BREAST CANCER

Insights into Patient Reported Outcomes

M.E. CLARIJS

Publication of this thesis was financially supported by the Erasmus MC Department of Surgery, Erasmus University Rotterdam, Nederlandse Vereniging voor Plastische Chirurgie, Congress Care, ABN AMRO, Chipsoft, GD Medical, and Monkeys & Bananas.

Cover design & Lay-out: Wouter Aalberts
Print by: Ridderprint | www.ridderprint.nl
ISBN: 978-94-6483-649-3

BREAST CANCER
INSIGHTS INTO PATIENT REPORTED OUTCOMES

BORSTKANKER
INZICHTEN IN PATIËNT GERAPPORTEERDE UITKOMSTEN

Thesis

to obtain the degree of Doctor from the
Erasmus University Rotterdam
by command of the
rector magnificus

Prof. dr. A.L. Bredenoord

and in accordance with the decision of the Doctorate Board

The public defence shall be held on

Tuesday, 30 January 2024 at 10:30 hrs

by

Marloes Elisabeth Clarijs,
born in Klundert, the Netherlands

Erasmus University Rotterdam

DOCTORAL COMMITTEE

Promotor	Prof. dr. C. Verhoef
Other members	Prof. dr. F.W.G. Leebeek Prof. dr. L. van der Poll Prof. dr. N.S. Klazinga
Co-promotor	Dr. L.B. Koppert

TABLE OF CONTENTS

PART III

APPENDICES

LIST OF ABBREVIATIONS

BCT	Breast Conserving Therapy
BPM	Bilateral Prophylactic Mastectomy
BRCA 1/2	BReast CAncer gene 1/2
CAT	Computer Adaptive Testing
HRQoL	Health-related Quality of Life
H2O	Health Outcomes Observatory
ICHOM	International Consortium for Health Outcome Measurement
IRT	Item Response Theory
MRI	Magnetic Resonance Imaging
NSM	Nipple-Sparing Mastectomy
NAC	Neo-Adjuvant Chemotherapy
NaC	Nipple-areolar Complex
PRO	Patient Reported Outcome
PROM	Patient Reported Outcome Measurement
QoL	Quality of Life
RECIST	Response Evaluation Criteria in Solid Tumors
RIF	Radiation-Induced Fibrosis
RILA	Radiation-Induced Lymphocyte Apoptosis
SSM	Skin-Sparing Mastectomy
VBHC	Value-Based Healthcare

Chapter 1

General introduction and outline of this thesis

Being diagnosed with breast cancer has a unimaginably large impact on a woman's life and that of her family. Breast cancer patients are facing many challenges during their oncologic and surgical treatment, which demands making choices. Although survival and recurrence rates are similar between different surgical breast cancer treatments, each treatment has a different level of impact on cosmetic outcome, physical and psychosocial wellbeing, and sexual functioning. These patient reported outcomes, often referred to as a patient's quality of life, may guide (surgical) treatment decision making. As the healthcare evolution into a value-based healthcare approach continues, the challenge lies in identifying, measuring, and improving outcomes. Outcomes that matter most to breast cancer patients, measured from a patient's own perspective.

ANATOMY OF THE FEMALE BREAST

A female breast contains different types of fatty, fibrous, and glandular tissue. The glandular tissue develops in puberty when hormonal stimulation triggers differentiation, consists of breast lobes and ducts which play an important role in lactation. The adipose tissue provides environment for the development of parenchyma.[1] The pectoral muscle is positioned posterior to the fibroglandular tissue, lying on the chest-wall. The pectoral muscle is separated from the fibroglandular tissue by the pectoral fascia. The pectoral fascia is firmly connected to the underlying muscle by many intramuscular septa, and has a role in proprioception, due to its many nerve endings, and in lymph drainage.[2] Medially, the breast extends from nearby the sternum and projects laterally in a tail upwards into the axilla. The nipples are a projection of the skin, containing outlets of the lactiferous ducts. The areola is containing sebaceous glands. The nipple-areolar complex is a tremendously important component of the breast, considering breastfeeding, its aesthetics and contribution to sexual pleasure.[3] During a woman's lifetime, the mammary glands undergo many changes. Variation in breasts in terms of shape, volume, density and symmetry in individuals depends on growth, cyclic expansion, age, and post-menopausal, post-partum, or pregnancy status.[1] Besides the anatomical features of the breast, the breast also serves as an female sexual characteristic.

BREAST CANCER

Incidence

Breast cancer is the most common cancer affecting women, with a yearly incidence rate of 47.8 per 100.000 females worldwide. In the Netherlands, approximately 17,000 women are diagnosed with breast cancer each year.[4-6] The survival rates of early-stage breast cancer

have increased over the last few years due to early detection and optimized treatments.[6,7] Unfortunately, there remains a group of patients with incurable disease. Metastatic breast cancer comprises 5-10% of breast cancer patients at time of diagnosis, and 20 to 50% of primary breast cancer patients will eventually develop metastatic disease. Unsurprisingly, metastases are the main cause of death in breast cancer patients, with a mortality rate of 13.6 globally. [8-10] Although there is a trend towards modest survival improvements, the 10% ten-year overall survival in Dutch metastatic breast cancer patients remains particularly poor.[4] Another female group related to breast cancer involves those with an increased risk of developing breast cancer. Genetic predisposition, with the inheritance of a pathogenic BRCA 1 or BRCA 2 gene mutation being the most common, and a family history of breast and/or ovarian disease are widely known risk factors. The risk of developing breast cancer by the age of 70 years is 57- 65 % in woman with a BRCA 1 mutation and 45-47% in woman with a BRCA 2 mutation.[11,12] Breast cancer risk management for mutation carriers encompass intensive surveillance aimed at early detection, or bilateral prophylactic mastectomy (BPM). [13,14]

DIAGNOSTICS

Over the last decade, there has been major improvement in diagnostics for breast cancer. The breast cancer work-up nowadays includes a trias of diagnostics, including physical examination, pre-operative imaging and cytopathological and/or histopathological evaluation. The golden standard for detecting breast cancer is mammography, a quick and cost-effective tool. In case of suspicious lesion palpable during clinical examination or seen on the mammogram, an additional breast ultrasonography is conducted in combination with a biopsy to confirm the breast cancer diagnosis.[15] Depending on the results, other imaging modalities such as axillary ultrasonography, breast MRI and/or FDG-PET or CT-scan are indicated to detect possible metastasis. The breast MRI is also incorporated in the evaluation of tumor diameter during neo-adjuvant chemotherapy treatment, and for the follow-up in a subset of high risk women.[16]

SURGICAL TECHNIQUES

The cornerstone of early-stage breast cancer treatment is surgical removal of the tumor mass. Traditionally, the radical mastectomy technique was introduced by Halsted, consisting of en-bloc resection of the breast, overlying skin, pectoral major muscle, and an extensive lymph node dissection. With the introduction of adequate imaging and systemic treatments, Halsted's radical mastectomy was abandoned after 70 years being the golden

standard.[17,18] Gradually over the years that followed, less extend surgery was performed until procedures that partially preserved the breast. Breast conserving treatment (BCT) involves excision of the primary tumor and evaluation of the axillary lymph nodes with sentinel lymph node biopsy, followed by adjuvant radiotherapy. The main goals of BCT were to provide survival equivalent compared to mastectomy, low rate of recurrence of the treated breast, and a cosmetically acceptable breast. Long-term results of randomized trials have demonstrated at least equal overall and disease-free survival rates for BCT and mastectomy in early-stage breast cancer.[19,20] A Dutch population-based study has even shown superior survival rates for BCT compared to mastectomy in T1-2N0-2M0 breast cancer patients, after correcting for possible confounders.[21] (neo-)Adjuvant systemic treatment, radiation therapy, anti-hormonal therapy and targeted therapies are important additional treatment modalities for non-metastatic breast cancer. Neo-adjuvant chemotherapy can lead to disease downstaging and tumor size reduction. As a result, it will make patients eligible for BCT and diminish the operated excision volume during surgery.[22,23] Although roughly 70 % of all breast cancer patients undergo BCT as an acceptable alternative to mastectomy, it is not always an option.[24] Radiation therapy may present itself with severe adverse effects, such as radiation-induced fibrosis, which impacts the cosmetic outcome and may lead to a partial mastectomy in certain cases that initially underwent BCT.[25] Other indications for a mastectomy with or without immediate or delayed autologous or implant-based reconstruction are high tumor breast volume, absence of donor site tissue or fear of recurrence. With the identification of patients at high risk for breast cancer in case of BRCA mutation, the frequency of BPM followed by autologous or implant-based reconstruction has increased. The landscape of breast reconstruction has changed significantly, and proven to reestablish a female's body image, satisfaction with breasts and quality of life.[26,27] Immediate breast reconstruction following mastectomy has shown favorable psychosocial and physical well-being outcomes compared to mastectomy alone.[28]

In general, a mastectomy is complete removal of the breast glandular tissue and in-breast neoplasia, however, different surgical mastectomy techniques exist. To improve aesthetic outcomes, mastectomy techniques have been refined to skin or nipple-sparing mastectomies (SSM, NSM).[17] The latter involves removal of glandular breast tissue with preservation of the native skin envelope, inframammary fold and nipple-areolar complex. Studies have shown that NSM is oncologically safe in patients with respect to specific selection criteria, such as a tumor-areolar distance of >2 cm, no detection of cancer in the nipple, and early stage breast cancer with favorable biological tumor characteristics.[29,30] Given this oncologic similarity, the decision between type NSM and SSM may be guided by cosmetic outcome, quality of life, and complication rate.

PATIENT REPORTED OUTCOMES

As survival rates of patients with early-stage breast cancer have improved over the last years together with comparable oncological outcomes for BCT and mastectomy, treatment decision-making should be guided by quality of life (QoL) and patient satisfaction. Therapeutic advances have also resulted in better outcomes for metastatic breast cancer patients with modest survival improvements, although without a curative intent. For metastatic breast cancer patients, goals of therapy include diminishing symptoms, delay of disease progression, and prolongation of overall survival with the least negative impact on QoL as possible. Given this, increasingly more attention is being paid to QoL issues within the breast cancer population. Patients with breast cancer often experience considerable burden related to numerous physical symptoms, psychosocial distress, impaired daily functioning during and after treatment. These aspects are expressed through patient-reported outcomes (PROs), captured with validated questionnaires also referred to as patient reported outcome measurements (PROMs). PROs have become an important endpoint in cancer treatment and research.[31,32] A key component of PROs is that the measure conveys information reported by the patient without the influence of an observer or clinician. A PROM can be disease specific, for example the Breast-Q for women undergoing breast surgery[33], or generic and therefore applicable to a plethora of disease populations. These subjective evaluations are self-completed and final scores are typically expressed as absolute numbers. Outcomes may be influenced by various factors, including gender, age, and other sociodemographic characteristics. PROMs allow clinicians to capture patient views, feelings, and subjective experiences unlike traditional measures. Standardized PROMs are validated to ensure certainty over changes in scores, changes over time, and that they measure the constructs they claim. Additionally, PROMs can be used for audit to examine service effectiveness, appropriateness, quality, and performance.[34,35] Nowadays, many PROMs exist as a result of developing disease-specific PROMs but also because criticism on the content or insufficient measurement properties of already existing PROMS.

A standardized outcome set, including PROMs, for early-stage breast cancer patients was developed by the International Consortium for Health Outcome Measurement (ICHOM) to align integrated routine PRO monitoring.[36] A standard set has not yet been composed voor metastatic breast cancer patients. The Academic Breast Cancer center of the Erasmus MC has gained experience in implementing PROs as part of the value based healthcare (VBHC) initiative, with collecting PROs on predefined time points using the institutes electronic PROM collection tool since 2015. The concept of VBHC was introduced by Michael Porter, a new patient-centric approach towards the organization of healthcare. The goal of VBHC is to achieve better health outcomes and an overall better patient experience at the same or lower cost.[35] Outcomes that are measured reflect the value of care instead of volume of services delivered. In a VBHC design, PROs have been incorporated

as an independent parameter for health outcomes in conjunction with clinical outcome measurements (provider-reported, i.e. survival rates, complications). This reflects the total cycle of care and QoL and disease burden in the long run. A global urge to improve the quality and efficiency of healthcare is fueling the rising popularity of VBHC. It has made a tremendous development and recognition in research, however, implementation of a VBHC framework and routinely administration of outcomes in hospitals has shown to be challenging.[32,37] It demands a change in culture within the healthcare organization and stakeholders, benchmarking, and continuously improvement to be able to learn from outcomes and improve the quality of care.

Aggregated PROM data from patient subgroups, disease-stage, treatments or otherwise together with provider-reported data will allow for comparing the care delivered within a single institute, or between institutes on national and international levels. The importance of collecting standardized health data to be used for benchmarking is acknowledged by many health care providers. Aggregated data may be used as quality indicators for improving quality of care, supported by outcome transparency through benchmarking. As one of the first, ICHOM was founded in 2012 with the aim to focus on health outcomes that matter to for many medical conditions. Up to May 2021, 39 standard outcome sets were published. Also new initiatives have arisen to achieve this vision, amongst which the Health Outcomes Observatory (H2O); a strategic alliance between the public and private sectors are creating a data and governance infrastructure system across Europe to foster a value based approach in healthcare systems.[38,39]

The ongoing transformations in healthcare require clinicians to be equipped with new competencies. Proper education can help to change a clinicians' belief about the importance of PROs in the consultation room. There are still some critical questions that remain with regards to statistical analysis, the psychometric evidence of PROMs highlighting the need for more research. Furthermore, to enhance PRO incorporation into daily clinical care, an adequate understanding of PROs by clinicians and providing clinical context for individual patients' scores is required. Baseline, reference and normative values are needed to fill the knowledge gap for the interpretation of PROs. Baseline values are essential to evaluate change over time, and therefore useful to measure the effect of treatment on QoL. Reference values allows for comparing an individual patient with its peers (e.g. based on age, type of surgery). Normative values describe outcomes of a defined population without the specific condition of interest. [40] For breast cancer, normative scores are baseline scores representing a women's quality of life, before the cancer diagnosis. Besides baseline, reference and normative PRO values, minimally clinical important differences describes the smallest patient derived score that is meaningful enough to change clinical management for an individual patient.[41] This may probably even be more interesting to clinicians, as they reflect something that patients perceive as beneficial instead of statistical significance

following treatment evaluations. Eventually, the goal is to promote a richer and fruitful dialogue between patient and healthcare professionals based on meaningful information.

Another method to measure the effectiveness of a health care intervention, with various terms used interchangeably, is the health-related quality of life (HRQoL). HRQoL is defined as the value assigned to duration of life as modified by the impairments, functional states, perceptions, and social opportunities that are influenced by disease, injury, treatment, or policy. The HRQoL outcomes are gathered using validated instruments, for which the EQ-5D-5L is often recommended. Outcomes can be converted into utility scores that reflect a certain health state and used to calculate quality adjusted life years for cost-effectiveness studies. Utility scores are disease, country, age and gender specific.[42]

OUTLINE OF THIS THESIS

Part I Patient reported outcomes in breast cancer patients

Part I of this thesis focuses on establishing normative scores, implementing patient reported outcomes, and measuring patient reported outcomes in different target groups. PROs and PROMs have gained popularity as important endpoints in research, based on the increasing number of publications in different disease areas. Initiatives have been committed to implement a VBHC framework within breast cancer care, in which PROs are routinely collected. The next step is to evaluate outcomes to improve the quality of care.

Normative values may provide both clinicians and patients more context when interpreting post-treatment scores, thereby potentially managing patients' expectations and improving patient–provider communication in the consultation room. In 2020, Dutch females with no medical history of breast cancer and/or prior breast-cancer related breast surgery were invited through social media platforms to complete questionnaires with the goal of obtaining normative values. In **Chapter 2**, the pre-operative Breast-Q module was used to determine age-dependent normative scores. These Dutch normative scores were also compared to other internationally published normative values.

Within the same aforementioned cohort, also the EQ-5D-5L questionnaire was distributed. Utility scores are a result of the conversion of EQ-5D-5L outcomes using pre-defined country-specific value sets. In **Chapter 3**, Dutch normative utility scores of heathy females were calculated. These normative utility values are needed for cost-effectiveness studies, as they are a comparator for health profiles of patients based on subgroups with similar age and gender. Furthermore, three different country-specific value sets were applied to the answers of the EQ-5D-5L of the Dutch cohort. This analysis was conducted to illustrate the impact of using different value sets on age-specific mean normative utility scores.

Using breast cancer related outcomes, both provider and patient reported outcomes, to improve shared-decision making and the care delivered, requires a routinely collected standard set of outcomes. Standardizing these measures might help to improve the implementation of PROs, and facilitates collecting and sharing data to establish valid comparisons in research. This is a prerequisite to learn about how they could impact the clinical care pathway. A standard set for early-stage breast cancer exists, and **Chapter 4** describes the need for a standardized approach in measuring QoL in metastatic breast cancer patients.

In **Chapter 5** we investigate the care-related quality of life of informal caregivers of breast cancer patients, by conducting a cross sectional evaluation of the CarerQoL Questionnaire. We will assess its association with breast cancer patients' QoL scores, to see whether the caregivers' QoL reflect the QoL of patients.

Quality of life and PROs may guide surgical-decision making in breast cancer patients when oncologic safety is similar between treatments. An example of this concept is the

nipple-sparing mastectomy, an emerging alternative for the skin-sparing mastectomy. **Chapter 6** describes a systematic review and meta-analysis that compares PROs and complication rates after nipple-sparing and skin-sparing mastectomy.

PART II A WAY TOWARDS PREDICTING BREAST CANCER OUTCOMES

Part II of this thesis describes research that is at the very beginning of the way towards predicting breast-cancer related outcomes.

In **Chapter 7** we evaluated a novel en patient-friendly imaging tool. The Automated Breast Volume Scanner (ABVS – ACUSON S2000TM, Siemens Medical Solutions) using three-dimensional ultrasonography, is studied for its accuracy for radiological tumor response evaluation in breast cancer patients who are treated with neo-adjuvant chemotherapy (NAC). This research builds on a previously published feasibility study, the RESPONDER I trial, which showed that the ABVS had excellent intra- and inter observer correlations, and superior patient satisfaction compared to the magnetic resonance imaging. In this current study, the sample size was extended to a 100 patients, and tumor volume and diameter measurements of the ABVS post-NAC were compared to histopathologic measurements in addition.

Radiation-induced fibrosis (RIF) is a late adverse event of breast conserving treatment, and is associated with severe symptoms for which invasive surgery is sometimes needed. There is a large patient-to-patient variability in the risk of developing RIF, related to treatment characteristics and individual radiosensitivity. The radiation-induced lymphocyte apoptosis (RILA) assay is a predictive assay to measure an individual's radiosensitivity. In **Chapter 8**, the RILA assay was optimized by using frozen blood samples to enhance clinical implementation, and used to assess the association between the RILA frequency of CD4 and CD8 T-lymphocytes and grade 3 RIF after breast conserving treatment. Potential patient, treatment and tumor related risk factors for RIF can be used for developing a predictive model for RIF that is useful in treatment decision making.

A study protocol that investigates whether preservation of the pectoral fascia decreases drain volume, seroma formation and diminishes postoperative complications is presented in **Chapter 9.** Many surgical guidelines recommend the removal of the pectoral fascia to ensure tumor free margins, however, there is no evidence to support this in BPM or early stage breast cancer. The pectoral fascia plays an role in lymphatic drainage, but whether removal of the pectoral fascia influences seroma formation following mastectomy remains unclear. Seroma and its sequela forms the mainstay of complications in breast cancer surgery, which will eventually delay and hamper reconstructive surgery. To answer our research question, women scheduled for BPM will be included in a within-subject design, meaning unilateral preservation and removal of the pectoral fascia within one patient.

REFERENCES

1. Javed A, Lteif A. Development of the human breast. *Semin Plast Surg.* 2013;27(1):5-12.
2. Stecco A, Masiero S, Macchi V, Stecco C, Porzionato A, De Caro R. The pectoral fascia: anatomical and histological study. *J Bodyw Mov Ther.* 2009;13(3):255-261.
3. Rivard AB, Galarza-Paez L, Peterson DC. Anatomy, Thorax, Breast. 2022.
4. Nederland IK. Kerncijfers over borstkanker uit de Nederlandse Kankerregistratie 1989-2019. 2020; https://iknl.nl/getmedia/2f489dc8-a103-4fd6-89fe-e266e589366f/borstkanker-in-nederland_flyer_2020.pdf. Accessed Accessed January 6, 2023.
5. Vondeling GT, Menezes GL, Dvortsin EP, et al. Burden of early, advanced and metastatic breast cancer in The Netherlands. *BMC Cancer.* 2018;18(1):262.
6. Cardoso F, Kyriakides S, Ohno S, et al. Early breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-updagger. *Ann Oncol.* 2019;30(8):1194-1220.
7. Tyczynski JE, Plesko I, Aareleid T, et al. Breast cancer mortality patterns and time trends in 10 new EU member states: mortality declining in young women, but still increasing in the elderly. *Int J Cancer.* 2004;112(6):1056-1064.
8. Cardoso F, Spence D, Mertz S, et al. Global analysis of advanced/metastatic breast cancer: Decade report (2005–2015). *Breast.* 2018;39:131-138.
9. Cardoso F, Costa A, Senkus E, et al. 3rd ESO-ESMO international consensus guidelines for Advanced Breast Cancer (ABC 3). *Breast.* 2017;31:244-259.
10. O'Shaughnessy J. Extending survival with chemotherapy in metastatic breast cancer. *Oncologist.* 2005;10 Suppl 3:20-29.
11. Engel C, Fischer C, Zachariae S, et al. Breast cancer risk in BRCA1/2 mutation carriers and noncarriers under prospective intensified surveillance. *Int J Cancer.* 2020;146(4):999-1009.
12. Kuchenbaecker KB, Hopper JL, Barnes DR, et al. Risks of Breast, Ovarian, and Contralateral Breast Cancer for BRCA1 and BRCA2 Mutation Carriers. *JAMA.* 2017;317(23):2402-2416.
13. Heemskerk-Gerritsen BA, Brekelmans CT, Menke-Pluymers MB, et al. Prophylactic mastectomy in BRCA1/2 mutation carriers and women at risk of hereditary breast cancer: long-term experiences at the Rotterdam Family Cancer Clinic. *Ann Surg Oncol.* 2007;14(12):3335-3344.
14. Ludwig KK, Neuner J, Butler A, Geurts JL, Kong AL. Risk reduction and survival benefit of prophylactic surgery in BRCA mutation carriers, a systematic review. *Am J Surg.* 2016;212(4):660-669.
15. Nederland IK. Breast Cancer. Dutch Guideline, version 2.0. 2012; https://www.lrcb.nl/resources/uploads/2017/02/Dutch-Breast-Cancer-Guideline-2012.pdf. Accessed Accessed on January 6, 2023.
16. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer.* 2009;45(2):228-247.
17. Freeman MD, Gopman JM, Salzberg CA. The evolution of mastectomy surgical technique: from mutilation to medicine. *Gland Surg.* 2018;7(3):308-315.
18. Kaidar-Person O, Offersen BV, Boersma LJ, et al. A multidisciplinary view of mastectomy and breast reconstruction: Understanding the challenges. *Breast.* 2021;56:42-52.
19. van Maaren MC, de Munck L, de Bock GH, et al. 10 year survival after breast-conserving surgery plus radiotherapy compared with mastectomy in early breast cancer in the Netherlands: a population-based study. *Lancet Oncol.* 2016;17(8):1158-1170.
20. Fisher B, Anderson S, Bryant J, et al. Twenty-year follow-up of a randomized trial comparing total mastectomy, lumpectomy, and lumpectomy plus irradiation for the treatment of invasive breast cancer. *N Engl J Med.* 2002;347(16):1233-1241.

21. Lagendijk M, van Maaren MC, Saadatmand S, et al. Breast conserving therapy and mastectomy revisited: Breast cancer-specific survival and the influence of prognostic factors in 129,692 patients. *Int J Cancer.* 2018;142(1):165-175.
22. Fisher B, Brown A, Mamounas E, et al. Effect of preoperative chemotherapy on local-regional disease in women with operable breast cancer: findings from National Surgical Adjuvant Breast and Bowel Project B-18. *J Clin Oncol.* 1997;15(7):2483-2493.
23. Newman LA, Buzdar AU, Singletary SE, et al. A prospective trial of preoperative chemotherapy in resectable breast cancer: predictors of breast-conservation therapy feasibility. *Ann Surg Oncol.* 2002;9(3):228-234.
24. Collins ED, Moore CP, Clay KF, et al. Can women with early-stage breast cancer make an informed decision for mastectomy? *J Clin Oncol.* 2009;27(4):519-525.
25. van Geel AN, Lans TE, Haen R, Tjong Joe Wai R, Menke-Pluijmers MB. Partial mastectomy and m. latissimus dorsi reconstruction for radiation-induced fibrosis after breast-conserving cancer therapy. *World J Surg.* 2011;35(3):568-572.
26. Lagendijk M, van Egdom LSE, Richel C, et al. Patient reported outcome measures in breast cancer patients. *Eur J Surg Oncol.* 2018;44(7):963-968.
27. Kouwenberg CAE, de Ligt KM, Kranenburg LW, et al. Long-Term Health-Related Quality of Life after Four Common Surgical Treatment Options for Breast Cancer and the Effect of Complications: A Retrospective Patient-Reported Survey among 1871 Patients. *Plast Reconstr Surg.* 2020;146(1):1-13.
28. van Bommel ACM, de Ligt KM, Schreuder K, et al. The added value of immediate breast reconstruction to health-related quality of life of breast cancer patients. *Eur J Surg Oncol.* 2020;46(10 Pt A):1848-1853.
29. Wu ZY, Kim HJ, Lee JW, et al. Breast Cancer Recurrence in the Nipple-Areola Complex After Nipple-Sparing Mastectomy With Immediate Breast Reconstruction for Invasive Breast Cancer. *JAMA Surg.* 2019;154(11):1030-1037.
30. Valero MG, Muhsen S, Moo TA, et al. Increase in Utilization of Nipple-Sparing Mastectomy for Breast Cancer: Indications, Complications, and Oncologic Outcomes. *Ann Surg Oncol.* 2020;27(2):344-351.
31. Snyder CF, Aaronson NK. Use of patient-reported outcomes in clinical practice. *Lancet.* 2009;374(9687):369-370.
32. van Egdom LSE, Oemrawsingh A, Verweij LM, et al. Implementing Patient-Reported Outcome Measures in Clinical Breast Cancer Care: A Systematic Review. *Value Health.* 2019;22(10):1197-1226.
33. Pusic AL, Klassen AF, Scott AM, Klok JA, Cordeiro PG, Cano SJ. Development of a new patient-reported outcome measure for breast surgery: the BREAST-Q. *Plast Reconstr Surg.* 2009;124(2):345-353.
34. Kotronoulas G, Kearney N, Maguire R, et al. What is the value of the routine use of patient-reported outcome measures toward improvement of patient outcomes, processes of care, and health service outcomes in cancer care? A systematic review of controlled trials. *J Clin Oncol.* 2014;32(14):1480-1501.
35. Porter ME, Teisber EO. *Redefining health care: creating value-based competition on results.* Harvard Business Press; 2006.
36. Ong WL, Schouwenburg MG, van Bommel ACM, et al. A Standard Set of Value-Based Patient-Centered Outcomes for Breast Cancer: The International Consortium for Health Outcomes Measurement (ICHOM) Initiative. *JAMA Oncol.* 2017;3(5):677-685.
37. Nguyen H, Butow P, Dhillon H, Sundaresan P. A review of the barriers to using Patient-Reported Outcomes (PROs) and Patient-Reported Outcome Measures (PROMs) in routine cancer care. *J Med Radiat Sci.* 2021;68(2):186-195.

38. Stamm T, Andrews M, Benard AHM, et al. Strengthening the Patient Voice in Health Outcome Measurement in Real-World Data in Europe - the Health Outcomes Observatory. *Value in Health.* 2022;25(12):S472-S472.
39. Stamm T, Bott N, Thwaites R, et al. Building a Value-Based Care Infrastructure in Europe: The Health Outcomes Observatory. *N Engl J Med Catalyst Innovations in Care Delivery.* 2021.
40. O'Connor PJ. Normative data: their definition, interpretation, and importance for primary care physicians. *Fam Med.* 1990;22(4):307-311.
41. Jaeschke R, Singer J, Guyatt GH. Measurement of health status. Ascertaining the minimal clinically important difference. *Control Clin Trials.* 1989;10(4):407-415.
42. Torrance GW. Utility approach to measuring health-related quality of life. *J Chronic Dis.* 1987;40(6):593-603.

PART I

PATIENT REPORTED OUTCOMES IN BREAST CANCER PATIENTS

Chapter 2

BREAST-Q Breast-Conserving Therapy Module: Normative Data From A Dutch Sample of 9059 Women

Arvind Oemrawsingh*, Marloes E. Clarijs*, Andrea L. Pusic, Hester F. Lingsma, Cornelis Verhoef, Jan A. Hazelzet, Linetta B. Koppert

*These authors contributed equally to this work.

Plastic and Reconstructive Surgery, Nov 2021

ABSTRACT

Background

The BREAST-Q, a patient-reported outcome measure for cosmetic and reconstructive breast surgery, is widely used in both clinical research and practice. The aim of this study was to acquire normative data of the BREAST-Q's Breast-Conserving Therapy module from a Dutch population sample and to compare it to existing normative BREAST-Q values.

Methods

Flyers with QR-codes, WhatsApp, and one academic center's Facebook and LinkedIn platforms were used to direct participants to self-complete an online version of four domains of the preoperative BREAST-Q Breast-Conserving Therapy module. BREAST-Q domain scores were log transformed to normalize the distribution. Univariable regression analyses were used to assess (non-linear) associations between age and BREAST-Q domain scores.

Results

Overall, 9 059 questionnaire responses were analyzed. Median BREAST-Q domain scores were 64.0 ± SD 18.0 ("Satisfaction with Breasts"), 69.0 ± SD 21.0 ("Psychosocial Wellbeing"), 92.0 ± SD 20 ("Physical Wellbeing") and 59.0 ± SD 15.0 ("Sexual Wellbeing"). Age as a linear term was associated with log-transformed "Satisfaction with Breasts", "Psychosocial Wellbeing" and "Physical Wellbeing", while "Sexual Wellbeing" was a quadratic functions of age. Prior non-breast cancer-related surgery was a significant predictor for higher log-transformed "Satisfaction with Breasts" ($\beta = 0.04$, $p < 0.001$) and higher "Sexual Wellbeing" ($\beta = -0.05$, $p < 0.001$) scores. Compared to previously published normative data, small differences were found in mean BREAST-Q domain scores (mean differences ranging between 2.45 – 6.24).

Discussion

Normative Dutch BREAST-Q scores follow similar patterns across domains in comparison to previously published normative data. Normative Dutch BREAST-Q data enables future comparisons in breast-related satisfaction and quality of life issues of Dutch breast cancer patients against their age-matched peers.

BACKGROUND

Approximately 17.000 women are diagnosed with breast cancer each year in the Netherlands of which 90% receive surgical treatment.[1,2] As the survival rates of patients with early-stage breast cancer have improved considerably in the Netherlands[3,4], increasingly more attention is being paid on health-related quality of life issues within this population.[5] Patients with breast cancer often experience considerable burden related to numerous physical symptoms, psychosocial distress and impaired function during and after treatment. [6,7] Clinicians have increasingly become more aware of the importance of the patient perspective on surgical outcomes, with the goal to improve the quality of clinical breast cancer care. [8,9]

The BREAST-Q, published in 2009, is a well-validated, multi-scale and widely-used patient-reported outcome measure for women undergoing breast surgery.[10] This condition-specific questionnaire measures the impact of oncological or reconstructive breast surgery on different HRQoL domains and has been used in a plethora of scientific publications in the past decade.[11] The use of patient-reported outcome measure scores in breast cancer care may improve patient-provider communication[12], enhance shared-decision making, and manage patients' expectations by informing them on the experiences of past patients[13]. In addition, as the use of patient-reported outcome measures in breast cancer clinical trials continues to rise, the availability of normative data may be helpful in enabling the interpretability and comparability of patient-reported outcome measure scores across different trial arms.

It has become clear that normative scores are needed to fill the knowledge gap in the interpretation of patient-reported outcome measures, especially to provide context for the interpretation of patient scores following various treatment strategies. Normative data describe outcomes of a defined population without the specific condition of interest.[14] Available normative BREAST-Q data have been published in two studies, both using samples of U.S. women with no previous history of breast cancer or breast surgery.[15,16] The aim of this study was to collect and describe normative data of the BREAST-Q from a Dutch sample and compare them to internationally published normative values.

METHODS

Web-Based Questionnaire

An anonymous opt-in web-based questionnaire was developed in LimeSurvey, a secure online survey tool provider.[17] This questionnaire contained the BREAST-Q and additional questions regarding age and history of breast cancer or breast surgery. The questionnaire was prefaced with a study information sheet and a consent statement box to check.

BREAST-Q, developed at Memorial Sloan Kettering Cancer Center (New York, N.Y.), is a surgery-specific instrument which assesses patient satisfaction and health-related quality of life in women undergoing different types of breast surgery.[10] Current BREAST-Q modules include Augmentation, Reduction/Mastopexy, and Breast Cancer, which includes scales for Mastectomy, Reconstruction, Breast Reconstruction Expectations, and Breast-Conserving Therapy.[18]

The current study used the second version (published in November of 2017) of the preoperative scale of the BREAST-Q Breast-Conserving Therapy Module. This module contains nine domains, of which three quality of life domains [physical well-being (10 items), psychosocial well-being (10 items), sexual well-being (six items)] and one satisfaction domain [satisfaction with breasts (four items)], were administered to participants in this study. Each scale is independent and all items are scored on a Likert scale. According to the BREAST-Q protocol[18], the total score of each domain is transformed separately using a Rasch model to a number within the range of 0 to 100. A higher score means higher satisfaction or better health-related quality of life.

The Dutch version was translated (both forward and backward translation) by a local academic before conception and design of this study.[18]

Recruitment of Study Participants and Data Collection

Three survey distribution techniques were chosen to reach as many potential respondents as possible. Firstly, digital and printed notifications with a QR code hyperlink (to the web-based questionnaire) were distributed by medical students in the city center of Rotterdam for 6.5 days. Secondly, members of the research team disseminated the hyperlink to friends and family and invited them to share it with others. Third, after a formal request was submitted, the Erasmus University Medical Center posted the survey link on its public Facebook and LinkedIn platforms. The status could be viewed and shared by people who are followers of the academic center's platforms.

Participants were required to self-complete this questionnaire on the recruitment website of the Erasmus MC, after reading the study information and giving informed consent. Participants were not compensated and those who failed to complete the questionnaire did not receive a reminder. Data were collected from January through July 2020 and stored in the LimeSurvey database. Participants who did not finish or submit the questionnaire, reported breast cancer in their history, or had discrepant responses (mastectomy reported in the history but no breast cancer reported), were not included in the analysis (Figure 1).

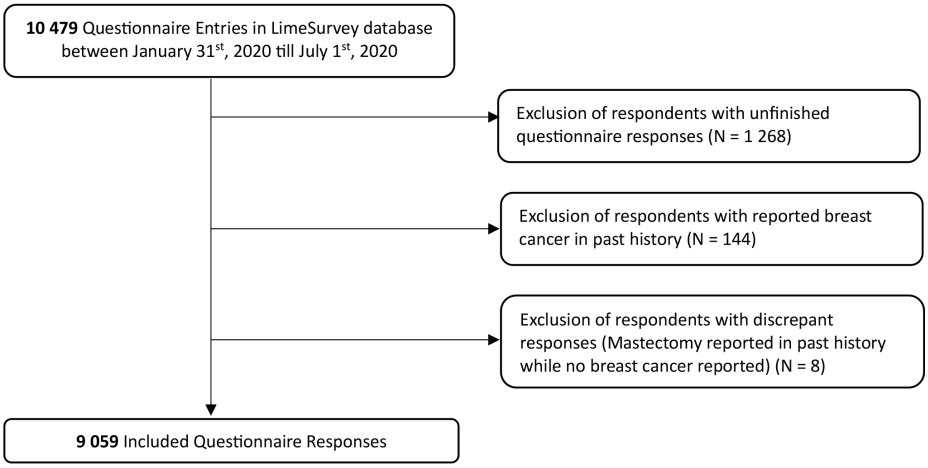


Figure 1: Flowchart of Respondent Selection

Statistical Analysis

Descriptive statistics, including medians and interquartile ranges, were calculated to present the normative BREAST-Q data. The Mann-Whitney U test (non-parametric) was performed to compare BREAST-Q domain scores between women with and without non-breast cancer-related surgery in their history. Skewness and kurtosis were calculated, with significant p values rejecting the null hypothesis for all domains. Therefore, natural log transformation was applied for all domain scores to normalize the distribution. Univariable models for each BREAST-Q domain were used to test for nonlinearity of the effect of age by comparing models with age as a linear versus age as a quadratic term. In addition, multivariable linear regression analysis was used to analyze whether there was a significant association between age and previous breast surgery unrelated to breast cancer (e.g. surgery for fibroadenoma, cosmetic surgery) and (log-transformed) BREAST-Q domain scores. Cases that contained one or more missing items in a domain of the preoperative BREAST-Q version were excluded from analysis for that subscale. The *t* test was used to compare means and standard deviations of the current study's normative scores with previously published normative data. Two-sided *p* values less than 0.05 were considered statistically significant. Statistical analyses were performed using SPSS, version 25.0 (IBM Corporation, Armonk, NY).

