	76	52.8%	631	58.6%	
	Academic hospital	27	13.9%	8	5.6%	61	5.7%	
Hospital type (hospital of breastreconstruction)[b]	General hospital	55	28.4%	42	30.4%	n/a	n/a	0.796
	Teaching hospital	112	57.7%	80	58.0%	n/a	n/a	
	Academic hospital	27	13.9%	16	11.6%	n/a	n/a	
Hospital volume (hospital of oncologic treatment)[c]	Low	48	24.7%	50	34.7%	380	35.3%	0.006
	Middle	60	30.9%	46	31.9%	361	33.5%	
	High	86	44.3%	48	33.3%	336	31.2%	

IBR, mastectomy with immediate breast reconstruction; DBR, mastectomy with delayed breast reconstruction
*Chi-square tested
[a] Only available if hormone receptor status was tested
[b] Hospitals were categorized as either general, teaching, or academic hospitals. Cancer-specialized centres were included in the category of academic hospitals.
[c] Number of surgical treated non-metastatic breast cancer patients in 2012, categorized as low (≤175), medium (175<245), and high (>=245) volume.

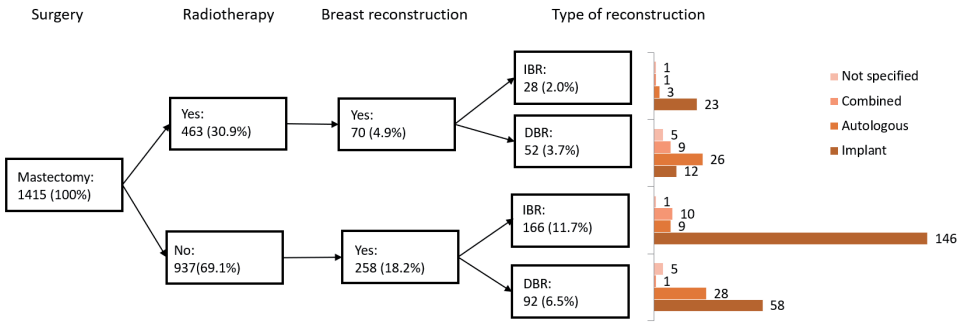

Figure 1. Treatment characteristics for surgical treated patients diagnosed between January and March 2012

IBR, mastectomy with immediate breast reconstruction; DBR, mastectomy with delayed breast reconstruction.
Percentages compared to population of patients treated with mastectomy (n=1415).
Absolute numbers of type of reconstruction are reported at the end of the corresponding bar.

Delayed breast reconstruction

DBR patients significantly more often received mastectomy at general hospitals compared to IBR patients (41.7% versus 28.9%, respectively, $p<0.001$). Implant-based DBR was performed most frequently (n=70, 48.6%), followed by autologous DBR (n=54, 37.5%; Table 2). However, autologous reconstructions were performed significantly more often in DBR patients than in IBR patients (6.2%), where implant-based reconstructions were leading (82.1%).

Mean time to DBR was 710 days (Table 1). In Fig. 2, time to DBR was categorized by TNM-staging. With an increasing tumour stage, DBR was performed later in time, starting ≥1 year following mastectomy ($p=0.019$). Patients treated with radiotherapy received DBR approximately one year later than patients without radiotherapy, with a mean time between diagnosis and DBR of 2.9 years (SD 1.26) versus 2.1 years (SD 1.23), respectively ($p=0.002$; results not shown in Fig. 2).

Table 2. Type of breast reconstruction for immediate and delayed breast reconstructions (n,%) for patients diagnosed between January and March 2012

	IBR (n=194)	%	DBR (n=144)	%	p-value*
Autologous	12	6.2%	54	37.5%	<0.001[b]
Combined autologous and implants	11	5.7%	10	6.9%	
Implants	169	82.1%	70	48.6%	
Not specified	2	1.0%	10	6.9%	

IBR, mastectomy with immediate breast reconstruction; DBR, mastectomy with delayed breast reconstruction.
*Chi-square tested

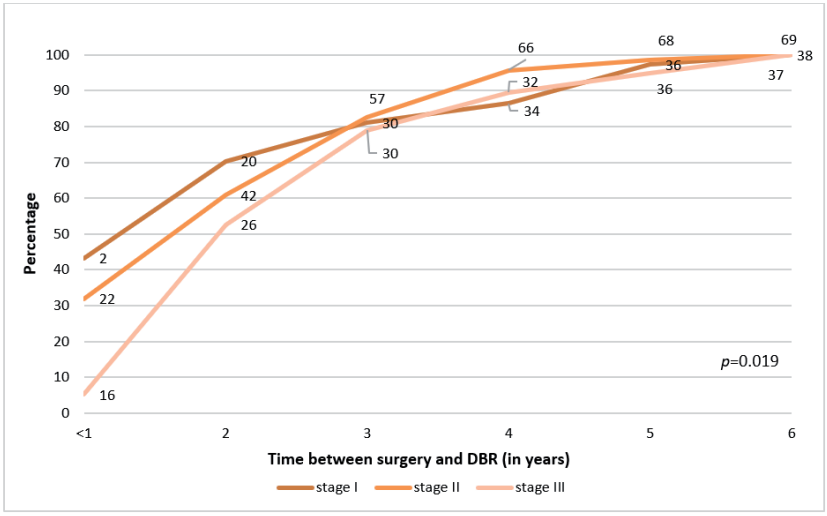

Figure 2. Time (in years) between mastectomy and DBR per TNM-stage; cumulative number of DBR (n=144).

DBR, mastectomy with delayed breast reconstruction.

Absolute cumulative numbers of patients with DBR are reported per year over each line.

Factors associated with the use of DBR

The following variables were significantly related to the use of DBR in univariable analyses and therefore included in the multivariable analyses: age, clinical T-stage and N-stage, grade, chemotherapy, radiotherapy, endocrine therapy, hospital type, and hospital volume. In the multivariable logistic regression analyses, the use of DBR was significantly and positively associated with age <35 years (OR 15.55, CI 8.37–28.93, p<0.001), age 35-49 (OR 4.18, CI 2.84–6.17, p<0.001), and receiving chemotherapy, either neoadjuvant chemotherapy (OR 2.59, CI 1.39–4.84, p<0.001) or adjuvant chemotherapy (OR 2.83, CI 1.75–4.56, p <0.001; Table 3).

As part of a sensitivity analysis, we performed a multivariable logistic regression for the factors related to any breast reconstruction (including both IBR and DBR) in contrast to mastectomy alone. Additionally to chemotherapy, radiotherapy was also associated with receiving breast reconstruction (OR 0.07, p<0.001), as were hospital type and volume (Table 4).

Factors associated with the time between mastectomy and DBR

The following variables were significantly related to time between mastectomy and DBR in univariable Cox regression analyses, and therefore included in the multivariable analyses: age, chemotherapy, radiotherapy, and endocrine therapy. In the multivariable analyses, a longer time between mastectomy and DBR was significantly associated with radiotherapy (HR 0.61, CI 0.42–0.89, p=0.011), and adjuvant chemotherapy (HR 0.53, CI 0.30–0.93, p=0.028; Table 5). Based on graphical investigation, proportionality was assumed for all variables.

Table 3. Logistic regression for the odds of delayed breast reconstruction versus mastectomy alone.

			Univariable		Multivariable		p-value*
		n=1221	OR	95% CI	OR	95% CI	
		Patient characteristics					
Age	<35	33	12.9	6.15 - 27.1	14.65	7.49 – 28.66	<0.001
	35-49	245	5.56	3.75 – 8.26	4.30	2.93 – 6.34	<0.001
	50-75	657	ref				
	75+	286	1	omitted		omitted	
		Tumour characteristics					
Clinical stage	T0	2		omitted		omitted	
	T1	459	Ref		Ref		
	T2	531	0.85	0.58 – 1.25	-	-	-
	T3	117	1.34	0.76 – 2.35	-	-	-
Lymph node status	N0	552	Ref		Ref		
	≥N1	635	1.21	0.85 - 1.72	-	-	-
	Not applicable	34	1	omitted	-	-	-
Grade	Grade I	160	ref		ref		
	Grade II	506	1.30	0.72 – 2.36	-	-	-
	Grade III	393	1.35	0.73 – 2.48	-	-	-
	Unknown	162	1.44	0.71 – 2.90	-	-	-
		Treatment characteristics					
Chemotherapy	No	579	Ref		Ref		
	Yes, adjuvant	484	5.57	3.50 – 8.89	2.99	1.84 – 4.85	<0.001
	Yes, neoadjuvant	145	4.36	2.38 – 7.98	2.85	1.52 – 5.35	0.001
Radiotherapy	No	810	Ref		Ref		
	Yes	411	1.13	0.79 – 1.62	-	-	-
Endocrine therapy	No	412	Ref		Ref		
	Yes	809	1.27	0.87 – 1.86	-	-	-
		Hospital factors					
Hospital type (hospital of oncologic treatment)[a]	General hospital	445	ref		ref		
	Teaching hospital	707	0.77	0.54 – 1.11	-	-	-
	Academic hospital	69	0.84	0.38 – 1.85	-	-	-
Hospital type (hospital of DBR)[a]	General hospital	43	ref		ref		
	Teaching hospital	81	1	omitted	-	-	-
	Academic hospital	16	1	omitted	-	-	-
Hospital volume (hospital of oncologic treatment)[b]	Low	430	ref		ref		
	Middle	407	0.97	0.63 – 1.48	-	-	-
	high	484	1.09	0.71 – 1.66	-	-	-
Goodness-of-fit	Prob > chi2 = 0.5925						
Area under ROC curve	0.7704						

DBR, mastectomy with delayed breast reconstruction; cT, clinical tumour-stage.
*Chi-square tested.
[a] Hospitals were categorized as either general, teaching, or academic hospitals. Cancer-specialized centres were included in the category of academic hospitals.
[b] Number of surgical treated non-metastatic breast cancer patients in 2012, categorized as low (≤175), medium (175-245), or high (>245) volume.

Table 4. Univariable and multivariable logistic regression for the odds of breast reconstruction (either IBR or DBR) versus mastectomy alone.

			Univariable		Multivariable		p-value*
		n=1221	OR	95% CI	OR	95% CI	
		Patient characteristics					
Age	<35	46	7.59	4.03 – 14.28	15.64	7.93 – 30.86	<0.001
	35-49	323	3.73	2.82 – 4.95	4.39	3.21 – 6.01	<0.001
	50-75	757	ref		ref		
	75+	289	0.04	0.01 – 0.13	0.06	0.02 – 0.21	<0.001
		Tumour characteristics					
Clinical stage	T0	4	2.55	0.36 – 18.29	8.28	0.43 – 158.0	0.160
	T1	558	Ref		Ref		
	T2	600	0.69	0.52 – 0.90	0.91	0.67 – 1.24	0.569
	T3	127	0.76	0.48 – 1.19	1.62	0.90 – 2.91	0.108
Lymph node status	N0	684	Ref		Ref		
	≥N1	693	0.65	0.51 – 0.83	1.14	0.84 – 1.53	0.407
	Not applicable	38	0.30	0.10 – 0.85	0.24	0.06 – 0.96	0.044
Grade	Grade I	198	ref		ref		
	Grade II	585	0.85	0.59 – 1.23	-	-	-
	Grade III	439	0.75	0.51 – 1.10	-	-	-
	Unknown	193	1.01	0.65 – 1.58	-	-	-
		Treatment characteristics					
Neoadjuvant chemotherapy	No	653	Ref		Ref		
	Yes, adjuvant	573	2.66	2.01 – 3.51	1.59	1.12 – 2.26	0.010
	Yes, neoadjuvant	172	2.32	1.57 – 3.44	2.47	1.45 – 2.23	0.001
Radiotherapy	No	976	Ref		Ref		
	Yes	439	0.62	0.47 – 0.82	0.07	0.05 – 0.10	<0.001
Anti-hormonal therapy	No	485	Ref		Ref		
	Yes	930	1.01	0.78 – 1.31	-	-	-
		Hospital factors					
Hospital type oncologic treatment[a]	General hospital	501	ref		ref		
	Teaching hospital	818	0.98	0.76 – 1.28	0.72	0.49 – 1.05	0.090
	Academic hospital	96	1.90	1.20 – 3.03	1.76	1.03 – 2.99	0.036
Hospital volume[b]	Low	478	ref		ref		
	Middle	467	1.14	0.83 – 1.55	1.66	1.12 – 2.45	0.011
	high	470	1.55	1.15 – 2.08	2.24	1.46 – 3.45	<0.001
Goodness-of-fit	Prob > chi2 = 0.0383						
Area under ROC curve	0.89						

IBR, mastectomy with immediate breast reconstruction; DBR, mastectomy with delayed breast reconstruction; cT, clinical tumour-stage; MDT, multidisciplinary team meeting.
*Chi-square tested.
[a] Hospitals were categorized as either general, teaching, or academic hospitals. Cancer-specialized centres were included in the category of academic hospitals.
[b] Number of surgical treated non-metastatic breast cancer patients in 2012, categorized as low (≤175), medium (175-245), or high (>245) volume.

Table 5. Cox regression for the time between mastectomy and delayed breast reconstruction (DBR).

			Univariable		Multivariable		p-value*
		n=144	HR	95% CI	HR	95% CI	
		Patient characteristics					
Age	<35	17	1.95	1.09 – 3.49	1.77	0.95 – 3.32	0.074
	35-49	77	1.08	0.75 – 1.55	1.47	0.99 - 2.20	0.058
	50-75	50	ref		ref		
	75+	0		omitted		omitted	
		Tumour characteristics					
Clinical stage	T0	58		omitted		omitted	
	T1	58	Ref		Ref		
	T2	19	0.73	0.50 – 1.06	-	-	-
	T3	9	1.16	0.67 – 1.99	-	-	-
Lymph node status	N0	61	Ref		Ref		
	≥N1	83	0.81	0.57 – 1.13	-	-	-
	Not applicable	0		omitted		omitted	
Grade	Grade I	15	ref		ref		
	Grade II	60	0.63	0.35 – 1.12	-	-	-
	Grade III	48	0.75	0.42 – 1.34	-	-	-
	Unknown	21	0.92	0.47 – 1.80	-	-	-
		Treatment characteristics					
Chemotherapy	No	24	Ref		Ref		
	Yes, adjuvant	94	0.59	0.37 – 0.94	0.53	0.30 – 0.93	0.028
	Yes, neoadjuvant	23	0.85	0.47 – 1.53	0.85	0.44 – 1.66	0.644
Radiotherapy	No	92	Ref		Ref		
	Yes	52	0.73	0.51 – 1.04	0.61	0.42 - 0.89	0.011
Endocrine therapy	No	42	Ref		Ref		
	Yes	102	0.71	0.49 – 1.02	0.94	0.63 – 1.41	0.778
		Hospital factors					
Hospital type (hospital of oncologic treatment)[a]	General hospital	60	ref		ref		
	Teaching hospital	76	0.91		-	-	-
	Academic hospital	8	1.24	0.64 – 1.28	-	-	-
Hospital type (hospital of DBR)[a]	General hospital	43	ref	0.56 – 2.74	ref		
	Teaching hospital	81	0.86	0.57 – 1.30	-	-	-
	Academic hospital	16	1.30	0.87 – 1.94	-	-	-
Hospital volume (hospital of oncologic treatment)[b]	Low	50	ref		ref		
	Middle	46	0.81	0.56 – 1.18	-	-	-
	high	48	0.85	0.47 – 1.54	-	-	-

DBR, mastectomy with delayed breast reconstruction; cT, clinical tumour-stage.
*Chi-square tested.
[a] Hospitals were categorized as either general, teaching, or academic hospitals. Cancer-specialized centres were included in the category of academic hospitals.
[b] Number of surgical treated non-metastatic breast cancer patients in 2012, categorized as low (≤175), medium (175-245), or high (>245) volume.

DISCUSSION

The objective of the current study was to investigate the breast cancer patient population opting for DBR in the Netherlands. Based on one quarter of newly diagnosed patients treated with mastectomy in 2012, DBR was performed in 10.2% (144/1,415) of patients, which is consistent with DBR rates of 9.3–13% from European literature (Denmark, the UK; 1999-2009)[26 27]. Breast cancer patients with DBR significantly differed from patients with IBR or mastectomy alone. DBR patients were significantly younger, were more often diagnosed with stage II breast cancer and axillary lymph node metastases and were more often treated with chemotherapy or radiotherapy. This corresponds with the rationale that patients who are considered eligible for IBR are generally diagnosed with stage I breast cancer, with a good prognosis and a negative sentinel lymph node without the indication for axillary lymphadenectomy or radiotherapy[14]. In addition, most DBR and mastectomy alone patients were treated at teaching or general hospitals, whereas IBR was mostly performed at academic or teaching hospitals[20 28]. This corroborates the findings of Alderman et al.[29], who demonstrated that breast reconstruction rates were most probably higher in breast cancer specialized centres and hospitals with a high clinical breast surgery volume, because of high referrals to plastic surgeons.

Although not exclusively explaining the use of DBR, age below 50 years and treatment with (neoadjuvant) chemotherapy were significantly associated with DBR. This is in contrast to current literature. Initiation of adjuvant chemotherapy is recommended within 6-12 weeks after mastectomy[8 30-32], and a recent large Dutch population-based study found that IBR did not reduce the likelihood of receiving adjuvant chemotherapy within 9 or 12 weeks following mastectomy[33]. This suggests that IBR does not delay the initiation of adjuvant chemotherapy to a clinically relevant extent[33], and thus DBR is not per se preferred over IBR when chemotherapy is indicated. Furthermore, literature has shown younger age is mainly related to higher IBR-rates[20 28 34], not to DBR-rates, and IBR-rates decrease significantly with increasing age[35]. Therefore, both associations may seem unexpected. However, our results could be explained by the following.

First, the decisions for IBR and DBR are interdependent, or as stated in our introduction section, part of a continuum of decisions. There are several reasons to prefer IBR over DBR, including cosmetic result and organizational benefits[6 8 19]. Patients who prefer a reconstruction but have a contra-indication for IBR, will most likely opt for DBR. The decision for DBR is therefore conditional to the decision regarding IBR, which may explain why we found no significant association of radiotherapy with DBR. This is illustrated by our sensitivity analysis. Radiotherapy was strongly negatively associated with receiving any breast reconstruction (IBR or DBR) in contrast to mastectomy alone (Table 4); a result from adding IBR patients to the regression analyses as reported in Table 3. Radiotherapy is reported as the most common reason to delay breast reconstruction until the acute side-effects of radiotherapy have been resolved, preferring DBR over IBR[8 12 14 15]. Our Cox regression analysis demonstrated that the time between mastectomy and DBR was significantly longer when radiotherapy was given; most patients were scheduled for DBR at least 2 years after radiotherapy completion.

The same may apply for age. Of all patients with a contra-indication for IBR, young patients may still opt for DBR, whereas older patients may be satisfied with mastectomy alone. This is partly explained by both patients' preferences and clinicians' beliefs. As older patients are more likely to have significant comorbidities, clinicians may find younger patients more eligible to undergo breast reconstruction[35]. Moreover, one may speculate that older patients more easily accept the loss of their breast(s) or may not want to undergo major surgery. Younger patients in contrast may be more aware of breast reconstruction possibilities[20] and may be more assertive to discuss this option with their physician[19].

Second, treatment practice has changed since 2012. Chemotherapy may be a proxy for disease severity and the prognosis of recurrence risk: DBR patients significantly more often had stage III disease and larger pre-treatment tumours. Therefore, reluctancy towards IBR may have caused physicians to advice DBR instead. At that time, IBR was more cautiously offered to patients indicated for chemotherapy[36], while current evidence-based guidelines state chemotherapy is not a contra-indication for IBR[33 37]. In our study we revealed a longer time between DBR in case of chemotherapy. The reason for this is not clear but could be patients were initially reluctant to undergo yet another stressful treatment in the hospital.

Implant-based breast reconstruction was the most frequently used technique (82.1% IBR; 48.6% DBR) in our cohort. Nowadays, however, autologous reconstructions are increasingly recommended[8], as lower rates of total reconstruction failure and better long-term patient satisfaction with aesthetic outcome compared to implant reconstruction have been reported[8 38]. In our radiated sub-population, the majority had received autologous breast reconstruction. The Dutch evidence-based guideline for breast reconstruction (2018) states that for DBR after radiotherapy it is preferable not to perform reconstruction with an implant only due to the high risk of implant loss[8], but rather add non-irradiated tissue to cover the implant or perform a full autologous reconstruction.