Anonymized data and syntax of statistical analyses that support the study findings are available from the principal investigator upon reasonable request.

Ethical Considerations

Formal approval from the local medical ethics review committee was not required because the Dutch Medical Research (Human Subjects) Act does not apply to this study. The legal team and department of communications of the Erasmus University Medical Center approved dissemination of the survey link on the institution's social media platforms.

RESULTS

Study Participants

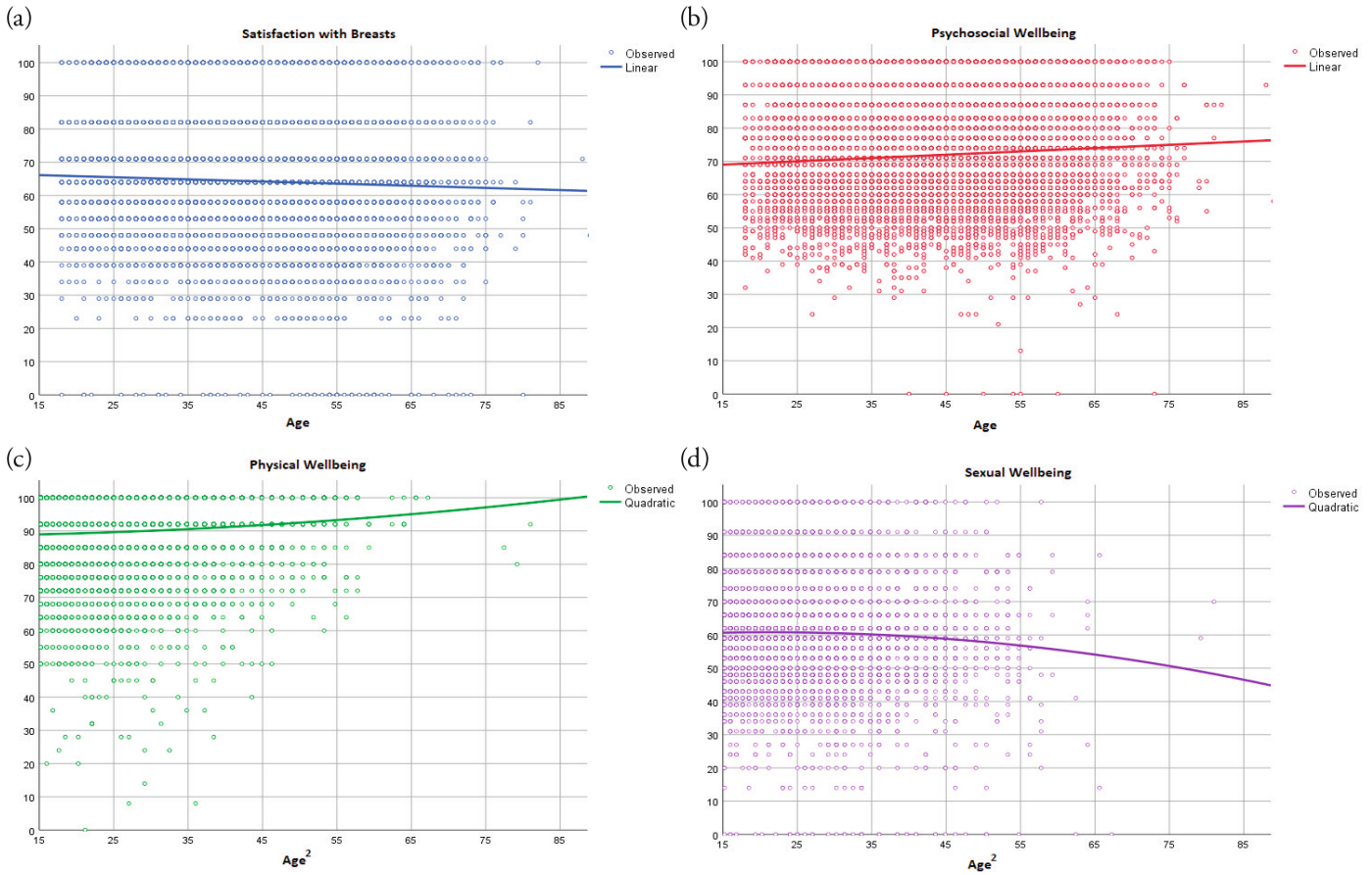
In total, 9 059 questionnaire entries were analyzed (Figure 1). Mean (±SD) age for the overall group was 44 ± 13 years, with most respondents representing the 40 to 49 and 50 to 59 age groups (Table 1). Eighty-one respondents (0.9 percent) did not complete the items of the sexual well-being domain. All other BREAST-Q domains were completed fully.

Table 1: Characteristics of respondents (N = 9059), January – July 2020

	N (%)
Age groups (years)	
18 – 29	1385 (15.3)
30 – 39	1776 (19.6)
40 – 49	2482 (27.4)
50 – 59	2424 (26.8)
60 – 69	837 (9.2)
≥ 70	155 (1.7)
Prior non-breast cancer-related surgery	
BCT (indication: Fibroadenoma)	22 (3.1)
Breast Reconstruction (Cosmetic)	86 (12.2)
Other	682 (96.7)

Dutch Normative BREAST-Q Scores

Overall, the median (±SD) BREAST-Q domain scores were 64.0 ± 18.0 (satisfaction with breasts), 69.0 ± 21.0 (psychosocial well-being), 89.54 ± 12.48 (physical well-being) and 60.38 ± 15.37 (sexual well-being). Median BREAST-Q domain scores stratified for age groups can be found in the Supplementary Material (Table 1). When comparing patients with (n = 705) versus without prior non-breast cancer-related surgery (n = 8 354), satisfaction with breasts was significantly higher (66.46 ± 20.26 vs. 64.05 ± 18.44, $p = 0.002$) and physical well-being was significantly lower (86.60 ± 14.26 vs. 89.79 ± 12.29, $p < 0.001$) for patients who had previous breast surgery.



Figures 2a-2d: Univariable Regression Plots Per Log-Transformed BREAST-Q Domain

Univariable Regression Analyses

Testing for linearity revealed age to be linearly associated with log-transformed satisfaction with breasts ($\beta = -0.001$; $p < 0.001$), psychosocial well-being ($\beta = 0.001$; $p < 0.001$) and physical well-being ($\beta = 0.001$; $p < 0.01$), while sexual well-being ($\beta = -3.7 \times 10^{-5}$; $p < 0.05$) was found to be a quadratic function of age (Figures 2). The model identified 34 years as the inflection point at which sexual well-being values began to decrease.

Multivariable Regression Analyses

Multivariable linear regression analyses (Table 2) confirmed age to be a significant predictor for log-transformed satisfaction with breasts ($\beta = -0.001$; $p < 0.001$), psychosocial well-being ($\beta = 0.001$; $p < 0.001$) and physical well-being ($\beta = 0.001$; $p < 0.001$). Whereas previous breast surgery unrelated to breast cancer was positively associated with log-transformed satisfaction with breasts ($\beta = 0.04$; $p < 0.001$), it had a negative association with physical well-being ($\beta = -0.05$; $p < 0.001$).

Table 2: Multi-Variable Linear Regression Coefficients For Log-Transformed BREAST-Q Domain Scores

	Satisfaction with Breasts		**Psychosocial Wellbeing**		**Physical Wellbeing**		**Sexual Wellbeing**	
Adjusted R^2	0.03		0.07		0.08		0	
	β	**p-value**	β	**p-value**	β	**p-value**	β	**p-value**
Age	–0.001	<0.001	0.001	<0.001	0.001	<0.001	0.001	NS
Previous breast surgery unrelated to breast cancer	0.04	<0.001	0.005	NS	–0.05	<0.001	0.014	NS

Comparison with Past Normative BREAST-Q Studies

Figure 3 demonstrates the variation in mean normative BREAST-Q domain scores between the current study and two internationally published studies by Mundy et al.[16] and Klifto et al.[15] on normative data of the BREAST-Q Reconstruction Module. Normative scores for satisfaction with breasts were statistically higher in the current study compared to Mundy et al. (mean difference = 6.24; $p < 0.001$) and Klifto et al. (mean difference = 4.94; $p < 0.001$), as well as for sexual well-being compared to Mundy et al. (mean difference = 4.38; $p < 0.001$) and Klifto et al. (mean difference = 3.78; $p < 0.001$). A significant score difference for psychosocial well-being was found between the current study and Klifto et al. (mean difference = 2.45; $p < 0.01$). Normative scores for physical well-being were lower compared to Mundy et al. (mean difference = 3.46; $p < 0.0001$), but higher compared to Klifto et al. (mean difference = 5.45; $p < 0.001$).

In contrast to the current study (β = 0.001; p = NS), Klifto et al.[15] found increasing age to be significantly associated with lower sexual well-being scores (β = –0.3; p = 0.018). Mundy et al.[16] demonstrated younger age (less than 40 years) to be associated with lower physical well-being scores, while the current study also revealed a minimal trend towards lower physical well-being scores in the younger age groups (Table 2).

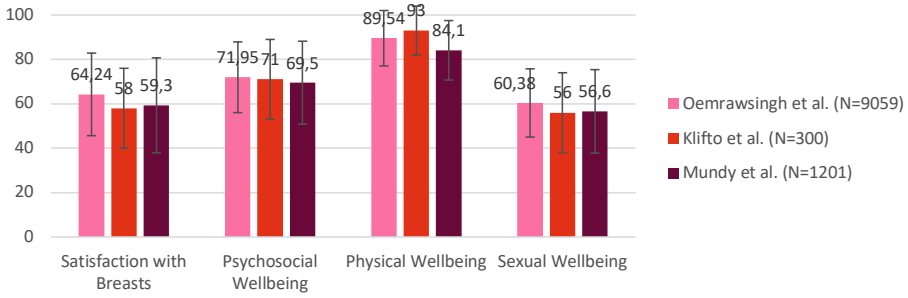


Figure 3: Variation in Normative BREAST-Q Domain Scores Across International Publications.
* Based on 8978 responses

DISCUSSION

Because a breast cancer diagnosis has significant effects on women, both psychologically and physically[19], it is essential that there are baseline scores available representative of women's quality of life before a potential cancer diagnosis. The BREAST-Q Preoperative Module was originally considered as an accurate baseline; however, these patients are aware of their underlying disease which immediately alters self-perception and quality of life.[15] According to normative data, one must take into account the degree of representation of the studied cohort. Previously published norm scores may not entirely reflect the normative scores for Dutch women because of the cultural differences between American and Dutch female populations. Thus, the aim of this study was to collect and describe normative BREAST-Q scores from a Dutch sample and to compare them with existing international normative data.

This study demonstrated through univariable regression analyses a negative linear relation between age and satisfaction with breasts. A positive association was observed between age and psychosocial well-being. Some research has demonstrated higher self-reported body image and self-esteem in middle-aged women compared to younger women[20], partially due to less self-objectification[21,22], but other studies have concluded that age alone is not consistently associated with women's overall body image.[23] This study identified prior breast surgery unrelated to breast cancer to be positively associated with higher satisfaction with breasts. These observations are in concordance with previous studies, which found improved breast satisfaction and quality of life following cosmetic breast surgery[24,25].

Unsurprisingly, prior breast surgery was associated with lower physical well-being scores, most likely because of prolonged complaints and physical discomfort (e.g. altered breast sensitivity, tenderness). A knowledge gap remains concerning how the strength between age and BREAST-Q domain scores is altered when corrected for other demographic variables. Neither age nor breast surgery unrelated to breast cancer seems to explain much of the variance in BREAST-Q domain scores, as is evident from the low R^2 values.

The current study also compared its normative BREAST-Q domain scores to U.S. scores published by Mundy et al. [16] and Klifto et al. [15] The differences between the current study's normative domain scores and those of the aforementioned studies could be due to both methodological differences and intercultural differences between European and American women in terms of body image or satisfaction with breasts. The normative scores reported by Mundy et al. were based not on a random sample but on the response of 1201 participants from the Army of Women (now the Love Research Army). The Love Research army is a strong community that is very aware of breast-related satisfaction and quality of life, possibly influencing responses and thus patient-reported outcome measure scores. The normative values reported by Klifto et al. were obtained at multiple Johns Hopkins clinic sites by recruiting nonpregnant women without a previous history of breast cancer at their routine gynecology appointments. Despite the different data population characteristics and methodologies across the three studies (different Breast-Q scales and different recruitment strategies), there was a similar pattern observed across all BREAST-Q domains among them. This observation suggests that score differences are most likely attributable to different recruitment strategies, and that, contrary to expectations, intercultural differences in the perception of breast-related quality of life have minimal influence on the normative scores. Using country-specific normative scores thus may not be necessary, if the assumption is that similar normative scores would be obtained from other Western countries.

Klifto et al. showed a β of –0.3 for the sexual well-being domain in their regression analysis, meaning an increase in age per year results in a 0.3 point decrease in score on a scale from 1 to 100. In the current study, an even smaller and nonsignificant β of 0.001 was observed. Although the result of Klifto et al. was significant, the question arises whether or in what extent such score differences on a scale from 1 to 100 are clinically important. It is thus not only important to take the statistical significance of patient-reported outcome measure score differences between ages into consideration, but also the extent to which these differences are clinically meaningful. To date, there are very few publications on minimal clinically important differences of the BREAST-Q[26,27], with varying definitions for minimal clinically important differences being used. Minimal clinically important difference indicates the smallest change in patient-reported outcome measure (domain) score that patients perceive to be important or beneficial and that would justify a change in patient management.[27-29] Voineskos et al. [27] determined, with distribution-based methods, a four-point MCID on the BREAST-Q Reconstruction Module (scale, 0 to

100), based on 3052 patients who underwent breast reconstruction. Minimal clinically important differences are estimates that are subject to change, depending on the study population (e.g. age, body mass index, socio-economic status, educational background) and the patient-reported outcome measurement of interest. Future research should focus more on calculating and validating minimal clinically important differences for BREAST-Q, as interpretability is a cornerstone in using patient-reported outcome measures for patient-centered care.

Strengths and Limitations

One of the key strengths of this study is the large size of the study sample. After the survey link was posted on the public Facebook and LinkedIn platforms of the Erasmus MC, a tremendous increase in respondents was observed. Because the questionnaire was widely available online and only in Dutch, the authors assume that respondents represent a heterogeneous Dutch population-based cohort in terms of geographical distribution. Population-based studies are often based on probability samples of a reference population; therefore, the exact sample strategy is important. [30] In this study, different recruitment methods were used to maximize the generalizability of the results. Compared to the population statistics in the Netherlands[31], both the age distribution and mean age of Dutch women (43.0 years in the population versus 44 years in the study) were similar. Although this study recruited a considerable number of respondents successfully, it is possible that health-conscious women or women with a strongly positive or negative body image were more likely to respond. The anonymity of the questionnaire may have partly remedied this effect but it may also have resulted in higher normative scores. The lack of sociodemographic characteristics (e.g. body mass index, family status, educational background, socioeconomic status) of the presented cohort prevents stating with certainty that this current study is population-based.

In this sample, 6.8 percent of respondents reported a history of non-breast cancer related-surgery, assumed to include breast implants, augmentation, reduction, and other cosmetic procedures. Some participants (n = 22) self-reported no history of breast cancer but also reported having breast-conserving surgery in the past. This discrepancy may be partially explained by patients being treated for benign tumors such as fibroadenomas. Because these cases also occur in the healthy female population, it still represents a normative cohort. Therefore, it was decided to only exclude patients who reported mastectomy but no history of breast cancer (n = 8). There is a possibility that this small number of patients has undergone preventive mastectomy, as approximately 40 percent of Dutch carriers of breast cancer gene mutation (BRCA 1/2) undergo bilateral risk-reducing mastectomy.[32] Previous breast surgery unrelated to breast cancer for cosmetic purposes or medical reasons may affect the scores differently (for example in the satisfaction with breasts scale). The

possible heterogeneity of the group with previous breast surgery unrelated to breast cancer must be taken into account when interpreting the results.

A limitation of this study was the considerable sample size differences across some age groups, with older age groups (60 years or older) being less represented in this study. For Dutch women receiving a diagnosis of breast cancer, the mean age is 57 to 62 years. [33,34] The mean ± age for the overall group in our sample was 44 years ± SD 13. This can be explained by the large number of respondents in the younger age groups, a potential consequence of using social media platforms. Older women may be less active on social media or may not have access to such platforms or a web-based questionnaire. Despite the fact that multiple recruitment methods were used, disproportionate sampling nevertheless emerged. However, the 40–49 and 50–59 age groups were represented by 2482 and 2424 participants, respectively, still providing adequate power for the analyses. Survey data commonly exhibits disproportionate sampling, either as a result of bias in the sampling procedure or by design. [35] In this study, however, the sample size differences between age groups is most likely attributable to the latter. Another limitation were the limited questions that captured respondents' demographic profile. It was decided not to include questions on marital status, educational background, annual income, and occupation, because authors were mindful of the fact that such sensitive questions can potentially affect survey outcomes by limiting the willingness of participants to complete the survey, the response rates to certain items, and the accuracy of responses. [36] As only two covariates (age and previous breast surgery unrelated to breast cancer) were collected and used as predictors for model fitting, no variable selection procedure (e.g., forward or backward selection) was performed. A follow-up study will collect more covariates and proceed with a variable selection procedure to control for possible selection bias. Finally, as with most survey studies, some selection bias may have occurred due to self-selection. In this study, it was not possible to determine the response rate for returned questionnaires as a registration log was not kept for those women that viewed the survey hyperlink but chose not to open it. It does have to be noted that there were no significant differences in domain scores between patients who completed (N=9059) and not fully completed (N=1268) the questionnaire.

CONCLUSION

This study provides age-dependent normative values for the BREAST-Q derived from a Dutch sample. These values may provide both clinicians and patients more context when interpreting post-surgical BREAST-Q scores, thereby potentially managing patients' expectations and improving patient-provider communication in the consultation room. This study has demonstrated that age alone has a weak association with BREAST-Q domain

scores on a scale of zero to 100. Small differences were found between the current study's Dutch normative BREAST-Q scores and previously published U.S. scores, while a similar pattern across domain scores was observed.

REFERENCES

1. Integraal Kankercentrum Nederland. [Accessed July 2020]. Kerncijfers over borstkanker uit de Nederlandse Kankerregistratie 1989-2019. https://iknl.nl/getmedia/2f489dc8-a103-4fd6-89fe-e266e589366f/borstkanker-in-nederland_flyer_2020.pdf Accessed Accessed 10 July 2020.
2. Vondeling GT, Menezes GL, Dvortsin EP, et al. Burden of early, advanced and metastatic breast cancer in The Netherlands. *BMC Cancer.* 2018;18(1):262.
3. Janssen-Heijnen MLG, van Steenbergen LN, Voogd AC, et al. Small but significant excess mortality compared with the general population for long-term survivors of breast cancer in the Netherlands. *Annals of Oncology.* 2014;25(1):64-68.
4. van Maaren MC, de Munck L, de Bock GH, et al. 10 year survival after breast-conserving surgery plus radiotherapy compared with mastectomy in early breast cancer in the Netherlands: a population-based study. *The Lancet Oncology.* 2016;17(8):1158-1170.
5. Slatman J. The meaning of body experience evaluation in oncology. *Health Care Anal.* 2011;19(4):295-311.
6. Michael YL, Kawachi I, Berkman LF, Holmes MD, Colditz GA. The persistent impact of breast carcinoma on functional health status: prospective evidence from the Nurses' Health Study. *Cancer.* 2000;89(11):2176-2186.
7. Stein KD, Syrjala KL, Andrykowski MA. Physical and psychological long-term and late effects of cancer. *Cancer.* 2008;112(11 Suppl):2577-2592.
8. Kool M, van der Sijp JR, Kroep JR, et al. Importance of patient reported outcome measures versus clinical outcomes for breast cancer patients evaluation on quality of care. *Breast.* 2016;27:62-68.
9. Tevis SE, James TA, Kuerer HM, et al. Patient-Reported Outcomes for Breast Cancer. *Ann Surg Oncol.* 2018;25(10):2839-2845.
10. Pusic AL, Klassen AF, Scott AM, Klok JA, Cordeiro PG, Cano SJ. Development of a new patient-reported outcome measure for breast surgery: the BREAST-Q. *Plast Reconstr Surg.* 2009;124(2):345-353.
11. Cohen WA, Mundy LR, Ballard TN, et al. The BREAST-Q in surgical research: A review of the literature 2009-2015. *J Plast Reconstr Aesthet Surg.* 2016;69(2):149-162.
12. Galina V, Laura B, Adam BS, et al. Measuring Quality of Life in Routine Oncology Practice Improves Communication and Patient Well-Being: A Randomized Controlled Trial. *Journal of Clinical Oncology.* 2004;22(4):714-724.
13. Wright JG. Evaluating the outcome of treatment. Shouldn't We be asking patients if they are better? *J Clin Epidemiol.* 2000;53(6):549-553.
14. O'Connor PJ. Normative data: their definition, interpretation, and importance for primary care physicians. *Fam Med.* 1990;22(4):307-311.
15. Klifto KM, Aravind P, Major M, et al. Establishing Institution-Specific Normative Data for the BREAST-Q Reconstruction Module: A Prospective Study. *Aesthet Surg J.* 2020;40(6):NP348-NP355.
16. Mundy LR, Homa K, Klassen AF, Pusic AL, Kerrigan CL. Breast Cancer and Reconstruction: Normative Data for Interpreting the BREAST-Q. *Plast Reconstr Surg.* 2017;139(5):1046e-1055e.
17. LimeSurvey. https://www.limesurvey.org/. Accessed 01-07-2020.
18. BREAST-Q Version 2.0©. http://qportfolio.org/wp-content/uploads/2018/12/BREAST-Q-USERS-GUIDE.pdf. Accessed 01-07-2020.
19. Metcalfe KA, Semple J, Quan M-L, et al. Changes in Psychosocial Functioning 1 Year After Mastectomy Alone, Delayed Breast Reconstruction, or Immediate Breast Reconstruction. *Annals of Surgical Oncology.* 2012;19(1):233-241.

20. Borland H, Akram S. Age is no barrier to wanting to look good: women on body image, age and advertising. *Qualitative Market Research: An International Journal.* 2007.
21. Greenleaf C. Self-objectification among physically active women. *Sex roles.* 2005;52(1-2):51-62.
22. Tiggemann M, Lynch JE. Body image across the life span in adult women: the role of self-objectification. *Dev Psychol.* 2001;37(2):243-253.
23. Myers TA. Book Review: Body Image: A Handbook of Science, Practice, and Prevention. SAGE Publications Sage CA: Los Angeles, CA; 2012.
24. Coriddi M, Angelos T, Nadeau M, Bennett M, Taylor A. Analysis of satisfaction and well-being in the short follow-up from breast augmentation using the BREAST-Q, a validated survey instrument. *Aesthet Surg J.* 2013;33(2):245-251.
25. Dreher R, Blaya C, Tenório JLC, Saltz R, Ely PB, Ferrão YA. Quality of Life and Aesthetic Plastic Surgery: A Systematic Review and Meta-analysis. *Plast Reconstr Surg Glob Open.* 2016;4(9):e862-e862.
26. Cano SJ, Klassen AF, Scott A, Alderman A, Pusic AL. Interpreting clinical differences in BREAST-Q scores: minimal important difference. *Plast Reconstr Surg.* 2014;134(1):173e-175e.
27. Voineskos SH, Klassen AF, Cano SJ, Pusic AL, Gibbons CJ. Giving Meaning to Differences in BREAST-Q Scores: Minimal Important Difference for Breast Reconstruction Patients. *Plast Reconstr Surg.* 2020;145(1):11e-20e.
28. Beaton DE, Boers M, Wells GA. Many faces of the minimal clinically important difference (MCID): a literature review and directions for future research. *Curr Opin Rheumatol.* 2002;14(2):109-114.
29. Jaeschke R, Singer J, Guyatt GH. Measurement of health status. Ascertaining the minimal clinically important difference. *Control Clin Trials.* 1989;10(4):407-415.
30. Szklo M. Population-based cohort studies. *Epidemiol Rev.* 1998;20(1):81-90.
31. https://www.cbs.nl/en-gb/visualisations/population-pyramid. Accessed Accessed 27-02-2021.
32. Heemskerk-Gerritsen BAM, Jager A, Koppert LB, et al. Survival after bilateral risk-reducing mastectomy in healthy BRCA1 and BRCA2 mutation carriers. *Breast cancer research and treatment.* 2019;177(3):723-733.
33. Johnson HM, Irish W, Muzaffar M, Vohra NA, Wong JH. Quantifying the relationship between age at diagnosis and breast cancer-specific mortality. *Breast cancer research and treatment.* 2019;177(3):713-722.
34. Lagendijk M, van Maaren MC, Saadatmand S, et al. Breast conserving therapy and mastectomy revisited: Breast cancer-specific survival and the influence of prognostic factors in 129,692 patients. *Int J Cancer.* 2018;142(1):165-175.
35. Maxwell A, Özmen M, Iezzi A, Richardson J. Deriving population norms for the AQoL-6D and AQoL-8D multi-attribute utility instruments from web-based data. *Qual Life Res.* 2016;25(12):3209-3219.
36. Tourangeau R, Yan T. Sensitive questions in surveys. *Psychological Bulletin.* 2007;133(5):859-883.

SUPPLEMENTARY MATERIAL

Table 1. BREAST-Q Scores (median with IQR) stratified by age group

Age groups (years)	N (%)	Satisfaction with breasts	Psychosocial well-being	Physical well-being	Sexual well-being
18 – 29	**1 385 (15.3)**	64 (53 – 77)	69 (60 – 80)	92 (80 – 100)	59 (50 – 66)
30 – 39	**1 776 (19.6)**	58 (53 – 71)	66 (60 – 80)	92 (80 – 100)	59 (50 – 66)
40 – 49	**2 482 (27.4)**	64 (53 – 71)	69 (60 – 83)	92 (80 – 100)	59 (50 – 66)
50 – 59	**2 424 (26.8)**	64 (53 – 71)	69 (62 – 87)	92 (85 – 100)	59 (50 – 70)
60 – 69	**837 (9.2)**	58 (48 – 71)	71 (62 – 87)	100 (85 – 100)	59 (48 – 66)
≥ 70	**155 (1.7)**	64 (53 – 71)	74 (64 – 87)	92 (85 – 100)	59 (48 – 67)
All patients	**9 059**	64 (53 – 71)	69 (60 – 83)	92 (80 – 100)	59 (50 – 66)*

*Based on 8 978 responses

Chapter 3

Health-related Quality of Life using the EQ-5D-5L: normative utility scores in a Dutch female population

Marloes E. Clarijs, Lindy M. Kregting,
Nicolien T. van Ravesteyn, Linetta B. Koppert, Ida J. Korfage

Quality of Life Research, Oct 2022

ABSTRACT

Purpose

Normative utility scores represent the health related quality of life of the general population, are of utmost importance in cost-effectiveness studies and should reflect relevant sexes and age groups. The aim of this study was to estimate EQ-5D-5L normative utility scores in a population of Dutch females, stratified by age, and to compare these scores to those of female populations of three other countries.

Methods

Dutch women completed the EQ-5D-5L online between January and July 2020. Mean normative utilities were computed using the Dutch EQ-5D-5L value set, stratified by age, tested for differences using the Kruskall-Wallis test, and compared to normative utility scores of female populations elsewhere. Additionally, to support the use of the Dutch EQ-5D-5L data in other settings, normative utility scores were also calculated by applying the value sets of Germany, United Kingdom and United States.

Results

Data of 9037 women were analyzed and the weighted mean utility score was 0.911 (SD 0.155, 95% CI 0.908–0.914). The mean normative utility scores differed between age groups, showing lower scores in older females. Compared to other normative utility scores of female populations, Dutch mean utilities were consistently higher except for age groups 18-24 and 25-34. With the three country-specific value sets, new age-specific mean normative utility scores were provided.

Conclusion

This study provides mean normative utility scores of a large cohort of Dutch females per age group, which were found to be lower in older age groups. Utility scores calculated with three other value sets were made available.

PLAIN ENGLISH SUMMARY

Health-related quality of life is a measure of the impact of disease and treatment on an individuals' disability and daily functioning. Health-related quality of life outcomes are gathered using questionnaires (e.g. EQ-5D-5L) and respondents' answers can be converted into a single utility score, that reflects an individual's health state at a particular point in time. These utility scores are used in cost-effectiveness studies. Utilities that are obtained in the general population, instead of patients with a specific disease, are called normative utilities. Differences in normative utility scores between countries, age groups and gender have been found and choosing the most accurate set of normative utility scores is important. However, Dutch age and gender specific normative utility scores for females are currently not available. This study converted the EQ-5D-5L results of 9037 women into mean normative utility scores stratified by age. Relatively high mean normative utility scores for the EQ-5D-5L in Dutch females were found in all age groups compared to female populations of other countries, with the lowest scores in older women. The EQ-5D-5L normative utility scores calculated with Dutch data and the value sets of Germany, United Kingdom and United States in this study support the use of the Dutch data in international cost-effectiveness studies when age and country-specific normative utility scores for women are not available.

INTRODUCTION

The effectiveness of a health care intervention or strategy can be measured in a variety of ways. A commonly used method is measuring and comparing the Health-related Quality of Life (HrQoL) between groups. HrQoL is a measure of the impact of disease and treatment on an individuals' disability and daily functioning. [1] It includes factors that are part of an individual's health, without non-health aspects such as economic circumstances, and is often used in cost-effectiveness studies. [2] HrQoL outcomes are gathered using questionnaires and respondents' answers can be converted into a single utility score, usually between 0 and 1, that reflects the personal desirability of an individual's health state at a particular point in time. [2] The EQ-5D-5L is often recommended as the instrument to obtain utility scores. [3] To enable the conversion for EQ-5D-5L outcomes, pre-defined country-specific value sets have been developed to this aim. [4]

In cost-effectiveness studies, utility scores are used to calculate quality adjusted life years (QALY's) for all relevant health states. If utility scores are not available for these health states, assumptions about such utilities have to be made. However, assumptions are sub-optimal compared to objectively measured utilities as this influences cost-effectiveness ratios and ultimately decision making. [5,6] Besides utilities for disease specific health states,

also utilities for the general population are considered to be relevant. These so-called 'normative utility scores' can be used as a comparator for health profiles of patients based on subgroups with similar age and gender. Additionally, they can be used to compensate for a loss in HrQoL due to factors that are not caused by the disease or intervention of interest.[7] Currently, many cost-effectiveness studies made the assumption of a utility of 1 (reflecting perfect health) for the general population. However, Versteegh et al. obtained utilities in a general Dutch population and the results suggested that utilities of the general population tend to be below 1.[8] This means that cost-effectiveness studies may overestimate the health of the general population, and thereby overestimate the loss in utility score caused by a disease or intervention. Therefore, up to date normative utility scores are needed to be used in cost-effectiveness studies.

Other countries have calculated normative utility scores using the EQ-5D and showed differences between genders.[9-11] In studies on women's health, using gender-specific normative EQ-5D utility scores of females only may be more accurate than population norms. Janssen et al. published EQ-5D index value population norms for 20 countries in Europe including the Netherlands.[12,13] Data of 2367 people, identified between 2001 and 2003, was used to calculate age stratified normative utility scores.[14] However, these results were based on the EQ-5D-3L, and the Dutch normative data for the EQ-5D-5L that was published thereafter, was not classified by gender.[8,13] This is a drawback for cost-effectiveness studies among only male or female populations.

Therefore, the aim of this study was to obtain EQ-5D-5L normative utility scores in a female Dutch cohort, stratified by age. In addition, these normative utility scores were compared to normative utility scores of female cohorts of other countries. Furthermore, three different country-specific value sets were applied to the answers of the EQ-5D-5L of the Dutch cohort. This analysis was conducted to illustrate the impact of using different value sets on age-specific mean normative utility scores, and to enable the use in cost-effectiveness studies in populations for which country-specific normative utility scores for women are not available.

METHODS

Study participants

Data were collected in a study that initially obtained normative data for the Breast-Q (a breast cancer specific quality of life questionnaire) (Oemrawsingh et al. (2021), in press). Dutch women were invited to complete a web-based survey that was disseminated through social media platforms of the Erasmus Medical Center between January and July 2020. Because the researchers focused on breast cancer, normative data should be based

on women unencumbered by the diagnosis of breast cancer. Therefore, women who were previously diagnosed with breast cancer were excluded from the survey.

Besides the Breast-Q, the survey also included the EQ-5D-5L. This current study made use of this EQ-5D-5L data.

Health related Quality of Life measured with the EQ-5D-5L

The Dutch version of the EQ-5D-5L was used to measure HrQoL. [3] The EQ-5D-5L is a non-disease-specific instrument, and consists of five dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety/depression), each with five levels of functioning, ranging from no problems to extreme problems. Eventually, 3125 different health states can be provided based on these five dimensions. A quality-adjustment weight or "utility" is a number anchored at 0 and 1, with "perfect health" carrying a weight of 1 and death carrying a weight of 0. A utility score below 0 is possible when a health state is valued worse than death. Utilities can be calculated after application of pre-defined values to a specific health state as indicated by a respondent. Utilities in this study were computed according to the Dutch tariffs for the EQ-5D-5L as established by Versteegh et al [8].

Statistical analysis

Descriptive statistics, including standard deviations and confidence intervals, were calculated to present the mean normative EQ-5D-5L index scores per age group. Age was categorized into seven subgroups; 18-24, 25-34, 35-44, 45-54, 55-64, 65-74 and ≥ 75 years. A weighted mean normative utility score was calculated taking into account the population size per age group of the Dutch population in 2020 (see Appendix, Figure 1) [15]. Because the data were not normally distributed, the Kruskal-Wallis test was used to compare mean utility scores between all age-groups. The data analyses were performed using IBM SPSS Statistics (Version 25) and R (Version 1.2).

Comparisons with three other countries

The mean normative utility scores per age-group were compared to normative utility scores for female populations in studies performed in Germany, South Australia, and the United States (US). [9-11] Furthermore, the country-specific value sets used in these studies (i.e. the value sets of Germany, the United Kingdom (UK) and the US) were also applied to the EQ-5D-5L data to convert them into utility scores. [16-18]

RESULTS

The total sample included 9037 females with a median age of 46.0 years (range 18-90 years). According to the responses of the individual EQ-5D-5L dimensions, most health

problems were identified in the pain/discomfort (41.2%) and anxiety/depression (29.5%) dimension (Table 1). The anxiety/depression dimension showed relatively high percentages of any health problems (level 2-5) in the younger age-groups, which decreased with increasing age. Health problems in the other dimensions increased when becoming older, which was most evident in the mobility dimension (Figure 1). The mean utility score was 0.917 (SD 0.110, 95% CI 0.915 – 0.920) with a left-skewed distribution, as 44.7% had a utility score of 1 (n = 4037). The weighted mean utility score was 0.911 (SD 0.155, 95% CI 0.908 – 0.914).

Table 1. Prevalence of EQ-5D-5L responses for the Dutch female normative population (N = 9037), stratified by age group.

	Mobility		**Self-care**		**Usual Activities**		**Pain/ Discomfort**		**Anxiety/ Depression**	
Level	**N**	**(%)**	**N**	**(%)**	**N**	**(%)**	**N**	**(%)**	**N**	**(%)**
					All ages					
1	8016	88.7	8899	98.5	7900	87.4	5328	59.0	6379	70.6
2	719	8.0	109	1.2	836	9.3	2871	31.8	2174	24.1
3	241	2.7	24	0.3	237	2.6	701	7.8	413	4.6
4	51	0.6	3	0.0	60	0.7	123	1.4	63	0.7
5	10	0.1	2	0.0	4	0.0	14	0.2	8	0.1
Any problems		*11.4*		*1.5*		*11.9*		*41.2*		*29.5*
					Age 18-24					
1	614	96.8	628	99.1	573	90.4	460	72,6	361	56.9
2	15	2.4	6	0.9	52	8.2	146	23.0	203	32.0
3	4	0.6	0	0.0	7	1.1	25	3.9	58	9.1
4	1	0.2	0	0.0	2	0.3	2	0.3	9	1.4
5	0	0.0	0	0.0	0	0.0	1	0.2	3	0.5
Any problems		*3.2*		*0.9*		*9.6*		*27.4*		*43*
					Age 25-34					
1	1498	95.5	1557	99.2	1419	90.4	1112	70.9	981	62.5
2	47	3.0	7	0.4	114	7.3	368	23.5	470	30.0
3	19	1.2	4	0.3	26	1.7	72	4.6	96	6.1
4	4	0.3	0	0.0	10	0.6	16	1.0	20	1.3
5	1	0.1	1	0.1	0	0.0	1	0.1	2	0.1
Any problems		*4.6*		*0.8*		*9.6*		*29.2*		*37.5*

Table 1. Prevalence of EQ-5D-5L responses for the Dutch female normative population (N = 9037), stratified by age group.