The nationwide and population-based character is a major strength of our study. However, the data obtained for this study was restricted to the time period between January and March 2012. Although this limits the size of our sample, our sample size calculation substantiates the number of included patients in our cohort. Because DBR is not routinely registered in the NCR, data had to be manually collected retrospectively over a time period of five years of follow-up. Still, within this quarter, patients who received DBR in a hospital different from were mastectomy was performed, may have been lost to follow-up. Patients may have decided independently for DBR at another hospital, leaving no paper trail at the hospital where the mastectomy was performed. These referral patterns are not easily identified by NCR's registrars, especially when time since diagnosis passes, probably resulting in a somewhat smaller number of identified DBR patients. In a study on IBR a 5% hospital transfer was seen[39], which implies little incompleteness in our study. Active follow-up for all patients in the NCR is advisable.

Several latent variables may have accounted for the reduced explanatory power of our multivariable logistic regression model for the use of DBR. Factors as patients' preferences and behaviour (smoking, BMI), surgeons' beliefs or hospital organizational factors probably also affect the use of DBR, as they do in IBR[20], but are not collected in detail in the NCR. For IBR patients, multiple hospital organizational factors were identified that could possibly also affect the use of DBR after mastectomy for stage I-III breast cancer in the Netherlands, including hospital type and volume, employment of a plastic surgeon, referral to a plastic surgeon, and the structural attendance of a plastic surgeon at the MDT[20].

The present study provides an overview of the use of DBR within the Dutch population of breast cancer patients treated with mastectomy within the last five years. Studies with long-term events since cancer treatment as primary outcome, such as recurrent disease, face the fact that clinical practice usually has changed over time since diagnosis because of improvements in cancer treatments. Similarly, this should be kept in mind when interpreting conclusions about DBR. Currently, BCT is considered at least equally safe as mastectomy[1]. Furthermore, IBR-rates in mastectomy patients have increased over the past years (from 14.8% in 2011 to 26.7% in 2015)[21]. Regarding which type of breast reconstruction is used, recent concerns about the association between the use of breast implants and anaplastic large cell lymphoma (ALCL)[40] could potentially further shift the preference to autologous reconstructions.

Our study is a starting point for future practice evaluation. In order to answer aforementioned questions, data on DBR should be registered on regular basis similar to IBR, taking into account the fact that DBR can be performed until years after the mastectomy. Future research is needed to identify the trend of DBR within the Netherlands over de last years, the variation between hospitals in performing DBR after mastectomy, and the effects of patients' and surgeons' preferences.

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Chapter 11

Summary, general discussion and future perspectives

In all parts of this thesis new diagnostic techniques, outcome measures and patients' preferences were evaluated with the overarching goal to evaluate, measure and improve the breast cancer care currently delivered. By evaluating outcomes that matter most to patients, this thesis strives towards a value-based and patient-centred breast cancer care.

NEW BREAST IMAGING IN TUMOUR RESPONSE EVALUATION

To improve diagnostic techniques and minimize the burden to breast cancer patients in the pre-operative setting, during neoadjuvant chemotherapy (NAC), we aimed to extend the applicability of (three-dimensional) breast ultrasonography. The Automated Breast Volume Scanner (ABVS – ACUSON S2000TM, Siemens Medical Solutions) is an observer-independent automated breast ultrasound technique that automatically scans the breast using a linear transducer. In **Chapter 2**, we performed the first study that evaluated the accuracy of the ABVS compared to breast MRI in measuring tumour response during and after completion of NAC in invasive breast cancer patients. A good correlation was found in the longest diameter for both the mid-NAC and post-NAC evaluation. In contrast to other studies[1 2], were three-dimensional volume measurements obtained and compared to longest diameter measurements. For volume measurements, a fair correlation was found in the mid-NAC evaluation and an excellent correlation in the post-NAC evaluation. Agreement with the RECIST response criteria was high with an absolute concordance in respectively 73% and 62.5% for mid-NAC and post-NAC response evaluation. Strengths of the study are the evaluation by two observers, showing an excellent intra-observer and inter-observer agreement for (3-D) ABVS measurements, and the evaluation of the acceptability for ABVS and breast MRI. Patients ranked the ABVS as much more acceptable as compared to breast MRI and appreciated the fact they could directly view the ultrasonography images during the examination. The study was however limited by its sample size and the availability of mainly tumour response evaluation measurements performed mid-NAC and not post-NAC (due to a considerable amount of (near) complete responses mid-NAC and no indication for post-NAC MRI). Consequently, the ability to compare the radiological response post-NAC with the pathological tumour response was limited. As the ABVS has proven to be advantageous over breast MRI with regard to cost, time, ease of interpretation by multiple clinicians, accessibility, avoidance of contrast agents, and with a diminished burden for patients and a high patient satisfaction rate, further evaluation is warranted. A second, larger, trial (RESPONDER II, NL6615) is, therefore, ongoing that compares the ABVS and MRI tumour response both during NAC and also post-NAC. The results of this larger sample size will be again compared with the pathological tumour response.

Future perspectives

As the effectiveness of systemic therapies improves, the rate of pathological complete response (pCR) in the neoadjuvant setting will increase. Assessment of pCR is thereby of valuable information, since the eradication of disease, from both breast and lymph nodes, is associated with improved survival when compared to the presence of residual disease[3]. Patients with chemother-

apy-sensitive tumours have an excellent outcome, such that additional systemic therapy may not be necessary[4]. This highlights one of the advantages of NAC, as it provides outcome information to physicians and patients in an early phase of treatment which may result in an opportunity to tailor treatment recommendations based on tumour response. Studies are now evaluating the role of additional systemic and/or locoregional therapy in both chemotherapy-sensitive and chemotherapy-resistant tumours[5 6]. For these trials, as well as in clinical practice, an accurate prediction of pCR becomes more important. Moreover, demanding a better radiological prediction of pCR than is currently achieved may prevent patients from unnecessary biopsies post-NAC[7 8]. Future research, including RESPONDER II, must indicate the role of the ABVS in this field.

The ABVS can also be used for purposes other than tumour response evaluation. The fundamental balance between a cleaner resection and a better aesthetic outcome is a key issue in breast-conserving surgery (BCS) and still very difficult to evaluate due to the lack of a reliable evaluation method. A previous study by Lagendijk et al., performed within our institute, has shown that 3-D ultrasonography measurements can be used as a preoperative tool to predict aesthetic outcome[9]. Using the ABVS it is shown that both breast volume and tumour volume have a significant and high association with the gold standard; i.e. water displacement method for the preoperative assessment of breast volume and the histopathological measurements of tumour volume[9]. Breast volume and tumour volume could be important for the aesthetic outcome prediction of breast-conserving therapy (BCT). Vos et al.[10] have shown that the tumour volume in relation to breast volume is a precise and independent predictor for the aesthetic result, and developed a decision model to compare the quality of life after BCT and mastectomy[11]. This model includes breast volume, tumour volume and the quadrant of the breast in which the tumour is located to predict the aesthetic outcome. Following these promising results, the ABVS was implemented in an ongoing randomized controlled trial: TURACOS trial[12]. In this trial, the ABVS is used to measure both breast volume and tumour volume in early-stage breast cancer patients opting for BCT. By using the decision model as developed by Vos et al., the objective of this trial is to provide evidence that a good aesthetic outcome following BCT can be predicted[12]. The trial enables us to evaluate the agreement between the aesthetic outcome as measured using patient-reported outcome measures (PROMs), and the objective aesthetic outcome as evaluated by an independent panel, as well as by digitalized measurement using BCCT.core software[13]. Combining both aforementioned study-subjects into one, this prediction model might be even helpful in predicting the odds that BCT is feasible after the completion of NAC.

PATIENT-REPORTED OUTCOME MEASURES

Considering comparable disease-specific outcomes and survival rates for both BCT and mastectomy, whether or not followed by breast reconstruction, evaluation of experiences and quality of life of women who have had breast surgery is needed to inform the decision-making process and to optimize the long-term health of those who are facing a new breast cancer diagnosis. The assessment of patients' quality of life and experiences using validated, clinically relevant, PROMs

is thereby critical. The studies presented in **Chapter 3** and **Chapter 4** were performed to gain insights into patient-reported outcomes (PROs) following breast cancer surgery amongst Dutch breast cancer patients and moreover, to provide reference scores for the comparison between surgical populations. PROMs, as proposed in the ICHOM outcome set for breast cancer[14], were collected in collaboration with the regional and national patients' advocate society (**Chapter 3**), and amongst breast cancer patients from the Erasmus MC Cancer Institute surgically treated between 2005 and 2016 (**Chapter 4**). The different results for PROMs following different types of breast surgery are in line with other studies, showing lower PROM scores in mastectomy patients and those who have had an implant-based breast reconstruction compared to patients undergoing BCT or autologous breast reconstruction[15-17]. Comparing PROs between BCT and autologous reconstruction, PROs are either comparable between both procedures or in favour of autologous reconstructions. Reference scores, as obtained in **Chapter 3** and **Chapter 4**, are pivotal when PROs are being used at the outpatient clinic to tailor and improve the care delivered. The data can be used to help guide personal choice with a candid discussion of all treatment options. Both studies were, thereby, the first studies to evaluate the complete set of PROMs as proposed in the ICHOM outcome set per type of breast surgery. However, these studies were both retrospective in nature and represented only a snapshot in time. A prospective evaluation of PROs along several designated time points would provide a more accurate comparison of the surgical procedures. Enabling comparison with baseline PROs will reflect the influence of different treatments better than a single score obtained. Measuring PROs during treatment has thereby the potential to monitor and detect changes in physical or psychological problems at the outpatient clinic. For example, an important finding when evaluating PROs in our patient population were the low response rates on the questions regarding sexual wellbeing, along with the low scores on the sexual wellbeing domain. Since the data on sexual functioning are hampered by the lower response rate and the lack of longitudinal data, the clinical applicability of these scores is limited. However, previous studies on sexual health in breast cancer patients have shown that 50-90% of women experience sexual dysfunction[18 19] and that breast cancer surgery has a negative impact[20]. Longitudinally PROM collection, with questions regarding sexual functioning, could open up the conversation and future consultation on sexuality in breast cancer patients at the outpatient clinic. Obtaining, and narrow, PROM reference scores for the different treatment strategies are then indispensable. It would also be interesting to evaluate the role of the patient's partner within this topic, as well as the will or the ease of discussing sexuality in the consultation room by the care provider, as both may influence the outcomes on sexual wellbeing.