	Mobility		Self-care		Usual Activities		Pain/ Discomfort		Anxiety/ Depression	
Level	**N**	**(%)**	**N**	**(%)**	**N**	**(%)**	**N**	**(%)**	**N**	**(%)**
					Age 35-44					
1	1902	91,7	2048	98.7	1841	88.8	1306	63.0	1430	68.9
2	124	6,0	23	1.1	173	8.3	611	29.5	545	26.3
3	39	1,9	3	0.1	47	2.3	133	6.4	88	4.2
4	7	0,3	0	0.0	13	0.6	22	1.1	10	0.5
5	2	0,1	0	0.0	0	0.0	2	0.1	1	0.0
Any problems		*8.3*		*1.2*		*11.2*		*37.1*		*30.5*
					Age 45-54					
1	2416	87.3	2715	98.1	2348	86.2	1488	53.8	2083	75.3
2	258	9.3	42	1.5	277	10.0	976	35.3	577	20.9
3	70	2.5	8	0.3	81	2.9	246	8.9	94	3.4
4	18	0.7	1	0.0	23	0.8	48	1.7	12	0.4
5	5	0.2	1	0.0	2	0.1	9	0.3	1	0.0
Any problems		*12.7*		*1.8*		*13.8*		*46.2*		*24.7*
					Age 55-64					
1	1285	82.0	1541	98.3	1342	85.6	774	49.4	1194	76.1
2	199	12.7	21	1.3	162	10.3	603	38.5	302	19.3
3	70	4.5	6	0.4	54	3.4	166	10.6	62	4.0
4	12	0.8	0	0.0	9	0.6	24	1.5	9	0.6
5	2	0.1	0	0.0	1	0.1	1	0.1	1	0.1
Any problems		*18.1*		*1.7*		*14.4*		*50.7*		*24.0*
					Age 65-74					
1	279	71.4	377	96.4	312	79.8	177	45.3	307	78.5
2	68	17.4	9	2.3	55	14.1	152	38.9	68	17.4
3	35	9.0	3	0.8	20	5.1	51	13.0	13	3.3
4	9	2.3	2	0.5	3	0.8	11	2.8	3	0.8
5	0	0.0	0	0.0	1	0.3	0	0.0	0	0.0
Any problems		*28.7*		*3.6*		*20.3*		*54.7*		*21.5*
					Age >75					
1	22	64.7	33	97.1	29	85.3	11	32.4	23	67.6
2	8	23.5	1	2.9	3	8.8	15	44.1	9	26.5
3	4	11.8	0	0.0	2	5.9	8	23.5	2	5.9
4	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
5	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Any problems		*35.3*		*2.9*		*14.7*		*67.6*		*32.4*

EQ-5D-5L answer levels = level 1 (no problems); level 2 (slight problems); level 3 (moderate problems); level 4 (severe problems); level 5 (inability / extreme problems).

Any problems = percentage of any problems (level 2-5) in the EQ-5D-5L dimensions according to age group.

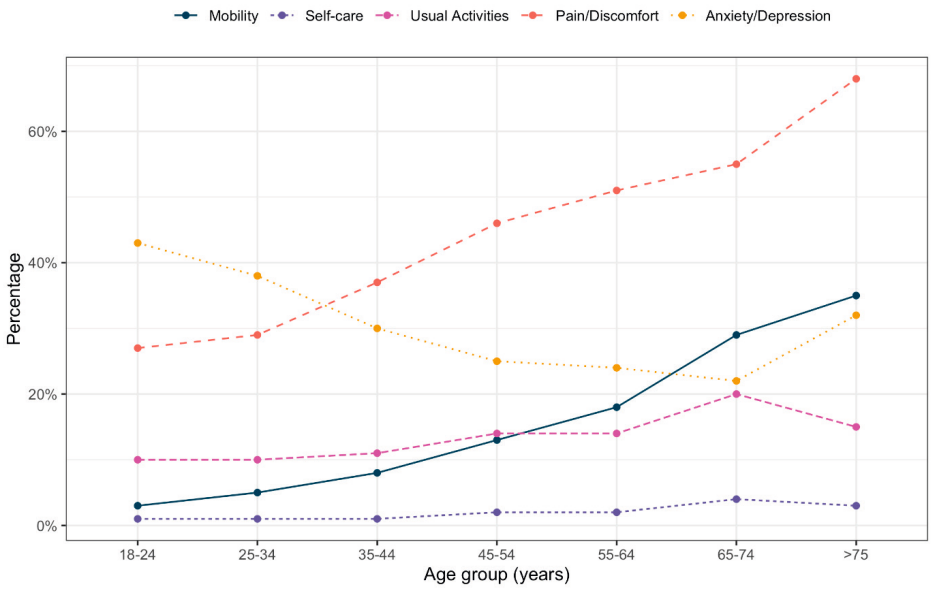


Figure 1. Frequencies of having "any problems" (level 2-5) in the EQ-5D-5L dimensions based on age group.

Primary outcome

The mean normative utility score ranged from 0.929 (SD 0.102) (age group 25-34) to 0.881 (SD 0.081) (age group >75). The highest mean normative utility scores were found in the three youngest age groups (between age 18 and 44 years) (Table 2). After age 45, mean normative utilities decreased with increasing age with lowest mean utility scores in the oldest age group (>75 years). The Kruskal-Wallis test revealed that there were statistically significant differences in mean normative utility scores between all age groups ($p < 0.001$). However, absolute differences were small.

Comparisons with three other countries

Compared to published normative utility scores for female populations in Germany, the US and South Australia, our mean normative utilities were consistently higher except for age groups 18-24 and 25-34 (Table 3).

The mean utility scores were recalculated after applying the country-specific value sets of Germany, the UK, and the US to the EQ-5D-5L answers of our Dutch cohort. This resulted in slightly higher mean utility scores for all age groups with all three value sets (Table 2). The mean utility scores were the highest when the German value set was applied.

Table 2. Mean utility scores, standard deviations and confidence intervals of four different utility value sets applied on the Dutch female normative EQ-5D-5L data (N = 9037).

Age group	N	Dutch value set (Versteegh et al. 2016)		German value set (Ludwig et al. 2018)		UK value set (Devlin et al. 2018)		US value set (Pickard et al. 2019)	
		Mean (SD)	*95% CI*	*Mean (SD)*	*95% CI*	*Mean (SD)*	*95% CI*	*Mean (SD)*	*95% CI*
18-24	634	.927 (.091)	0.920-0.934	.953 (.075)	0.947-0.959	.933 (.083)	0.926-0.939	.934 (.094)	0.926-0.941
25-34	1569	.929 (.102)	0.924-0.934	.953 (.087)	0.949-0.957	.935 (.094)	0.930-0.940	.935 (.110)	0.929-0.940
35-44	2074	.925 (.102)	0.921-0.930	.950 (.087)	0.946-0.954	.933 (.095)	0.929-0.937	.931 (.114)	0.926-0.936
45-54	2767	.913 (.120)	0.908-0.917	.939 (.106)	0.935-0.943	.925 (.106)	0.921-0.929	.918 (.131)	0.913-0.923
55-64	1568	.907 (.112)	0.902-0.913	.936 (.098)	0.931-0.941	.919 (.102)	0.914-0.925	.910 (.127)	0.904-0.916
65-74	391	.890 (.131)	0.877-0.903	.919 (.117)	0.859-0.888	.901 (.123)	0.889-0.914	.884 (.154)	0.869-0.900
>75	34	.881 (.081)	0.854-0.910	.918 (.066)	0.895-0.941	.894 (.084)	0.864-0.923	.877 (.108)	0.839-0.915

N = number of participants per age-group, SD = standard deviation, CI = confidence interval.
UK = United Kingdom, US = United States.

Table 3. Mean normative utility scores based on the EQ-5D-5L in other female populations stratified by age group.

Age group	**The Netherlands**		**Germany Grochtdreis et al. (2019)**		**South Australia McCaffrey et al. (2016)**		**United States Jiang et al. (2021)**	
	N	*Mean (SD)*	*N*	*Mean (SD)*	*N*	*Mean (SD)*	*N*	*Mean (SD)*
18-24	634	0.93 (0.09)	230	0.94 (0.08)	226	0.95 (0.08)	53	0.93 (0.09)
25-34	1569	0.93 (0.10)	363	0.92 (0.10)	224	0.95 (0.11)	130	0.92 (0.11)
35-44	2074	0.93 (0.10)	386	0.88 (0.17)	241	0.91 (0.13)	95	0.85 (0.21)
45-54	2767	0.91 (0.12)	494	0.86 (0.19)	253	0.87 (0.16)	102	0.81 (0.24)
55-64	1568	0.91 (0.11)	399	0.86 (0.20)	226	0.88 (0.15)	67	0.83 (0.21)
65-74	391	0.89 (0.13)	346	0.85 (0.25)	193	0.87 (0.16)	57	0.82 (0.22)
>75	34	0.88 (0.08)	366	0.77 (0.31)	122	0.82 (0.15)	61	0.83 (0.18)
Total	**9037**	**0.92 (0.11)**	**2584**	**0.86 (0.20)**	**1486**	**0.90 (0.14)**	**565**	**0.86 (0.19)**

N = number of participants per age-group, SD = standard deviation, SE = standard error.

DISCUSSION

We obtained normative utility scores by using the EQ-5D-5L in a sample of 9037 Dutch females and found relatively high utility values for Dutch females aged 18 to >75 years old. In general, the mean normative utilities were lower in the older age groups although absolute differences were small. Applying the country-specific value sets of Germany, UK and US to the EQ-5D-5L answers of our Dutch sample resulted in consistently higher mean utility scores in all age groups as compared to the mean utility scores calculated with the Dutch value set.

Our mean normative utility scores in the younger age groups were slightly lower than previously found in female populations of other countries. [9-11] This difference may be caused by the sampling method. Young people that are less healthy may spend more time on their computer, mobile phones or social media than healthy adolescents who are possibly able to do more activities. Therefore, they might have been more likely to encounter the study invitation and more inclined to complete a questionnaire on their health. The normative utility data of female populations of other countries was collected between 2013 and 2017. [9-11] The lower Dutch utilities in the younger age groups compared to those of previous studies might be explained by an increase in mental health problems in adolescents over the last years as observed in the Netherlands. [19] The data of this study was collected during the start of the COVID-19 pandemic, which also led to more anxiety and mental health issues particularly in females and adolescents, and may have contributed to lower utility scores. [20] Besides, it appears as if the use of the Dutch value set is partially responsible for the differences in utility scores in younger age groups (up to 35 years), because the differences in utility becomes smaller when the German, UK, and US value sets were used. In contrast, our mean normative utility scores in the older age groups were higher than those in female populations of other countries. Particular in these age groups, the differences were enlarged by the use of the German, UK and US value sets. That is, these differences cannot be explained by the value sets themselves.

The oldest age group (>75 years) showed a relatively high mean normative utility, as none of the participants scored level four and five across all dimensions. This might indicate that older Dutch women have a relatively good quality of life, and possibly better than older women elsewhere. In contrast to a recently published Russian article reporting normative utility scores, Dutch women did not show many problems in the self-care dimension for all age groups. [21] In the current study, the frequency of having any problems in the anxiety/depression dimension decreased with increasing age, but was consistent across all age groups in the Russian population. Although the pattern of having any problems in the mobility dimension was similar in both studies, the frequency in the older age group was considerably higher in the Russian population. [21] However, the high mean normative utilities may also be related to most participants being between 75 and 80 years of age, and

no one being older than 90 years. Because more health issues appear with increasing age, this may explain the differences with other studies if they included older participants. [21-23] In addition, the sample of older participants (n=34) was relatively small, which reduces the generalizability. Another explanation is the use of social media as a recruitment method, which may have caused some selection bias. Older females that are able and willing to complete a questionnaire through an online survey are potentially in better health. [24] On the other hand, internet is easily accessible in the Netherlands and internet use is higher than in most other western countries, also in older people. [25] Interestingly, Jiang et al. has shown differences in outcome between face-to-face and online sampling, with higher EQ-5D-5L index scores in the face-to-face population for most age groups. [9] However, the index scores of the older participants (i.e. above the age of 65) were slightly higher in the online population. [9]

We found statistically significant differences in mean normative utility scores between the age groups. However, we expected larger age-specific absolute differences beforehand based on results of previous normative studies (both males and females) in the Netherlands. [26] Nevertheless, we recommend to use age and gender specific reference values, as they are important for cost-effectiveness studies and can have a substantial effect on outcomes. [5,6] It would be interesting to investigate to what extent our age-specific values alter the outcomes of cost-effectiveness analyses. To note, our normative utility scores are mainly intended to answer women-specific research questions, and they might not be directly comparable to future normative utility scores of Dutch males as they are not generated from the same sample.

The key strengths of our study are the use of the EQ-5D-5L to obtain normative utility scores and the large sample size. The EQ-5D-5L is more sensitive than the EQ-5D-3L version which has several limitations (e.g. ceiling effects in patient populations, non-detection of small differences or changes in patients with mild conditions). [27-29] Furthermore, the sample size of our cohort was substantially larger (at least three times) than the samples in previous studies, and in combination with the more sensitive 5-level version of the EQ-5D, our study may have resulted in more reliable outcomes. [9-12] Another strength is that we provide age-specific mean utility scores specifically for women. These could be used an up-to-date reference point in research and Dutch health policy evaluations, such as breast and cervical cancer screening strategies, and health policies for pregnancy and childbirth. Importantly, our study did not gather demographic data which makes it difficult to state anything about the representativeness of the population. We used a web-based survey that was disseminated through the institutes' social media platforms, which are all accessible for the general population. To be able to complete the survey, access to internet was required. Especially in the Netherlands, internet use has increased over the last decade and is nowadays extremely high as 95% of total population has access to internet. [30] This makes the internet-user population very similar to the general population. Even back in 2013,

internet was the main source to search for health information (83%) in the Netherlands, and social media is frequently used for this purpose. [31] The percentage of social media use is more than 90% for the age group of 18-54 years, and between 76% and 89% in the age group of 55-64 years of the Dutch population. [32] Although we cannot assume that all female internet-users have seen our survey, we believe that the survey reached a large and representative part of the Dutch female population. Despite our large sample size the group of elderly females was relatively small. In other countries where internet availability is less developed, using this sampling method might be more of an issue because certain populations are possibly left out.

To date, it is unclear if and to which extent utility measurements on a national level can be generalized to other countries. However, there are differences between the country-specific value sets even between countries that were expected to have quite similar populations, socioeconomic status, health systems, or attitudes to health. [13] Therefore, using a country-specific value set is encouraged. [33,34] In this study, a subset of value sets of three other countries was used to calculate utility scores based on the answers to the EQ-5D-5L of our Dutch female cohort. This was done to illustrate the impact of using different value sets on age-specific mean normative utility scores, and also to provide age-specific mean normative utility scores to be used in cost-effectiveness studies in countries of which country-specific normative utility scores for women are lacking. For example, if a breast cancer study would be conducted in the UK, researchers probably prefer to use the UK value set to determine the utilities in patients. In order to allow for proper comparisons with the general population, they can also best use normative utilities calculated with the UK value set. If age-specific mean normative utility scores for women in the UK are not available, the normative utility scores calculated with the UK value set in this study may be a good alternative. Reporting the normative utility scores for different value sets enlarges the applicability in multiple international studies.

CONCLUSIONS

In this study, we presented age specific normative utility scores for the EQ-5D-5L in Dutch females using different value sets. We found lower mean normative utilities in older age groups. Relatively high normative utility scores were found in all age groups, compared to those in other female populations. Furthermore, utility scores were calculated with value sets of three other countries which can be used as normative comparisons in international patient populations.

REFERENCES

1. Karimi M, Brazier J. Health, Health-Related Quality of Life, and Quality of Life: What is the Difference? *Pharmacoeconomics*. Jul 2016;34(7):645-9.
2. Torrance GW. Utility approach to measuring health-related quality of life. *J Chronic Dis*. 1987;40(6):593-603.
3. Herdman M, Gudex C, Lloyd A, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). *Qual Life Res*. Dec 2011;20(10):1727-36.
4. EQ-5D Valuation Standard Value Sets. EuroQoL EQ-5D. Updated 08-06-2021. Accessed 01-07-2021, https://euroqol.org/eq-5d-instruments/eq-5d-5l-about/valuation-standard-value-sets/
5. de Kok I, Korfage IJ, van den Hout WB, et al. Quality of life assumptions determine which cervical cancer screening strategies are cost-effective. *Int J Cancer*. Jun 1 2018;142(11):2383-2393.
6. Omidvari AH, Lansdorp-Vogelaar I, de Koning HJ, Meester RGS. Impact of assumptions on future costs, disutility and mortality in cost-effectiveness analysis; a model exploration. *PLoS One*. 2021;16(7):e0253893.
7. Brazier J, Ara R, Azzabi I, et al. Identification, Review, and Use of Health State Utilities in Cost-Effectiveness Models: An ISPOR Good Practices for Outcomes Research Task Force Report. *Value Health*. Mar 2019;22(3):267-275.
8. Versteegh M VK, Evers S, de Wit, GA, Prenger, R, Stolk E. Dutch Tariff for the Five-Level Version of EQ-5D. *Value Health*. Jun 2016;19(4):343-52.
9. Jiang R, Janssen MFB, Pickard AS. US population norms for the EQ-5D-5L and comparison of norms from face-to-face and online samples. *Qual Life Res*. Mar 2021;30(3):803-816.
10. McCaffrey N, Kaambwa B, Currow DC, Ratcliffe J. Health-related quality of life measured using the EQ-5D-5L: South Australian population norms. *Health Qual Life Outcomes*. Sep 20 2016;14(1):133.
11. Grochtdreis T, Dams J, Konig HH, Konnopka A. Health-related quality of life measured with the EQ-5D-5L: estimation of normative index values based on a representative German population sample and value set. *Eur J Health Econ*. Aug 2019;20(6):933-944.
12. Janssen MF, Szende A, Cabases J, Ramos-Goni JM, Vilagut G, Konig HH. Population norms for the EQ-5D-3L: a cross-country analysis of population surveys for 20 countries. *Eur J Health Econ*. Mar 2019;20(2):205-216.
13. Janssen B. SA. Self-Reported Population Health: An International Perspective based on EQ-5D. In: Szende A. JB, Cabases J. (eds). ed. *Population Norms for the EQ-5D*. Springer; 2014.
14. Konig HH, Bernert S, Angermeyer MC, et al. Comparison of population health status in six european countries: results of a representative survey using the EQ-5D questionnaire. *Med Care*. Feb 2009;47(2):255-61.
15. Statistics Netherlands; StatLine. Updated 07-09-2020]. Accessed 04-08-2021, https://opendata.cbs.nl/statline/#/CBS/nl/
16. Pickard AS, Law EH, Jiang R, et al. United States Valuation of EQ-5D-5L Health States Using an International Protocol. *Value Health*. Aug 2019;22(8):931-941.
17. Devlin NJ, Shah KK, Feng Y, Mulhern B, van Hout B. Valuing health-related quality of life: An EQ-5D-5L value set for England. *Health Econ*. Jan 2018;27(1):7-22.
18. Ludwig K, Graf von der Schulenburg JM, Greiner W. German Value Set for the EQ-5D-5L. *Pharmacoeconomics*. Jun 2018;36(6):663-674.
19. Nuijen J, vDoesum T, vBon-Martens M. Landelijke Monitor Depressie. Eerste peiling: trends tot en met 2019. Trimbos Instituut; Netherlands Institute of Mental Health and Addiction; 2021.

20. Kunzler AM, Rothke N, Gunthner L, et al. Mental burden and its risk and protective factors during the early phase of the SARS-CoV-2 pandemic: systematic review and meta-analyses. *Global Health*. Mar 29 2021;17(1):34.
21. Holownia-Voloskova M, Tarbastaev A, Golicki D. Population norms of health-related quality of life in Moscow, Russia: the EQ-5D-5L-based survey. *Qual Life Res*. Mar 2021;30(3):831-840.
22. Jaul E, Barron J. Age-Related Diseases and Clinical and Public Health Implications for the 85 Years Old and Over Population. *Front Public Health*. 2017;5:335. doi:10.3389/fpubh.2017.00335
23. Niccoli T, Partridge L. Ageing as a risk factor for disease. *Curr Biol*. Sep 11 2012;22(17):R741-52.
24. Kelfve S, Kivi M, Johansson B, Lindwall M. Going web or staying paper? The use of web-surveys among older people. *BMC Med Res Methodol*. Oct 8 2020;20(1):252.
25. How popular is internet use among older people? Eurostat. Updated 17-05-2021]. Accessed 27-09-2021, https://ec.europa.eu/eurostat/web/products-eurostat-news/-/edn-20210517-1
26. Janssen B. SA. Population Norms for the EQ-5D. In: Agota Szende BJ, Juan Cabases, ed. *Self-Reported Population Health: An International Perspective based on EQ-5D*. Springer; 2013:19-30:chap 3.
27. Janssen MF, Pickard AS, Golicki D, et al. Measurement properties of the EQ-5D-5L compared to the EQ-5D-3L across eight patient groups: a multi-country study. *Qual Life Res*. Sep 2013;22(7):1717-27.
28. Janssen MF, Bonsel GJ, Luo N. Is EQ-5D-5L Better Than EQ-5D-3L? A Head-to-Head Comparison of Descriptive Systems and Value Sets from Seven Countries. *Pharmacoeconomics*. Jun 2018;36(6):675-697.
29. Devlin N, Brazier J, Pickard AS, Stolk E. 3L, 5L, What the L? A NICE Conundrum. *Pharmacoeconomics*. Jun 2018;36(6):637-640.
30. Centraal Bureau voor de Statistiek. Households–connection to the internet. Accessed May 16, 2022. Accessed May 16, 2022. https://opendata.cbs.nl/statline/#/CBS/nl/dataset/83291NED/table?ts=1560934345782]
31. Van de Belt TH, Engelen LJ, Berben SA, Teerenstra S, Samsom M, Schoonhoven L. Internet and social media for health-related information and communication in health care: preferences of the Dutch general population. *J Med Internet Res*. Oct 2 2013;15(10):e220.
32. Centraal Bureau voor de Statistiek. Who use social media the most? Accessed May 20, 2022. Accessed May 20 2022. https://longreads.cbs.nl/the-netherlands-in-numbers-2020/who-use-social-media-the-most/]
33. Lamers LM, McDonnell J, Stalmeier PF, Krabbe PF, Busschbach JJ. The Dutch tariff: results and arguments for an effective design for national EQ-5D valuation studies. *Health Econ*. Oct 2006;15(10):1121-32.
34. Norman R, Cronin P, Viney R, King M, Street D, Ratcliffe J. International comparisons in valuing EQ-5D health states: a review and analysis. *Value Health*. Nov-Dec 2009;12(8):1194-200.

SUPPLEMENT

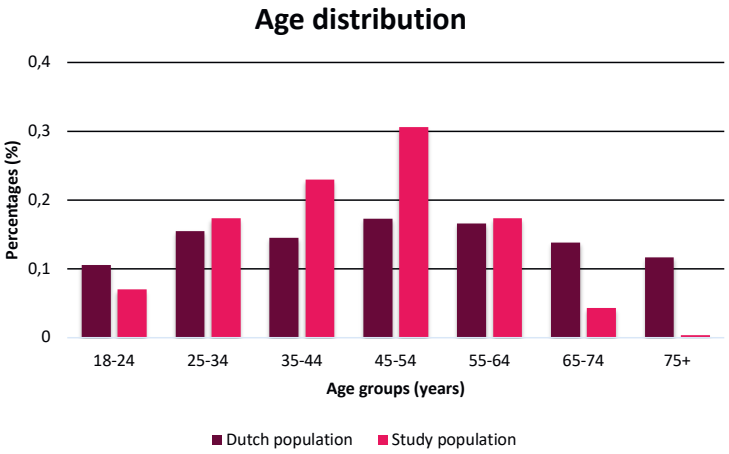


Figure 1. Age group distribution for this current cohort (n = 9037) and the female Dutch population in 2020 (n = 7.1 million) used for the weighted mean normative utility score calculation.

Chapter 4

Measuring Quality of Life Using Patient-Reported Outcomes in Real-World Metastatic Breast Cancer Patients: The Need for a Standardized Approach

Marloes E. Clarijs, Jacob Thurell, Friedrich Kühn, Carin A. Uyl-de Groot, Elham Hedayati, Maria M. Karsten, Agnes Jager and Linetta B. Koppert

Cancers (Basel), May 2021

ABSTRACT

Metastatic breast cancer (MBC) patients are almost always treated to minimize the symptom burden, and to prolong life without a curative intent. Although the prognosis of MBC patients has improved in recent years, the median survival after diagnosis is still only 3 years. Therefore, the health-related quality of life (HRQoL) should play a leading role in making treatment decisions. Heterogeneity in questionnaires used to evaluate the HRQoL in MBC patients complicates the interpretability and comparability of patient-reported outcomes (PROs) globally. In this review, we aimed to provide an overview of PRO instruments used in real-world MBC patients and to discuss important issues in measuring HRQoL. Routinely collecting symptom information using PROs could enhance treatment evaluation and shared decision-making. Standardizing these measures might help to improve the implementation of PROs, and facilitates collecting and sharing data to establish valid comparisons in research. This is a prerequisite to learn about how they could impact the clinical care pathway. In addition, the prognostic value of intensified PRO collection throughout therapy on survival and disease progression is promising. Future perspectives in the field of PROs and MBC are described.

SIMPLE SUMMARY

Metastatic breast cancer (MBC) remains incurable despite treatment improvements. The health-related quality of life is a multidimensional entity which covers physical, psychological and social dimensions. It is an important outcome particularly in patients with metastatic disease, as the primary goal of therapy is no longer curation, but to provide the best possible quality of life weighted against treatment risks and adverse symptoms. Patient-reported outcomes reflecting the quality of life are usually measured with validated questionnaires to evaluate treatment strategies based on symptom burden and to improve care delivery. This review shares insights into the role of patient-reported outcome measurements in MBC patients and describes the heterogeneity of current questionnaires. We conclude that an up-to-date and standardized outcome set is needed, containing relevant domains referring to individual needs to improve the quality of life assessment among MBC patients. This is a prerequisite to learn about how they could impact the clinical care pathway.

INTRODUCTION

Breast cancer is the most common cancer diagnosis among women, with a yearly incidence rate of 47.8 per 100,000 females worldwide that is still gradually increasing. [1] The past few years have seen rapid improvements in treatment strategies for breast cancer, both in the area of locoregional and systemic treatment. Although survival rates of early-stage breast cancer have increased over the last few years [2,3], there remains a group of patients with incurable disease. Globally, metastatic breast cancer (MBC) comprises 5–10% of breast cancer patients at the time of diagnosis, and 20% to 50% of primary breast cancer patients will eventually develop metastatic disease. [4,5] Unsurprisingly, metastases are the worldwide major cause of death in breast cancer patients with a mortality rate of 13.6, resulting in more than half a million deaths in 2020. [6] The estimated 5-year overall survival in MBC is 27%, which is still particularly poor. [7] However, therapeutic advances have also resulted in better outcomes for MBC patients, such as modest survival improvements, although without a curative intent.[5,8,9] Goals of therapy include diminishing symptoms, delay of disease progression, and prolongation of overall survival with the least negative impact on quality of life as possible. [4] Breast cancer patients face difficult challenges throughout their trajectory of disease, including numerous physical symptoms, emotional distress and impaired daily functioning. [8,9] These physical and psychosocial consequences of breast cancer diagnosis and treatment are reflecting the health-related quality of life (HRQoL), which has been increasingly recognized as an important endpoint in cancer treatment. [10,11] In MBC patients, the disease itself causes quality of life limiting symptoms and together with treatment-related symptoms, the impact on HRQoL may even be more substantial. The recently published Decade Rapport of Cardoso and colleagues showed a decline in overall quality of life in MBC patients over the last decade, based on a quantitative analysis of the EuroQol questionnaire. [6] The authors believe that this is as a result of unmet needs, less support and inconsistency of reported HRQoL data in MBC patients. The HRQoL is typically evaluated by patient-reported outcomes (PRO) and can be assessed by using validated instruments known as patient-reported outcome measurements (PROMs). The use of PROs has been associated with better patient satisfaction, quality of care and health outcomes. [12] While general cancer-related PRO measures have been used in MBC research, often to compare novel treatment strategies, previous studies recommend standardized and disease-specific HRQoL assessment methods. [13-15] In MBC patients with a future perspective of living longer with metastatic disease in particular, signaling changes in HRQoL during treatment is of great importance to maintain the quality of life weighed against the treatment benefits and toxicity. This demands a different approach compared to early stage breast cancer patients and emphasizes the need for an up-to-date HRQoL instrument dictated to patients with MBC.

The goal of this review is to describe the current use of questionnaires in real-world MBC patients by providing an overview of the available literature. We will highlight the importance of routinely monitoring appropriate PROs throughout treatment, including the implications and benefits of using PROs in daily clinical practice. This review concludes with opportunities and recommendations for the harmonized approach of HRQoL measurement applicability in MBC patients in clinical breast cancer care.

MATERIALS AND METHODS

Literature Search Strategy

This paper is partly based on a systematic literature search using different online resources; MedLine, Web of Science Core Collection, Cochrane database and Embase. Search terms used were 'metastatic breast cancer' AND 'quality of life' AND 'questionnaire' OR 'patient reported outcome' OR 'quality of life assessment', and additional related terms to maximize the sensitivity of the search. The search was conducted in December 2020 and a total of 1736 articles matched the search term.

Patient-Reported Outcomes

Patient-centered health care is the cornerstone of current cancer care, and underlines the importance of collecting PROs. [13] PROs are defined as direct feedback on a patient's health condition from a patient's perspective and, therefore, PRO scores reflect the individual HRQoL without external interpretation. [16] Since the entrance of the HRQoL concept, several research organizations have developed questionnaires to transform this subjective concept into measurable scores. Some questionnaires can be used additionally for specific purposes, for example the EuroQoL Five-Dimension Scale (EQ-5D) to calculate health-utility scores for cost-effectiveness analyses or the BREAST-Q® to evaluate breast surgery. [17,18] Besides questionnaires that are applicable for various diseases, more condition-specific instruments have been developed including breast cancer. An overview of available and validated questionnaires used in cancer patients is shown in Table 1.

Each instrument has specific questions attributed to domains that cover health issues, for example physical symptoms, daily functioning or emotional wellbeing. Thus, answers to every specific domain result in an individual score. Scores of separate domains can be summarized to generate a total score, and in general higher scores reflect better HRQoL. PROs were primarily invented to evaluate treatment strategies and thereby support clinical decisions. The collection of PROs at standard time points provides short-term information on treatment and disease burden, but longitudinal collection can also signal changes over time, which is helpful in starting a conversation at the outpatient clinic about certain domains wherein distress is identified. [25] With the growing experience in

PROs over the last few years, they have earned their place as an important outcome in cancer research. [10,11] Many institutes worldwide have already integrated routine PRO monitoring with standardized outcome sets into patient portals and electronic systems, following an initiative of The International Consortium for Health Outcomes Measurement (ICHOM). [26] ICHOM developed standardized outcome sets for a range of diseases, not necessarily with the intention to devise new outcomes measures, but to align on which well-validated PROMs providers and clinicians should use. A standard set for primary breast cancer already exists, and although a metastatic set has been composed for other cancers, this has not yet been done for MBC. [26]

Table 1. Concrete examples of patient-reported outcome measurements (PROMs) used in cancer patients with questionnaire characteristics.

Questionnaire	Subscales	No. of Items	Response Scale (Likert-Scale)	Scoring System	Recall Period
EORTC QLQ-C30 [19]	Generic	30	4-point	0–100	Past 7 days to 4 weeks
EORTC QLQ-BR23 [20] (updated EORTC QLQ-BR45)	Breast Cancer Subscale	23	4-point	0–100	Past 7 days to 4 weeks
FACT-ES [21]	Endocrine Therapy Subscale	46	5-point	0–184	Past 7 days
FACT-B [22]	Breast Cancer Subscale Trial Outcome Index	37	5-point	0–148 0–96	Past 7 days
EQ-5D-5L EQ-5D-3L [17]	Generic	6	5-point 3-point	Health states and VAS-score 0–100	Today
BREAST-Q (pre- and post-operative) [18]	Mastectomy, Breast Conserving Therapy and Reconstruction module	4–11 (depending on subscale)	3, 4 and 5-point	0–100	Past 7 days
MOS SF-36 [23]	Generic	36	3, 5 and 6 point	0–100	Past 4 weeks
RSCL [24]	Generic	39	4 point	0–135	Past 7 days

EORTC-QLQ = European Organisation for Research and Treatment of Cancer Quality-of-Life Questionnaire C-30, Breast cancer-23 and Breast cancer-45; FACT-B/ES = Functional Assessment of Cancer Therapy–Breast and Endocrine Subscale; EQ-5D = EuroQoL-5 dimensions; MOS SF-36 = Medical Outcomes Study-Short Form 36; RSCL = Rotterdam Symptom Checklist.

Inclusion and Exclusion Criteria

The criteria for inclusion in this review were studies published in the last 20 years and using questionnaires or patient-reported outcomes to evaluate quality of life in real-world MBC patients. The value of PROs as outcomes in clinical trials comparing systemic treatment regimens or other interventions in MBC patients have already been described in previously published reviews. [27-29] Although clinical trials evaluating PROs provide important insights in quality of life, the use of PROMs in such studies may serve a different purpose than the use for monitoring during daily clinical care. It was decided to focus on real-world MBC patients and that this specific topic was beyond the scope of the review. Articles based on clinical trials were, therefore, excluded. Studies focusing on locally advanced breast cancer only or focusing on other cancer types were not selected. Advanced breast cancer refers to both MBC (distant dissemination of the disease) and locally advanced disease. Locally advanced breast cancer includes primary cancers with extensive nodal or skin involvement, and is in general treated with a curative intent. Even though there is a risk of recurrent disease with distant metastasis in the following years[4], the main subject of this current paper is only MBC. Studies that included both non-metastatic and metastatic patients, but analyzed them separately, were also included.

RESULTS

Included Articles

Selection based on title and abstract was done by two researchers (M.C. and L.K.). In total, 48 articles were accepted for full text reading by both authors of which twenty articles ultimately met the inclusion criteria and are discussed throughout this review, see Figure 1.

Study Characteristics

The results of the literature search for citations meeting the inclusion criteria are summarized in Table 2. Six articles used PROs for evaluating the HRQoL during treatment, not necessarily to compare different treatment strategies, but to observe the influence of treatment on the QoL in MBC patients. Fourteen of the selected articles presented cross-sectional questionnaire-based studies.

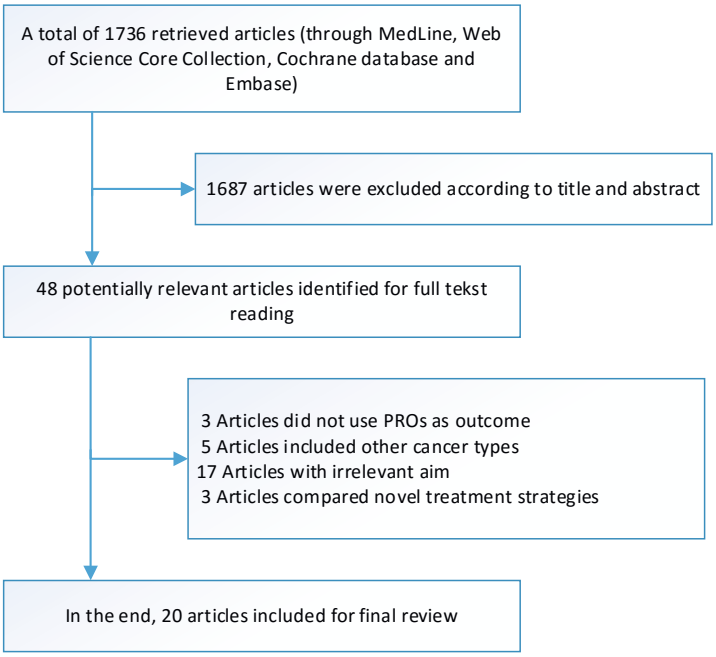


Figure 1. Flow diagram of relevant article selection.

Questionnaires and Patient-Reported Outcome (PRO) Domains

The European Organisation for Research and Treatment of Cancer Quality-of-Life Questionnaire (EORTC QLQ-C30) was most frequently used in studies [30-33,50], often supplemented by the EORTC QLQ-BR23. [34-37] Other questionnaires that were identified, often combined with others, included the short form (SF-36) [31,38], Functional Assessment of Cancer Therapy–Breast Subscale (FACT-B) [39-42] and EuroQoL (EQ)-5D[39,45,46]. Several articles used other individual and less common PRO questionnaires. One study investigated the differences between HRQoL scores of 68 MBC patients compared to the general population, using multiple validated questionnaires. Of 96 included patients, 68 patients were diagnosed with MBC and 31 were receiving a form of adjuvant therapy. Analyses were done for the complete cohort as HRQoL did not differ between the MBC and adjuvant therapy group. Lower HRQoL scores were found in MBC patients across all used instruments and the EORTC QLQ-C30 captured most aspects of HRQoL. However, no adjustments for possible confounders, such as type of therapy or comorbidities were made in their univariate analysis. [37] Age above 65 and one or more comorbidities were associated with lower EQ-5D scores according to the stratified analysis of Claessens et al., but their sample size was not sufficient for multivariate regression analyses. The latter could probably have better explored the relationship between potential risk factors and

Table 2. Instruments used for health-related quality of life (HRQoL) measurements in metastatic breast cancer (MBC) patients.