As the majority of the patients in **Chapter 3** agreed that PROs could add in improving the current breast cancer care delivered, these findings highlight the value of the initiatives undertaken, seeking to enhance the quality of surgical care by taking a more patient-centric approach. Herewith, an important step towards extensive use of PROMs in clinical practice and the implementation of value-based healthcare (VBHC) within Erasmus MC's breast cancer care was made. Driven by the raised desire for longitudinal PRO collection and evaluation, our value-based breast cancer care strategy was then implemented. This strategy, as described in **Chapter 5**, is based on the

principle to create value for our breast cancer patients by the measurement of (patient-reported) health outcomes. Herewith the focus lies on outcome-measures not on volume-measures that only facilitate processes but do not reflect outcome. A breast cancer outcomes set that is in line with the ICHOM standard set was integrated into our clinical practice by using an adapted data collection tool that is linked to our electronic health record (EHR). Patients within our institute now receive PROMs at baseline and at predetermined time points throughout their care cycle to discuss these outcomes with their healthcare providers and tailor their supportive therapies where necessary. The PROMs used in this set are all validated questionnaires, specific to the questions at hand. Positive feedback about the initiative was obtained from both patients and healthcare providers. PROs add in information provision, giving a more complete view about the patient, the provided care, and the impact of the treatment given on patients' health-related quality of life (HRQoL) outcomes. The ability to prioritize topics for discussion at the outpatient visits and to monitor and manage symptoms consequently improved patient-provider communication and enhanced shared-decision-making.

Several tools for PRO collection are available nowadays and used in clinical breast cancer care, of which we have provided an overview in **Chapter 6**. PROM administration methods and their facilitators and barriers were studied, as well as the impact of PRO collection on patients, providers, and care processes. In line with our own experiences with PRO collection (**Chapter 5**), we have found that PROM interventions were generally developed to improve symptom management, to identify psychosocial problems, to facilitate patient-centred care and treatment-specific monitoring during treatment phases, and to improve patient-provider communication. The advantages of the use of electronic PRO collection systems were found, which strengthen the way our VBHC-strategy was implemented and integrated into the patient's EHR. Collecting PROs electronically provides a certain flexibility in assessment location (clinic versus home), frequency and duration of PRO follow-up[21]. Consequently, the usability increases, along with a lower response burden, higher completion-rates, and thus fewer missing data (when compared to paper-based PROMs). All the aforementioned findings in turn can lead to better PROM scores and higher patient satisfaction[22-24]. In **Chapter 6** it was also found that most PROM collection tools either focused on monitoring a specific treatment phase or on the entire breast cancer trajectory. In our opinion should routine PROM assessment integrate both and, moreover, be combined with the appropriate PROM to ensure optimal patient engagement and management of care. Within our outcome set, we included an additional time point for breast cancer patients treated with neoadjuvant systemic therapy to measure the degree of chemotherapy-induced peripheral neuropathy. Besides, as we collect a surgery-specific PROM as the BREAST-Q, the PRO collection is based on the individual patient's treatment pathway (i.e. type of surgery performed).

Following the successful implementation of a standardized outcome set that encompassed both provider- and patient-reported outcomes (**Chapter 5**), we strive towards expanding our initiative amongst the women at risk for breast cancer. In **Chapter 8** we compared PROs of *BRCA1/2* mutation carries after either bilateral prophylactic mastectomy followed by immediate breast reconstruc-

tion (BPM-IBR) or during breast surveillance to optimize shared-decision-making in their breast cancer risk management. The Hospital Anxiety and Depression Scale (HADS) and the BREAST-Q were administered amongst unaffected *BRCA1/2* mutation carriers. With all HADS scores below the upper limit of normal, no signs of anxiety or depression were seen in both the surveillance and the BPM-IBR group. For the BREAST-Q questionnaire, slightly better mean scores were seen for the surveillance group as compared to BPM-IBR, except for the psychological wellbeing module. Moreover, the difference in physical wellbeing with chest module was significantly worse for BPM-IBR. As baseline scores were not available due to the cross-sectional retrospective design of this study, initial anxiety levels for developing breast cancer were not available. Being diagnosed with a *BRCA1/2* mutation is however associated with physical and psychological trauma, and (amongst others) patient's (psychosocial) characteristics, coping, and type of risk management strategy chosen are of influence on PROs. Changes in PROM scores over time are thus expected. This, again, emphasizes the necessity of longitudinal PRO collection starting at baseline. Moreover, given the results of a previous study within our institute[25], future possibilities should be explored to obtain reference values which could add value in shared decision-making concerning breast cancer risk management in this population. Within this study, it was shown that for *BRCA1* BPM was associated with lower mortality-rates than surveillance and that for *BRCA2* surveillance was as effective as BPM regarding breast cancer-specific survival[25]. This underscores the importance of adequate counselling *BRCA1/2* mutation carriers regarding their choice between breast surveillance and BPM. Knowledge of PROM outcomes concerning the quality of life after this choice is thereby of great value.

Pressures as aging populations, increasing numbers of people with (multiple) chronic conditions, and high survival rates following breast cancer surgery, along with the greater focus on patient-centred care, have raised the demand for VBHC[26]. However, defining VBHC is still a challenge. The concept of VBHC-delivery, as envisioned by Porter, is a structure for rebuilding global healthcare systems with the overarching goal of value for patients[27]. To establish this indisputable goal of improving value for patients, outcomes of importance to patients and their costs should be measured and these results should be compared to others inside and outside the organisation. This creates the possibility to compare the care delivered within a single healthcare institute as well as between different institutes, on both national and international levels. A challenge in this is standardizing PROMs that are meaningful to patients across different cultural and geographical settings. If routine PROM collection is to be implemented in clinical practice, it is recommended to implement a standardized outcome set, such as the ICHOM standard sets[28], because it is one of the requirements for benchmarking treatments and healthcare providers. Regional, national, or even international efforts to adopt an identical outcome set creates the possibility for benchmarking and comparative research on a much broader scale.

Future perspectives

Quality of life is an important endpoint of breast cancer treatment, and the effects of various interventions on a woman's quality of life are of major interest. As our surgical techniques are becoming more sophisticated, we need to be able to look at them with a much more sophisticated lens in terms of research. PROMs could be used as a tool to facilitate comparisons of different surgical techniques from a patient perspective. PROMs make it then able to learn from patients, from their point of view, whether or not one approach is better than the other for that individual patient in terms of HRQoL endpoints. We, therefore, desire reliable prognostic information tailored to the individual patient; i.e. practical data that can help surgeons and patients tease out the optimal surgical approach and help to set reasonable expectations in anticipation of the specific surgical procedure selected. Predictive modelling has the purpose of informing patients and guiding clinicians in decision-making on treatment decisions. Given the growing trend in the application of machine learning methodologies, we investigated the possibility of developing an algorithm to predict patient-reported HRQoL endpoints in breast cancer patients treated with surgery (**Chapter 7**). To this extent, we used the dataset as described in **Chapter 4**. Unfortunately, in this dataset, we were not successful because of the lack of baseline scores and the, for machine learning, a relatively small sample size. To realize an effective clinical prediction model, information regarding patients' starting position is crucial. The lack of preoperative psychological profiles or PROM scores is, however, a weakness in various other studies or healthcare institutes. This emphasizes, even more, the urgent need of collecting PROMs at baseline. A prospective comparison of preoperative and postoperative PROs might be able to give more definite answers. The next step toward further validation of this approach to the prediction of HRQoL endpoints would be to work with a more complete dataset, including baseline PROs and lifestyle measures. Since PRO collection is considered standard of care at our institute (**Chapter 5**), a prospective dataset is nowadays gathered, which will grow progressively over time. This prospective dataset, including baseline PROs and longitudinal PROs for a period of at least 5 years, should be used to further test the possibilities of developing a predictive tool.

Furthermore, due to the introduction of oncoplastic surgery techniques into the breast-conserving surgery area, a significant number of new surgeries have been generalized. There is an almost absolute lack of knowledge of the aesthetic outcome of these surgeries as well as its impact on a woman's HRQoL. The correlation of the aesthetic outcome with patients' HRQoL is not standardized and very difficult to evaluate anyway. Although several challenges impede bringing aesthetic evaluation into daily clinical practice now, it is expected to be a critical component in future breast cancer management workflows[43]. As artificial intelligence breakthroughs are achieved in current research, the next logical step is to improve the overall aesthetic evaluation also resorting to machine learning. The introduction of objective methods to measure the aesthetic outcome like BCCT.core[13], brings possibilities to adapt machine learning methodologies to integrated disparate measures into a global assessment of the aesthetic result. Using machine learning it is possible to extract predesigned features from the patients photograph[29]. For example, the most relevant anatomical

landmarks as the incisura jugularis, nipples, and breast contours, with particular emphasis in the endpoints. The algorithm can learn to compute features directly form the photograph, including the best set of attributes (distances, textural differences, etc.), and to use those features in the analysis of the aesthetic outcome. The first incursion in explaining the automatic aesthetic assessment has already been made[29 30], promising accountability for the future. However, there is still a lack of big data and extensive international studies. An sizeable repository of photographs of locoregional treated breast cancer patients will enable the development, testing and validation of machine learning based methodologies to improve aesthetic evaluation and overall quality of life follow-up. These methodologies enables us to build on top of the present efforts for locoregional surgeries, adapting the models for the aesthetic evaluation of the vast offer of breast cancer treatments. Finally, the current journey towards more objective methods excluded patients self-assessment from the evaluation process. It seems fundamental to unite these two perspectives of HRQoL, researching methods for the evaluation of the aesthetic outcomes of breast cancer treatments integrating objective methods *and* significant factors derived from patients' input. The aforementioned, currently ongoing, TURACOS trial is an example of such a trial. This prediction model may add information in the conflict between obtaining tumour free resection margins for oncologic control and conserving breast symmetry and aesthetics. But moreover will the PROs obtained inform us whether or not women choose BCT over other surgical techniques in terms of the patient's self-esteem and HRQoL. Ultimately are patients' preferences, if obtained in multiple cohorts, expected to enable an improved objective shared-decision-making in future breast cancer patients

FOLLOW-UP CARE AND DELAYED BREAST RECONSTRUCTIONS

Most patients should be allowed to make their decisions based on their psychological state, values, and preferences, with the proviso that it is oncologically safe. For patients, it is vital to be fully informed about the pros and cons of the different approaches and have realistic expectations about what a specific treatment can achieve. Only when a patient has enough information to make an informed choice, a decision can be made[31]. The quality of the shared-decision-making process, therefore, might affect the eventual effect on the value of the care delivered, in terms of outcomes, costs and organizational efforts[32]. Currently, the arrangements for follow-up care meet the needs of breast cancer patients suboptimally[33-35]. This is also reflected in the literature study described in **Chapter 9**. By exploring the evidence on preferences for and patient involvement in decisions about breast cancer follow-up care, the potential for personalising follow-up care among breast cancer patients was evaluated. The decisions described concerned subjects as surveillance for recurrence or the development of secondary breast cancer, recurrence-risk reduction by anti-hormonal treatment, consultations relating to physical and psychological (late) effects and improving the HRQoL after breast cancer. It was found that patients are currently not involved in all decisions about the content of the form of follow-up that affect them during follow-up, nor it was optimally acknowledged they had preferences towards these decisions. Decisions about follow-up consultations, anti-hormonal treatment, and menopausal symptoms were considered not to be sensitive to patient preferences. Decisions about breast reconstructions in turn were regarded to be very sensitive to patient pref-

erences. Moreover, were patients usually involved in breast reconstruction decision-making. These findings resulted in the recommendation to further personalise breast cancer follow-up care, as it is expected to lead to care that is of greater relevance and value to individual patients.

Breast cancer patients who undergo a mastectomy as part of their treatment can face a potentially life-changing decision, namely whether or not to have their breast reconstructed, and if so, what kind of reconstruction. For patients receiving radiotherapy to reduce the risk of local recurrence, this decision becomes even more challenging. As identified in **Chapter 9** were decisions regarding breast reconstructive surgery considered sensitive to patient preferences, and were patients usually involved in breast reconstruction decision-making. Considering the enormous value that a breast reconstruction can bring, including the rebuilding of the breast and restoring a woman's body image and her HRQoL, decisions regarding breast reconstruction are vitally important within breast cancer care. To make a deliberate decision it is crucial to be fully informed about the different methods available. As information regarding immediate breast reconstructions (IBR, i.e. reconstruction applied during the mastectomy) is widely available in the Netherlands[36-38], partly due to systematic recording of all surgically treated breast cancer patients by the Netherlands Cancer Registry (NCR), the focus within the last part of this thesis lays on delayed breast reconstructions (DBR, i.e. reconstruction applied at a given point in time after the mastectomy). Besides, decisions regarding DBR are more often made after a mastectomy is performed and can remain relevant until years after the initial surgical procedure. In **Chapter 10** it was found that DBR was performed in about 10% of the patients curatively treated with mastectomy for stage I-III breast cancer. Within this cohort, DBR patients were significantly younger, were most often diagnosed with stadium II breast cancer, with nodal involvement, were treated with chemotherapy and/or radiotherapy, and were more often treated at a teaching hospital. The mean time between mastectomy and DBR was 2.4 years (range 1 – 6 years). Age and chemotherapy were identified as predictive factors, as they increased the probability of receiving DBR. Implant-based reconstructions were performed most often, followed by autologous reconstructions, despite treatment with postmastectomy radiotherapy. As for the effect of radiotherapy on the type of DBR: in our radiated sub-population, the largest group had autologous reconstructions. When radiotherapy or adjuvant chemotherapy was performed the time between mastectomy and DBR was extended. The information provided can be helpful in future shared decision-making about breast reconstructive options. Further research is needed to identify the trend of DBR within the Netherlands over de last couple of years, the variation in hospitals in performing DBR after mastectomy, and patients' and surgeon's preferences. Patients who are facing the decision about breast reconstructive surgery may benefit greatly from the perspective of patients who have had the procedures.

Future perspectives

Multiple (patient-reported) treatment-related health problems are identified up to five years after the breast cancer diagnosis, variating per treatment modality (i.e. (neoadjuvant) systemic therapy, type of (reconstructive) breast surgery, and radiotherapy)[39-41]. It is difficult to predict which patients will

encounter medical, physical, and psychological late effects of breast cancer and its treatment[43]. One gap in knowledge we are now striving to fill, is the one regards (late) effects of radiotherapy, because whether or not to receive radiotherapy has a major influence on treatment outcomes. Although in general BCT is associated with good aesthetic outcomes, up to 30% of patients are affected by a severe form of radiation induced fibrosis (RIF) of the radiated breast[44-46]. Moreover, symptoms after RIF as skin induration and thickening, loss of elasticity, lymphoedema, limited joint mobility, pain and an impaired aesthetic outcome, have a negative impact on a woman's HRQoL and a marked effect on the subsequent psychological outcome[47]. Preoperative insight into which women will and which women will not be affected by radiation toxicity gives a woman with a high risk of RIF the possibility to deviate from breast-conserving therapy and opt for a mastectomy (whether or not followed by (immediate) breast reconstruction) that does not necessarily requires radiotherapy. However, there is a large patient-to-patient variability and the severity of RIF is known to be affected by differences in treatment characteristics as maximum radiation dose, boost treatment, and intrinsic radiosensitivity[48 49]. The latter is characterized by patient related factors such as age, breast volume, smoking and/or profound biological differences[46 50 51]. However, the determination of an individual's normal tissue radiosensitivity is seldom possible before treatment. Current practice standard therefore commonly prescribe radiation dose according to clinical scenarios, without regard to the genotype or phenotype of the individual being irradiated. An important biological difference, which can explain the differences in individual radiosensitivity, is the presence of senescence in cells (i.e. permanent arrest state of cell division), which can be induced by ionizing radiotherapy in fibroblasts and other cellular types[52]. It is suggested that by analysing characteristic features of senescence, the individual radiosensitivity, and thus the risk of RIF, can be predicted[52 53]. Since RIF is expected to negatively affect the aesthetic outcome and a woman's HRQoL, the multivariable adjusted association between senescence and RIF after BCT should be further explored. In addition, it is relevant to measure the impact of RIF from patients' point of view. PROMs specific for RIF in breast cancer patients will illustrate the clinical relevance of developing a prediction tool for RIF, but has not been properly evaluated yet. Future trial should therefore not focus on predicting individual radiosensitivity only[54], but should include PROMs as well. If developing RIF indeed decreases the patient-reported HRQoL substantially, it would be clinically relevant to use cell senescence measurements in the shared decision-making process of the choice of breast cancer treatment.

It is plausible that follow-up could be more personalized by predicting which health symptoms may occur in patients. Follow-up care could also become more effective by targeting those health symptoms for which the biggest impact on the patient's life is expected. Successful management of these symptoms would have a large effect on breast cancer survivorship. Again, PROMs could be used for symptom monitoring and management, and to identify other health-related actualities. Prospective PRO collection, starting at baseline and continued during treatment until after treatment completion, is therefore recommended.

Based on the VBHC-initiative, there is an international trend towards increased shared-decision-making in diagnosis and treatment. PROM scores and patients' preferences, as obtained within this thesis, helps us to manage and improve health-related outcomes. In addition, PROs can contribute to the evaluation of the clinical relevance of outcome prediction. Further personalisation of (follow-up) care may lead to care that is of great value for the individual patient, with the possible consequence of reducing overtreatment and / or undertreatment. However, it needs to be emphasized that treatment and follow-up choices must be made within proven clinical guidelines.

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Chapter 12

Nederlandse samenvatting / Dutch Summary

In alle delen van dit proefschrift worden nieuwe diagnostische technieken, uitkomstmaten en voorkeuren van patiënten geëvalueerd, met het overkoepelende doel om de huidige borstkankerzorg te meten, te sturen en te verbeteren. Door zorg uitkomsten te evalueren die het meest belangrijk worden geacht voor borstkankerpatiënten, wordt in dit proefschrift gestreefd naar een waardegedreven borstkankerzorg waarbij de patiënt centraal staat.

NIEUWE BEELDVORMENDE TECHNIEK IN DE TUMORRESPONS EVALUATIE

Met het doel de belasting voor borstkankerpatiënten in de preoperatieve behandelfase te minimaliseren, wordt in het eerste deel van dit proefschrift gekeken naar de mogelijkheden om diagnostische technieken te verbeteren.