Selected Article	Study Objective	Study Design	Study Population	Administered PROM
Aranda, S. et al., 2005 [30]	To identify the support- and information needs in urban MBC patients	Cross-sectional multicenter study	105 Australian patients from four different hospitals in Melbourne with MBC. 61% response rate.	EORTC QLQ-C30 and SCNC
Kokkonen, K. et al., 2017 [31]	To assess the functional capacity and quality of life of Finnish MBC patients	Cross-sectional observational study	128 Finnish patients with ongoing treatment for MBC, treated at Helsinki University Hospital. 61% response rate.	BDI, HAQ, RAND SF-36 and EORTC QLQ-C30
Lima, E.O.L. et al., 2020 [32]	To assess QoL in hospitalized MBC patients	Cross-sectional observational study	199 (145 with stage IV) Brazilian patients with locally advanced (stage IIB, IIIA, B and C) or MBC (stage IV) that were hospitalized in Rio de Janeiro.	EORTC QLQ-C30
Müller, V. et al., 2018 [33]	To assess the impact of disease-progression on HrQoL in MBC patients	Retrospective, longitudinal, observational study	326 MBC patients from the PRAEGNANT database	EORTC QLQ-C30
Adamowicz et al., 2020 [34]	To assess QoL in MBC patients dependent on treatment-choice	Prospective, multicenter observational study	351 Polish MBC patients undergoing first-line palliative chemotherapy, HER2-treatment or endocrine therapy at two hospitals in Gdansk.	EORTC QLQ-C30 and BR23
Costa, W.A. et al., 2017 [35]	To assess the influence of pain on QoL in breast cancer patients undergoing treatment	Cross-sectional study	400 Brazilian breast cancer patients from one hospital were included. Of these, 160 patients had MBC and were analyzed separately.	McGill Pain Questionnaire, EORTC QLQ-C30 and BR-23
Karamouzis, M. et al., 2007 [36]	To evaluate QoL parameters in patients with MBC	Prospective, randomized, single-center study	210 women with MBC patients receiving chemotherapy vs supportive care	EORTC QLQ-C30 and BR23

Table 2. Instruments used for health-related quality of life (HRQoL) measurements in metastatic breast cancer (MBC) patients.

Selected Article	Study Objective	Study Design	Study Population	Administered PROM
Wallwiener, M. et al., 2016 [37]	To assess the HRQoL of MBC patients and breast cancer patients under adjuvant treatment compared with the general population.	Cross-sectional, single-center study	96 German patients with MBC or under adjuvant treatment for breast cancer. Response rate 80%.	EORTC QLQ-C30, and BR23, EQ-5D-5L and EQ-VAS.
Amado, F. et al., 2006 [38]	To evaluate changes in QoL among MBC patients receiving treatment	Prospective, observational survey study	40 Brazilian MBC patients that were about to start palliative treatment. Data was collected before start (baseline) and after 6 and 12 weeks of treatment.	BDI, SF-36
Ecclestone, C. et al., 2016 [39]	To examine the symptom burden and QoL in MBC patients	Cross-sectional observational study	174 Canadian MBC patients with only bone metastasis compared to MBC patients with visceral and/or bone metastasis.	ESAS, FACT-B
Meisel, J.L. et al., 2012 [40]	To evaluate psychological adjustment of women living long-term with metastatic disease	Cross-sectional study	28 eligible US women, of which 18 completed the questionnaires.	HADS, IES-R, DUFSS, FACT-B
Reed, E. et al., 2012 [41]	To explore QoL, experience of care and support needs in MBC patients	Cross-sectional study	235 women with MBC off two U.K. cancer centers (N = 110) and online survey (N = 125).	FACT-B
Shin, J.A. et al., 2016 [42].	To study the QoL, depression and anxiety in patients with MBC	Cross-sectional, study	140 US MBC patients, stratified by endocrine therapy (40) and chemotherapy (100)	HADS, FACT-B (TOI)
Claessens, A.K. et al., 2020 [43]	To evaluate the QoL using the EQ-5D-3L in Dutch advanced breast cancer patients	Cross-sectional study	92 Dutch patients with MBC were analyzed.	EQ-5D-3L
Slovacek, L. et al., 2010 [44]	To evaluate global QoL and depression among MBC patients	Prospective, cross-sectional study	41 Czech patients in a program of palliative cancer care	EQ-5D, ZSDS

Table 2. Instruments used for health-related quality of life (HRQoL) measurements in metastatic breast cancer (MBC) patients.

Selected Article	Study Objective	Study Design	Study Population	Administered PROM
Love, A.W. et al., 2004 [45]	To identify possible depression in MBC patients	Cross-sectional screening study	74 patients with depression were identified.	HADS, BDI-SF
Park, E.M. et al., 2018 [46].	To determine factors associated with anxiety and depression in young MBC patients	Cross-sectional study	54 women with de novo MBC from an ongoing prospective, multicenter cohort of women diagnosed <40 years.	HADS, CARES-SF, MOS
Turner, J. et al., 2005 [47]	To investigate psychosocial aspects of MBC	Cross-sectional study	66 women diagnosed with MBC under ongoing treatment at two large hospitals in Australia.	HADS, IES, CARES-SF, MSAS
Barnadas, A. et al., 2019 [48]	The applicability of the BOMET-QoL-10 measure in MBC patients	Prospective, observational, multicenter study	172 breast cancer patients with bone metastasis at 15 GEICAM hospitals in Spain.	BOMET-QoL-10
Cleeland, C.S. et al., 2014 [49]	To evaluate baseline PROs in patients with MBC and first-line hormonal, targeted or chemotherapy	Cross-sectional study	152 patients of VIRGO observational study, 104 received chemotherapy and 48 endocrine therapy.	MDASI, WPAI:SHP, RSCL

BDI = Beck Depression Inventory; SCNC = Supportive Care Needs Survey; WPAI:SHP = Work Productivity and Activity Impairment Questionnaire; HAQ = Health assessment questionnaire; SF-MPQ = ; ESAS = Edmonton Symptom Assessment System; MDASI = MD Anderson Symptom Inventory; IES-R = Revised Impact of Events Scale; DUFSS = Duke-University of North Carolina (UNC) Functional Social Support; ZSDS = Zung self-rating depression score; MSAS = Memorial Symptom Assessment Scale; CARES-SF = Cancer Rehabilitation Evaluation System-Short Form; MOS = Medical Outcomes Study Social Support Survey; BOMET-QoL-10 = Bone Metastasis Quality of Life measure; HADS = Hospital Anxiety and Depression Scale; GEICAM = Spanish Breast Cancer Research Group

HRQoL. [43] Different results were found in two other studies, in which older women had better psychological symptom scores than younger women. [41,47] According to the study of Costa et al., pain was prevalent in early-stage, locally advanced and metastatic disease, but only correlated with a decrease in QoL among MBC patients in a separate analysis. [35]

Impact of Treatment on Health-Related Quality of Life (HRQoL)

Chemotherapy, Endocrine and Targeted Therapy

Six studies assessed the HRQoL in MBC patients undergoing systemic therapy, either to evaluate single therapy or to compare endocrine and chemotherapy. The studies were difficult to compare due to heterogenic study design and outcome measurements. Amado et al. concluded that patients with low performance status at baseline seemed to have the greatest benefit on HRQoL following oncological treatment. [38] Although measured with different PRO instruments, similar results were found in the study of Cleeland et al. They also found younger age to be associated with greater symptom severity and reduced HRQoL. After adjustment for age, no difference in PRO outcomes were observed between the chemotherapy and endocrine therapy groups. [49] Chemotherapy was associated with greater symptom severity and lower functional wellbeing than endocrine or targeted therapy in two studies. [34,41] The overall quality of life measured with the EORTC QLQ-C30 after treatment did not differ from before for all treatments. [34] Kokkonen et al. also found worse physical functioning in MBC patients receiving chemotherapy, and the most common symptoms included pain and fatigue. However, most patients also underwent breast surgery prior to systemic treatment and they did not adjust for additional endocrine or targeted therapy. [31] HRQoL scores were higher in patients receiving chemotherapy versus supportive care, but results must be interpreted with caution as 40% of the supportive care group received palliative radiotherapy which possibly decreased the HRQoL. [36]

Bisphosphonate Treatment and Bone Metastasis

Bone metastases frequently occur in MBC patients for which there are a variety of treatment options, including bisphosphonates. Three studies focused on MBC patients with bone metastasis and showed lower QoL compared to patients without bone metastasis. [41,43,50] One study indicated that bisphosphonate treatment was associated with better wellbeing. The authors did not adjust the results for additional treatments, disease progression and several other factors that could impact the association. Results were possibly biased as patients with only visceral metastasis were also included, although biphosphonate treatment is not effective in these cases. [39] The study of Barnadas et al., a subanalysis of patients receiving specific treatment for bone metastatis versus no treatment revealed clinically significant improvement in HRQoL. [48]

Depression and Anxiety

The Hospital Anxiety and Depression Scale and Back Depression Inventory were mostly administered in screening for depression and anxiety, but also for general QoL outcomes. [38,40,42,45-47] Overall, mean HADS scores for anxiety were higher, signifying greater burden, than depression scores. Love et al. found similar outcomes for the HADS and BDI questionnaire, although the BDI-SF performed better in screening for depression in MBC patients. [45] Multiple regression analysis by Shin et al. showed a higher prevalence of clinical depressive and anxiety symptoms in patients receiving chemotherapy compared with endocrine therapy. However, chemotherapy was not an independent risk factor of these outcomes and lower QoL in the chemotherapy group possibly caused higher levels of depression and anxiety. [42] In patients living 5 years or longer with MBC, the overall quality of life was good, but low scores were found in emotional subscales. Half of the eligible patients did not respond due to illness severity and the authors did not distinguish between type of therapy. [40]

Disease Progression

The retrospective study of Müller et al. showed that disease progression was associated with a more than 2-fold risk (hazard ratio of 2,22) of experiencing minimally important deterioration in HRQoL based on the EORTC QLQ-C30. Regarding mean HRQoL scores, no differences were found between patients with and without progression. [33]

Hospitalization

The study of Lima et al. assessed the HRQoL in hospitalized MBC patients. The global health status averaged 32.04, which is lower than in other studies of MBC patients in the outpatient setting. The global health status was significantly lower in stage IV patients. This is probably explained by the fact that hospitalization itself and the symptoms causing admission reduce the HRQoL. [32]

DISCUSSION

As the breast-cancer specific PRO measurements were developed for early-stage breast cancer, translating them to patients with MBC can be challenging and difficult. [51] The 20 papers that were included, used 17 different PROMs to monitor the QoL in real-world MBC patients. As previously mentioned, clinical trials using PROs to evaluate novel or different chemotherapy regimens in MBC patients were excluded. However, the questionnaires used in real-world MBC patients as described in this current review are in line with PROs used in randomized clinical trials according to previously published systematic reviews. [14,27-29,52] These results together show that there is still large heterogeneity in instru-

ments used for PRO measurement in MBC patients. The various questionnaires, subscales and scoring systems leading to disaggregated data of PROs may complicate the answers to research questions or hypotheses. [12,53] A standardized outcome set may be a prerequisite to improve the interpretation of PROs in daily clinical care but also in clinical trials and to recognize them as an important endpoint.

Most MBC patients do not qualify for surgical treatment and the effect of surgical removal of the primary tumor on survival and quality of life is not convincing. [54-56] Chemotherapy, endocrine therapy and targeted immunotherapy with biological agents have been modified over recent years with increasing effectiveness. [57,58] For oncologists administering novel treatments with respect to the benefit-risk ratio for patients is challenging. Because treatment options sometimes have similar efficacy based on traditional outcomes such as survival or tumor response, but have different toxicity, new indicators such as HRQoL or symptom burden can be used to support treatment decisions. [59] However, the impact of systemic agents on the HRQoL remains a subject of controversy. Some studies have shown that endocrine therapy and trastuzumab can improve the overall QoL following treatment by diminishing symptoms. [34,60] Chemotherapy is effective in relieving cancer-related symptoms and disease control, but can negatively impact well-being, especially in patients with a poor baseline HRQoL. A study of 378 women with advanced breast cancer receiving chemotherapy, showed that appetite and physical wellbeing at baseline were independent predictors of overall and progression free survival. Women with poor baseline HRQoL received fewer cycles of chemotherapy and experienced more toxicity. Thus, HRQoL itself can be an independent predictor of chemotherapy efficacy. [36,61]

Despite promising effects, intense treatments are causing severe side effects which can also deteriorate the patient's quality of life, sometimes making it worse enough to discontinue treatment. One study showed treatment non-adherence in one-third of breast cancer patients receiving endocrine therapy due to adverse events. [62] Therefore, it is important to include patients in the decision-making process and jointly decide whether they are eligible for more or less aggressive treatment regimens, and how they can trade-off side effects and QoL. QoL monitoring with use of PROs can be helpful in this process, as worsening of adverse symptoms can be signaled early and information as well as guidance of the patient might be improved. [59] Unfortunately, today's available PRO instruments for MBC patients do not always seem sufficient to detect changes in HRQoL. Therefore, demonstrating possible variation in HRQoL scores between different systemic treatments in clinical trials is difficult and complicates clinical decision-making. [52,63]

Some studies that examined the completion of questionnaires, however, found low rates of patient adherence, sometimes associated with disease severity and the inability to complete questionnaires. [12] Another possible cause is the lack of information given about the potential and importance of PROs as well as the meaning of the resulting scores. If outcomes are discussed or explained by physicians in the outpatient clinic, poor adherence

to completion of questionnaires will most likely be avoided. Patients might feel uncomfortable starting a conversation about emotional or social problems, unless their physician initiated a discussion on these topics. HRQoL questionnaires may contribute to ease these conversations by being a helpful tool to identify problematic health issues. [25] To overcome the aforementioned barriers, creating dashboards that visually present the scores of a specific patient in simplified pictures, graphics or tables can be more informative than only abstractive numbers. Additionally, individual patient scores can be compared with scores of breast cancer patients with the same biological or treatment-related characteristics also known as reference scores. [64] Normative data reflect outcomes of a population unencumbered by a disease or specific condition, and can be used by both clinicians and patients to provide more context when interpreting PROs. The consensus in cancer research is still that conclusions are based on statistical significant differences. However, in the evaluation of PROs it is not only important to take the statistical significance into consideration, but also the extent to which these differences are clinically meaningful, also known as minimal clinical important differences (MCID). MCIDs are the smallest changes in PROM scores, that are important and relevant enough for an individual patient to justify a modification in patient management. [65] MCIDs can be determined for individual questionnaires and both MCIDs and thresholds can support the clinical evaluation of PROs. To date, these reference data for MBC patients are scarce.

FUTURE PERSPECTIVES

In a constantly improving and changing health care system, where patient-centered care is being more prioritized, measuring HRQoL should be a routine clinical assessment. Although many researchers and clinicians agree, a wide variety of questionnaires resulting in different values make it difficult for healthcare professionals to become familiar with PRO data and could also hamper the exchange of information between treating physicians and disciplines. Particularly in the field of breast cancer research, with major developments in PROs over de last years, the necessity for comparable outcome data is apparent. Yet traditional questionnaires each result in an instrument-specific score that is difficult to compare. One approach to address this challenge is the development of common metrics for the specific outcomes of interest such as fatigue and depression. [66,67] Common metrics are statistical models based on modern test theory (item response theory, IRT), that cover multiple questionnaires and, therefore, allow different questionnaires to be scored on a common scale. However, standardizing outcome sets has also been proven effective and efficient, enabling the comparison of quality of life scores between institutes. [13,26]

Some clinicians are concerned about the patient burden due to frequent questionnaire assessments. However, it is likely that intensified surveillance and detection of short-term

changes in metastatic disease will require shorter time intervals and more frequent surveys than in early-stage breast cancer patients. For example, in a landmark study evaluating an intensified digital PRO elicitation, Denis et al. defined a time interval of only one week between self-reports during lung cancer treatment. [68] Initiatives such as the EORTC or PROMIS developed IRT-based, construct-specific measurement models and established standardized item banks, offering the prospect of a less burdensome and more valid PRO assessment through tailored short forms and computerized adaptive testing (CAT). [69,70] CAT describes an assessment of the respective construct (e.g., pain, fatigue, physical functioning) which specifically asks questions deemed most informative based on currently available information. This results in greater precision without extending the test length which might decrease the effort, respectively, the burden, for patients to answer the questionnaires. [71] Even if institutions struggle to implement CAT due to technical prerequisites, an IRT-based standard set for metastatic breast cancer would only need to include the domains of interest rather than specific questionnaires or items. Use of common metrics and construct-specific item-banks would enable comparable data despite different items or instruments.

Another interesting topic is the additional prognostic value of PRO-supported care on survival. Studies have shown an increase in overall survival through intensified HRQoL monitoring using, among others, the EQ-5D and FACT-L. [68,72] In a randomized controlled trial by Basch et al. including 766 metastatic cancer patients, digital PRO assessment for symptom monitoring in the intervention group led to an alert email to the treating center in case of symptom deterioration. The control group received the usual care with symptom monitoring during routine clinical visits only. Patients in the PRO group showed significantly higher HRQoL scores at 6 months after enrollment and overall survival increased by 5 months compared with usual care. [72,73] Moreover, in a study among 121 lung cancer patients taking a similar approach, Denis et al. presented an overall survival of 22.5 months in the PRO group compared to 14.9 months in the control group. [68] Against this backdrop, one can assume that PRO monitoring might facilitate an early detection of symptoms associated with adverse events or disease progression, thus enabling timely countermeasures, which ultimately result in improved overall survival. In addition, a recent meta-analysis of Efficace et al. identified several PRO domains (e.g., fatigue, appetite loss) to be independent predictors for overall survival in metastatic cancer patients. [74] The strongest association was found with physical functioning, showing a 12% increase in risk of death for every 10-point decrease on a scale of 1 to 100. The results underline the importance of baseline measurements and the systematic administration of PROs to also capture prognostic information. However, PROs comprise more than only symptom burden and, apart from possible aforementioned survival benefits, minimizing the physical and psychosocial impact of MBC is important in itself. Studies performed in MBC patients to identify the optimal patient-centered approach for electronic PRO

collection in routine clinical care concluded that physical symptoms or treatment toxicity are not always a priority, but financial concerns or emotional well-being even so, and that PRO collection should be multidimensional. [30,75] The EORTC QoL questionnaires are used frequently in cancer research and the need for an MBC specific questionnaire has not gone unnoticed by the EORTC workgroup. They are currently working on a comprehensive questionnaire for HRQoL assessment in MBC patients, with the aim to conduct phases 1 to 3 of the module development process in the next two years. The European Innovative Medicines Initiatives Funded Health Outcomes Observatory (H2O) project is a recently developed initiative to improve the quality of care by creating 'health outcomes observations', which also aims to collect standardized health data, among which (metastasized) breast cancer.

CONCLUSIONS

Current treatment developments for MBC patients can impact the symptom burden and quality of life, emphasizing the importance of HRQoL measurements. We believe that an important step in accelerating value-based health care for MBC patients is to implement a standard set of PROs for routine clinical care. An appropriate and standardized set could be used in evaluating treatment strategies and making clinical decisions. It will increase the interpretability of PROs and allow for comparisons in MBC outcomes. Eventually, national and international benchmarking will help to develop a stronger theoretical foundation for future research and lead to improvements in daily breast cancer care. The value of PROs and specific domains for the prediction of survival outcomes or disease progression should be studied further.

ACKNOWLEDGMENTS

The authors wish to thank Elise Krabbendam (Biomedical Information Specialists) from the Erasmus MC Medical Library for developing and updating the search strategies.

REFERENCES

1. Breast cancer: estimated incidence, mortality and prevalence worldwide International Agency for Research on Cancer. Accessed Accessed 22-01-2021, http://globocan.iarc.fr/old/FactSheets/cancers/breast-new.asp [Accessed on 22-01-2021)
2. Mettlin C. Global breast cancer mortality statistics. *CA Cancer J Clin*. May-Jun 1999;49(3):138-44.
3. Tyczynski JE, Plesko I, Aareleid T, et al. Breast cancer mortality patterns and time trends in 10 new EU member states: mortality declining in young women, but still increasing in the elderly. *Int J Cancer*. Dec 20 2004;112(6):1056-64.
4. Cardoso F, Costa A, Senkus E, et al. 3rd ESO-ESMO international consensus guidelines for Advanced Breast Cancer (ABC 3). *Breast*. Feb 2017;31:244-259.
5. O'Shaughnessy J. Extending survival with chemotherapy in metastatic breast cancer. *Oncologist*. 2005;10 Suppl 3:20-9.
6. Cardoso F, Spence D, Mertz S, et al. Global analysis of advanced/metastatic breast cancer: Decade report (2005–2015). Article. *Breast*. 2018;39:131-138.
7. Sundquist M, Brudin L, Tejler G. Improved survival in metastatic breast cancer 1985-2016. *Breast*. Feb 2017;31:46-50.
8. Michael YL, Kawachi I, Berkman LF, Holmes MD, Colditz GA. The persistent impact of breast carcinoma on functional health status: prospective evidence from the Nurses' Health Study. *Cancer*. Dec 1 2000;89(11):2176-86.
9. Stein KD, Syrjala KL, Andrykowski MA. Physical and psychological long-term and late effects of cancer. *Cancer*. Jun 1 2008;112(11 Suppl):2577-92.
10. Snyder CF, Aaronson NK. Use of patient-reported outcomes in clinical practice. *Lancet*. Aug 1 2009;374(9687):369-70.
11. Marshall S, Haywood K, Fitzpatrick R. Impact of patient-reported outcome measures on routine practice: a structured review. *J Eval Clin Pract*. Oct 2006;12(5):559-68.
12. van Egdom LSE, Oemrawsingh A, Verweij LM, et al. Implementing Patient-Reported Outcome Measures in Clinical Breast Cancer Care: A Systematic Review. *Value Health*. Oct 2019;22(10):1197-1226. 10.1016/j.jval.2019.04.1927
13. Porter ME, Larsson S, Lee TH. Standardizing Patient Outcomes Measurement. *N Engl J Med*. Feb 11 2016;374(6):504-6.
14. Reed E, Kössler I, Hawthorn J. Quality of life assessments in advanced breast cancer: Should there be more consistency? Review. *Eur J Cancer Care*. 2012;21(5):565-580.
15. Pe M, Dorme L, Coens C, et al. Statistical analysis of patient-reported outcome data in randomised controlled trials of locally advanced and metastatic breast cancer: a systematic review. Review. *Lancet Oncol*. 2018;19(9):e459-e469.
16. Bredart A, Marrel A, Abetz-Webb L, Lasch K, Acquadro C. Interviewing to develop Patient-Reported Outcome (PRO) measures for clinical research: eliciting patients' experience. *Health Qual Life Outcomes*. Feb 5 2014;12:15.
17. EuroQol G. EuroQol--a new facility for the measurement of health-related quality of life. *Health Policy*. Dec 1990;16(3):199-208.
18. Pusic AL, Klassen AF, Scott AM, Klok JA, Cordeiro PG, Cano SJ. Development of a new patient-reported outcome measure for breast surgery: the BREAST-Q. *Plast Reconstr Surg*. Aug 2009;124(2):345-353.
19. McLachlan SA, Devins GM, Goodwin PJ. Validation of the European Organization for Research and Treatment of Cancer quality of life questionnaire (QLQ-C30) as a measure of psychosocial function in breast cancer patients. Article. *Eur J Cancer*. 1998;34(4):510-517.

20. Sprangers MA, Groenvold M, Arraras JI, et al. The European Organization for Research and Treatment of Cancer breast cancer-specific quality-of-life questionnaire module: first results from a three-country field study. *J Clin Oncol*. Oct 1996;14(10):2756-68.
21. Fallowfield LJ, Leaity SK, Howell A, Benson S, Cella D. Assessment of quality of life in women undergoing hormonal therapy for breast cancer: Validation of an endocrine symptom subscale for the FACT-B. Article. *Breast Cancer Res Treat*. 1999;55(2):189-199.
22. Brady MJ, Cella DF, Mo F, et al. Reliability and validity of the Functional Assessment of Cancer Therapy-Breast quality-of-life instrument. *J Clin Oncol*. Mar 1997;15(3):974-86.
23. McHorney CA, Ware JE, Jr., Lu JF, Sherbourne CD. The MOS 36-item Short-Form Health Survey (SF-36): III. Tests of data quality, scaling assumptions, and reliability across diverse patient groups. *Med Care*. Jan 1994;32(1):40-66.
24. de Haes JC, van Knippenberg FC, Neijt JP. Measuring psychological and physical distress in cancer patients: structure and application of the Rotterdam Symptom Checklist. *Br J Cancer*. Dec 1990;62(6):1034-8.
25. Detmar SB, Muller MJ, Schornagel JH, Wever LD, Aaronson NK. Health-related quality-of-life assessments and patient-physician communication: a randomized controlled trial. *JAMA*. Dec 18 2002;288(23):3027-34.
26. Ong WL, Schouwenburg MG, van Bommel ACM, et al. A Standard Set of Value-Based Patient-Centered Outcomes for Breast Cancer: The International Consortium for Health Outcomes Measurement (ICHOM) Initiative. *JAMA Oncol*. May 1 2017;3(5):677-685.
27. Ghislain I, Zikos E, Coens C, et al. Health-related quality of life in locally advanced and metastatic breast cancer: methodological and clinical issues in randomised controlled trials. *Lancet Oncol*. 07 2016;17(7):e294-e304.
28. Krohe M, Hao Y, Lamoureux RE, et al. Patient-reported outcomes in metastatic breast cancer: A review of industry-sponsored clinical trials. Article. *Breast Cancer Basic Clin Res*. 2016;10:93-102.
29. Turner-Bowker DM, Hao Y, Foley C, et al. The use of patient-reported outcomes in advanced breast cancer clinical trials: a review of the published literature. Review. *Curr Med Res Opin*. 2016;32(10):1709-1717.
30. Aranda S, Schofield P, Weih L, et al. Mapping the quality of life and unmet needs of urban women with metastatic breast cancer. Article. *Eur J Cancer Care*. 2005;14(3):211-222.
31. Kokkonen K, Saarto T, Mäkinen T, et al. The functional capacity and quality of life of women with advanced breast cancer. Article. *Breast Cancer*. 2017;24(1):128-136.
32. Lima EOL, Silva MMD. Quality of life of women with locally advanced or metastatic breast cancer. Article. *Rev Gaucha Enferm*. 2020;41:e20190292.
33. Müller V, Nabieva N, Häberle L, et al. Impact of disease progression on health-related quality of life in patients with metastatic breast cancer in the PRAEGNANT breast cancer registry. Article. *Breast*. 2018;37:154-160.
34. Adamowicz K, Baczkowska-Waliszewska Z. Quality of life during chemotherapy, hormonotherapy or antiHER2 therapy of patients with advanced, metastatic breast cancer in clinical practice. Article. *Health Qual Life Outcomes*. 2020;18(1)
35. Costa WA, Monteiro MN, Queiroz JF, Gonçalves AK. Pain and quality of life in breast cancer patients. Article. *Clinics (Sao Paulo)*. 2017;72(12):758-763.
36. Karamouzis MV, Ioannidis G, Rigatos G. Quality of life in metastatic breast cancer patients under chemotherapy or supportive care: A single-institution comparative study. Article. *Eur J Cancer Care*. 2007;16(5):433-438.

37. Wallwiener M, Simoes E, Sokolov AN, Brucker SY, Fasching PA, Graf J. Health-related quality of life in metastatic and adjuvant breast cancer patients. Article. *Geburtshilfe Frauenheilkd*. 2016;76(10):1065-1073.
38. Amado F, Lourenço MTC, Deheinzelin D. Metastatic breast cancer: Do current treatments improve quality of life? A prospective study. Article. *Sao Paulo Med J*. 2006;124(4):203-207.
39. Ecclestone C, Chow R, Pulenzas N, et al. Quality of life and symptom burden in patients with metastatic breast cancer. Article. *Supportive Care Cancer*. 2016;24(9):4035-4043.
40. Meisel JL, Domchek SM, Vonderheide RH, et al. Quality of life in long-term survivors of metastatic breast cancer. Article. *Clin Breast Cancer*. 2012;12(2):119-126.
41. Reed E, Simmonds P, Haviland J, Corner J. Quality of life and experience of care in women with metastatic breast cancer: A cross-sectional survey. Article. *J Pain Symptom Manage*. 2012;43(4):747-758.
42. Shin JA, El-Jawahri A, Parkes A, Schleicher SM, Knight HP, Temel JS. Quality of Life, Mood, and Prognostic Understanding in Patients with Metastatic Breast Cancer. Article. *J Palliative Med*. 2016;19(8):863-869.
43. Claessens AKM, Ramaekers BLT, Lobbezoo DJA, et al. Quality of life in a real-world cohort of advanced breast cancer patients: a study of the SONABRE Registry. Article in Press. *Qual Life Res*. 2020.
44. Slovacek L, Slovackova B, Slanska I, Petera J, Priester P. Quality of life and depression among metastatic breast cancer patients. Article. *Med Oncol*. 2010;27(3):958-959.
45. Love AW, Grabsch B, Clarke DM, Bloch S, Kissane DW. Screening for depression in women with metastatic breast cancer: A comparison of the Beck Depression Inventory Short Form and the Hospital Anxiety and Depression Scale. Article. *Aust New Zealand J Psychiatry*. 2004;38(7):526-531.
46. Park EM, Gelber S, Rosenberg SM, et al. Anxiety and Depression in Young Women With Metastatic Breast Cancer: A Cross-Sectional Study. Article. *Psychosomatics*. May-Jun 2018;59(3):251-258.
47. Turner J, Kelly B, Swanson C, Allison R, Wetzig N. Psychosocial impact of newly diagnosed advanced breast cancer. Article. *Psycho-Oncol*. May 2005;14(5):396-407.
48. Barnadas A, Munoz M, Margeli M, et al. BOMET-QoL-10 questionnaire for breast cancer patients with bone metastasis: the prospective MABOMET GEICAM study. *J patient rep outcomes*. Dec 21 2019;3(1):72.
49. Cleeland CS, Mayer M, Dreyer NA, et al. Impact of symptom burden on work-related abilities in patients with locally recurrent or metastatic breast cancer: Results from a substudy of the VIRGO observational cohort study. Article in Press. *Breast*. 2014.
50. Davie A, Carter GC, Rider A, et al. Real-world patient-reported outcomes of women receiving initial endocrine-based therapy for HR+/HER2- advanced breast cancer in five European countries. Article. *BMC Cancer*. 2020;20(1).
51. Danesh M, Belkora J, Volz S, Rugo HS. Informational needs of patients with metastatic breast cancer: what questions do they ask, and are physicians answering them? Article. *J Cancer Educ*. 2014;29(1):175-180.
52. Goodwin PJ, Black JT, Bordeleau LJ, Ganz PA. Health-related quality-of-life measurement in randomized clinical trials in breast cancer - Taking stock. Review. *J Natl Cancer Inst*. 2003;95(4):263-281.
53. Bottomley A, Pe M, Sloan J, et al. Analysing data from patient-reported outcome and quality of life endpoints for cancer clinical trials: a start in setting international standards. *Lancet Oncol*. Nov 2016;17(11):e510-e514.
54. Badwe RA, Parmar V, Hawaldar RW, et al. Surgical removal of primary tumor in metastatic breast cancer: impact on health-related quality of life (HR-QOL) in a randomized controlled trial (RCT). Journal: Conference Abstract. *Journal of clinical oncology*. 2014;32(15)

55. Bjelic-Radisic V, Fitzal F, Knauer M, et al. Primary surgery versus no surgery in synchronous metastatic breast cancer: Patient-reported quality-of-life outcomes of the prospective randomized multicenter ABCSG-28 Posytive Trial. Article. *BMC Cancer*. 2020.
56. Tosello G, Torloni MR, Mota BS, Neeman T, Riera R. Breast surgery for metastatic breast cancer. Review. *Cochrane Database Syst Rev*. 2018.
57. Gennari A, Conte P, Rosso R, Orlandini C, Bruzzi P. Survival of metastatic breast carcinoma patients over a 20-year period: a retrospective analysis based on individual patient data from six consecutive studies. *Cancer*. Oct 15 2005;104(8):1742-50.
58. Tevaarwerk AJ, Gray RJ, Schneider BP, et al. Survival in patients with metastatic recurrent breast cancer after adjuvant chemotherapy: little evidence of improvement over the past 30 years. *Cancer*. Mar 15 2013;119(6):1140-8.
59. Cardoso F, Senkus-Konefka E, Fallowfield L, Costa A, Castiglione M, Group EGW. Locally recurrent or metastatic breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. May 2010;21 Suppl 5:v15-9.
60. Osoba D, Slamon DJ, Burchmore M, Murphy M. Effects on quality of life of combined trastuzumab and chemotherapy in women with metastatic breast cancer. Article. *J Clin Oncol*. 2002;20(14):3106-3113.
61. Lee CK, Stockler MR, Coates AS, Gebski V, Lord SJ, Simes RJ. Self-reported health-related quality of life is an independent predictor of chemotherapy treatment benefit and toxicity in women with advanced breast cancer. Article. *Br J Cancer*. 2010;102(9):1341-1347.
62. daCosta DiBonaventura M, Copher R, Basurto E, Faria C, Lorenzo R. Patient preferences and treatment adherence among women diagnosed with metastatic breast cancer. *Am Health Drug Benefits*. Oct 2014;7(7):386-96.
63. Adamowicz K, Jassem J, Katz A, Saad ED. Assessment of quality of life in advanced breast cancer. An overview of randomized phase III trials. *Cancer Treat Rev*. Aug 2012;38(5):554-8.
64. Mierzynska J, Taye M, Pe M, et al. Reference values for the EORTC QLQ-C30 in early and metastatic breast cancer. Article. *Eur J Cancer*. 2020;125:69-82.
65. Musoro JZ, Coens C, Fiteni F, et al. Minimally important differences for interpreting EORTC QLQ-C30 scores in patients with advanced breast cancer. Article. *JNCI Cancer Spectr*. 2019;3.
66. Friedrich M, Hinz A, Kuhnt S, Schulte T, Rose M, Fischer F. Measuring fatigue in cancer patients: a common metric for six fatigue instruments. *Quality of Life Research*. 2019/06/01 2019;28(6):1615-1626.
67. Choi SW, Schalet B, Cook KF, Cella D. Establishing a common metric for depressive symptoms: linking the BDI-II, CES-D, and PHQ-9 to PROMIS depression. *Psychol Assess*. Jun 2014;26(2):513-27.
68. Denis F, Basch E, Septans AL, et al. Two-Year Survival Comparing Web-Based Symptom Monitoring vs Routine Surveillance Following Treatment for Lung Cancer. *JAMA*. Jan 22 2019;321(3):306-307.
69. Cella D, Riley W, Stone A, et al. The Patient-Reported Outcomes Measurement Information System (PROMIS) developed and tested its first wave of adult self-reported health outcome item banks: 2005-2008. *J Clin Epidemiol*. Nov 2010;63(11):1179-94.
70. Petersen MA, Aaronson NK, Arraras JI, et al. The EORTC CAT Core-The computer adaptive version of the EORTC QLQ-C30 questionnaire. *Eur J Cancer*. Sep 2018;100:8-16.
71. Cella D, Gershon R, Lai JS, Choi S. The future of outcomes measurement: item banking, tailored short-forms, and computerized adaptive assessment. *Qual Life Res*. 2007;16 Suppl 1:133-41.
72. Basch E, Deal AM, Dueck AC, et al. Overall Survival Results of a Trial Assessing Patient-Reported Outcomes for Symptom Monitoring During Routine Cancer Treatment. *JAMA*. Jul 11 2017;318(2):197-198.

73. Basch E, Deal AM, Kris MG, et al. Symptom monitoring with patient-reported outcomes during routine cancer treatment: A randomized controlled trial. Article. *J Clin Oncol*. 2016;34(6):557-565.
74. Efficace F, Biganzoli L, Piccart M, et al. Baseline health-related quality-of-life data as prognostic factors in a phase III multicentre study of women with metastatic breast cancer. Article. *Eur J Cancer*. May 2004;40(7):1021-1030.
75. Mougalian SS, Aminawung JA, Presley CJ, et al. Prioritization of patient-reported outcomes by women with metastatic breast cancer. Note. *JCO Clin Cancer Inform*. 2019;3.

Chapter 5

Quality of life, patient satisfaction, and complications after nipple-sparing versus skin-sparing mastectomy followed by immediate breast reconstruction

A systematic review and meta-analysis

Marloes E. Clarijs, Noelle J.M.C. Vrancken Peeters, Sophie A.F van Dongen, Linetta B. Koppert, Andrea L. Pusic, Marc A.M. Mureau*, Bianca F.M. Rijken*

*Both authors contributed equally to the study.

Plastic and Reconstructive Surgery, Jan 2023

ABSTRACT

Background

Nipple-sparing mastectomy (NSM) has emerged as an alternative procedure for skin sparing mastectomy (SSM), followed by immediate breast reconstruction. Because oncological safety appears similar, patient-reported outcomes (PROs) and complication risks may guide decision-making in individual patients. Therefore, the aim of this systematic review was to compare PROs and complication rates after NSM and SSM.

Methods

A systematic literature review evaluating NSM versus SSM was performed using Embase, Medline and Cochrane databases. Methodological quality of the included studies was assessed using the Newcastle-Ottawa Quality Assessment Form for Cohort Studies. Primary outcomes were PROs and complications. Studies that evaluated Breast-Q scores were used to perform meta-analyses on five Breast-Q domains.

Results

Thirteen comparative studies including 3895 patients were selected from 1202 articles found. Meta-analyses of the Breast-Q domains showed a significant mean difference of 7.64 in the Sexual Well-being domain ($p = 0.01$) and 4.71 in the Psychosocial Well-being domain ($p = 0.03$), both in favor of NSM. Using the specifically designed questionnaires, no differences in overall satisfaction scores were found. There were no differences in overall complication rates between the two groups.

Conclusions

Patient satisfaction scores were high after both NSM and SSM, however, NSM led to a higher sexual and psychosocial well-being. No differences in complication rates were found. In combination with other factors, such as oncological treatments, complication risk profile, and fear of cancer recurrence, the decision for NSM or SSM has to be made on an individual basis and only if NSM is considered to be oncologically safe.

BACKGROUND

Breast cancer is one of the most commonly diagnosed female cancers with an increasing incidence globally. [1] An important part of curative treatment of breast cancer involves surgical removal of the tumor mass. Over the last years, surgical treatment has been refined to improve aesthetic outcomes with comparable oncological results. Although the trend has shifted towards breast conserving therapy, including oncoplastic reconstruction techniques, a mastectomy with reconstruction still may be the best treatment in case of a high tumor breast volume ratio, absence of donor site tissue or fear of recurrence. [2] Therefore, new surgical techniques for mastectomy, such as skin or nipple-sparing mastectomy (SSM and NSM, respectively), have been developed to improve aesthetic appearances. With the identification of patients at high risk for breast cancer in case of BRCA mutation, the rate of prophylactic bilateral mastectomies and the desire for NSM has increased. [3]

NSM involves removal of all glandular breast tissue with preservation of the native skin envelope, inframammary fold (IMF) and nipple areolar complex (NAC), while SSM involves the removal of all glandular breast tissue and IMF without NAC preservation. [4] The NAC is a tremendously important component of the breast, considering the aesthetics and contribution to sexual pleasure. The main reason to preserve the NAC is for aesthetic purposes, and previous studies reported an improvement in patient satisfaction and psychological benefit after NSM. [4-6] Although SSM can be followed by NAC reconstruction, the NAC is unique in its appearance and therefore difficult to reconstruct accurately. Outcomes of NAC reconstruction vary across previous studies. [7-9]

Despite an increasing number of women choosing NSM for aesthetic reasons, the oncological safety of the procedure had been questioned. The main concern about preserving the NAC is exposing patients to a higher risk of occult NAC tumor involvement. Because the retro-areolar tissue is not fully removed, more terminal duct lobular units could be left behind compared to SSM. [10,11] Nevertheless, previous research has shown equal local recurrence rates and overall survival outcomes in carefully selected breast cancer patients after NSM compared to conventional mastectomies. [4,12-15] The National Comprehensive Cancer Network suggested that NSM is feasible in patients with a tumor-areolar distance of >2 cm, no detection of cancer in the nipple, and early stage breast cancer with favorable biological tumor characteristics. [16] Although the oncological safety was outside the scope of this review, attention is needed for the selection criteria of NSM patients.

Given similar oncologic outcomes, NSM might offer better aesthetic results and higher patient satisfaction compared to SSM, suggesting NSM might be superior to SSM[17], which can be measured using patient-reported outcomes (PROs). On the other side, NAC preservation may cause an increased risk of complications, such as necrosis, wound healing problems, infections (with implant loss) or nipple displacement and this may negatively affect PROs. The aim of this systematic review was to evaluate PROs and complication

risks in patients undergoing NSM versus patients undergoing SSM followed by immediate breast reconstruction.

METHODS

Literature search

A systematic search was performed in Embase, Medline and Cochrane databases according to the PRISMA guidelines (Preferred Reporting Items for Systematic Reviews and Meta-Analysis), from inception to March 30th 2021. A search string was drafted with the help of an experienced librarian using search terms related to "nipple sparing mastectomy" and "patient-reported outcomes". The exact search syntaxes are available in Supplemental Digital Content 1.

Eligibility criteria

Studies were included if they evaluated patient-reported outcomes after NSM with SSM as control group. SSM was defined as removal of breast glandular tissue including excision of the NAC, with preservation of the skin envelope. NSM involved removal of the breast glandular tissue, preserving the skin envelope and a thin NAC flap. If an immediate reconstruction was performed, studies using total mastectomy (TM) and simple mastectomy with nipple reconstruction (SNR) were considered to be the same procedure as a skin-sparing mastectomy. To facilitate comparison, only articles including quantitative PRO measurements were utilized. Both unilateral and bilateral procedures, as well as autologous or (expander)implant-based breast reconstructions were included. Studies were excluded that (1) included male patients, (2) reported SSM without differentiating between skin sparing or nipple sparing surgery, (3) did not compare cohorts, and (4) described gender transition surgery.

Study selection

Two independent authors (MC and NVP) initially reviewed all articles based on title and abstract. Discrepancies of inclusion were resolved by discussion in which an additional author was involved (BR) and consensus was found in all cases. Systematic reviews were excluded. An in-debt analysis of the full-text was performed.

Data extraction

Data extraction from studies included the methodological and baseline clinical aspects of the studies, e.g. year of publication, study design, cohort selection, sample size, age of subjects, specific PRO measurement, complications, and time from surgery to completion of questionnaires (follow-up). Mean scores and standard deviations for each Breast-Q domain

were abstracted. The domains included Satisfaction with Breasts, Physical Well-being, Psychosocial Well-being, Sexual Well-being, and Satisfaction with Outcome. Authors were contacted by email to request unpublished data. Data collection was independently done by two researchers (NVP and SD), and checked by a third researcher afterwards (MC).

Quality assessment

Both authors (NVP and SD) independently assessed the risk of bias in included studies using the Newcastle Ottawa Scale (NOS) for non-randomized studies. The articles were rated based on selection, comparability and ascertainment of exposure or outcome of interest, resulting in a score from zero to eight. The Newcastle Ottawa scale can be converted into Agency for Healthcare Research and Quality (AHRQ) standards, which divides the quality of studies in good, fair and poor quality. [18] Disagreements were settled by consensus.

Statistical analysis

Breast-Q data were pooled with random-effect meta-analyses to determine the mean differences and 95% confidence intervals (CIs). The I^2 was used to assess heterogeneity, expressed as the percentage of variability across studies. An I^2 greater than 50% was considered to represent significant heterogeneity. Weights were calculated based on the inverse variance method. Breast-Q scores range from 0 to 100, with higher scores representing better satisfaction or well-being. [19] The RevMan software was used to calculate standard deviations from other related statistics, such as standard errors and confidence intervals, if articles did not report standard deviations. If required, the statistics of two groups (e.g. younger/older age groups) were combined according to the formulas for combining summary statistics. The exact formulas are described in the Cochrane Handbook (Chapter 6.5.2.1 and 6.5.2.10). [20] Funnel plots were created to display the risk of publication bias. All statistical analyses were conducted using Review Manager (Version 5.4.1) and p-values ≤ 0.05 were considered statistically significant. [21]

RESULTS

Search results

After deduplication, a total of 1202 citations were identified. By screening title and abstract, 38 potentially relevant articles were selected, of which 16 articles were selected for full text evaluation. Finally, 13 articles including 3895 patients met the criteria for inclusion in this systematic review (Figure 1). The study specific characteristics are summarized in Table 1.

Table 1. Study characteristics

Article ID	Title	Study Type	Country	NSM (n)	Control (n)	Age (years)	Outcome	Type of reconstruction	Bilateral mastectomy (%), Yes	Intraoperative or adjuvant radiotherapy (%)	Timing questionnaire post-surgery
Bailey et al. 2017[5]	Quality-of-Life Outcomes Improve with Nipple-Sparing Mastectomy and Breast Reconstruction	RO	USA	32	32	Mean: NSM (48.9) - SSM (46.3)	BREAST-Q	NSM: autologous (43.7%) SSM: autologous (43.8%) or expander-implant or direct-to-implant	NSM: 31 (96.6%) SSM: 27 (84.4%)	NSM: 5 (15.6%) SSM: 7 (21.9%)	>6 months
Dosset et al. 2016[25]	Prospective evaluation of skin and nipple-areola sensation and patient satisfaction after nipple-sparing mastectomy."	PO	USA	38	15	Mean: NSM (49) – SSM (43)	Breast Evaluation Questionnaire and Body Image after Breast Cancer Questionnaire	Immediate expander-implant (94%) or autologous (6%)	NSM: 33 (87%) SSM: 15 (100%)	NSM: 3 (8%) SSM: 0	12 months
Kim et al. 2019[29]	Comparative Study of Nipple–Areola Complex Position And Patient Satisfaction After Unilateral Mastectomy and Immediate Expander–Implant Reconstruction Nipple-Sparing Mastectomy Versus Skin-Sparing Mastectomy	RO	Korea	55	85	Mean: NSM (42.7) - SSM (45.6)	Specifically designed questionnaire	Immediate expander-implant	Only unilateral procedures	NSM: 6 (10.9%) SSM: 12 (14.1%)	Unknown
Mesdag et al. 2017[6]	Nipple sparing mastectomy for breast cancer is associated with high patient satisfaction and safe oncological outcomes	RO	France	63	89	Median: NSM (49,5) - SSM (50)	Specifically designed questionnaire	Immediate expander-implant (18.4%) or direct-to-implant (81.6%)	NR (mostly unilateral procedures)	NSM: 30.2% SSM: 10.1%	Median: 42 months (IQR: 18–58)

Table 1. Study characteristics

Article ID	Title	Study Type	Country	NSM (n)	Control (n)	Age (years)	Outcome	Type of reconstruction	Bilateral mastectomy (%), Yes	Intraoperative or adjuvant radiotherapy (%)	Timing questionnaire post-surgery
Metcalfe et al. 2015[17]	Long-Term Psychosocial Functioning in Women with Bilateral Prophylactic Mastectomy: Does Preservation of the Nipple-Areolar Complex Make a Difference?	CS	Canada	53	84	Mean: 41 (range 24–69)	BREAST-Q IES HADS Decision Regret Scale	NR	Only bilateral procedures	NR	50 ± 31 months
Opsomer et al. 2020[27]	Nipple reconstruction in autologous breast reconstruction after areola-sparing mastectomy	RO	Belgium	55	348	Mean: 48.3	BREAST-Q	Autologous*	NSM: 22 (40%) SSM: 83 (23.9%)	NSM: 7 (12.7%) SSM: 107 (30.7%)	64.3 ± 18.9 months
Ritter et al. 2021[23]	The impact of age on patient-reported outcomes after oncoplastic versus conventional breast cancer surgery	PO	Switzerland	32	31	NR	BREAST-Q	NSM: autologous (100%)** SSM: NR	NR	NR	35 ± 25 months
Rojas et al. 2017[28]	The impact of mastectomy type on the Female Sexual Function Index (FSFI), satisfaction with appearance, and the reconstructed breast's role in intimacy	RO	USA	8	36	Median: NSM (46,5) - SSM (50,5)	FSFI	NR	NSM: 5 (62.5%) SSM: 17 (42.2%)	NSM: 0 SSM: 7 (19.4%)	>1 year
Romanoff et al. 2018[24]	A Comparison of Patient-Reported Outcomes After Nipple-Sparing Mastectomy and Conventional Mastectomy with Reconstruction.	RO	USA	219	1647	Mean: NSM (44), TM (48)	BREAST-Q	Immediate expander-implant	NSM: 174 (79%) TM: 1012 (61%)	NSM: 9 (4%) TM: 353 (21%)	658 days (IQR: 442–1189)

Table 1. Study characteristics

Article ID	Title	Study Type	Country	NSM (n)	Control (n)	Age (years)	Outcome	Type of reconstruction	Bilateral mastectomy (%), Yes	Intraoperative or adjuvant radiotherapy (%)	Timing questionnaire post-surgery
Santosa et al. 2019[22]	Comparing Nipple-sparing Mastectomy to Secondary Nipple Reconstruction: A Multi-institutional Study.	PO	USA	286	314	Mean: NSM (44.0) – SNR (48.4)	BREAST-Q	Immediate expander-implant or direct-to-implant	NSM: 216 (75.5%) SNR: 184 (58.6%)	NSM: 28 (9.8%) SNR: 18 (5.7%)	24 months
Ueda et al. 2008[31]	Cosmetic outcome and patient satisfaction after skin-sparing mastectomy for breast cancer with immediate reconstruction of the breast	PO	Japan	33	41	Mean: NSM (44) -SSM (47)	Specifically designed questionnaire	NSM: 97% autologous (1 implant) SSM: 100% autologous***	NR	NSM: 1 (3%) SSM: 1 (2%)	50 months NSM 53 months SSM 47 months
Van Verschuer et al. 2016[30]	Patient Satisfaction and Nipple-Areola Sensitivity After Bilateral Prophylactic Mastectomy and Immediate Implant Breast Reconstruction in a High Breast Cancer Risk Population	PO	Nether-lands	20	25	Median: NSM (37) - SSM (34)	BREAST-Q	Immediate expander-implant	Only bilateral procedures	NSM: 2 (10%) SSM (0%)	Median (range) NSM: 27 months (10-58) SSM: 65 months (43-136)
Wei et al. 2016[26]	Psychosocial and Sexual Well-Being Following Nipple-Sparing Mastectomy and Reconstruction	PO	USA	52	202	Mean: NSM (44,9) - SSM (45,7)	BREAST-Q	Immediate expander-implant	NSM: 37 (71%) SSM: 132 (65%)	NSM: 6 (11.8%) SSM: 15 (7.4%)	NSM: 18.3 (±17) SSM: 32.9 (±21)

RO = retrospective cohort study, PO = prospective cohort study, CS = cross-sectional survey study, NSM = nipple-sparing mastectomy, SSM = skin-sparing mastectomy, IES = Impact of Event Scale, HADS = Hospital Anxiety and Depression scale, FSFI = Female Sexual Function Index, TM = Total Mastectomy, SNR = simple mastectomy with nipple reconstruction, NR = not reported.

* Deep Inferior Epigastric Perforator (DIEP) flap, Superior Gluteal Artery Perforator flap, or Lumbar Artery Perforator flap

** DIEP flap.

*** DIEP flap, Latissimus Dorsi Myocutaneous flap, or Transverse Rectus Abdominus Myocutaneous flap.

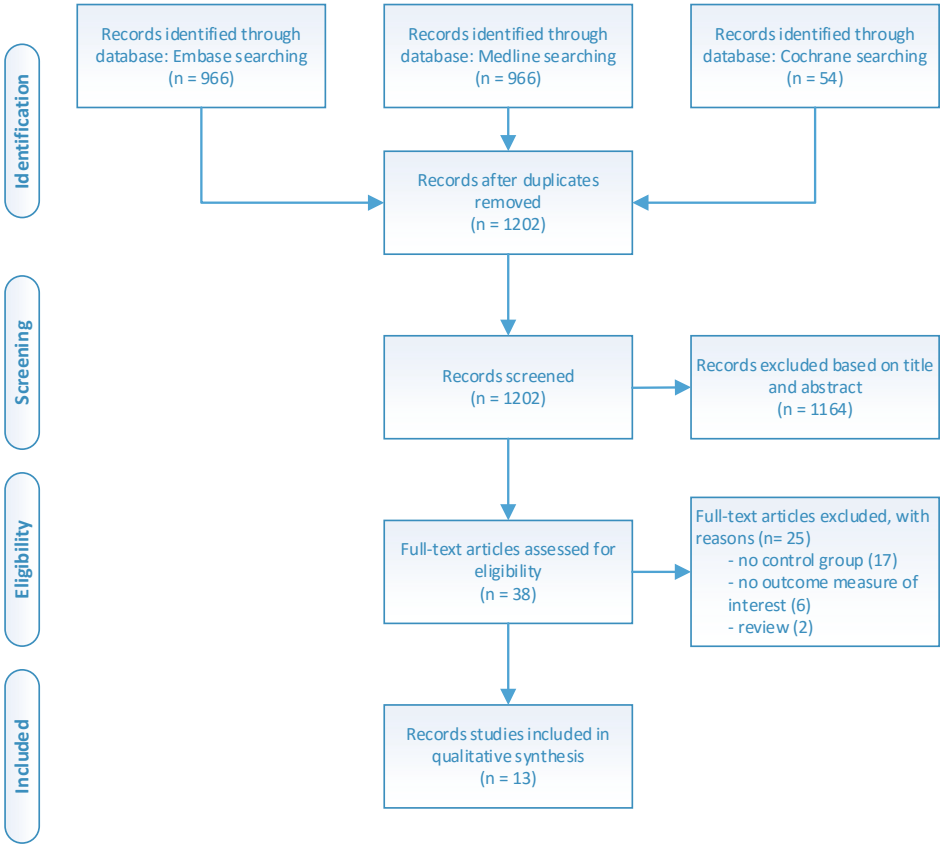


Figure 1. Flowchart study selection

Study characteristics

The intervention of interest was NSM, the comparator was SSM, always followed by immediate breast reconstruction. In three studies, a total mastectomy or 'simple mastectomy with nipple reconstruction' was used as the control group. [22-24] Seven articles were retrospective cohort studies, while six were prospective cohort studies. There was one cross-sectional survey study. [17] The studies were conducted in the United States (N=6), Europe (N=4), Canada (N=1), and Asia (N=2). Studies included women diagnosed with invasive breast cancer or DCIS. Four studies included both breast cancer patients and patients with a BRCA mutation opting for prophylactic mastectomy. [22,24-26] Seven studies included both unilateral and bilateral mastectomies[5,22,24-28], one study only unilateral[29], and two studies only bilateral (prophylactic) mastectomies[17,30]. Three studies did not specify this, resulting in at least 1436 unilateral and 2170 bilateral mastectomies. Six studies evaluated (expander)implant based reconstructions[6,22,24,26,29,30]. Three studies included both (expander)implant-based and autologous[5,23,25], and two studies only autologous

breast reconstructions[27,31]. Sample sizes ranged from 44 to 1866 patients, with a mean of 73 patients for NSM and 227 patients for SSM. Eight studies used the Breast-Q of which different domains were selected, five studies used another questionnaire. Studies had a mean follow-up time starting from six months after surgery. Nipple reconstruction after SSM was reported in seven studies of which four studies specified the type of nipple reconstruction after SSM (e.g. intradermal tattooing, local transposition flaps). [6,22,24,26,27,29,30]

Quality assessment

Six studies were rated as good, eight studies were rated as fair and one study was rated as poor. Adjustment for potential confounding was not consistent across studies; seven studies adjusted for age, four adjusted for prognostic factors such as tumor grade and treatment, while other studies adjusted for income or insurance status (Table 2). The funnel plots did not indicate a risk of publication bias (see Figure S1-5 in Supplemental Digital Content 2).

Meta-analyses of Mean Breast-Q Scores

Seven studies were included in the meta-analyses to evaluate mean Breast-Q scores. [5,17,22,23,26,27,30] A meta-analysis was performed for each domain: Satisfaction with Breasts, Psychosocial Wellbeing, Physical Well-being, Sexual Wellbeing, and Satisfaction with Outcome (Figures 2a-e). There was a significant mean difference of 7.96 in Sexual Wellbeing ($p = 0.003$) and 4.77 in Psychosocial Well-being ($p = 0.01$), both in favor of NSM. No statistically significant differences between NSM and SSM in Satisfaction With Breasts (2.04, $p = 0.51$), Satisfaction With Outcome (2.80, $p = 0.64$) and Physical Well-being (1.37, $p = 0.42$) were found.

Although Romanoff et al. [24] evaluated Breast-Q scores of NSM and TM patients, they were unable to share their data. Therefore, the data is missing in the meta-analyses. Their results showed that, after adjusting for relevant clinical variables (e.g. age, unilateral vs. bilateral mastectomy, chemotherapy, radiotherapy and baseline Breast-Q score), only Psychosocial and Physical Well-being were significantly higher in the NSM group.

Table 2. Quality Assessment of non-randomized studies based on the NOS and AHRQ

Article ID	Selection				Comparability	Outcome			NOS	AHRQ
	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of Exposure	Outcome of interest was not present at start of study	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome§	Follow-up long enough for outcomes to occur	Adequacy of follow-up of cohorts	**Total score**	
Bailey 2017	1	1	1	1	1	-	0	1	6	Fair
Dosset 2016	1	1	1	1	0	-	1	1	6	Fair
Kim 2019	1	1	1	1	2	-	0	0	6	Fair
Mesdag 2017	1	1	1	1	0	-	1	0	5	Fair
Metcalfe 2015	1	1	1	1	2	-	1	1	8	Good
Opsomer 2020	1	1	1	1	0	-	1	0	4	Poor
Ritter 2021	1	1	1	1	1	-	1	1	6	Fair
Rojas 2017	1	1	1	1	1	-	1	0	5	Fair
Romanoff 2018	1	1	1	1	2	-	1	1	8	Good
Santosa 2019	1	1	1	1	2	-	1	0	7	Good
Ueda 2008	1	1	1	1	0	-	1	0	5	Fair
Van Verschuer 2016	1	1	1	1	0	-	1	1	6	Fair
Wei 2016	1	1	1	1	2	-	1	1	7	Good

NOS Score = Newcastle-Ottawa Scale; AHRQ = Agency for Healthcare Research and Quality.

Maximum score is 8 (selection = 4, comparability = 2, and outcome = 2).

§ Patient-reported outcomes are self-reported.

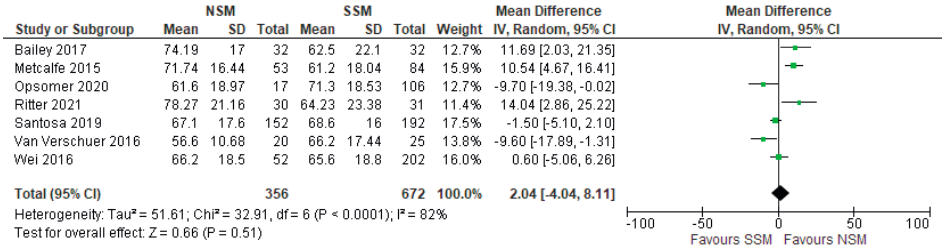


Figure 2a Satisfaction With Breasts

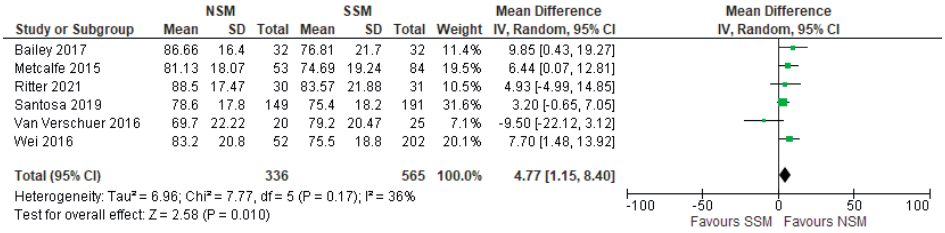


Figure 2b Psychosocial Well-being

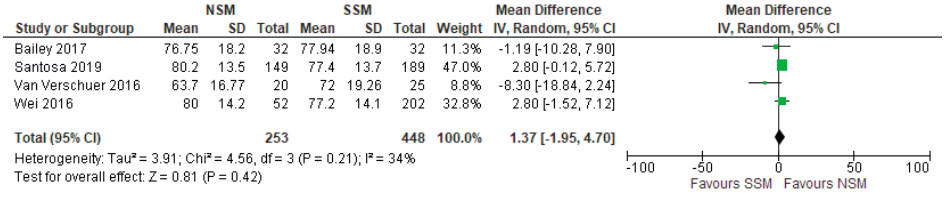


Figure 2c Physical Well-being

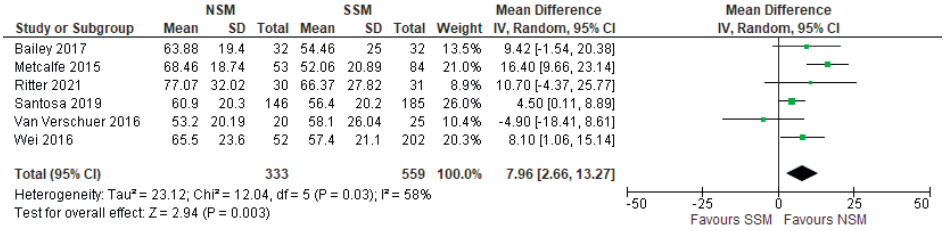


Figure 2d Sexual Well-being

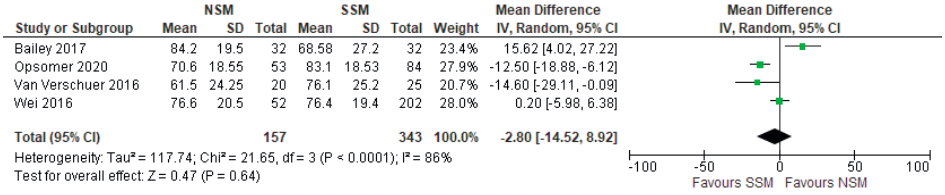


Figure 2e Satisfaction With Outcome

Figure 2a-e. Forest plots for the Satisfaction With Breasts (a), Psychosocial Well-being (b), Physical Well-being (c), Sexual Well-being (d) and Satisfaction With Outcome (e) domains of the Breast-Q

Other Patient Reported Outcomes

Besides the Breast-Q, other specifically designed questionnaires were used to study quality of life as well, e.g. harmony between breasts and sexual well-being. Ueda et al. [31] showed that according to the QOL-ACD-B response, the mean scores for patient satisfaction did not differ between SSM and NSM and were similar to those of patients undergoing breast conserving therapy. Mesdag et al. [6] used their own specifically designed questionnaire that was partially adapted from the Breast-Q, as specific questions about nipple sensitivity or harmony between breasts were added. Most patients in the total cohort (NSM (n=41), SSM (n=63) or SSM with nipple reconstruction (n=35)) were very satisfied with the overall aspect of the reconstructed breast (n = 73, 76.8%), and there were no differences in satisfaction rates between the three groups. Focusing on the aesthetic results of the NAC, patient satisfaction with NSM was comparable to that of patients with secondary NAC reconstruction (NSM n = 27 (75%) vs. SSM n = 18 (60%), p = 0.202). Considering harmony between breasts, patients in the NSM group had a lower satisfaction rate compared to patients with SSM and nipple reconstruction (NSM n = 14 (37.8%) vs. SSM n = 19 (63.3%), p = 0.038). Rojas et al. [32] reported that there were no significant differences in postoperative total median Female Sexual Function Index (FSFI) scores between the groups. Interestingly, women who underwent SSM experienced a significantly higher sexual satisfaction score than women who underwent NSM (median 5.2 vs. 4.8, p = 0.005). Kim et al. [29] used a NAC-specific questionnaire comprising 9 items in which each item was scored on a 5-point Likert scale. Their study showed a similar satisfaction about breast reconstruction between the NSM and SSM group (3.48 in NSM vs 3.51 in SSM, p = 0.913). In addition, the NAC sensitivity score was significantly better in the NSM group compared to the SSM group (2.12 vs 1.84 respectively, p = 0.003). NAC position was better in the SSM group (2.88 in NSM compared to 3.80 in SSM, p = 0.001). Verschuer et al. [30] found almost total loss of sensitivity in the NSM group, which was significantly lower compared to non-operated females, measured with Semmes Weinstein monofilaments (mean 1.9 vs. 4.7, p < 0.01). Dosset et al. [25] used a Breast Evaluation Questionnaire and Body Image after Breast Cancer Questionnaire to evaluate quality of life. Similar to Kim et al. [29], they found that patients who underwent SSM were more satisfied with nipple position (p = 0.03). There was significant loss in (monofilament) sensation following mastectomy compared to preoperative sensation.

Complications

Complication rates were reported in eight studies (Table 3). One study found more delayed wound healing in NSM patients (18/55 (32.7%) vs. 15/85 (17.6%), p = 0.04), including postoperative NAC necrosis, but total reconstruction failure was more common in SSM patients (6/85 (7.1%) vs 0/55, p = 0.043). [29] One study reported more overall complications in the NSM group, including primarily minor infections and minimal mastectomy flap ne-

crosis (p = 0.046). [24] One study showed a similar two-year complication (76/286 (26.6%) vs. 69/314 (22.0%), p = 0.73) and reconstruction failure rate (19/286 (6.6%) vs. 9/314 (2.9%), p = 0.90) between NSM and SSM. [22] The other five studies could also not find a significant difference in the overall complication rates between NSM and SSM. [5,6,22,26,30]

Table 3. Comparison of complications between nipple-sparing and skin-sparing mastectomy

Article ID	Type of complication(s)	SSM N (%)	NSM N (%)	P-value
Bailey et al. 2017[5]	No significant difference in any complication rates			*NR*
	Tissue expander infection	4 (7.1%)	6 (10.3%)	0.74
	Delayed wound healing complications	1 (1.8%)	2 (3.4%)	1.0
Kim et al. 2019[29]	Tissue expander-associated complications	27 (31.8%)	21 (38.2%)	0.435
	Delayed wound healing complications	15 (17.6%)	18 (32.7%)	0.04*
	Expander removal	5 (5.9%)	0	0.067
	Implant associated complications	10 (12.5%)	10 (18.2%)	0.361
	Final reconstruction failure	6 (7.1%)	0	0.043*
Mesdag et al. 2017[6]	No significant difference in overall complications	16 (18%)	14 (22.2%)	0.52
	Rate of skin-flap necrosis	6 (6.7%)	0	0.042*
	Prosthesis contracture rate	2 (2.2%)	7 (11.1%)	0.034*
	NAC necrosis		4 (6.4%)	*NR*
	Reconstruction failure	8 (9%)	2 (3.2%)	0.20
Opsomer et al. 2021[27]	Wound problems at nipple level	11 (3.2%)	6 (10.9%)	0.013*
	Necrosis of the nipple§	22 (6.3%)	9 (16.4%)	*NR*
Romanoff et al. 2018[24]	Overall complications			0.046*
	None	1444 (88%)	179 (82%)	
	Minor	160 (10%)	32 (15%)	
	Major	43 (3%)	8 (4%)	
Santosa et al. 2019[22]	No significant difference in overall complications	69 (22%)	76 (26.6%)	0.079
	Mastectomy flap necrosis	15 (4.8%)	25 (8.7%)	0.024*
	Reconstructive failure	9 (2.9%)	19 (6.6%)	0.081
Van Verschuer et al. 2016[30]	No significant difference in overall complications	9 (38%)	12 (60%)	0.14
	NAC necrosis§	2 (8%)	0	*NR*
	Mastectomy skin flap necrosis	0	1 (5%)	*NR*
Wei et al. 2016[26]	No significant difference in overall complications			0.207
	None	180 (89.1%)	43 (82.7%)	
	≥1 complication	22 (10.9%)	9 (17.3%)	

NSM = nipple-sparing mastectomy; SSM = skin-sparing mastectomy; NR = not reported.
§ spared and reconstructed nipple.
*p value < 0.05.

DISCUSSION

The aim of this study was to conduct a systematic review and meta-analysis to compare PROs and complication rates between NSM and SSM. Statistically significant differences in favor of NSM were found in the Psychosocial and Sexual Wellbeing domains of the Breast-Q. The studies that analyzed PROMs other than the Breast-Q found no differences in overall satisfaction scores. In general, nipple sensitivity was better, while nipple position was worse in NSM patients. Most studies did not show significant differences in overall complication rates, however wound related complications and NAC necrosis were more prevalent in NSM patients. [22,24,27,33]

A previously published systematic review that mainly focused on oncological outcomes after NSM and SSM did not find any differences in local recurrence rates 5-year or disease free survival. [4] Although aesthetic outcomes, patient reported outcomes, and quality of life were evaluated as well, no scientific conclusions could be drawn due to the lack of standardized assessment tools. We used outcomes of the well-validated Breast-Q that may have allowed for more reliable comparisons in our meta-analyses. Other modified questionnaires may not be specific enough to detect small differences in quality of life between surgical techniques. Such detailed aspects of psychosocial or physical well-being can be highly relevant to evaluate outcomes after breast reconstructive surgery and this requires a reliable and validated questionnaire, for which the Breast-Q has become the golden standard. [19]

An interesting finding was that a higher satisfaction of the nipple position was found in the SSM group. A possible explanation is that the position of the nipple can be adjusted to the new aesthetic contour of the breast during nipple reconstruction, while after NAC preservation the position of the nipple is more determined within the skin flap. Moreover, use of a tissue expander may deteriorate the position of the NAC during expansion, specifically in ptotic breasts. In exceptional cases, expanding the skin with or without the pectoral muscle results in an unacceptable position of the NAC which has to be corrected by NAC removal and reconstruction. Consequently, this might have a substantial impact on patient well-being. In patients with ptotic breasts, the new NAC position is even more difficult to predict after tissue expansion and therefore NSM is not always an option. [34-36] Satisfaction with nipple position may also depend on whether the procedure was performed uni- or bilaterally, as in prophylactic mastectomies in BRCA mutation carriers. [37] In the study of Verschuer et al, a trend towards higher satisfaction with nipple position was seen in patients with bilateral SSM and nipple reconstruction. [30] Strictly, uni- and bilateral mastectomies should be separately analyzed in order to obtain more reliable outcomes.

Post-operative NAC sensitivity was investigated in three studies using different measurements. Two studies used an objective method with Semmes Weinstein filaments and both found almost no NAC sensation in the NSM group compared to non-operated controls

or pre-operative sensation. [25,30] In contrast, the third study found a higher NAC sensitivity score in the NSM group versus SSM based on a questionnaire. [29] Previous literature describes the influence of incision type on postoperative sensation, with periareolar incisions causing more sensation loss compared to inframammary incision. [38] Remarkably, Verschuer and Dosset et al. used different incisions and both found substantial loss of sensation. [25,30] For some patients, nipple reconstruction after SSM is an important final step to complete the aesthetic aspect of the breast and may improve PROs. [7,39] Although some articles provided a detailed description of the procedures for nipple reconstruction, the timing of reconstruction was not reported. [6,17,24,26,27,29,30] In general, nipple reconstruction is performed at least three months after surgery and includes local transposition flaps, intradermal tattooing, or a combination of both. Since PROs were collected starting from six months post-surgery, we assumed that the nipple reconstruction had been completed before administration of the questionnaires.

This review included articles based on different kinds of reconstructions (e.g. autologous or (expander)implant-based reconstruction), which may have led to a heterogeneous sample. Although this may have influenced PROs[40,41], there was not sufficient data for a subgroup meta-analysis. Moreover, outcomes of the individual articles did not show a trend based on type of reconstruction.

Radiation can have adverse effects on the skin or breast implant, but the influence of adjuvant radiotherapy on aesthetic outcomes and satisfaction was poorly documented. One study showed that a higher number of patients received adjuvant radiotherapy in the NSM group compared to the SSM group, causing more capsular contractures and therefore resulted in a lower satisfaction with harmony between breasts. Despite this finding, reconstruction failure was similar between NSM and SSM patients. Moreover, an association between radiotherapy and risk of NAC necrosis was not found. [6] According to the Breast-Q scores, one study revealed adjuvant radiotherapy as a significant negative predictor for the Satisfaction with Breasts, Sexual Well-being, and Satisfaction with Outcome domains. [24] In contrast, Wei et al. did not found an association between radiotherapy and the Sexual Well-being domain. [26]

Strengths and limitations

One of the key strengths of the present review is the evaluation of validated Breast-Q scores that allowed us to perform several meta-analyses. Heterogeneity in patient reported outcome measurements (PROMs) limited such comparisons in a previous study. [4] Most of the included articles were of good quality. Besides PROs, a clear overview of the complications was also provided, as they may influence PROs. Unfortunately, there was some selective reporting bias in one article. [24] Summary data for the mean pre-operative Breast-Q scores was missing and not available upon request. Despite the fact that their statistical data could not be included in our meta-analyses, they found similar results in

the Breast-Q domains. Second, the follow-up for completion of the questionnaires varied between studies from six months up to eleven years. Previous research has shown that a longer follow-up results in improved quality of life outcomes. [24,42] Therefore, results of our meta-analyses must be viewed with caution. Another limitation was the non-randomized design of all studies. Thus, it is likely that patients were not eligible for both types of breast surgery and baseline characteristics may have differed. This could have led to confounding by indication, for example if patients had ptotic or non-ptotic breasts and underwent unilateral or bilateral procedures. The amount of skin preserved in SSM patients was unclear due to different provided definitions of SSM (e.g. total, non-nipple sparing or simple mastectomies with implant based reconstructions), which may have had a small effect on the outcomes and this should be taken into account when interpreting the findings.

The Breast-Q is able to detect differences between pre- and postoperative scores, but the cross-sectional or retrospective design of the studies prohibited such comparisons.

CONCLUSION

Our meta-analyses showed significant differences in the Psychosocial Well-being and Sexual Well-being domains of the BREAST-Q in favor of NSM. Although complication types varied between NSM and SSM, there was no significant difference in the overall complication rate or reconstruction failure. For patients with an indication for mastectomy with immediate reconstruction who value the preservation of their NAC, NSM could be seen as a superior treatment. NSM should therefore be offered to selected patients with an indication or wish for mastectomy with immediate reconstruction, and in whom NSM is oncologically safe.