In **hoofdstuk 2** wordt de eerste studie beschreven die de nauwkeurigheid van de *Automated Breast Volume Scanner* (ABVS) evalueert in het meten van de tumorrespons tijdens en na voltooiing van neoadjuvante chemotherapie (NAC) bij patiënten met invasieve borstkanker. De resultaten van de ABVS werden vergeleken met die van de borst-MRI (gouden standaard). Er werd een goede correlatie gevonden in de langste diameter respons voor zowel de tussentijdse evaluatie (mid-NAC) als de evaluatie na het voltooien van NAC (post-NAC). Een sterk punt van dit onderzoek is dat, in tegenstelling tot andere studies[1 2], ook driedimensionale volumemetingen uitgevoerd werden naast de diametermetingen. Voor volumemetingen werd een redelijke correlatie gevonden tussen de ABVS en de MRI in de mid-NAC evaluatie, en een uitstekende correlatie in de post-NAC evaluatie. De overeenstemming met de RECIST-responscriteria was eveneens hoog, met een absolute overeenstemming van, respectievelijk, 73% en 62,5% voor de mid-NAC evaluatie en post-NAC-respons. Andere sterke punten zijn de evaluatie door twee onafhankelijke onderzoekers werd verricht, met een uitstekende overeenkomst tussen beide onderzoekers, en de evaluatie van de patiënttevredenheid ten aanzien van de MRI en ABVS. In tegenstellig tot de MRI werd de ABVS als zeer acceptabel beoordeeld. Patiënten waardeerden daarnaast het feit dat de echografiebeelden direct konden worden bekeken tijdens het onderzoek. De studie was echter beperkt door de steekproefomvang en de beschikbaarheid van voornamelijk tumorresponsevaluatiemetingen mid-NAC en niet post-NAC. Dit laatste was een gevolg van de complete radiologische tumorrespons die bij het merendeel van de patiënten gezien werd bij de mid-NAC evaluatie, waardoor er geen indicatie bestond voor het herhalen van de MRI post-NAC. Derhalve werd de ABVS post-NAC ook achterwegen gelaten en was het vermogen om de radiologische respons post-NAC te vergelijken met de histopathologische tumorrespons beperkt. Aangezien de ABVS voordelig is gebleken ten opzichte van borst-MRI met betrekking tot kosten, tijd, interpretatiegemak door meerdere clinici, toegankelijkheid, het vermijden van contrastmiddelen met tevens een hoge patiënttevredenheid, is verdere evaluatie gerechtvaardigd. Daarom is er een tweede, grotere studie (RESPONDER II, NL6615) opgezet die de ABVS- en MRI-tumorrespons vergelijkt, zowel mid-NAC als ook post-NAC. In deze studie worden eveneens de resultaten vergeleken met de histopathologische tumorrespons.

PATIËNT-GERAPPORTEERDE UITKOMSTMATEN

Gezien heden ten dage vergelijkbare ziekte specifieke-uitkomsten en overlevingspercentages voor zowel mammasparende therapie (MST) als voor mastectomie worden bereikt, kan evaluatie van de kwaliteit van leven en patiënttevredenheid van reeds behandelde patiënten bijdragen aan het besluitvormingsproces en lange termijn uitkomsten van diegene die in de toekomst geconfronteerd zullen worden met de diagnose borstkanker. De beoordeling van de kwaliteit van leven en ervaringen van patiënten met behulp van gevalideerde, klinisch relevante vragenlijsten, is daarbij van cruciaal belang.

De studies gepresenteerd in **hoofdstuk 3** en **hoofdstuk 4** zijn uitgevoerd om inzicht te krijgen in door patiënten gerapporteerde uitkomsten (PROs) na borstkankeroperaties bij Nederlandse borstkankerpatiënten. Met behulp van deze uitkomsten streven we er eveneens naar referentiescores te verkrijgen om met behulp van PROs de vergelijking tussen verschillende chirurgische populaties te kunnen maken (i.e. MST, mastectomie en borstreconstructie, autoloog of met behulp van implantaten). Patiënt-gerapporteerde uitkomstmaten (PROMs), overeenkomend met de ICHOM-uitkomstenset voor borstkanker[3], werden verzameld in samenwerking met de regionale en nationale patiëntenverenigingen (**hoofdstuk 3**) en onder alle borstkankerpatiënten van het Erasmus MC Kanker Instituut welke chirurgisch werden behandeld tussen 2005 en 2016 (**hoofdstuk 4**). De verkregen PROs, per type borstchirurgie, komen overeen met resultaten van andere studies en tonen lagere PROM-scores bij borstkankerpatiënten die een mastectomie of een borstreconstructie met implantaten ondergingen. Dit is in tegenstelling tot MST of een autologe borstreconstructie, waar juist hogere scores worden gerapporteerd[4-6]. Wanneer we PROs vergelijken tussen MST en autologe reconstructies, zijn PROs of vergelijkbaar tussen beide procedures of in het voordeel van autologe reconstructies. Referentiescores, zoals verkregen in **hoofdstuk 3** en **hoofdstuk 4**, zijn cruciaal wanneer PROs worden ingezet tijdens poliklinische controles om de geleverde zorg te meten, te sturen en te verbeteren. De gegevens kunnen worden gebruikt om de persoonlijke keuze te begeleiden bij het bespreken van alle behandelingsopties.

Beide studies waren daarbij de eerste studies die de complete set van PROMs evalueren zoals voorgesteld in de ICHOM-uitkomstenset per type borstchirurgie. Deze studies waren echter beide retrospectief van aard en vormden slechts een momentopname. Een prospectieve evaluatie van PROs op verschillende tijdstippen gedurende de behandeling en follow-up zou een meer nauwkeurige vergelijking van de chirurgische procedures bieden. Een vergelijking met baseline PROs zal daarbij nog beter de invloed van verschillende behandelingen weergeven dan een enkele score. Het meten van PROs tijdens de behandeling kan veranderingen in fysieke of psychische problemen detecteren, welke vervolgens poliklinisch kunnen worden opgepakt en vervolgd. Een belangrijke bevinding bij het evalueren van PROs in onze patiëntenpopulatie waren de lage responspercentages op de vragen over seksueel welzijn, samen met de lage PROM-scores op het domein van seksueel welzijn. Omdat de gegevens over seksueel functioneren worden gekleurd door de lagere respons en het ontbreken van longitudinale gegevens, is de klinische toepasbaarheid van deze scores beperkend. Eerdere onderzoeken naar seksuele gezondheid bij borstkanker-

patiënten hebben echter aangetoond dat 50-90% van de vrouwen seksuele disfunctie ervaart[7 8] en dat borstkankeroperaties een negatief effect hebben[9]. Longitudinale PROM-verzameling, met vragen over seksueel functioneren, zal het gesprek over seksualiteit bij borstkankerpatiënten in de polikliniek kunnen openen. Het verkrijgen van PROM-referentiescores voor de verschillende behandelstrategieën is dan onontbeerlijk. Daarnaast zou het ook interessant zijn om de rol van de partner van de patiënt binnen dit onderwerp te evalueren, evenals de wil of het gemak van het bespreken van seksualiteit in de spreekkamer door de zorgverlener, omdat beide de uitkomsten van seksueel welzijn mogelijk beïnvloeden.

De meerderheid van de patiënten in **hoofdstuk 3** vond dat PROs zouden kunnen bijdragen aan de verbetering van de huidige geleverde borstkankerzorg. Dit benadrukt de waarde van de genomen initiatieven, die erop gericht zijn de kwaliteit van de chirurgische zorg te verbeteren door een meer patiëntgerichte benadering te volgen. Hiermee is een belangrijke stap gezet in de richting van het gebruik van PROMs in de kliniek en de implementatie van waardegedreven zorg (v*alue-based healthcare,* VBHC) binnen de borstkankerzorg van het Erasmus MC. Gedreven door de wens voor longitudinale PRO-verzameling en PRO-evaluatie, werd een strategie voor waardegedreven borstkankerzorg geïmplementeerd. Deze strategie, zoals beschreven in **hoofdstuk 5**, is gebaseerd op het principe om waarde te creëren voor onze borstkankerpatiënten door het meten van (door de patiënt gerapporteerde) gezondheidsresultaten. Hierbij ligt de focus op uitkomstmaten, en niet op volumemetingen die alleen processen weergeven maar geen uitkomst weerspiegelen. Een set van uitkomstmaten voor borstkanker, die in overeenstemming is met de ICHOM-uitkomstenset, werd in onze klinische praktijk geïntegreerd met behulp van een nieuw ontwikkelde tool voor gegevensverzameling die is gekoppeld aan het elektronische patiëntendossier (EPD). Borstkankerpatiënten binnen ons instituut ontvangen nu PROMs bij aanvang en op vooraf bepaalde tijdstippen gedurende hun gehele behandeltraject en de bijbehorende follow-up. De PROM-resultaten worden poliklinisch met de behandeld arts besproken en zo kan, waar nodig, ondersteunende therapie worden aangeboden. De PROMs die in deze set worden gebruikt, zijn allen gevalideerde vragenlijsten, specifiek voor het betreffende zorgpad waar de patiënt zich in bevindt. Zowel patiënten als zorgverleners gaven positieve feedback ten aanzien van het initiatief. PROs geven meer informatievoorziening, met een volledieger beeld van de patiënt, de geboden zorg en de impact van de behandeling op de gezondheid gerelateerde kwaliteit van leven van de patiënt. De mogelijkheid om prioriteit te geven aan onderwerpen voor discussie tijdens de poliklinische bezoeken en om de symptomen te monitoren en te beheren, verbeterde de communicatie tussen de patiënt en de arts en verbeterde tevens de gezamenlijke besluitvorming.

In **hoofdstuk 6** wordt een overzicht gegeven van de verschillende tools voor PRO-verzameling die heden ten dagen beschikbaar zijn en gebruikt worden in de borstkankerzorg. PROM-verzamelmethoden en hun facilitators en belemmeringen werden bestudeerd, evenals de impact van PRO-verzameling op patiënten, zorgverleners en zorgprocessen. In overeenstemming met onze eigen ervaringen met PRO-verzameling (**hoofdstuk 5**), hebben we geconstateerd dat PROM-interventies over het algemeen werden ontwikkeld om de symptoomdetectie te verbeteren,

psychosociale problemen te identificeren, patiëntgerichte zorg en behandeling specifieke monitoring tijdens bepaalde behandelingsfasen te vergemakkelijken, en om de communicatie tussen patiënt en zorgverlener te verbeteren. Gevonden werd dat, met name, het gebruik van elektronische PRO-verzamelsystemen voordelen heeft. Dit spreekt voor de manier waarop onze eigen VBHC-strategie werd geïmplementeerd en geïntegreerd in het EPD van de borstkankerpatiënt. Het elektronisch verzamelen van PROs biedt namelijk een zekere flexibiliteit in de locatie waar de PROMs kunnen worden ingevuld (kliniek versus thuis), en in de frequentie en duur van PRO-follow-up[10]. Dit leidt tot een betere bruikbaarheid, en samen met een lagere responslast tot een hoger voltooiingspercentages en dus minder ontbrekende gegevens (in vergelijking met papieren PROMs). Alle bovengenoemde bevindingen kunnen op hun beurt weer leiden tot verbeterde PROM-scores en een hogere patiënttevredenheid[11-13]. Tevens werd in **hoofdstuk 6** gevonden dat de meeste PROM-verzamelingstools zich ofwel op het monitoren van een specifieke behandelingsfase ofwel op het gehele borstkankertraject concentreerden. Naar onze mening moeten routinematige PROM-collectie beide integreren en bovendien worden gecombineerd met de juiste PROM om een optimale patiëntbetrokkenheid en zorgmanagement te waarborgen. In onze uitkomstenset namen we een extra collectiemoment op voor borstkankerpatiënten die werden behandeld met neoadjuvante systemische therapie om de mate van door chemotherapie geïnduceerde perifere neuropathie te meten. Bovendien, aangezien we chirurgie-specifieke PROMs afnemen (namelijk de BREAST-Q), is de PRO-collectie gebaseerd op het behandeltraject van de individuele patiënt (d.w.z. het type chirurgie dat wordt uitgevoerd).