REFERENCES

1. WHO. Early diagnosis and screening. *World Health Organization* 2020; WHO Available at: https://www.who.int/cancer/prevention/diagnosis-screening/breast-cancer/en/, 2015.
2. Kouwenberg CAE, Kranenburg LW, Busschbach JJ, Mureau MAM. Why Breast-Conserving Therapy Should be Considered Treatment of Choice in Early-Stage Breast Cancer Patients. *Ann Surg Oncol.* 2021.
3. Jakub JW, Peled AW, Gray RJ, et al. Oncologic safety of prophylactic nipple-sparing mastectomy in a population with BRCA mutations: A multi-institutional study. *JAMA Surg.* 2018;153(2):123-129.
4. Agha RA, Al Omran Y, Wellstead G, et al. Systematic review of therapeutic nipple-sparing versus skin-sparing mastectomy. *BJS Open.* 2019;3(2):135-145.
5. Bailey CR, Ogbuagu O, Baltodano PA, et al. Quality-of-Life Outcomes Improve with Nipple-Sparing Mastectomy and Breast Reconstruction. *Plast Reconstr Surg.* 2017;140(2):219-226.
6. Mesdag V, Régis C, Tresch E, et al. Nipple sparing mastectomy for breast cancer is associated with high patient satisfaction and safe oncological outcomes. *J Gynecol Obstet Hum Reprod.* 2017;46(8):637-642.
7. Goh SC, Martin NA, Pandya AN, Cutress RI. Patient satisfaction following nipple-areolar complex reconstruction and tattooing. *J Plast Reconstr Aesthet Surg.* 2011;64(3):360-363.
8. Harcourt D, Russell C, Hughes J, White P, Nduka C, Smith R. Patient satisfaction in relation to nipple reconstruction: the importance of information provision. *J Plast Reconstr Aesthet Surg.* 2011;64(4):494-499.
9. Jabor MA, Shayani P, Collins DR, Jr., Karas T, Cohen BE. Nipple-areola reconstruction: satisfaction and clinical determinants. *Plast Reconstr Surg.* 2002;110(2):457-463; discussion 464-455.
10. Edge SB. Nipple-sparing mastectomy: How often is the nipple involved? *J Clin Oncol.* 2009;27(30):4930-4932.
11. van Verschuer VM, van Deurzen CH, Westenend PJ, et al. Prophylactic nipple-sparing mastectomy leaves more terminal duct lobular units in situ as compared with skin-sparing mastectomy. *Am J Surg Pathol.* 2014;38(5):706-712.
12. Galimberti V, Morigi C, Bagnardi V, et al. Oncological Outcomes of Nipple-Sparing Mastectomy: A Single-Center Experience of 1989 Patients. *Ann Surg Oncol.* 2018;25(13):3849-3857.
13. Voltura AM, Tsangaris TN, Rosson GD, et al. Nipple-Sparing mastectomy: Critical assessment of 51 procedures and implications for selection criteria. *Ann Surg Oncol.* 2008;15(12):3396-3401.
14. Valero MG, Muhsen S, Moo TA, et al. Increase in Utilization of Nipple-Sparing Mastectomy for Breast Cancer: Indications, Complications, and Oncologic Outcomes. *Ann Surg Oncol.* 2020;27:344-351.
15. Wu ZY, Kim HJ, Lee JW, et al. Breast Cancer Recurrence in the Nipple-Areola Complex after Nipple-Sparing Mastectomy with Immediate Breast Reconstruction for Invasive Breast Cancer. *JAMA Surg.* 2019;154(11):1030-1037.
16. National Comprehensive Cancer Network; Guidelines Invasive Breast Cancer. . 2021; https://www.nccn.org/home, 2021.
17. Metcalfe KA, Cil TD, Semple JL, et al. Long-Term Psychosocial Functioning in Women with Bilateral Prophylactic Mastectomy: Does Preservation of the Nipple-Areolar Complex Make a Difference? *Ann Surg Oncol.* 2015;22(10):3324-3330.
18. GA Wells BS, D O'Connell, J Peterson, V Welch, M Losos, P Tugwell. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp.

19. Pusic AL, Klassen AF, Scott AM, Klok JA, Cordeiro PG, Cano SJ. Development of a new patient-reported outcome measure for breast surgery: the BREAST-Q. *Plast Reconstr Surg.* 2009;124(2):345-353.
20. Julian PT Higgins TL, Jonathan J Deeks. Choosing effect measures and computing estimates of effect. 2021; https://training.cochrane.org/handbook/current/chapter-06, 2021.
21. *RevMan Web 2020* [computer program]. The Cochrane Collaboration; 2020.
22. Santosa KB, Qi J, Kim HM, et al. Comparing Nipple-sparing Mastectomy to Secondary Nipple Reconstruction: A Multi-institutional Study. *Ann Surg.* 2019.
23. Ritter M, Ling BM, Oberhauser I, et al. The impact of age on patient-reported outcomes after oncoplastic versus conventional breast cancer surgery. *Breast Cancer Res Treat.* 2021;187(2):437-446.
24. Romanoff A, Zabor EC, Stempel M, Sacchini V, Pusic A, Morrow M. A Comparison of Patient-Reported Outcomes After Nipple-Sparing Mastectomy and Conventional Mastectomy with Reconstruction. *Ann Surg Oncol.* 2018;25(10):2909-2916.
25. Dossett LA, Lowe J, Sun W, et al. Prospective evaluation of skin and nipple-areola sensation and patient satisfaction after nipple-sparing mastectomy. *J Surg Oncol.* 2016;114(1):11-16.
26. Wei CH, Scott AM, Price AN, et al. Psychosocial and Sexual Well-Being Following Nipple-Sparing Mastectomy and Reconstruction. *Breast J.* 2016;22(1):10-17.
27. Opsomer D, Vyncke T, Depypere B, Stillaert F, Van Landuyt K, Blondeel P. Nipple reconstruction in autologous breast reconstruction after areola-sparing mastectomy. *J Plast Reconstr Aesthet Surg.* 2021;74(6):1223-1228.
28. Rojas K, Onstad M, Raker C, Clark M, Stuckey A, Gass J. The impact of mastectomy type on the Female Sexual Function Index (FSFI), satisfaction with appearance, and the reconstructed breast's role in intimacy. *Breast Cancer Res Treat.* 2017;163(2):273-279.
29. Kim H, Park SJ, Woo KJ, Bang SI. Comparative Study of Nipple-Areola Complex Position and Patient Satisfaction After Unilateral Mastectomy and Immediate Expander-Implant Reconstruction Nipple-Sparing Mastectomy Versus Skin-Sparing Mastectomy. *Aesthetic Plast Surg.* 2019;43(2):313-327.
30. van Verschuer VM, Mureau MA, Gopie JP, et al. Patient Satisfaction and Nipple-Areola Sensitivity After Bilateral Prophylactic Mastectomy and Immediate Implant Breast Reconstruction in a High Breast Cancer Risk Population: Nipple-Sparing Mastectomy Versus Skin-Sparing Mastectomy. *Ann Plast Surg.* 2016;77(2):145-152.
31. Ueda S, Tamaki Y, Yano K, et al. Cosmetic outcome and patient satisfaction after skin-sparing mastectomy for breast cancer with immediate reconstruction of the breast. *Surgery.* 2008;143(3):414-425.
32. Rojas K, Onstad M, Raker C, Clark MA, Stuckey A, Gass J. The impact of mastectomy type on the Female Sexual Function Index (FSFI), satisfaction with appearance, and the reconstructed breast's role in intimacy. *Breast Cancer Res Treat.* 2017;163(2):273-279.
33. Kracoff S, Benkler M, Allweis TM, Ben-Baruch N, Egozi D. Does nipple sparing mastectomy affect the postoperative complication rate after breast reconstruction? Comparison of postoperative complications after nipple sparing mastectomy vs skin sparing mastectomy. *Breast J.* 2019;25(4):755-756.
34. Hudson DA, Skoll PJ. Complete one-stage, immediate breast reconstruction with prosthetic material in patients with large or ptotic breasts. *Plast Reconstr Surg.* 2002;110(2):487-493; discussion 494-486.
35. Rusby JE, Gui GP. Nipple-sparing mastectomy in women with large or ptotic breasts. *J Plast Reconstr Aesthet Surg.* 2010;63(10):e754-755.
36. Spear SL, Willey SC, Feldman ED, et al. Nipple-sparing mastectomy for prophylactic and therapeutic indications. *Plast Reconstr Surg.* 2011;128(5):1005-1014.
37. Taylor EM, Wilkins EG, Pusic AL, et al. Impact of Unilateral versus Bilateral Breast Reconstruction on Procedure Choices and Outcomes. *Plast Reconstr Surg.* 2019;143(6):1159e-1168e.

38. Araco A, Araco F, Sorge R, Gravante G. Sensitivity of the nipple-areola complex and areolar pain following aesthetic breast augmentation in a retrospective series of 1200 patients: periareolar versus submammary incision. *Plast Reconstr Surg.* 2011;128(4):984-989.
39. Bykowski MR, Emelife PI, Emelife NN, Chen W, Panetta NJ, de la Cruz C. Nipple-areola complex reconstruction improves psychosocial and sexual well-being in women treated for breast cancer. *J Plast Reconstr Aesthet Surg.* 2017;70(2):209-214.
40. Kouwenberg CAE, de Ligt KM, Kranenburg LW, et al. Long-Term Health-Related Quality of Life after Four Common Surgical Treatment Options for Breast Cancer and the Effect of Complications: A Retrospective Patient-Reported Survey among 1871 Patients. *Plast Reconstr Surg.* 2020;146(1):1-13.
41. Lagendijk M, van Egdom LSE, Richel C, et al. Patient reported outcome measures in breast cancer patients. *Eur J Surg Oncol.* 2018;44(7):963-968.
42. Hu ES, Pusic AL, Waljee JF, et al. Patient-reported aesthetic satisfaction with breast reconstruction during the long-term survivorship Period. *Plast Reconstr Surg.* 2009;124(1):1-8.

SUPPLEMENTS

Search Strategy. The search syntaxes for the Embase, Medline, and Cochrane databases.

EMBASE

('subcutaneous mastectomy'/de OR 'subcutaneous nipple sparing mastectomy'/de OR 'nipple sparing mastectomy'/de OR 'areola sparing mastectomy'/de OR ((nipple/de OR 'breast areola'/de) AND mastectomy/de AND preservation/de) OR (((subcutan*) NEAR/3 (mastectom* OR breast-amputat* OR breast-resect* OR mammectom*)) OR ((nipple OR areola) NEAR/3 (sparing OR preserv* OR retain* OR retention* OR conservation* OR conserving OR graft*) AND (mastectom* OR breast-amputat* OR breast-resect* OR mammectom*))):ab,ti,kw) AND ('treatment outcome'/de OR 'patient-reported outcome'/de OR 'cancer recurrence'/de OR 'cancer free survival'/de OR 'cancer survival'/de OR 'cancer mortality'/de OR mortality/de OR 'survival'/de OR reoperation/de OR 'complication'/de OR 'postoperative complication'/de OR 'necrosis'/de OR 'breast necrosis'/de OR 'surgical infection'/de OR 'infectious complication'/de OR 'hematoma'/de OR 'seroma'/de OR 'epidermolysis'/de OR 'prosthesis complication'/de OR 'prosthesis loosening'/de OR 'cancer specific survival'/de OR 'disease free survival'/de OR 'overall survival'/de OR 'skin necrosis'/de OR (outcome* OR recorren* OR disease-free OR cancer-free OR surviv* OR mortalit* OR reoperation* OR complication* OR necrosis* OR necrotic* OR hematoma* OR haematoma* OR epidermolys* OR seroma* OR (Prosthesis NEAR/3 (loss)) OR ((surgical OR wound) NEAR/3 infection*) OR ((oncological) NEAR/3 (safety))):ab,ti,kw) NOT ('sex reassignment'/mj OR transsexualism/mj OR 'transgender'/mj OR 'male breast cancer'/mj OR (sex-reassignment* OR transsexual* OR transgender* OR male-breast-cancer):ti) NOT ('case report'/de OR (case-report*):ti) NOT ([animals]/lim NOT [humans]/lim) NOT [conference abstract]/lim AND [english]/lim

MEDLINE

(Mastectomy, Subcutaneous/ OR ((Nipples/) AND Mastectomy/ AND Preservation, Biological/) OR (((subcutan*) ADJ3 (mastectom* OR breast-amputat* OR breast-resect* OR mammectom*)) OR ((nipple OR areola) ADJ3 (sparing OR preserv* OR retain* OR retention* OR conservation* OR conserving OR graft*) AND (mastectom* OR breast-amputat* OR breast-resect* OR mammectom*))).ab,ti,kf.) AND (Treatment Outcome/ OR Patient Reported Outcome Measures/ OR Recurrence / OR Mortality/ OR Survival/ OR Reoperation/ OR complication.fs. OR Postoperative Complications/ OR Necrosis/ OR Surgical Wound Infection/ OR Hematoma/ OR Seroma/ OR Prosthesis Failure/ OR Disease-Free Survival/ OR (outcome* OR recorren* OR disease-free OR cancer-free OR surviv* OR mortalit* OR reoperation* OR complication* OR necrosis* OR necrotic* OR hematoma* OR haematoma* OR epidermolys* OR seroma* OR (Prosthesis ADJ3

(loss)) OR ((surgical OR wound) ADJ3 infection*) OR ((oncological) ADJ3 (safety))). ab,ti,kf.) NOT (exp *Sex Reassignment Procedures/ OR * Transsexualism/ OR * Transgender Persons/ OR * Breast Neoplasms, Male/ OR (sex-reassignment* OR transsexual* OR transgender* OR male-breast-cancer).ti.) NOT (case reports/ OR (case-report*).ti.) NOT (exp animals/ NOT humans/) AND english.la.

COCHRANE

((((subcutan*) NEAR/3 (mastectom* OR breast-amputat* OR breast-resect* OR mammectom*)) OR ((nipple OR areola) NEAR/3 (sparing OR preserv* OR retain* OR retention* OR conservation* OR conserving OR graft*) AND (mastectom* OR breast-amputat* OR breast-resect* OR mammectom*))):ab,ti,kw) AND ((outcome* OR recorren* OR disease-free OR cancer-free OR surviv* OR mortalit* OR reoperation* OR complication* OR necrosis* OR necrotic* OR hematoma* OR haematoma* OR epidermolys* OR seroma* OR (Prosthesis NEAR/3 (loss)) OR ((surgical OR wound) NEAR/3 infection*) OR ((oncological) NEAR/3 (safety))):ab,ti,kw)

Funnel plots. Funnel plots were created to display the risk of publication bias for each domain of the Breast-Q.

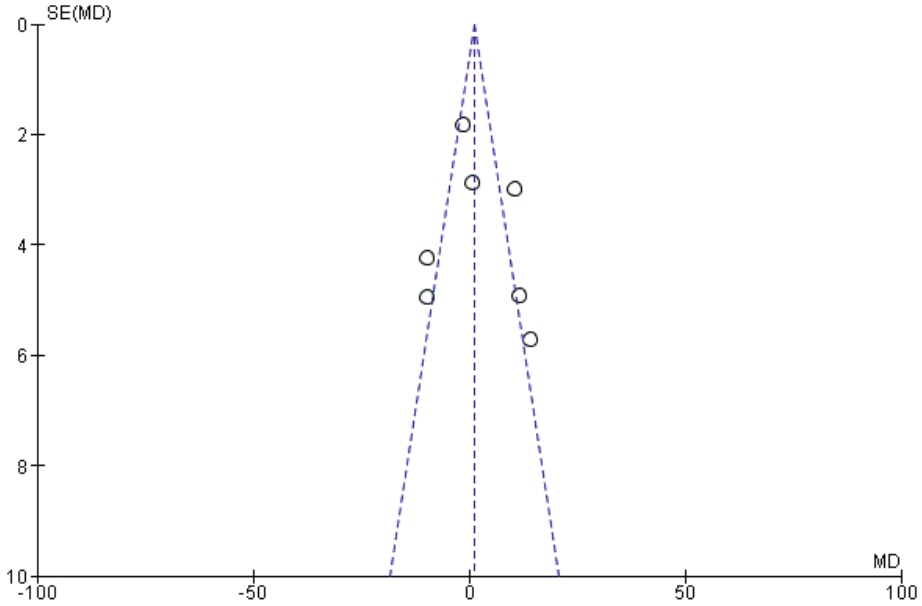


Figure S1. Satisfaction With Breasts

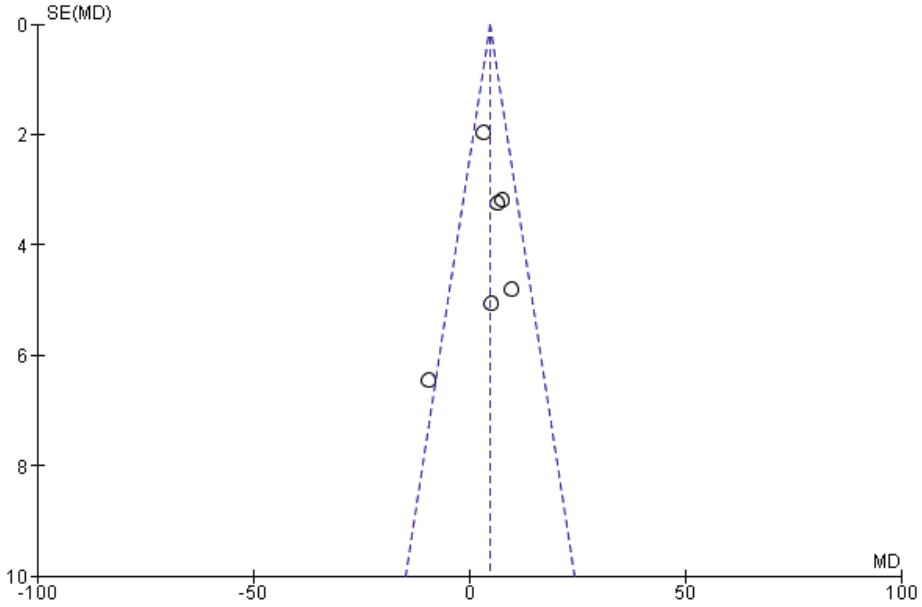


Figure S2. Psychosocial Well-being

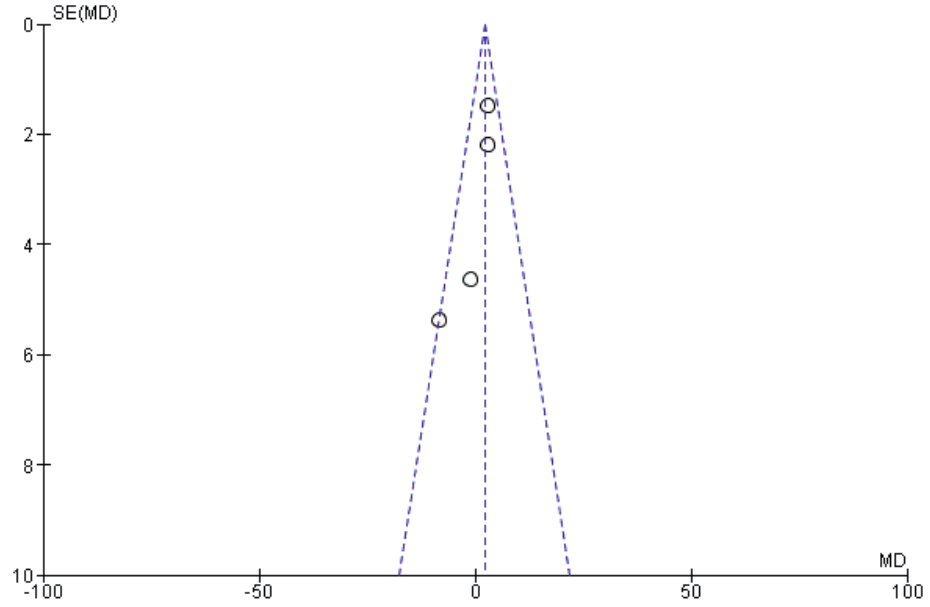


Figure S3. Physical Well-being

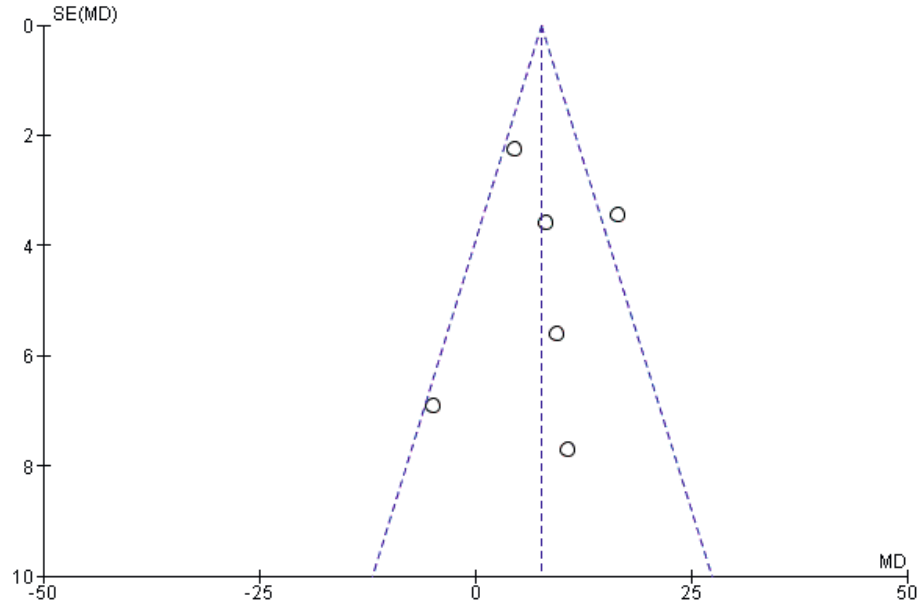


Figure S4. Sexual Well-being

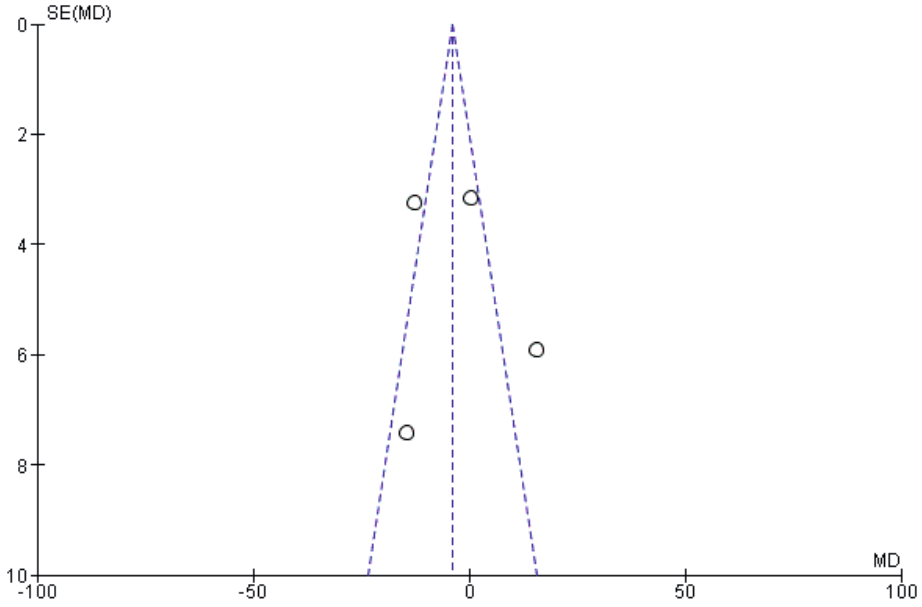


Figure S5. Satisfaction With Outcome

Chapter 6

Quality of Life of Caregivers of Breast Cancer Patients: a cross-sectional evaluation

Marloes E. Clarijs, Arvind Oemrawsingh, Mirelle E.E. Bröker, Cornelis Verhoef, Hester Lingsma, Linetta B. Koppert

Health and Quality of Life Outcomes, Feb 2022

ABSTRACT

Background: The aim of this study was to evaluate the care-related quality of life in caregivers of breast cancer patients, to assess its association with breast cancer patients' health-related quality of life (HRQoL), and to identify its potential predictors.

Methods: Caregivers of breast cancer patients at six and twelve months follow up were identified through the institutes electronic patient reported outcome measurement collection tool. The Care-related Quality of Life Instrument (CarerQoL) was used to obtain CarerQoL utility scores by applying a pre-existent set of Dutch tariffs and the CarerQoL VAS score, which represented the overall happiness of caregivers. The associations between breast cancer patients' EQ-5D-5L and EORTC QLQ-C30 scores and caregivers' CarerQoL scores was determined with Spearman's correlation coefficients. Associations between log transformed CarerQol scores and patient and caregiver characteristics were analyzed with multivariable linear regression analyses.

Results: A total of 116 completed CarerQoL questionnaires were analyzed. Most caregivers were male spouses or partners (81.4%) with a mean age of 55.7 ± 16.4. The median CarerQoL utility score was 92.4/100 and median CarerQoL VAS was 8.0/10. We found weak correlations between CarerQoL VAS scores and patients' EQ-5D-5L utility score (0.301, p=0.002) and EQ VAS score (0.251, p=0.009), and between EORTC QLQ-C30 scores and CarerQol VAS (0.339, p<0.001) and utility score (0.236, p=0.015). There was a negative association between chemotherapy and log-transformed CarerQoL utility score (B=–0.063, p=0.001) and VAS score (B=–0.044, p=0.038) at six months follow-up.

Conclusions: This study provides the first evaluation of the CarerQoL in caregivers of Dutch breast cancer patients. Caregivers' happiness was associated with breast cancer patients' HRQoL. Our results can be used as reference values for future care-related quality of life evaluations.

PLAIN ENGLISH SUMMARY

Breast cancer patients face many difficulties during their cancer journey and often need the support of their caregivers. Despite the fact that successfully providing informal care can have positive effects on caregivers' wellbeing, it may also have a negative impact on their quality of life. Monitoring the quality of life using a standardized questionnaire, such as the CarerQoL questionnaire, may result in early detection of possible quality of life issues. In this study, we evaluated 116 caregivers and found overall high CarerQoL scores. The scores showed a positive relation to the patients' quality of life. Lower CarerQoL scores at six months after surgery were found in caregivers of patients who received chemotherapy. Our research underlines the importance to include caregivers of breast cancer patients in clinical practice, provides reference values for future research, and the results can be used to manage the caregivers' expectations prior to treatment.

BACKGROUND

In the Netherlands, approximately 23% of the population provides informal care for various health indications. [1] Survival rates for breast cancer patients have improved over the last years. [2] Informal care plays an essential part during their diagnostic and treatment process. Having a social network ensures access to informal care which may even positively affect breast cancer outcomes. [3,4]

The term 'informal care' is often interpreted in the context of chronically ill or severely disabled patients in need of daily support and care. However, there is a wide variation in definitions of informal care and it is provided in many forms and in all kinds of situations. Informal care may include support during medical visits, managing wound or drain care, managing medication intake or other activities of daily living, and is performed voluntary by non-professional people without compensation. In addition to physical care, the social-emotional support of caregivers has a positive effect during decision making and processing. [5]

As shortening of hospital-based care and early hospital discharge after breast surgery has been shown to improve clinical outcomes[6,7], support for at-home recovery is often required. Additionally, systemic therapies (e.g. chemotherapy) are increasingly being offered to women with breast cancer, which may cause uncomfortable side effects requiring care at home. Breast cancer patients face many difficult decisions during their cancer journey. These situations illustrate that the burden of caregivers is growing. Caregivers often feel obliged to provide informal care to their relatives. Despite the fact that successfully providing informal care can have positive effects on caregivers' wellbeing, it may also have a negative impact on their lives. [8] Stress or anxiety induced by continuous caregiving

may result in health issues and indirectly affect the care recipient. [9,10] Monitoring the care-related quality of life of caregivers by using a standardized questionnaire may result in early detection of possible financial, relational or health problems. [11,12] Thus, engaging caregivers during the treatment of breast cancer patients and optimizing the communication between provider, patient and caregiver may lead to better patient outcomes and breast cancer care.

The primary aim of the current study was to evaluate the care-related quality of life in caregivers of breast cancer patients using the Care-related Quality of Life Instrument (CarerQoL). The primary outcome was the CarerQoL utility score. The second aim was to correlate the CarerQoL utility and VAS scores with health-related quality of life (HRQoL) scores of breast cancer patients and to identify potential predictors.

METHODS

Recruitment of Study Participants

Two strategies were used for data collection. Firstly, breast cancer patients that reached 6 or 12 months follow-up after surgery and their caregivers were contacted by post including the study's background and aim. Breast cancer patients were requested to discuss study participation with their caregiver and to eventually make a joint decision. If caregivers were willing to be enrolled, an additional recruitment letter was sent to them. After the informed consent form was signed by both caregiver and researcher, participants received a brief explanation and hyperlink to the questionnaire by email. Two reminders were sent to participants who failed to complete the questionnaire after 2 and 4 weeks. Participants who did not complete the questionnaire were not included in the analysis. Secondly, the CarerQol has been disseminated through the Erasmus University Medical Center's electronic patient reported outcome measurement (PROM) collection tool ("Zorgmonitor") in late 2019, as part of standard care for newly diagnosed breast cancer patients and their caregivers. [13] Data from these completed CarerQoL questionnaires at 6 or 12 months postoperatively were also used for analyses. The 6 or 12 months follow up moments for completion of the CarerQoL were already determined in the PROMs collection tool prior to the concept of this study. Therefore, only breast cancer patients at 6 or 12 months post-surgery were approached during the active recruitment to maintain consistency in time since treatment.

Data collection

CarerQoL data were prospectively collected from August 2019 to February 2021 and stored in a "LimeSurvey" database, a secure online survey tool provider. [14] Characteristics of breast cancer patients were retrospectively collected, including age and type of breast surgery. Neo-adjuvant or adjuvant systemic therapy, endocrine therapy and radiotherapy were collected as a dichotomous outcome (yes/no).

Outcome Measurements

CarerQoL

The CarerQoL, developed in 2006[15], is a caregiver reported measure combining a description of the caregiving situation (CarerQol-7D) with a valuation of informal care in terms of quality of life (CarerQol VAS, a visual analogue scale for general happiness). The current study used a Dutch translation of the first version (2006). The translation was performed by the institute for Medical Technology Assessment prior to the conception and design of this study. [16]

The CarerQol-7D comprises seven burden dimensions, of which 5 negative and 2 positive, each with 3 possible answer options. This includes (± indicating positive/negative dimension) fulfillment of care giving (+), relational problems (–), mental health problems (–), problems with combining daily activities (–), financial problems (–), social support (+) and physical health problems (–).Answers on the negative dimensions of the CarerQol-7D receive a value of 0 (a lot), 1 (some) or 2 (no); answers on the positive dimensions receive a value of 0 (no), 1 (some), or 2 (a lot). After summing the values for the seven dimensions, the overall sum score indicates the impact of informal care on caregivers. The higher the score (range 0-14), the better the caregiver experiences providing informal care. The CarerQol utility score is a weighted sum score using utility tariffs, based on preferences of the general public for the different caregiving situations. Dutch tariffs have been published. [17] The CarerQoL VAS score ranges from 0 (worst experience of the caregiver about the informal care situation) to 10 (best experience of the caregiver about the informal care situation). The psychometric properties of the CarerQol have been investigated in previous studies. The CarerQoL demonstrated no floor or ceiling effects, with high feasibility and a reasonable degree of internal consistency in a study that used data of informal carers in Australia. [18] The CarerQoL has been validated in a large heterogeneous cohort of caregivers in the Netherlands, but not for breast cancer caregivers specifically. [19-21] Other validation studies were performed in caregivers of patients with dementia, caregivers of patients in a palliative setting, and in a large cohort of informal caregivers of older persons. [22-24]

Health-related Quality of life in breast cancer patients

HRQoL of breast cancer patients was measured with the cancer specific European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) and the EQ-5D-5L. [25,26] The EORTC QLQ-C30 is a 30-item questionnaire composed of a global quality of life (QoL) subscale, functional subscales and cancer-related symptom scales. Responses to all items were converted to a 0–100 scale. For functional and global QoL scales, higher scores represent a better level of functioning/QoL than lower scores; for symptom-oriented scales, higher scores represent greater symptom severity. [25] The score for global health status was used to compare HRQoL scores in this study. The EORTC QLQ-C30 is validated for oncology clinical research. [27] It has also been validated and found to be responsive in breast cancer patients and therefore commonly used in breast cancer research investigating HRQoL. [25,28,29]

The EQ-5D-5L is a standardized, non-disease specific instrument to describe the HRQoL using five dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression), each with five levels of functioning, ranging from no problems to extreme problems. [26] A quality-adjustment weight or "utility" is a number anchored at 0 and 1, with "perfect health" carrying a weight of 1 and death carrying a weight of 0. In this study, the pre-defined EQ-5D-5L value set of the Netherlands was used to compute utility scores based on a specific health state as indicated by a respondent. [30] The EQ VAS score is related to the EQ-5D-5L and used to rate the overall health on a scale from 0 (worst imaginable health state) to 100 (best imaginable health state). [26] The EQ-5D-5L is widely recognized as a HRQoL measurement tool for cancer patients and has been validated in breast cancer patients. [31,32]

Statistical Analysis

Descriptive statistics, including frequencies and proportions were used to describe patient and caregiver characteristics. Medians and inter-quartile ranges (IQR) were used to present the results of the overall CarerQoL sum scores. All scores were tested for normality with the Kolmogorov-Smirnov and Shapiro-Wilk test. Scores were not normally distributed and natural log transformation was applied to all CarerQoL, EORTC QLQ-C30 and EQ-5D-5L scores. The distribution of responses to the CarerQoL-7D were calculated in percentages for each of the seven dimensions, and for 6 and 12 months post-surgery separately. Univariate and multivariable linear regression analysis were used to assess the association between kind of relationship with patient, patient's age, type of surgery, adjuvant breast cancer treatments and log transformed CarerQoL scores. Because of the high number of male caregivers and the missing values of caregivers' age in most cases, these variables were not included in the regression models. The multivariable linear regression analysis was stratified for time since treatment (6 and 12 months). The effect of the predictors was expressed as beta's and the total amount of variance explained by the models in

R^2. The Spearman's rho was used to describe the correlation of caregivers scores and the EQ VAS and EORTC QLQ-C30 scores of their respective breast cancer patient. The interpretation of the Spearman's correlation coefficients was based on the following standards: 0.1-0.19 (very weak), 0.2-0.39 (weak), 0.4-0.59 (moderate), 0.6-0.79 (strong), and 0.8-1 (very strong). [33] Two-sided p-values < 0.05 were considered statistically significant. Statistical analyses were performed using SPSS, Version 25.0 (IBM Corporation, Armonk, NY, USA) and R, Version 1.2.

Ethical Considerations

Formal approval from the local Medical Ethics Review Committee was waived as the Dutch Medical Research (Human Subjects) Act did not apply to this study.

RESULTS

Study participants

From July till September 2020, a total of 153 breast cancer patients with their respective caregivers received an invitation to participate in the study. Eventually 34 caregivers responded and signed informed consent, of which two caregivers did not complete the questionnaire after sending two reminders, resulting in a response rate of 22%. Additionally, 84 completed CarerQoL questionnaires were identified in the electronic PROMs collection tool ("Zorgmonitor"). Thus, a total of 116 CarerQoL questionnaires from 2019 to 2020 were analyzed; 67 caregivers in the six months and 49 caregivers in the twelve months post-surgery group. A total of 32 caregivers completed the CarerQoL at both follow-up moments.

The majority of caregivers were male (81.4%) and the median age was 60.5 (IQR 25.0) (Table 1a). Most participants were the care recipient's spouse or partner with a family consisting either of a partner alone or a partner and children. Median age of breast cancer patients was 54.0 (IQR 25.0) and 39.7% received chemotherapy, either neo-adjuvant or adjuvant, 58.6% received radiotherapy and 46.6% were treated with endocrine therapy (Table 1b). None of the patients had metastatic disease.

Table 1a and b. Characteristics of caregivers and breast cancer patients (N= 116), 2019-2021.

(a)

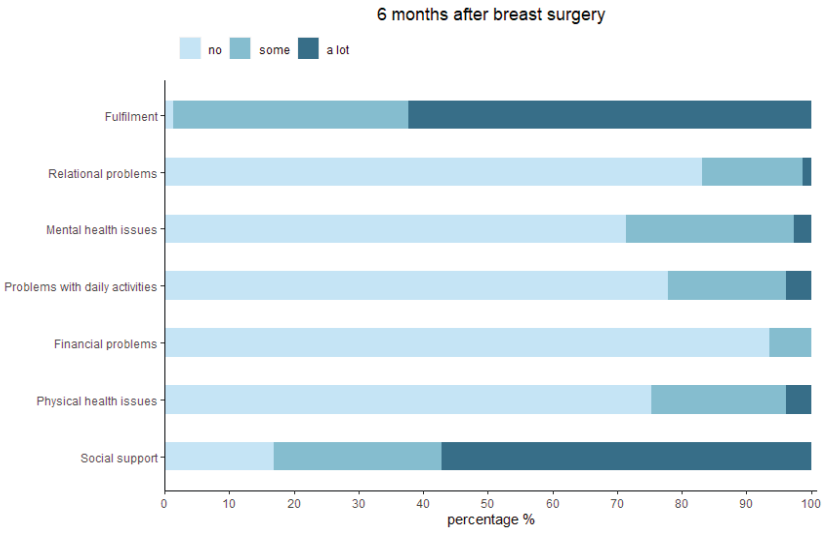
Informal caregivers (N=116)	
	Median (IQR)
Age	60.5 (25.0)
Missing (n=68)	
	N (%)
Gender	
Male	94 (81.0)
Female	18 (15.5)
Unknown	4 (3.4)
Relation with breast cancer patient	
Spouse/Partner	96 (82.7)
Other (parent, child, friend)	20 (15.4)
Family status	
Alone	8 (6.8)
Partner	40 (33.9)
Child(ren)	2 (1.7)
Partner and child(ren)	58 (49.2)
Unknown	10 (8.5)

(b)

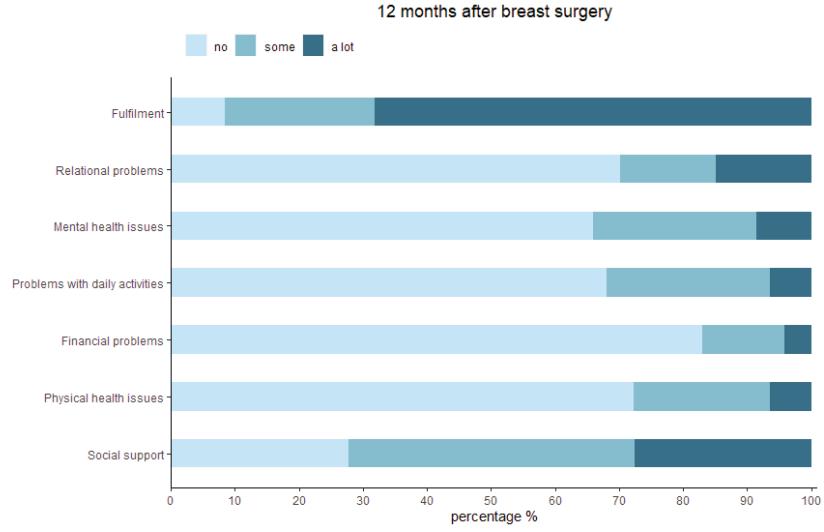
Breast cancer patient or "care recipient" (N = 116)	
	Median (IQR)
Age	54.0 (25)
	N (%)
Type of breast surgery	
Lumpectomy	51 (44.1)
Mastectomy	41 (35.3)
Reconstruction	24 (20.7)
Radiotherapy	68 (58.6)
Endocrine therapy	54 (46.6)
Chemotherapy	46 (39.7)
Neo adjuvant chemotherapy	31 (26.7)
Adjuvant chemotherapy	21 (18.1)

Primary outcome

After applying the Dutch set of tariffs to each dimension of the CarerQoL-7D, the median utility score was 92.4/100 (IQR 14.9). According to the positive dimensions, most caregivers experienced some or a lot of fulfillment (98.5% vs. 91.8%) and support when needed (85.1% vs. 71.4%) at six versus twelve months (Figure 1a and 1b). Median score for the CarerQol VAS score was 8.0/10 (IQR 1.0) (Table 2).



(a)



(b)

Figure 1a and 1b. Distribution of responses to the CarerQol-7D in caregivers of breast cancer patients after 6 and 12 months follow-up (n= 67 and n=49, respectively).

Table 2. Median CarerQoL, EQ-5D-5L and EORTC QLQ-C30 scores (N=116).

	Median (IQR)	6 months follow-up (N=67)	12 months follow-up (N=49)
Informal caregivers			
CarerQoL Utility Score	92.4 (14.9)	92.3 (14.7)	93.6 (16.6)
CarerQoL VAS Score	8.0 (1.0)	7.0 (1.0)	8.0 (1.0)
Breast cancer patients or "care recipient"			
EQ-5D-5L Utility Score	0.835 (0.137)	0.818 (0.144)	0.883 (0.156)
EQ VAS Score	80 (25)	80 (20)	80 (26)
EORTC QLQ-C30 Global health status	83.3 (25)	75 (16.66)	83.3 (16.7)

CarerQoL = Carer Quality of Life, VAS = Visual Analogue Scale, IQR = interquartile range

Correlations between Caregivers' and Breast Cancer Patients' Quality of Life Scores

The CarerQoL VAS score was positively but weakly correlated with the patients' EQ-5D-5L utility score (0.301, p = 0.002), EQ VAS score (0.251, p = 0.009) and EORTC QLQ-C30 global health status (0.339, p < 0.001). The CarerQoL utility score showed a weak correlation with patient's EORTC QLQ-C30 global health status (0.236, p = 0.015). See Table 3.

Table 3. Spearman's correlation coefficients (N = 116).

	CarerQol VAS Score	**CarerQoL utility score**	**EQ VAS score**	**EQ-5D-5L utility score**	**EORTC QLQ-C30 Global health status**
CarerQoL VAS Score		0.520 (p <0.001)*	0.251 (p = 0.009)*	0.301 (p = 0.002)*	0.339 (p <0.001)*
CarerQoL utility Score	0.520 (p <0.001)*		0.023 (p = 0.810)	0.148 (p = 0.126)	0.236 (p = 0.015)*
EQ VAS score	0.251 (p = 0.009)*	0.023 (p = 0.810)		0.678 (p<0.001)*	0.608 (p<0.001)*
EQ-5D-5L Utility score	0.301 (p = 0.002)*	0.148 (p = 0.126)	0.678 (p<0.001)*		0.556 (p<0.001)*

CarerQoL = Carer Quality of Life, VAS = Visual Analogue Scale. EQ-5D-5L utility and EQ VAS scores and EORTC QLQ-C30 Global health status of breast cancer patients.
**Correlation is significant at the level 0.05 (two-tailed).*

Univariable and Multivariable Regression Analyses

Data of 116 caregivers at six and twelve months follow up was included in the univariable regression analysis, in which four caregiver characteristics and five patient characteristics were analyzed. Relationship between caregiver and breast cancer patient (partner/spouse versus other) was positively related with caregivers' log transformed CarerQoL utility score

(B = 0.106, p = 0.034). Chemotherapy was associated with the CarerQoL utility score (B = -0.097, p = 0.019) and to a lesser extent with the CarerQoL VAS score (B = 0.036, p = 0.125). This was also the case for the association between age of breast cancer patient and CarerQoL utility score (B= 0.001, p = 0.034) and CarerQoL VAS score (B=0.002, p= 0.078).

The multivariable regression analysis revealed chemotherapy as a significant negative predictor for the log transformed CarerQoL utility score (B = -0.063, p = 0.001) and log transformed CarerQoL VAS score (B = -0.044, p = 0.038) at six months follow-up. Adjusted R^2 for the models was 0.188 and 0.165 respectively. At twelve months follow up, results for the log transformed CarerQoL utility score were B = -0.010 (p = 0.758, Adjusted R^2 =0.126) and B = -0.042 (p = 0.601, Adjusted R^2 = -0.121) for the CarerQoL VAS score (Table 4).

Table 4a and b. Multivariable linear regression coefficients for the log-transformed CarerQoL utility and VAS score after 6 and 12 months follow-up.

(a) T = 6 months

	CarerQoL utility Score			**CarerQoL VAS score**		
	Beta	**Std. error**	**Sig.**	**Beta**	**Std. error**	**Sig.**
Age breast cancer patient	-7.289E-5	0.001	0.924	0.001	0.001	0.092
Relationship between caregiver and breast cancer patient	0.020	0.018	0.278	-0.008	0.021	0.718
Chemotherapy	**-0.063**	**0.018**	**0.001***	**-0.044**	**0.020**	**0.038***
Radiotherapy	0.036	0.030	0.242	0.058	0.035	0.1
Adjuvant endocrine therapy	-0.002	0.017	0.920	0.019	0.019	0.334
Type of surgery						
Lumpectomy	Ref			Ref		
Mastectomy	0.044	0.026	0.091	0.028	0.030	0.352
Reconstruction	0.035	0.037	0.341	0.039	0.042	0.360

**Significance at the level 0.05 (two-tailed).*

(b) T = 12 months

	CarerQoL Utility Score			**CarerQoL VAS score**		
	Beta	**Std. error**	**Sig.**	**Beta**	**Std. error**	**Sig.**
Age breast cancer patient	-3,433E-5	0.001	0.977	-0.001	0.003	0.778
Relationship between caregiver and breast cancer patient	-0.002	0.028	0.954	-0.031	0.070	0.656
Chemotherapy	-0.010	0.031	0.758	-0.042	0.079	0.601
Radiotherapy	-0.061	0.051	0.237	-0.091	0.128	0.484
Adjuvant endocrine therapy	-0.009	0.028	0.735	0.018	0.070	0.797
Type of surgery						
Lumpectomy	Ref			Ref		
Mastectomy	-0.032	0.046	0.701	-0.011	0.115	0.925
Reconstruction	-0.033	0.062	0.591	-0.117	0.155	0.455

**Significance at the level 0.05 (two-tailed).*

DISCUSSION

While much effort is generally expended on providing social support for breast cancer patients during treatment, little attention has been paid to the needs of the caregiver in daily practice. The primary aim of this study was to evaluate the quality of life of caregivers of breast cancer patients using the CarerQoL utility and VAS score. In addition, the association with breast cancer patients' HRQoL and potential predictors of the caregivers' quality of life were evaluated.

The results of this survey indicates that the overall care-related quality of life of caregivers is good, based on a median CarerQoL utility score of 87.0/100 and VAS score of 8.0/10 . The caregivers of breast cancer patients in our cohort formed a homogeneous group, as most caregivers were male spouses or partners. The role of caregiving may be experienced differently between spouses and non-spouses (e.g. close friends or relatives).[34] Worldwide, caregivers of cancer patients are most often females, experiencing higher levels of caregiving burden. On the contrary, levels of distress may be determined by gender, with females having higher distress levels regardless of their role (e.g. patient or caregiver).[35] Our results suggest that caregiving does not completely disrupt caregivers' lives and relationships with breast cancer patients, but could affect the seven dimensions of the social environment in some cases. The question rises to what extent changes in scores are considered to be clinically meaningful. Minimal clinically important differences (MCID) indicate the smallest change in PROM scores which subjects perceive to be important or beneficial, and which would justify an intervention or change in management.[36] MCIDs for the CarerQoL or measures to determine MCIDs for caregivers have not been described previously. The CarerQoL was initially developed for economic evaluations of healthcare, as health care interventions impact both patients and the caregiver burden. When the total societal perspective is evaluated in such cost-effectiveness studies, the optimal approach would be to also include informal care outcomes. However, this may be the most universal questionnaire to evaluate the care-related quality of life in caregivers of cancer patients.

One of the strengths of this study is that the caregivers' CarerQol scores were correlated to HRQoL scores of breast cancer patients. A positive but weak to moderate correlation was observed between the CarerQoL scores of caregivers and the HRQoL scores of breast cancer patients. It was assumed that care-related quality of life scores of caregivers could reflect the HRQoL of breast cancer patients and vice versa. In caregiving for other diseases, such as Alzheimer or Parkinson's disease, the caregiver burden was inversely associated with the quality of life of patients.[37,38] However, our results suggest that although the HRQoL of breast cancer patients diminishes over time, this does not directly impact the care-related quality of life of caregivers. Such observations can possibly be used to manage the caregivers' expectations prior to treatment.

Another strength is using the CarerQoL Instrument to evaluate the care-related quality of life in caregivers of breast cancer patients, as this has never been described in the literature before. Translating the results of previous caregiver-related studies into daily practice remains challenging. For example, outcomes based on a review of Lopes et al. are only useful to a certain extent as objective measurements are lacking. [34] In three other studies, the psychosocial impact of caregiving in women with advanced breast cancer in a palliative setting or recurrent disease was described. [39-41] Overall, they conclude that patient's physical and emotional factors can predict the caregivers' quality of life. According to the Short Form 36 questionnaire, better quality of life scores in patients and caregivers were found if the caregiver was spouse. Formal comparisons with our results was difficult, as this current cohort did not include metastasized or recurrent breast cancer and one study did not use validated questionnaires. The breast cancer patients that were linked to the caregivers in this study made up a small and heterogeneous group according to the treatment characteristics. Treatment strategies for breast cancers have different symptom burden and duration of therapy, which may have an impact on the intensity of care provided by caregivers. This may also influence the tasks and medical support carried out by caregivers. Our results suggest that chemotherapy in breast cancer patients was negatively associated with quality of life scores of caregivers, but previous research found inconsistent results. [42-44] According to a study of Nijboer et al., numerous background characteristics of the caregiver may influence the quality of life, including age, gender, living situation, socioeconomic status and type of relationship between care recipient and caregiver. [45] Another study investigated potential determinants that influence the quality of life of Chinese caregivers of specifically breast cancer patients. Quality of life was measured with the Short Form-36 questionnaire. Although they found several significant associated predictors (income, educational level and symptom severity) which were unfortunately not included in our analyses, similar non-significant correlations for overlapping variables were found. [42] As chemotherapy may contribute to symptom severity, this may explain the negative association with our CarerQoL scores at six months follow up and that the effect on quality of life is normalized after one year. The relationship with breast cancer patients was not investigated, as only spouses were included in their study.

Study limitations

Several limitations were identified in this study. Firstly, although several reminders were sent to participants to complete the questionnaire, one third responded. The low response rate may be due to the fact that caregivers did not directly identify themselves as such. As previously mentioned, caregivers often experience the provision of informal care as an obligation to their family, and something that goes without saying. This may have resulted in some selection bias. On the other side, by disseminating the survey directly to caregivers, we maybe have reached more persons lending informal care who would normally not

define themselves as caregivers, for instance because their burden is low. The suboptimal response rate could have influenced the normal distribution of CarerQoL scores, for which log transformation was applied. It is possible that the caregivers with a low burden and relatively good quality of life may be more likely to complete a survey. However, caregivers that have a higher burden may be more self-conscious of their care-related problems, recognize the importance of such research, and are willing to participate in a survey.

Secondly, the lack of socio-demographic characteristics of caregivers prevents to precisely describe the cohort that was studied. Educational level and current work situation can be important explanatory factors of the care-related quality of life. Such variables were only registered for those caregivers that completed the questionnaire after active recruitment and not during standard breast cancer care. Due to the low response rate, these data were not sufficient enough to use in the analysis.

Lastly, the questionnaires were only administered to caregivers of patients of a tertiary hospital with a specialized academic breast cancer center in which more younger women or advanced stages of breast cancer are treated. Therefore, the results may not be generalizable to patients of general hospitals.

CLINICAL IMPLICATIONS

Results highlight the need to include caregivers of breast cancer patients in clinical practice, and provide reference values in a predefined cohort of caregivers of breast cancer patients. The CarerQoL has already been implemented in the institutes electronic PROM collection tool since 2019. Providing feedback and discussing questionnaire outcomes is important to maintain adherence and to act upon if quality of life is diminishing. However, physicians usually do not have a doctor-patient relationship with the caregiver. An implication for clinical practice could be exchanging the CarerQoL outcomes with general practitioners. They could evaluate the quality of life scores of caregivers but also provide additional support or care for the caregiver if needed. In addition, caregivers could benefit from self-management tasks in managing their own quality of life. The CarerQoL may be a suitable tool in optimizing self-management to prevent caregiver-related health issues.

CONCLUSIONS

This is the first study that evaluated the CarerQoL Instrument in caregivers of breast cancer patients. Most caregivers felt happy as they were satisfied and experienced fulfillment in their role as caregiver. A minority of the caregivers indicated some problems in their relationship, mental and physical health, finances, or daily activities. Caregivers' happiness

was associated with breast cancer patients' HRQoL. Chemotherapy was a negative predictor for logtransformed CarerQoL utility and VAS scores as six months follow-up. Results of this study can be used as a reference for future quality of life evaluations in caregivers of breast cancer patients.

FERENCES

1. Schellingerhout R. The informal caregiver. In J Timmermans (Ed), Informal care Care of and to informal carers. 2003:33–57.
2. van der Meer DJ, Kramer I, van Maaren MC, et al. Comprehensive trends in incidence, treatment, survival and mortality of first primary invasive breast cancer stratified by age, stage and receptor subtype in the Netherlands between 1989 and 2017. Int J Cancer. May 1 2021;148(9):2289-2303.
3. House JS, Landis KR, Umberson D. Social relationships and health. Science. Jul 29 1988;241(4865):540-5.
4. Kroenke CH, Kubzansky LD, Schernhammer ES, Holmes MD, Kawachi I. Social networks, social support, and survival after breast cancer diagnosis. J Clin Oncol. Mar 1 2006;24(7):1105-11.
5. Maly RC, Umezawa Y, Ratliff CT, Leake B. Racial/ethnic group differences in treatment decision-making and treatment received among older breast carcinoma patients. Cancer. Feb 15 2006;106(4):957-65.
6. Bundred N, Maguire P, Reynolds J, et al. Randomised controlled trial of effects of early discharge after surgery for breast cancer. BMJ. Nov 7 1998;317(7168):1275-9.
7. Wells M, Harrow A, Donnan P, et al. Patient, carer and health service outcomes of nurse-led early discharge after breast cancer surgery: a randomised controlled trial. Br J Cancer. Aug 16 2004;91(4):651-8.
8. Schulz R, Newsom J, Mittelmark M, Burton L, Hirsch C, Jackson S. Health effects of caregiving: the caregiver health effects study: an ancillary study of the Cardiovascular Health Study. Ann Behav Med. Spring 1997;19(2):110-6.
9. van Ryn M, Sanders S, Kahn K, et al. Objective burden, resources, and other stressors among informal cancer caregivers: a hidden quality issue? Psychooncology. Jan 2011;20(1):44-52.
10. Goren A, Gilloteau I, Lees M, DaCosta Dibonaventura M. Quantifying the burden of informal caregiving for patients with cancer in Europe. Support Care Cancer. Jun 2014;22(6):1637-46.
11. Lefranc A, Perol D, Plantier M, Chatelain P, de Rohan-Chabot H, Schell M. Assessment of informal caregiver's needs by self-administered instruments: a literature review. European Journal of Public Health. 10 01 2017;27(5):796-801.
12. Deeken JF, Taylor KL, Mangan P, Yabroff KR, Ingham JM. Care for the caregivers: a review of self-report instruments developed to measure the burden, needs, and quality of life of informal caregivers. J Pain Symptom Manage. Oct 2003;26(4):922-53.
13. GemsTracker. Updated 17-09-2020. Accessed 17-09-2020, 2020. https://gemstracker.org/
14. LimeSurvey. Updated 21-10-2020. Accessed 21-10-2020, 2020. https://www.limesurvey.org/
15. Brouwer WB, van Exel NJ, van Gorp B, Redekop WK. The CarerQol instrument: a new instrument to measure care-related quality of life of informal caregivers for use in economic evaluations. Qual Life Res. Aug 2006;15(6):1005-21.
16. Hoefman RJ VEN, Brouwer WBF. iVICQ. iMTA Valuation of Informal Care Questionnaire. Updated 17-09-2020. Accessed 17-09-2020, https://www.imta.nl/carerqol/]
17. Hoefman RJ, van Exel J, Rose JM, van de Wetering EJ, Brouwer WB. A discrete choice experiment to obtain a tariff for valuing informal care situations measured with the CarerQol instrument. Medical Decision Making. 01 2014;34(1):84-96.
18. McCaffrey N, Bucholc J, Rand S, et al. Head-to-Head Comparison of the Psychometric Properties of 3 Carer-Related Preference-Based Instruments. Value Health. Nov 2020;23(11):1477-1488.
19. Hoefman RJ, van Exel J, Brouwer WB. Measuring the impact of caregiving on informal carers: a construct validation study of the CarerQol instrument. Health Qual Life Outcomes. Oct 21 2013;11:173.

20. Hoefman RJ, van Exel NJ, Looren de Jong S, Redekop WK, Brouwer WB. A new test of the construct validity of the CarerQol instrument: measuring the impact of informal care giving. Qual Life Res. Aug 2011;20(6):875-87.
21. Hoefman RJ, van Exel NJ, Foets M, Brouwer WB. Sustained informal care: the feasibility, construct validity and test-retest reliability of the CarerQol-instrument to measure the impact of informal care in long-term care. Aging Ment Health. Nov 2011;15(8):1018-27.
22. Voormolen DC, van Exel J, Brouwer W, et al. A validation study of the CarerQol instrument in informal caregivers of people with dementia from eight European countries. Qual Life Res. Feb 2021;30(2):577-588.
23. Hoefman R, Al-Janabi H, McCaffrey N, Currow D, Ratcliffe J. Measuring caregiver outcomes in palliative care: a construct validation study of two instruments for use in economic evaluations. Qual Life Res. May 2015;24(5):1255-73.
24. Lutomski JE, van Exel NJ, Kempen GI, et al. Validation of the Care-Related Quality of Life Instrument in different study settings: findings from The Older Persons and Informal Caregivers Survey Minimum DataSet (TOPICS-MDS). Qual Life Res. May 2015;24(5):1281-93.
25. McLachlan SA, Devins GM, Goodwin PJ. Validation of the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (QLQ-C30) as a measure of psychosocial function in breast cancer patients. Eur J Cancer. Mar 1998;34(4):510-7.
26. Herdman M, Gudex C, Lloyd A, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). Qual Life Res. Dec 2011;20(10):1727-36.
27. Bottomley A, Aaronson NK, European Organisation for R, Treatment of C. International perspective on health-related quality-of-life research in cancer clinical trials: the European Organisation for Research and Treatment of Cancer experience. J Clin Oncol. Nov 10 2007;25(32):5082-6.
28. Osoba D, Zee B, Pater J, Warr D, Kaizer L, Latreille J. Psychometric properties and responsiveness of the EORTC quality of Life Questionnaire (QLQ-C30) in patients with breast, ovarian and lung cancer. Qual Life Res. Oct 1994;3(5):353-64.
29. Michels FA, Latorre Mdo R, Maciel Mdo S. Validity, reliability and understanding of the EORTC-C30 and EORTC-BR23, quality of life questionnaires specific for breast cancer. Rev Bras Epidemiol. Jun 2013;16(2):352-63.
30. Versteegh M VK, Evers S, de Wit, GA, Prenger, R, Stolk E. Dutch Tariff for the Five-Level Version of EQ-5D. Value Health. Jun 2016;19(4):343-52.
31. Lee CF, Ng R, Luo N, et al. The English and Chinese versions of the five-level EuroQoL Group's five-dimension questionnaire (EQ-5D) were valid and reliable and provided comparable scores in Asian breast cancer patients. Support Care Cancer. Jan 2013;21(1):201-9.
32. Pickard AS, De Leon MC, Kohlmann T, Cella D, Rosenbloom S. Psychometric comparison of the standard EQ-5D to a 5 level version in cancer patients. Med Care. Mar 2007;45(3):259-63.
33. Dancey CP, Reidy J. Statistics without maths for psychology. Pearson/Prentice Hall; 2007.
34. Lopes VB, Lobo APA, Da Silva Junior GB, Melo AK, Lamboglia CG, Silva C. The experience of male spouses in the context of breast cancer: a systematic review of the literature. Psychol Health Med. Jan 2018;23(1):89-98.
35. Hagedoorn M, Sanderman R, Bolks HN, Tuinstra J, Coyne JC. Distress in couples coping with cancer: a meta-analysis and critical review of role and gender effects. Psychol Bull. Jan 2008;134(1):1-30.
36. Beaton DE, Boers M, Wells GA. Many faces of the minimal clinically important difference (MCID): a literature review and directions for future research. Curr Opin Rheumatol. Mar 2002;14(2):109-14.

37. Schrag A, Hovris A, Morley D, Quinn N, Jahanshahi M. Caregiver-burden in parkinson's disease is closely associated with psychiatric symptoms, falls, and disability. Parkinsonism Relat Disord. Jan 2006;12(1):35-41.
38. Conde-Sala JL, Garre-Olmo J, Turro-Garriga O, Lopez-Pousa S, Vilalta-Franch J. Factors related to perceived quality of life in patients with Alzheimer's disease: the patient's perception compared with that of caregivers. Int J Geriatr Psychiatry. Jun 2009;24(6):585-94.
39. Grunfeld E, Coyle D, Whelan T, et al. Family caregiver burden: results of a longitudinal study of breast cancer patients and their principal caregivers. CMAJ. Jun 8 2004;170(12):1795-801.
40. Coristine M, Crooks D, Grunfeld E, Stonebridge C, Christie A. Caregiving for women with advanced breast cancer. Psychooncology. Oct-Nov 2003;12(7):709-19.
41. Northouse LL, Mood D, Kershaw T, et al. Quality of life of women with recurrent breast cancer and their family members. J Clin Oncol. Oct 01 2002;20(19):4050-64.
42. Zhu P, Fu JF, Wang B, et al. Quality of life of male spouse caregivers for breast cancer patients in China. Asian Pac J Cancer Prev. 2014;15(10):4181-5.
43. Siegel K, Raveis VH, Mor V, Houts P. The relationship of spousal caregiver burden to patient disease and treatment-related conditions. Ann Oncol. Jul 1991;2(7):511-6.
44. Shaffer KM, Jacobs JM, Nipp RD, et al. Mental and physical health correlates among family caregivers of patients with newly-diagnosed incurable cancer: a hierarchical linear regression analysis. Support Care Cancer. Mar 2017;25(3):965-971.
45. Nijboer C, Triemstra M, Tempelaar R, Sanderman R, van den Bos GA. Determinants of caregiving experiences and mental health of partners of cancer patients. Cancer. Aug 15 1999;86(4):577-88.

PART II

A WAY TOWARDS PREDICTING BREAST CANCER OUTCOMES

Chapter 7

Three-dimensional breast ultrasonography and virtual reality imaging; a sufficient replacement for MRI in neo-adjuvant chemotherapy tumor-response evaluation? Results of the RESPONDER II trial

Marloes E. Clarijs, Noelle J.M.C. Vrancken Peeters, Anton H.J. Koning, Carolien H.M. van Deurzen, Agnes Jager, Cecile de Monye, Mirelle Bröker, Cornelis Verhoef, Laurentine S.E. van Egdom, Linetta B. Koppert

European Radiology, under review

ABSTRACT

Background*:* Neoadjuvant chemotherapy (NAC) can lead to disease down staging in patients with invasive breast cancer and MRI is the golden standard for tumor response evaluation. The aim of this study is to assess the accuracy of three-dimensional (3-D) ultrasounds obtained with the Automated Breast Volume Scanner (ABVS) for the tumor diameter and volume response evaluations during and after NAC compared to MRI and final histopathological examination.

Method*:* A multi-center, prospective, observational study was conducted in the Academic Breast Cancer Centre Rotterdam in women with histologically proven invasive breast cancer receiving NAC. The V-Scope software was used for the 3-D visualization of ABVS and MRI images on an in-house developed desktop Virtual Reality system. Tumor response was evaluated according to longest diameter and volume measurements pre-, mid- and post-NAC. The intraclass correlation coefficient (ICC) reflected the correlation between tumor diameter and volume response on (3-D) ABVS and (3-D) MRI. Absolute concordance between post-NAC response and histopathological evaluation was evaluated.

Results*:* Analyses included 96 patients for pre- and mid-NAC evaluations, and 57 patients for post-NAC evaluation. MRI and ABVS showed absolute concordance in 66% for the mid-NAC and 63% for the post-NAC evaluation. A 'good' significant correlation between ABVS and MRI was found for the difference in longest diameter measurement for the first (ICC 0.64 (95%CI 0.51-0.75)) and second (ICC 0.68 (95%CI 0.50-0.80)) response evaluation. For volume measurements, 'good' and 'excellent' significant correlations for the first (ICC 0.69 (95% CI 0.57-0.78) and second (ICC 0.98 (95% CI 0.96-0.99)) response evaluation were found. Post-NAC ABVS and MRI showed absolute concordance with histopathologic response in 71% versus 50%, respectively. Patients' acceptability ratings were higher for the ABVS compared to MRI.

Conclusion*:* ABVS showed good to excellent correlations with the MRI tumor diameter and volume response in breast cancer patients receiving NAC. Because the ABVS is advantageous over MRI in terms of costs, ease and acceptability, it should be considered as a sufficient alternative.

INTRODUCTION

Preoperative or neoadjuvant chemotherapy (NAC) is an option for patients with early-stage or locally advanced breast cancer, and a significant increase in the use of NAC has been observed in the Netherlands.[1] NAC can lead to disease down staging and tumor size reduction. As a result, this will make patients eligible for breast conserving surgery and safely diminish the operated excision volume during surgery.[2-4] Being able to assess the susceptibility of the tumor to systemic therapy in vivo during NAC allows for necessary adjustments in treatment regimen.

Currently, the most accurate imaging modality to assess the response evaluation during NAC is Magnetic Resonance Imaging (MRI). However, both over- and underestimation have been found in residual tumor on breast MRI compared to final histopathological evaluation of the tumor.[5-7] For every radiographic technique, the tumor response during and after NAC is evaluated by an unidimensional method that assesses the longest diameter of the target lesion(s), as described in the 'Response Evaluation Criteria in Solid Tumours' (RECIST).[8] With the development of three-dimensional image modalities, volume measurements showed excellent agreement with real tumor volume without making assumptions on shape.[9,10] In studies using 3-D MRI images, the tumor *volume* response evaluations were more accurate to histopathologic findings and predicting pathologic complete response (pCR) compared to *diameter* response.[10-12] Achieving pCR after NAC represents better disease free survival and overall survival, depending on molecular subtype.[13,14] An adequate response evaluation is therefore pivotal, and requires standardized and objective measurement techniques with high reproducibility.

In clinical breast cancer care, there is a need for an easily available radiographic technique that is faster, less expensive, patient friendly, able to do tumor *volume* response evaluations in addition to the longest *diameter* response during NAC together with equal performance as MRI. The Automated Breast Volume Scanner (ABVS) is an operator-independent sonographic technique, which provides standardized, automated, and reproducible whole breast ultrasounds.[15] The ABVS has the ability to reconstruct 3-D images and consequently tumor volume response measurements in addition to the longest diameter. The ABVS is proven to be superior compared to 2-D ultrasound in predicting histological tumor size.[16,17] A previous feasibility study was conducted in our institute (RESPONDER I trial, NTR6799) to evaluate the accuracy of the ABVS.[18] The ABVS showed a good correlation with MRI tumor response evaluation during NAC, an excellent intra- and inter-observer agreement, and high patient satisfaction. Due to the small sample size, no conclusions could be drawn regarding the concordance with final histopathological evaluation. Because of the pilot design and the missing post-NAC ABVS evaluations in the majority of the patients, the inclusion was prolonged and results will be discussed in this current study. Additionally,

post-NAC (3-D) ABVS scans were performed in all patients to evaluate the accuracy of ABVS in the post-NAC response and the concordance with histopathological evaluation.

METHODS

Patient population

Patients eligible for this multicenter study were prospectively included at the Academic Breast Cancer Centre Rotterdam (Erasmus MC Cancer Institute) and Franciscus Gasthuis & Vlietland Hospital in Rotterdam, the Netherlands. Data was collected from August 2017 until December 2022. The inclusion criteria were 1) women with histologically proven invasive breast cancer, 2) above the age of 18, and 3) scheduled for NAC. Patients with a clinical T4 stage (tumor of any size growing into the chest wall or skin) were identified as non-measurable and excluded. Tumors growing in non-breast tissue are sonographically difficult to distinguish. In some cases, the acoustic shadow of the nipple on the ABVS prevents to visualize retro-mammilar lesions precisely enough. Retro-mammilar lesions were excluded if this complicated the diameter and volume measurements. Lesions were classified according to the TNM classification system (7th edition).[19] Tumor differentiation grade was assessed by using the pre-NAC biopsies. Surrogate subtypes were defined according to the St. Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer.[20] The cut-off point for estrogen receptor and progesterone receptor positivity was defined as ≥ 10% positive cells[21], and Her2 expression positivity was defined according to the international guidelines.[22]

Study procedures

Treatment

All patients received NAC according to the institute's standard protocols, based on the national guidelines. After NAC, patients underwent either breast-conserving surgery, mastectomy with or without (immediate or delayed) reconstruction, or an oncoplastic reconstruction of the breast.

V-scope software for longest diameter and volume measurements

The V-Scope software was used for the 3-D visualization of ABVS and MRI images on a desktop system. This driving V-scope software was developed by the department of Bioinformatics, Erasmus MC, Rotterdam. The breast is projected as a hologram and can be viewed with special 3-D glasses on a dedicated workstation. The specific image can be sized, turned and cropped, and the targeted lesion can be selected using a wireless joystick.[23] Longest diameter measurements were obtained by measuring the distance

between two specified points in a 3-D space, using digital rulers. Specific thresholds for the grey-level of the voxels were chosen to calculate the volume based on a segmentation algorithm. More detailed information about the diameter and volume measurements using the V-Scope desktop system can be found elsewhere.[23,24]

MRI and three-dimensional MRI of the breast

The routinely diagnostic breast MRI was performed with a 1.5 Tesla system (Siemens Healthineers – Erlangen, Germany) or a 1.5 Tesla (Philips Healthcare – Best, the Netherlands). The MRI was performed according to standard protocol, including dynamic contrast-enhanced images. All patients were positioned in prone position with the breast pending in a dedicated double breast surface coil. Premenopausal women were scanned on day 5–15 of the menstrual cycle. Pre-contrast injection imaging protocol consisted of a low resolution localizing sequence, a transversal T2 weighted fat-suppressed sequence (TE/TR 42/67000, FOV 34 cm, slice thickness 5.0 mm, matrix 32×224). VIBRANT (T1) transversal 3-D sequences were performed (TE/TR 1.0/34, FOV 34 cm, slice thickness 2.2 mm, flip angle 10°, matrix 388×388) pre- and post-contrast injection (using 7.5 cc Gadovist or 15 cc ProHance, 2cc/s), followed by a final post contrast sagittal VIBRANT sequence (TE/TR 1.0/34, FOV 34 cm, slice thickness 3 mm, flip angle 10°, matrix 388×388). Subtraction images were obtained with the use of a software subtraction function. The longest diameter was single measured by experienced breast radiologists on the dynamic T1 sequences using digital rulers on a breast MRI workstation. The V-scope software was used for the 3-D visualization of the MRI images, after which the longest diameter and volume measurements were assessed.

ABVS and three-dimensional ultrasound of the breast

The ABVS (Siemens ACUSON S2000TM) is designed to acquire ultrasound images using a linear transducer that scans the entire breast in an automated fashion.[15] The transducer scans volume slabs while acquiring 0.5mm thick images in the transverse plane. The resulting ultrasound can be evaluated in multi imaging-planes simultaneously (i.e. axial, coronal and sagittal plane) and viewed repeatedly off-line. The V-scope software was used to visualize the ABVS images in 3-D, after which volume measurements were done. Three researchers (MC, NVP and LE) performed the ABVS. Because of an excellent intra-observer and inter-observer agreement for the mid-NAC and post-NAC response evaluation found in the RESPONDER I trial, two researchers (MC and LE) individually measured the tumor diameter and volume once.[18]

Response evaluation

Pre-defined time points for the response evaluations were used according to standard care. This included a baseline assessment pre-treatment (pre-NAC), the first response evalua-

tion after three or four courses depending on the chemotherapy schedule (mid-NAC), and a second evaluation pre-operatively if applicable (post-NAC). Every patient was intended to receive a third ABVS after finishing NAC, regardless the fact whether a post-NAC MRI was performed. In case of complete response on the mid-NAC MRI, the post-NAC MRI was omitted. Response was calculated as percentage difference compared to baseline (pre-NAC) measurements, and categorized according to the RECIST criteria for longest diameter. Changes in the RECIST criteria according to the first (mid-NAC vs. pre-NAC) and second (post-NAC vs. pre-NAC) response evaluations were compared between ABVS and MRI. Additionally, response was evaluated by comparing the tumor volumes using both the 3-D MRI and 3-D ABVS. Histopathologic response evaluation was performed by an experienced breast pathologist, using the scoring system as described by Pinder et al.[25] This was compared with the second (RECIST) response evaluation based on the post-NAC ABVS and MRI.

Acceptability

Patient satisfaction was expressed as an acceptability score for both the breast MRI and ABVS, reflecting the total experience during examination. Acceptability was scored using a 5-point Likert Scale in which 5 represents 'high acceptability' to 1 being 'not acceptable' (Supplementary Figure 1). The questionnaire was completed by patients after the first study visit.

Data collection

Electronic patient files were viewed to collect baseline characteristics of all patients, including age, tumor laterality, morphology (type of carcinoma), histopathology (tumor type, size, grade, TNM classification, and response evaluation), disease stage and treatment characteristics. Both longest diameter and tumor volume measurements for the ABVS and MRI were analyzed by two researchers individually (MC and LE).

Statistical analysis

Descriptive statistics, including medians and inter-quartile ranges (IQRs), were used to present volume and diameter measurements for the (3-D) MRI and (3-D) ABVS. The longest diameter response was evaluated according to the RECIST guidelines (progressive disease (PD) > 20% increase, stable disease (SD) < 20% increase to <30% decrease, and partial response (PR) > 30% decrease in longest diameter). Complete response (CR) was defined as no target lesion visible in the breast [8]. Both the tumor diameter and volume response evaluations of the (3-D) MRI and (3-D) ABVS were compared by calculating the intraclass correlation coefficient (ICC). The ICC is the proportion of the total variance that is not due to measurement error. The strength of reliability of the ICC was interpreted according to the benchmarks of Cichetti et al.[26] An ICC of < 0.40, 0.40 – 0.59,

0.60 – 0.74 and 0.74 – 1.00 was rated as 'poor', 'fair', 'good' and 'excellent' respectively. The absolute longest diameter and volume measurements obtained by (3-D) MRI were compared to the longest diameter and volume measurements obtained by (3-D) ABVS. A p-value of ≤0.05 was considered to be statistically significant. All data was analyzed using IBM SPSS statistics (current version 25.0, Chicago, IL, USA) and R (current version 4.1.0, R Foundation for statistical computing, Vienna, Austria).