Na de succesvolle implementatie van een gestandaardiseerde uitkomstenset die zowel harde uitkomstmaten als door de patiënt gerapporteerde uitkomsten omvat (**hoofdstuk 5**), streven we ernaar ons initiatief uit te breiden onder de vrouwen met een verhoogd risico op borstkanker. In **hoofdstuk 8** hebben we PROs van *BRCA1* en *BRCA2* genmutatiedraagsters vergeleken die een bilaterale profylactische mastectomie gevolgd door een directe borstreconstructie (BPM-IBR) hadden ondergaan met genmutatiedraagsters die borstkankerscreening (surveillance) ondergaan, met het doel de gedeelde besluitvorming rondom borstkankerrisico-reducerende opties te optimaliseren. De *Hospital Anxiety and Depression Scale* (HADS) en de BREAST-Q werden afgenomen onder *BRCA1* en *BRCA2* genmutatiedragers. Met alle HADS-scores onder de 8, de bovengrens van normaal, werden geen tekenen van angst of depressie gezien in zowel de surveillance als de BPM-IBR-groep. Voor de BREAST-Q-vragenlijst werden iets betere gemiddelde scores gezien voor de surveillancegroep in vergelijking met BPM-IBR, behalve voor de module voor psychologisch welzijn. Bovendien was het verschil in de module voor fysiek welzijn (borsttevredenheid) aanzienlijk slechter voor BPM-IBR. Omdat baselinescores niet beschikbaar waren vanwege het retrospectieve, cross-sectionele, studiedesign, waren aanvankelijke angstniveaus voor het ontwikkelen van borstkanker niet beschikbaar. Gediagnosticeerd worden met een *BRCA1/2*-mutatie wordt echter geassocieerd met fysiek en psychologisch trauma. De (psychosociale) kenmerken, coping en de gekozen borstkankerrisico-reducerende strategie hebben invloed op PROs. Veranderingen in PROM-scores in de loop van de tijd mogen dus worden verwacht. Dit benadrukt nogmaals de noodzaak van longitudinale PRO-verzameling vanaf het moment van diagnose. Bovendien

moeten, mede gebaseerd op de resultaten van een eerdere studie binnen ons instituut[14], mogelijkheden worden onderzocht om referentiewaarden te verkrijgen die van toegevoegde waarde zijn in de gedeelde besluitvorming rondom borstkankerrisico-reducerende strategieën in deze populatie. Binnen deze studie[14] werd aangetoond dat voor een *BRCA1* genmutatie BPM geassocieerd was met lagere sterftecijfers dan surveillance, en dat voor *BRCA2* surveillance even effectief was als BPM wat betreft borstkanker-specifieke overleving. Deze resultaten onderstrepen het belang van adequate begeleiding van *BRCA1/2* genmutatiedragers met betrekking tot hun keuze tussen surveillance en BPM(-IBR). Kennis van PROs met betrekking tot de kwaliteit van leven na deze keuze is daarbij van grote waarde.

Predictiemodellen hebben tot doel patiënten te informeren en clinici te begeleiden bij de besluitvorming rondom behandelingen. Gezien de groeiende trend in de toepassing van *machine learning* voor predictie, hebben we in **hoofdstuk 7** de mogelijkheid onderzocht om een algoritme te ontwikkelen om patiënten gerapporteerde kwaliteit van leven-eindpunten te voorspellen bij chirurgisch behandelde borstkankerpatiënten. Hiertoe hebben we de dataset gebruikt zoals beschreven in **hoofdstuk 4**. Helaas waren we met deze dataset niet succesvol vanwege het ontbreken van baselinescores en de, voor *machine learning*, relatief kleine steekproefomvang. Om een effectief klinisch predictiemodel te realiseren, is informatie over de startpositie van patiënten cruciaal. Het ontbreken van preoperatieve psychologische profielen en/of PROM-scores is echter eveneens een zwakte in verschillende andere studies of zorginstellingen. Dit benadrukt nog meer de dringende behoefte om PROs bij aanvang te verzamelen. Een prospectieve vergelijking van preoperatieve en postoperatieve PROs kan wellicht meer definitieve antwoorden geven. De volgende stap in de richting van verdere validatie van deze benadering voor de voorspelling van kwaliteit van leven-eindpunten zou zijn om te werken met een completere dataset, inclusief baseline PROs en levensstijlgegevens. Omdat PRO-verzameling wordt beschouwd als standaardzorg in ons instituut (**hoofdstuk 5**), wordt momenteel een prospectieve dataset verzameld, die in de loop van de tijd geleidelijk zal worden uitgebreid. Met behulp van deze dataset hopen we de ontwikkeling een dergelijk predictiemodel in de nabije toekomst te kunnen realiseren.

NAZORG EN UITGESTELDE BORSTRECONSTRUCTIES

Hoewel sommige patiënten geen keuze hebben wat betreft de behandelingsstrategie berustend op de tumorkenmerken en -stadium, dient er wel rekening worden gehouden met de autonomie en wensen en voorkeuren van de patiënt. Uiteraard zolang het oncologisch veilig is. Voor patiënten is het uiterst belangrijk om volledig op de hoogte te zijn van de voor- en nadelen van de verschillende behandelstrategieën en om realistische verwachtingen te hebben over wat een specifieke behandeling kan bereiken. Alleen wanneer een patiënt voldoende informatie heeft om een geïnformeerde keuze te maken, kan een beslissing worden genomen[15]. De kwaliteit van het gedeelde besluitvormingsproces kan daarom van invloed zijn op het uiteindelijke effect op de waarde van de geleverde zorg, in termen van resultaten, kosten en organisatorische inspanningen[16]. Momenteel voldoen de regelingen voor de nazorg aan de behoeften van borstkankerpatiënten suboptimaal[17-19]. Dit komt

eveneens naar voren in de literatuurstudie die is beschreven in **hoofdstuk 9**. In deze studie werd de preferentie-sensitiviteit van en de patiëntbetrokkenheid bij beslissingen rondom de borstkanker nazorg geëvalueerd. Tevens werd het potentieel voor het personaliseren van nazorg bij borstkankerpatiënten onderzocht. Dit betrof onderwerpen als surveillance (recidief dan wel secundaire borstkanker), vermindering van het recidiefrisico door anti-hormonale behandeling, consultaties in het kader van fysieke en psychologische (late) effecten, en verbetering van de kwaliteit van leven na borstkanker. Er werd vastgesteld dat borstkankerpatiënten momenteel niet altijd betrokken zijn bij beslissingen rondom de inhoud en de vorm van de follow-up die op hen van toepassing is, noch werd optimaal erkend dat patiënten voorkeuren hebben voor de manier waarop hun nazorg wordt ingericht. Beslissingen over poliklinische follow-up afspraken, anti-hormonale behandeling en symptomen van de menopauze werden niet preferentie-sensitief geacht. Beslissingen over borstreconstructies werden op hun beurt als zeer preferentie-sensitief beschouwd Bovendien waren patiënten meestal betrokken bij de besluitvorming over borstreconstructie. Deze bevindingen resulteerden in de aanbeveling om de nazorg voor borstkanker verder te personaliseren, omdat dit naar verwachting zal leiden tot zorg die van grotere relevantie en waarde is voor individuele patiënten.

Patiënten met borstkanker die een mastectomie ondergaan als onderdeel van hun behandeling, kunnen voor de, potentieel leven veranderende, vraag komen te staan al dan de borst te laten reconstrueren, en zo ja, wat voor reconstructie. Voor patiënten die radiotherapie krijgen om het risico op lokaal recidief te verminderen, wordt deze beslissing nog uitdagender. Zoals geïdentificeerd in **hoofdstuk 9** werden beslissingen met betrekking tot borstreconstructie preferentie-sensitief beschouwd en waren borstkankerpatiënten meestal ook betrokken bij de besluitvorming rondom borstreconstructie. Gezien de enorme waarde die een borstreconstructie kan opleveren, namelijk het reconstrueren van een borst en het herstellen van het lichaamsbeeld van een vrouw en haar gezondheid gerelateerde kwaliteit van leven, zijn beslissingen met betrekking tot borstreconstructie van vitaal belang binnen borstkankerbehandeling. Om een weloverwogen beslissing te kunnen nemen, is het cruciaal om volledig op de hoogte te zijn van de verschillende beschikbare methoden. Aangezien informatie over directe borstreconstructies (IBR, reconstructie ten tijde van de mastectomie) algemeen beschikbaar is in Nederland[20-22], deels als gevolg van systematische registratie van alle chirurgisch behandelde borstkankerpatiënten door de Nederlandse Kankerregistratie (NCR), ligt de focus in het laatste deel van dit proefschrift op uitgestelde borstreconstructies (DBR). Beslissingen met betrekking tot DBR worden vaker genomen nadat een mastectomie is uitgevoerd en kunnen daarom relevant blijven tot jaren na de initiële chirurgische procedure. In **hoofdstuk 10** werd gevonden dat DBR werd uitgevoerd bij ongeveer 10% van de patiënten die curatief werden behandeld met mastectomie voor stadium I-III borstkanker. Binnen dit cohort waren DBR-patiënten aanzienlijk jonger, meestal gediagnostiseerd met stadium-II borstkanker, met aanwezigheid van lymfekliermetastasen, werden ze behandeld met chemotherapie en/of radiotherapie en werden ze vaker behandeld in een perifeer (opleidings-)ziekenhuis. De gemiddelde tijd tussen mastectomie en DBR was 2,4 jaar (range 1 - 6 jaar). Adjuvante behandeling met radiotherapie of chemotherapie verlengde de tijd tussen mastectomie en DBR. Leeftijd onder de 50 jaar en chemotherapie werden

geïdentificeerd als voorspellende factoren, omdat ze de kans op DBR verhoogden. Implantaat-reconstructies werden het vaakst uitgevoerd, gevolgd door autologe reconstructies. Wat betreft het effect van radiotherapie op het type DBR: in onze bestraalde subpopulatie had de grootste groep autologe reconstructies. De verkregen informatie kan nuttig zijn bij toekomstige gedeelde besluitvorming over reconstructieve opties voor borsten. Patiënten die worden geconfronteerd met beslissingen over reconstructieve borstoperaties kunnen veel baat hebben bij het perspectief van patiënten die een dergelijke procedures hebben gehad. Verder onderzoek is nodig om de trend van DBR in Nederland over de afgelopen jaren, de variatie in ziekenhuizen bij het uitvoeren van DBR na mastectomie en de voorkeuren van patiënten en chirurgen te identificeren.

Mede dankzij het VBHC-initiatief is er een internationale trend naar meer gedeelde besluitvorming bij de behandeling van, onder andere, borstkanker. PROM-scores en voorkeuren van patiënten, zoals verkregen binnen dit proefschrift helpen ons bij het beheren en verbeteren van gezondheidsgerelateerde resultaten. Bovendien kunnen PROs bijdragen aan de evaluatie van de klinische relevantie van het ontwikkelen van predictie modellen. Verdere personalisatie van (na)zorg kan leiden tot zorg die van grote waarde is voor de individuele patiënt, en mogelijk zelfs leiden tot minder over- dan wel onderbehandeling. Echter, het moet worden benadrukt dat behandelings- en vervolgkeuzes moeten worden blijven gemaakt binnen de bewezen klinische richtlijnen.

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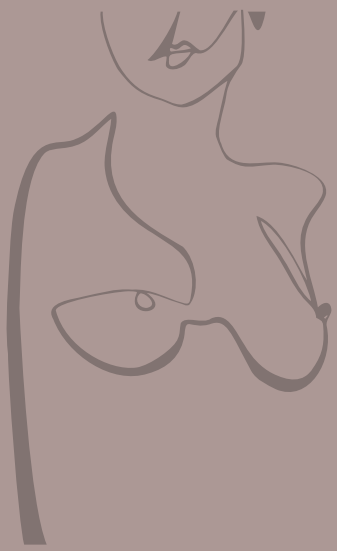
Appendices



LIST OF PUBLICATIONS

Three-dimensional ultrasonography of the breast; An adequate replacement for MRI in neoadjuvant chemotherapy tumour response evaluation? – RESPONDER trial
L.S.E. van Egdom, M. Lagendijk, E.H.M. Heijkoop, A. Jager, A.H.J. Koning, C.H.M. van Deurzen, W. van Lankeren, L.B. Koppert.
Published: Eur J Radiol. 2018 Jul;104:94-100. doi: 10.1016/j.ejrad.2018.05.005.

Patient reported outcome measures in breast cancer patients
M. Lagendijk, **L.S.E. van Egdom**, C. Richel, P. Veenstra, C. Verhoef, H.F. Lingsma, L.B. Koppert
Published: Eur J Surg Oncol. 2018 Jul;44(7):963-968. doi: 10.1016/j.ejso.2018.03.009.

Patient Reported Outcome Measures May Add Value in Breast Cancer Surgery
M. Lagendijk, **L.S.E. van Egdom**, F.E.E. van Veen, E.L. Vos, M.A.M. Mureau, CD. Verhoef, H.F. Lingsma, L.B. Koppert
Published: Ann Surg Oncol. 2018 Nov;25(12):3563-3571. doi: 10.1245/s10434-018-6729-6.

Implementation of Value Based Breast cancer Care
L.S.E. van Egdom, M.L. Lagendijk, M. van der Kemp, J. van Dam, M.A.M. Mureau, J.A. Hazelzet, L.B. Koppert
Published: Eur J Surg Oncol. 2019 Jul;45(7):1163-1170. doi: 10.1016/j.ejso.2019.01.007.

Reply to: Moving forward with value-based healthcare: The need for a scientific approach
L.S.E. van Egdom, J.A. Hazelzet, L.B. Koppert
Published: Eur J Surg Oncol. 2019 Jul;45(7):1300. doi: 10.1016/j.ejso.2019.04.022.

Implementing Patient-Reported Outcome Measures (PROMs) in Clinical Breast Cancer Care: a Systematic Review
L.S.E. van Egdom*, A. Oemrawsingh*, L.M. de Jong-Verweij, H.L. Lingsma, L.B. Koppert, C. Verhoef, N.S. Klazinga, J.A. Hazelzet,
Published: Value Health. 2019 Oct;22(10):1197-1226. doi: 10.1016/j.jval.2019.04.1927.

Opportunities for personalized follow-up care among patients with breast cancer: A scoping review to identify preference-sensitive decisions
K. van der Ligt, **L.S.E. van Egdom**, L.B. Koppert, S. Siesling, J.A. van Til
Published: Eur J Cancer Care (Engl). 2019 May;28(3):e13092. doi: 10.1111/ecc.13092.

Patient-Reported Outcome Measures may optimize shared decision-making for cancer risk management in BRCA mutation carriers
L.S.E. van Egdom, M.A. de Kock, I. Apon, M.A.M. Mureau, C. Verhoef, J.A. Hazelzet, L.B.

Koppert
Published: Breast Cancer. 2019 Dec 12. doi: 10.1007/s12282-019-01033-7.

Machine learning with PROs in Breast Cancer Surgery; Caution: collecting PROs at baseline is important.
L.S.E. van Egdom, A.L. Pusic, C. Verhoef, J.A. Hazelzet, L.B. Koppert
Published: Breast J. 2020 Mar 11. doi: 10.1111/tbj.13804.

Current clinical practice and determinants of the use of delayed breast reconstruction in the Netherlands.
L.S.E. van Egdom, K. de Ligt, L. de Munck H. Rakhorst, M.A.M. Mureau, L.B. Koppert, S. Siesling
Submitted.

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PhD PORTFOLIO

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Copromotor: dr. L.B. Koppert, MD, PhD

1. PhD training		
	Year	**ECTS**
General academic skills		
Research Integrity	2018	0.3
BROK (Good Clinical Practice)	2018	1.5
In-depth courses		
Biostatics Methods I: Basic Principles (CC02), NIHES	2017	5.7
Value Based Health Care; from theory to implementation, ESP76	2017	0.7
CPO course, Patient Oriented Research: design, conduct and analysis	2017	0.3
Presentations		
12th European Breast Cancer Conference, Barcelona, Spain (poster)	2020	0.5
Value Based Health Care meeting, Erasmus MC	2018	1.0
38th ESSO Congress, European Cancer Organisation, Budapest, Hungary (x2)	2018	1.5
9e Rotterdamse Borstkanker Symposium	2018	1.0
Chirurgendagen 2018, NVVH (x2)	2018	1.5
3D ultrasonography in breast cancer research, Department of Bioinformatics, Erasmus MC	2017	1.0
ACE Health Care Quality , Erasmus MC	2017	1.0
Attendance at (inter)national Conferences and Seminars		
38th ESSO Congress, European Cancer Organisation, Budapest, Hungary	2018	0.5
Chirurgendagen/Annual meeting Dutch association of Surgery	2018	0.5
Value Based Health Care & Research, Rotterdam	2018	0.5
11th European Breast Cancer Congress (EBCC-11), Barcelona, Spain	2018	1.0
18e Wondcongres, Rotterdam	2017	0.3
Borstkanker Behandeling Beter Symposium, Rotterdam	2017-19	1.0
Bilthoven Breast Meeting, Alexander Monro Ziekenhuis, Bilthoven	2017	0.1
Quality of Life after cancer treatment Symposium, IHG, Dordrecht	2017	0.3
Organisational skills		
21e Wondcongres 2020, Rotterdam, the Netherlands	2020	2.0
20e Wondcongres 2019, Rotterdam, the Netherlands	2019	2.0
31e Symposium Experimenteel Onderzoek Heelkundige Specialismen (SEOHS)	2018	2.0

2. Teaching activities		
	Year	**ECTS**
Tutor for medical Bachelor students	2018-19	2.0
Examination of Basic Life Support of medical students	2017-18	1.0
Supervising Master theses		
'Two years Value Based Breast Cancer Care' – Cathy van Horik (Erasmus MC)	2018	1.0
'Development of a 3D numerical breast model' – Robin Govers (TU Delft)	2018	1.0
'PROMs in BRCA 1 and 2 gene mutation carriers' – Merel de Kock (Erasmus MC)	2019	1.0
'Ultrasound breast models'- Eva Scherders (TU Delft)	2019	1.0

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Laurentine van Egdom was born on March 21st, 1991 in Bunnik, the Netherlands. As the middle child of three, she grew up in Bilthoven where she completed both elementary school and high school. In 2009 she started medical school at the Erasmus University in Rotterdam. Throughout medical school and the regular internships, her interest in plastic and reconstructive surgery grew into the ambition to become a plastic surgeon. After obtaining her medical degree Laurentine started as a surgical resident at the Department of Surgery at the Franciscus Gasthuis & Vlietland, Rotterdam, the Netherlands (dr. T.M.L. Klem). During this period her interest in the oncological breast surgery grew and with a lot of enthusiasm, she started as a PhD-candidate at the Department of Surgical Oncology at the Erasmus MC Cancer Institute in August 2017 (Prof. C. Verhoef, Prof. J.A. Hazelzet, dr. L.B. Koppert). Motivated to improve the quality of life of breast cancer patients, Laurentine seized the opportunity to work as a research trainee in November 2018 at the Patient-Reported Outcome & Value Experience (PROVE) Centre of the Dana Farber Cancer Institute/ Brigham Women's Hospital, Boston, Massachusetts, United States of America (dr. A.L. Pusic). From January 2019 until July 2019, Laurentine worked as a resident at the Department of Plastic and Reconstructive Surgery of the Erasmus University Medical Centre, Rotterdam, the Netherlands (dr. A.J.M. Luijsterburg). Laurentine started her plastic surgery residency training per October 2019 in the Ikazia hospital, Rotterdam, the Netherlands (dr. P.T. den Hoed).