Sample size calculation

The total number of patients was estimated using the method suggested by Zou.[27] With the assumptions of a number of observations (k) of two and a two-sided alpha (α) of 0.05, and assuming a true ICC ($H_0 : \varrho_0$) of 0.85 with a power of 90%, the required sample size was estimated at 96 patients. Excluded patients were replaced until the total number of inclusions was reached.

$H_0 : \rho_0 = 0.85$ at $\alpha = \beta = 0.05$ with $k = 2$

Ethical Considerations

Formal approval of the local medical ethics review committee of the Erasmus MC was obtained for this study (file number MEC-2015-647). All patients gave written informed consent prior to the first study procedures. Patient's anonymity and confidentiality were ensured throughout the study by the use of study codes replacing identifying information. The first author had access to digital records of study codes and patient information.

RESULTS

A total of 106 patients scheduled for NAC were eligible for inclusion. Six patients were excluded as they prematurely discontinued NAC due to severe side effects (n=2), liver metastasis without curative intent (n=1), and the decision for upfront surgery (n=3). The tumor was not visible on the pre-NAC ABVS in four patients. Eventually, 96 patients were eligible for analysis. All patients were women and underwent a pre-NAC and mid-NAC ABVS and MRI (n=96). A post-NAC MRI and post-NAC ABVS was performed in 58 and 90 patients, respectively (Figure 1). Patient and tumor characteristics are shown in Table 1. The majority (90.6%) of the carcinomas evaluated were invasive ductal carcinomas. Median longest diameter in cm on the ABVS and MRI and median volumes in cm^3 of the 3-D ABVS and 3-D MRI for the pre-NAC, mid-NAC and post-NAC evaluations can be found in Table 2.

Table 1. Baseline patient characteristics (n = 96).

Median age in years (IQR)	45 (34 – 54)
	N (%)
Gene mutation	
BRCA 1	8 (8.3)
BRCA 2	2 (2.1)
No	68 (70.8)
Unknown[a]	18 (18.8)
Laterality	
Left	43 (44.8)
Right	49 (51.0)
Bilateral	4 (4.2)
Morphology	
Invasive ductal carcinoma (NST)	87 (90.6)
Invasive lobulair carcinoma	3 (3.1)
Other	6 (6.2)
cTstage	
cT1	21 (21.8)
cT2	70 (72.9)
cT3	5 (5.2)
cNstage	
Negative	41 (42.7)
Positive	54 (57.3)
Surrogate molecular subtype	
Luminal A	34 (35.4)
Luminal B	15 (15.6)
Triple negative/basal like	35 (36.5)
HER2-enriched	12 (12.5)
pNstage (SNB)	
pN0	31 (32.3)
pN0 (itc +)	4 (4.2)
pN1	16 (16.7)
Not applicable[b]	45 (46.9)
ypTstage	
ypT0[c]	35 (36.5)
ypTis	10 (10.4)
ypT1	38 (39.7)
ypT2	11 (11.5)
ypT3	2 (2.1)
ypNstage	

Table 1. Baseline patient characteristics (n = 96).

Median age in years (IQR)	45 (34 – 54)
	N (%)
ypN0	48 (50.0)
ypN1	14 (14.6)
ypN2	2 (2.1)
ypN3	3 (3.1)
Not applicable[d]	29 (30.2)
DCIS present	
Yes	40 (41.7)
No	56 (58.3)

NAC = neoadjuvant chemotherapy, 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, NST = No Special Type. [a] Gene mutation testing not indicated.
[b] If by histopathological or cytopathological biopsy a lymph node metastasis is diagnosed, no pre-NAC SNB was performed.
[c] Complete pathologic response
[d]Not applicable in case of negative pre-NAC SNB

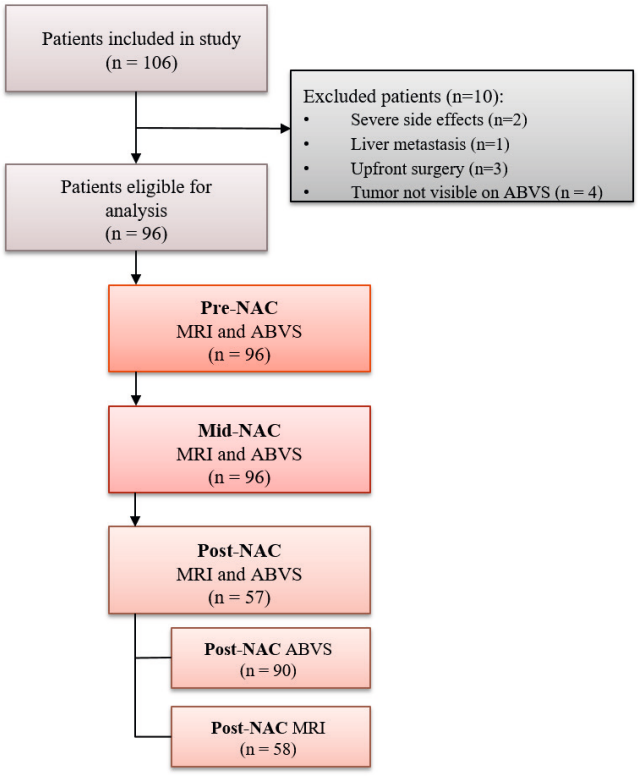


Figure 1. Flow chart patient inclusion and response evaluation

Table 2. Median longest diameter (cm) and tumor volume (cm3) pre-NAC, mid-NAC and post-NAC based on the MRI and ABVS.

	Pre-NAC (n = 96)	**Mid-NAC** (n = 96)	**Post-NAC**[a] (n = 57)
	cm (IQR)	cm (IQR)	cm (IQR)
Longest diameter			
MRI (radiologist)	2.6 (1.9 – 3.5)	1.6 (0.9 – 2.2)	1.1 (0 – 1.7)
MRI (V-scope)	2.6 (1.9 – 3.3)	1.5 (0.9 – 2.3)	1.0 (0 – 1.7)
ABVS (V-scope)	2.5 (1.8 – 3.1)	1.4 (0.8 – 2.0)	0.7 (0 – 1.5)
	cm^3 (IQR)	cm^3 (IQR)	cm^3 (IQR)
Tumor volume			
3-D MRI (V-scope)	4.1 (1.5 – 6.9)	0.7 (0.1 – 1.9)	0.2 (0 – 0.6)
3-D ABVS (V-scope)	2.2 (1.1 – 3.8)	0.4 (0.1 – 1.1)	0.2 (0 – 0.6)

NAC=neoadjuvant chemotherapy, MRI=Magnetic Resonance Imaging, ABVS=Automated Breast Volume Scanner, IQR = interquartile range.

[a]Number of patients with both post-NAC ABVS and MRI diameter and volume measurements.

First diameter response evaluation (mid-NAC)

Absolute concordance between ABVS and MRI was found in 66% (63/96) of the patients, according to the RECIST response evaluation mid-NAC (Table 3a). Results showed a significant and 'good' correlation for the first diameter response between the ABVS and MRI (radiologist) and MRI (V-scope) with an ICC 0.64 (95%CI 0.51-0.75) and 0.68 (95%CI 0.56-0.78) respectively, p <0.01 (Table 4).

Table 3a. First response according to RECIST based on mid-NAC *diameter* evaluation (n = 96).

Progressive disease		**MRI (radiologist)**			
		Stable disease	Partial response	Complete response	
ABVS (V-scope)	Progressive disease	0	3	0	0
	Stable disease	0	26[a]	6	1
	Partial response	0	12	26[a]	2
	Complete response	0	4	5	11[a]

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

[a]Absolute concordance between MRI and ABVS RECIST response evaluation.

Table 3b. Second response according to RECIST based on post-NAC *diameter* evaluation (n = 57).

Progressive disease		**MRI (radiologist)**			
		Stable disease	Partial response	Complete response	
ABVS (V-scope)	Progressive disease	1[a]	0	0	0
	Stable disease	0	4[a]	2	0
	Partial response	0	6	17[a]	2
	Complete response	0	3	8	14[a]

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

Table 4. ICC (95% confidence interval) for first (n = 96) and second (n = 57) diameter and volume response.

	First diameter response		**Second diameter response**	
	MRI (radiologist)	MRI (V-scope)	MRI (radiologist)	MRI (V-scope)
ABVS (V-scope)	0.64 (0.51-0.75)*	0.68 (0.56-0.78)*	0.68 (0.50-0.80)*	0.70 (0.53-0.80)*
	First volume response		**Second volume response**	
	3-D MRI (V-scope)		3-D MRI (V-scope)	
3-D ABVS (V-scope)	0.69 (0.57-0.78)*		0.98 (0.96-0.99)*	

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

Second diameter response evaluation (post-NAC)

Absolute concordance between ABVS and MRI was found in 63% (36/57) of the patients, according to the RECIST response evaluation post-NAC (Table 3b). Results showed a significant and 'good' correlation for the second longest diameter response between the ABVS and MRI (radiologist) and MRI (V-scope) with an ICC 0.68 (95%CI 0.50-0.80) and 0.70 (95%CI 0.53-0.80) respectively, p < 0.01 (Table 4).

Volume response evaluations (mid- and post-NAC)

The correlation between the first volume response for 3-D MRI and 3-D ABVS was 'good' with an ICC 0.69 (95% CI 0.57-0.78). For the second volume response, 'excellent' correlation was found (ICC 0.98 (95% CI 0.96-0.99), p <0.01) (Table 4).

Histopathologic response evaluation (post-NAC)

The ABVS and histopathologic response evaluation (pCR versus no pCR) performed by the pathologist showed absolute concordance in 71% (64/90) based on the longest diameter

(RECIST) and pathological response evaluation. For the MRI, absolute concordance was found in 50% (29/58) (Table 5 and 6). Based on the RECIST response category, the ICC for the histopathologic evaluation versus the post-NAC ABVS and MRI were 0.55 (95% CI 0.387 – 0.679, p < 0.01) and 0.29 (95% CI 0.036 – 0.508, p = 0.013), respectively.

Table 5. *Diameter* response evaluation according to histopathology examination and post-NAC MRI (n = 58)

Complete response		**Histopathology**		
		Partial response	**Stable disease**	
MRI (radiologist)	Complete Response	12[a]	4	0
	Partial response	10	17[a]	0
	Stable disease	3	11	0[a]
	Progressive disease	1	0	0

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

Table 6. *Diameter* response evaluation according to histopathology examination and post-NAC ABVS (n = 90)

Complete response		**Histopathology**		
		Partial response	**Stable disease**	
ABVS (V-scope)	Complete Response	36[a]	9	0
	Partial response	6	27[a]	0
	Stable disease	0	10	1[a]
	Progressive disease	1	0	0

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

Patient satisfaction

Patient satisfaction was expressed as acceptability, and the ABVS and MRI were ranked as 'very acceptable' in 86.5% and 27.1%, respectively (Figure 2). None of the patients ranked the ABVS as 'moderately acceptable' or 'not acceptable', in contrast to the MRI (19.8% and 4.2%, respectively).

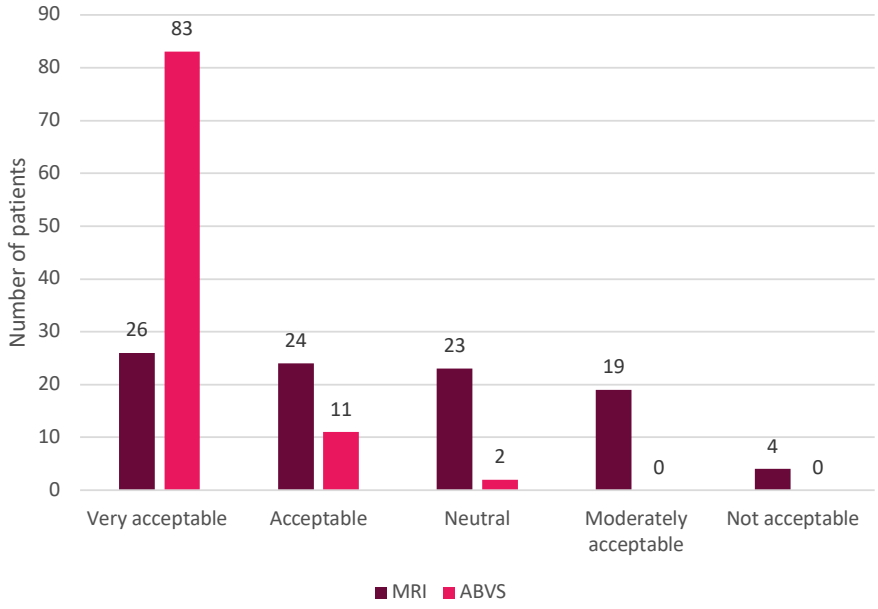


Figure 2. Patient satisfaction regarding breast MRI and ABVS (n = 96 patients).

DISCUSSION

Accurate evaluation of the tumor response during and after NAC is important for individualizing treatments and reducing local recurrence rates. Over the years, the percentage of patients who underwent breast MRI before neo-adjuvant treatment has increased.[1,28] The ABVS is known to be less expensive, quicker, and easily accessible without the need for contrast agents compared to MRI and therefore a promising technique for the tumor response evaluation in patients receiving NAC. A 'good' correlation was found between MRI and ABVS for the mid- and post-NAC diameter evaluation. Agreement in the RECIST response criteria for longest diameter was high for the ABVS and MRI, with an absolute concordance in 66% and 63% mid-NAC and post-NAC respectively. According to the histopathologic response evaluation, the RECIST response evaluation of the post-NAC ABVS showed a higher absolute concordance (71%) compared to post-NAC MRI (50%). Moreover, patients found the ABVS much more acceptable than the MRI, with various reasons such as; less time consuming, no loud noises, no need for an intravenous needle, no physical discomfort during scan, suggesting the ABVS is less burdensome (data not shown).

A strength of this study is that 3-D volume measurements for the MRI and ABVS images were estimated in addition to the longest diameter, and that the post-NAC evaluations were compared to the histopathological response. With a ICC of 0.69 (first response) and 0.98 (second response), the 3-D ABVS showed to be a reliable method for tumor volume measurements compared to 3-D MRI. As the response evaluations might be more clinically relevant than absolute longest diameter comparisons, the RECIST criteria were used for analyses. Although widely accepted, RECIST also knows some disadvantageous. RECIST ignores tumor volume response (as it only includes unidimensional size changes), and does not take into account changes in contrast intensity on MRI images. In addition, RECIST response category for stable disease has a very broad range (30% decrease to 20% increase) which might reflect different prognostic risk profiles.[8] More studies are focusing on volume responses, as correct estimates of tumor response using linear measurements is limited in irregular lesions with irregular growth of shrinkage. The response of breast tumors, especially estrogen positive/HER2neu-negative lesions, to NAC can show a crumble (fragmentation) effect rather than a regular shrinkage pattern in three dimensions.[29] Thus, a response can be present but might not be expressed in simply measuring unidimensional tumor size. In addition, individual reader decisions about where to place linear measurements within a complex lesion add variability to the response evaluation, and can lead to discordant assessments.[30] For tumor volume evaluation, consensus regarding response criteria or cut-off values are lacking which limited the analyses using 3-D ABVS and MRI volume response and histopathologic evaluation in this present study. Data of our study may be used to determine cut-off values for tumor volume response evaluation and to assess its prognostic value with breast cancer survival.[31]

Reasons for overestimation of the volume and diameter measurements were seen in patients with tumor necrosis, unclear tumor borders, or multi-centric tumors. If surrounded DCIS was present, the measurements on the ABVS seemed to be less accurate and this is a limitation of the ABVS. In retrospect, the artefact of the marker was sometimes misinterpret as residual tumor on the ABVS in some cases with proven histopathological complete response because of acoustic shadowing. The visualization of breast tumors varies significantly between ultrasound and MRI due to their distinct imaging modalities. While ultrasonography uses high-frequency sound waves to produce images, MRI utilizes strong magnetic fields and radio waves to generate detailed images of internal anatomy. In terms of tumor visualization, US is primarily used to detect masses and characterize their texture, while MRI provides more comprehensive and detailed information about the tumor as a result of contrast-agents, and the ability to detect neo-vascularization.[32] Therefore, the effect on response measurements is assumed to be larger with MRI than ultrasonography. Additionally, US may not be as effective as MRI in detecting small or subtle tumors, particularly those that are located near the chest wall/pectoral muscle or nipple.

On the other side, patients with claustrophobia, (electronic) implants, or a contrast-agent allergy are contraindicated for MRI and could benefit from the ABVS. Also, multiple MRI examinations is quite expensive. As 3-D ABVS volume measurements showed higher absolute concordance with histopathologic evaluation, incorporating this into daily clinical care could be of additional value. The RESPONDER I trial performed the 3-D MRI measurements in the I-Space, which was recently replaced by the I-Wall.[18,23] The projection technology of the I-Wall in combination with the costs of an MRI scan is expensive for routine day-to-day use. Therefore, the desktop virtual reality system, on which both the (3-D) MRI and ABVS were viewed in this study, is a great solution. In clinical practice, this means that only an extra workstation is needed for the radiologist to perform volume measurements. Ideally, the work-up for breast cancer patients scheduled for NAC includes a pre-NAC MRI and ABVS, and in case of good tumor visualization on the ABVS, the follow-up during NAC is continued with ABVS only. Extra volume measurements may take minimal additional time, however, this can be tackled with upcoming radiomics and machine learning techniques.

To eventually predict pCR, MRI is known for a high specificity but low sensitivity. With increasing pCR rates during the last decade due to optimized treatment, more physicians are asking for possibilities to diagnose pCR with noninvasive methods. pCR prediction is of high interest because a valid prediction of residual tumor absence could strongly influence the extent of surgery and can predict long-term survival based on molecular breast cancer subtypes.[13,14] Predicting pCR in breast cancer patients using MRI-based radiomics appears to be promising.[33] The field of radiomics is based on the hypothesis that there is a relation between imaging features and biological information. The central challenge is how to integrate diverse, multimodal information (clinical, imaging and molecular data) in a quantitative manner to provide specific clinical predictions that accurately and robustly estimate patient outcomes as a function of the possible decisions.[34] Radiomics models often use MRI or computer tomography images, and ultrasound is not recommended, however, the ABVS is automated and reproducible. The main disadvantage of the ABVS is the difficulty of examining the axillary region due to the large transducer. For the response evaluation during NAC, complete response is based on the absence of both the target lesion(s) in the breast as well as axillary lesions. Predicting CR is therefore hampered by the fact that the ABVS does not visualize the breast and axilla at once. A solution could be to use the handheld 2-D ultrasound transducer to examine the axilla. Although tumor response prediction can currently not be based on the 3D ultrasound alone, it may add value or even perform equal to the MRI based radiomics model which could be subject of future research.

Another application for the response evaluation with the ABVS in the neoadjuvant setting, is for breast cancer patients that receive neoadjuvant endocrine therapy (NET). In post-menopausal breast cancer patients with hormone positive carcinomas, NET can be

an alternative treatment for NAC. Also, pre-menopausal patients with the Luminal A-like subtype and without an indication for NAC may benefit from NET.[35] NET is usually given for 6-9 months before surgery and continued postoperatively, and the use of NET is increasing. Response to NET can also be expressed as a Ki67 drop or with 2D ultrasound, nonetheless, the ABVS might be an adequate alternative.

CONCLUSIONS

The ABVS showed equal performance compared to MRI (golden standard) for tumor response evaluations in breast cancer patients receiving NAC based on diameter and 3-D volume measurements, and better concordance with histopathologic response evaluation. Tumor volume measurements could add value in tumor response evaluations in general rather than unidimensional diameter solely. As the ABVS was preferred over MRI by the majority of the patients, it could be an adequate alternative in the response evaluation during NAC.

ACKNOWLEDGEMENTS

The authors would like to thank the Borstkliniek of the Franciscus Gasthuis and Vlietland Hospital and all patients for their participation in this study.

REFERENCES

1. Maliko N, Bijker N, Bos ME, Wouters MW, Vrancken Peeters MT, Audit NBC. Patterns of care over 10 years in young breast cancer patients in the Netherlands, a nationwide population-based study. *Breast.* 2022;66:285-292.
2. Spronk PER, Volders JH, van den Tol P, Smorenburg CH, Vrancken Peeters M. Breast conserving therapy after neoadjuvant chemotherapy; data from the Dutch Breast Cancer Audit. *Eur J Surg Oncol.* 2019;45(2):110-117.
3. Woeste MR, Bhutiani N, Donaldson M, McMasters KM, Ajkay N. Evaluating the effect of neoadjuvant chemotherapy on surgical outcomes after breast conserving surgery. *J Surg Oncol.* 2021;123(2):439-445.
4. Simons JM, Jacobs JG, Roijers JP, et al. Disease-free and overall survival after neoadjuvant chemotherapy in breast cancer: breast-conserving surgery compared to mastectomy in a large single-centre cohort study. *Breast Cancer Res Treat.* 2021;185(2):441-451.
5. Marinovich ML, Macaskill P, Irwig L, et al. Agreement between MRI and pathologic breast tumor size after neoadjuvant chemotherapy, and comparison with alternative tests: individual patient data meta-analysis. *BMC Cancer.* 2015;15:662.
6. Park J, Chae EY, Cha JH, et al. Comparison of mammography, digital breast tomosynthesis, automated breast ultrasound, magnetic resonance imaging in evaluation of residual tumor after neoadjuvant chemotherapy. *Eur J Radiol.* 2018;108:261-268.
7. Lobbes MB, Prevos R, Smidt M, et al. The role of magnetic resonance imaging in assessing residual disease and pathologic complete response in breast cancer patients receiving neoadjuvant chemotherapy: a systematic review. *Insights Imaging.* 2013;4(2):163-175.
8. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer.* 2009;45(2):228-247.
9. Lagendijk M, Vos EL, Ramlakhan KP, et al. Breast and Tumour Volume Measurements in Breast Cancer Patients Using 3-D Automated Breast Volume Scanner Images. *World J Surg.* 2018;42(7):2087-2093.
10. Choi WJ, Kim WK, Shin HJ, Cha JH, Chae EY, Kim HH. Evaluation of the Tumor Response After Neoadjuvant Chemotherapy in Breast Cancer Patients: Correlation Between Dynamic Contrast-enhanced Magnetic Resonance Imaging and Pathologic Tumor Cellularity. *Clin Breast Cancer.* 2018;18(1):e115-e121.
11. Partridge SC, Gibbs JE, Lu Y, et al. MRI measurements of breast tumor volume predict response to neoadjuvant chemotherapy and recurrence-free survival. *AJR Am J Roentgenol.* 2005;184(6):1774-1781.
12. Hylton NM, Blume JD, Bernreuter WK, et al. Locally advanced breast cancer: MR imaging for prediction of response to neoadjuvant chemotherapy--results from ACRIN 6657/I-SPY TRIAL. *Radiology.* 2012;263(3):663-672.
13. Liedtke C, Mazouni C, Hess KR, et al. Response to neoadjuvant therapy and long-term survival in patients with triple-negative breast cancer. *J Clin Oncol.* 2008;26(8):1275-1281.
14. von Minckwitz G, Blohmer JU, Costa SD, et al. Response-guided neoadjuvant chemotherapy for breast cancer. *J Clin Oncol.* 2013;31(29):3623-3630.
15. Wojcinski S, Farrokh A, Hille U, et al. The Automated Breast Volume Scanner (ABVS): initial experiences in lesion detection compared with conventional handheld B-mode ultrasound: a pilot study of 50 cases. *Int J Womens Health.* 2011;3:337-346.
16. Girometti R, Zanotel M, Londero V, Linda A, Lorenzon M, Zuiani C. Automated breast volume scanner (ABVS) in assessing breast cancer size: A comparison with conventional ultrasound and magnetic resonance imaging. *Eur Radiol.* 2018;28(3):1000-1008.

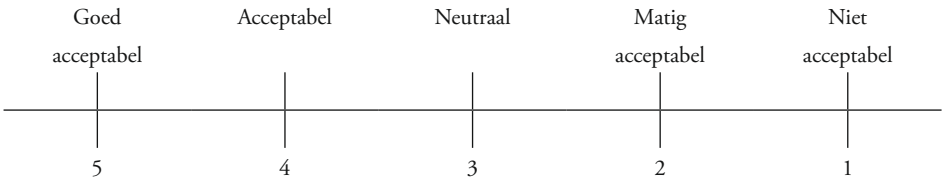
17. Schmachtenberg C, Fischer T, Hamm B, Bick U. Diagnostic Performance of Automated Breast Volume Scanning (ABVS) Compared to Handheld Ultrasonography With Breast MRI as the Gold Standard. *Acad Radiol.* 2017;24(8):954-961.
18. van Egdom LSE, Lagendijk M, Heijkoop EHM, et al. Three-dimensional ultrasonography of the breast; An adequate replacement for MRI in neoadjuvant chemotherapy tumour response evaluation? - RESPONDER trial. *Eur J Radiol.* 2018;104:94-100.
19. Sobin LH, Gospodarowicz M, Wittekind C. *TNM Classification of Malignant Tumors.* New York: John Wiley & Sons, Inc; 2009.
20. Goldhirsch A, Wood WC, Coates AS, et al. Strategies for subtypes--dealing with the diversity of breast cancer: highlights of the St. Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2011. *Ann Oncol.* 2011;22(8):1736-1747.
21. Federatie Medisch Specialisten. Richtlijnendatabase. Richtlijn Borstkanker. 2012; https://richtlijnendatabase.nl/richtlijn/borstkanker/pathologie/receptorbepaling.html. Accessed 13-06-2023.
22. Wolff AC, Hammond MEH, Allison KH, et al. Human Epidermal Growth Factor Receptor 2 Testing in Breast Cancer: American Society of Clinical Oncology/College of American Pathologists Clinical Practice Guideline Focused Update. *Arch Pathol Lab Med.* 2018;142(11):1364-1382.
23. Baken L, van Gruting IM, Steegers EA, van der Spek PJ, Exalto N, Koning AH. Design and validation of a 3D virtual reality desktop system for sonographic length and volume measurements in early pregnancy evaluation. *J Clin Ultrasound.* 2015;43(3):164-170.
24. Vos EL, Koning AH, Obdeijn IM, et al. Preoperative prediction of cosmetic results in breast conserving surgery. *J Surg Oncol.* 2015;111(2):178-184.
25. Pinder SE, Provenzano E, Earl H, Ellis IO. Laboratory handling and histology reporting of breast specimens from patients who have received neoadjuvant chemotherapy. *Histopathology.* 2007;50(4):409-417.
26. Cicchetti DV. Guidelines, criteria, and rules of thumb for evaluating normed and standardized assessment instruments in psychology. *Psychological Assessment.* 1994;6(4):284–290.
27. Zou GY. Sample size formulas for estimating intraclass correlation coefficients with precision and assurance. *Stat Med.* 2012;31(29):3972-3981.
28. van Bommel AC, Spronk PE, Vrancken Peeters MT, et al. Clinical auditing as an instrument for quality improvement in breast cancer care in the Netherlands: The national NABON Breast Cancer Audit. *J Surg Oncol.* 2017;115(3):243-249.
29. Loo CE, Straver ME, Rodenhuis S, et al. Magnetic resonance imaging response monitoring of breast cancer during neoadjuvant chemotherapy: relevance of breast cancer subtype. *J Clin Oncol.* 2011;29(6):660-666.
30. Goldmacher GV, Conklin J. The use of tumour volumetrics to assess response to therapy in anticancer clinical trials. *Br J Clin Pharmacol.* 2012;73(6):846-854.
31. Wesdorp NJ, Bolhuis K, Roor J, et al. The Prognostic Value of Total Tumor Volume Response Compared With RECIST1.1 in Patients With Initially Unresectable Colorectal Liver Metastases Undergoing Systemic Treatment. *Annals of Surgery.* 2021;2(4):p e103.
32. Jeswani T, Padhani AR. Imaging tumour angiogenesis. *Cancer Imaging.* 2005;5:131-138.
33. Granzier RWY, van Nijnatten TJA, Woodruff HC, Smidt ML, Lobbes MBI. Exploring breast cancer response prediction to neoadjuvant systemic therapy using MRI-based radiomics: A systematic review. *Eur J Radiol.* 2019;121:108736.
34. Lambin P, van Stiphout RG, Starmans MH, et al. Predicting outcomes in radiation oncology--multifactorial decision support systems. *Nat Rev Clin Oncol.* 2013;10(1):27-40.
35. Leal F, Liutti VT, Antunes dos Santos VC, et al. Neoadjuvant endocrine therapy for resectable breast cancer: A systematic review and meta-analysis. *Breast.* 2015;24(4):406-412.

SUPPLEMENTARY MATERIALS 1 - ACCEPTABILITY QUESTIONNAIRE

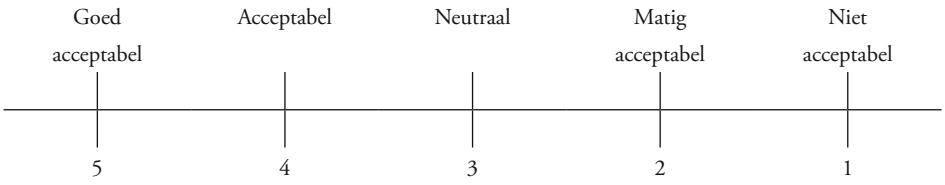
Erasmus MC – Acceptatiescore MRI en 3D-echo

Wij zijn geïnteresseerd in uw gevoel over de borst-MRI en de 3D-echografie van uw borst(en). Wij vragen u om hieronder aan te geven hoe acceptabel uw de onderzoeken vindt. Wilt u alle vragen zelf beantwoorden door het getal/antwoord te omcirkelen dat het meest op u van toepassing is. Er zijn geen 'juiste' of 'onjuiste' antwoorden. De antwoorden die u geeft zullen strikt vertrouwelijk en anoniem behandeld worden.

MRI borst(en)



3D-echo borst(en)



Chapter 8

An Optimized Protocol using frozen immune cells to Evaluate the Association between Radiation-induced T-Lymphocyte Apoptosis and Radiation-induced Fibrosis after Breast Conserving Therapy

---

Marloes E. Clarijs, Romy van der Groef, Dik C. van Gent, Femke E. Froklage, Nadine Davelaar, Erik Lubberts, Linetta B. Koppert, Marta E. Capala

Submitted

ABSTRACT

Objective: The objectives of this study were to optimize the radiation-induced lymphocyte apoptosis (RILA) assay using frozen immune cells, to analyze the association between RILA frequencies in CD4 and CD8 T-lymphocytes and grade 3 radiation-induced fibrosis (RIF) after breast conserving therapy (BCT), and to identify potential risk factors of RIF.

Materials and Methods: First, the RILA assay was performed on both freshly obtained and frozen peripheral blood mononuclear cells (PBMCs) that were isolated from blood samples of ten healthy volunteers. Second, Dutch female breast cancer patients with ≤ grade 1 (controls, n = 13) or grade 3 (cases, n = 17) fibrosis on the LENT-SOMA scale were included in this non-matched case-control study. Subsequently, study participants' (n = 30) RILA frequencies of CD4 and CD8 T-lymphocytes were assessed by flow cytometry using frozen PBMCs. Potential clinical risk factors of RIF were identified by obtaining treatment-, patient- and tumour-related characteristics from digital patient files.

Results: Similar RILA frequencies in frozen and freshly obtained PBMCs were found. The odds ratio of a 10% increase in T-lymphocyte RILA frequency was 1.58 (95% CI 0.85-3.33, p=0.16) and 1.13 (95% CI 0.62-2.10, p=0.68) for CD4 and CD8 T-lymphocytes respectively. Additionally, auto-immune disease, total axillary dissection, boost volume, total irradiated volume, and acute radiation dermatitis were significant clinical risk factors for RIF.

Conclusions: This is the first study to show that the RILA assay is feasible using frozen PBMCs, suggesting an easier method to use in clinical practice. No statistically significant association was found between a decreased RILA frequency of CD4 or CD8 T-lymphocytes and an increased risk of developing grade 3 RIF in this relatively small clinical study. However, acute radiation dermatitis (grade 2) and presence of an immunological disease in patients were identified as novel risk factors for RIF.

INTRODUCTION

In Western countries, 70% of breast cancer patients undergo breast conserving therapy (BCT).[1,2] BCT includes local excision of the primary tumour followed by adjuvant breast radiotherapy. BCT has demonstrated at least equal overall and disease-free survival rates as compared to mastectomy in early breast cancer.[3-5] As a result, treatment decisions are currently guided by cosmetic outcomes and quality of life (QoL). [6] Although BCT is associated with reasonably good cosmetic outcomes, radiation-induced fibrosis (RIF) of the breast occurs as a late adverse event in a substantial subset of patients (10-30%) after BCT.[7-9] Symptoms associated with RIF are skin induration and thickening, impaired cosmesis, loss of elasticity, limited joint mobility, lymphedema and pain.[10] In some cases, RIF can only be treated with (partial) mastectomy followed by reconstructive surgery. Such procedures are invasive and contain serious risks, which emphasizes that RIF can be considered as a serious treatment complication of BCT.[11]

There is a large patient-to-patient variability in the risk of developing RIF. The severity of RIF is related to treatment characteristics and individual radiosensitivity.[12,13] Individual radiosensitivity itself is characterized by patient-related factors, such as age, breast volume and smoking status, or by profound biological differences.[9,14,15] The presence of senescent cells is one of these important biological features that could explain the differences in individual radiosensitivity. Nguyen et al.[16] suggested that the individual risk of RIF could be predicted based on the reduced apoptosis of senescent cells.[16] The study of Crompton et al.[17] demonstrated that the risk of RIF was positively correlated with reduced apoptosis in the radiation-induced lymphocyte apoptosis (RILA) assay. Building on this result, other studies demonstrated that a low RILA frequency of CD4 and/or CD8 T-lymphocytes is associated with a higher risk of RIF.[18] However, these studies did not correct for all possible confounding factors and it remained unclear whether CD4 or CD8 T-lymphocytes should be used in the RILA assay. Current functional RILA assay protocols, for example the protocol of Crompton et al., use freshly obtained blood samples that need to be processed and analyzed within 48 hours.[17] From a clinical point of view, implementing such an assay in the routine breast cancer care may be hampered by the availability of time, personnel and equipment in the laboratory. A possible solution for this could be the use of frozen peripheral blood mononuclear cells (PBMCs) isolated from blood samples. Moreover, an up-to-date assessment of patient and treatment related risk factors for RIF is currently not available. The latter warrants new research to capture all risk factors of RIF, which can be of great importance in the development of future preoperative predictive models to identify patients likely to develop severe RIF and to optimize shared-decision making.

The aims of this study were to optimize the RILA assay by using frozen PBMCs to enhance clinical implementation, to assess the association between the RILA frequency of

CD4 and CD8 T-lymphocytes and grade 3 RIF after BCT in breast cancer patients, and to identify potential patient, treatment and tumour related risk factors for RIF.

MATERIALS AND METHODS

Study Population

Healthy volunteers were recruited at the Erasmus University Medical Centre for the optimization of the RILA assay. Patients who initially underwent BCT for non-metastatic, histologically proven invasive breast cancer (pT1-3N0-2a) or ductal carcinoma in situ (DCIS) at the Erasmus MC Cancer Institute were included. All study participants had either grade 1 (controls) or grade 3 (cases) RIF on the Late Effects Normal Tissues – Subjective, Objective, Management, Analytic (LENT-SOMA) scale[19]. Cases and controls were included from January 2021 till May 2021. Exclusion criteria were males and patients who were unable to provide written informed consent. Participants were invited to a one-time hospital visit.

Ethical Considerations

Formal approval from the institution's Medical Ethics Review Committee was obtained prior to start of the study (MEC-2020-0484). Written informed consent was obtained from all participants before participation in the study.

Optimization of RILA assay

The RILA procedure of CD4 and CD8 T-lymphocytes was initially adapted from the studies of Crompton et al.[20] and Menz et al.[21] To assess whether frozen patient samples could be used in this study, the RILA assay was performed on freshly obtained samples, and frozen PBMCs isolated from blood samples of the same ten healthy volunteers. The RILA assay was identical in both the healthy volunteers (fresh and frozen blood samples) and patients (frozen blood samples).

Radiation-induced CD4 and CD8 T-lymphocyte Apoptosis procedure

In this study, two 9-ml heparinized blood samples were obtained from each participant during a one-time hospital visit. PBMCs were isolated using density gradient medium Ficoll-Paque PLUS (GE Healthcare) within 24 hours and firstly stored at -80°C in a freezing container to effectuate gradual freezing of 1°C/minute and were subsequently transferred to in liquid nitrogen until use. PBMC were frozen in RPMI supplemented with 20% Dimethyl sulfoxide (DMSO (Merck Millipore)) and 20% heat inactivated fetal calf serum. After inclusion of all patients, PBMCs were thawed and resuspended in Roswell Park Memorial Institute (RPMI) 1640 supplemented with L-glutamine (BioW-

hittaker®, Lonza), 100 U/ml penicillin/streptomycin (BioWhittaker®, Lonza) and 20% heat inactivated fetal calf serum (HI-FCS; Gibco, Thermofisher Scientific) to remove the DMSO. The diluted samples were counted with trypan blue to exclude dead cells in the cell count and 1 million cells were plated in 3 ml culture medium per well in 6-well plates, irradiated at 0 and 8 Gy X-rays RS320 (Xstrahl Live Sciences) and incubated at 37°C with 5% CO_2 for 48 hours. The irradiated PBMCs were labelled with CD3-BV421 (SK7 clone, BioLegend), CD4-APC (RPA-T4 clone, BioLegend), and CD8-BUV737 (SK1 clone, BD Biosciences) monoclonal antibodies. After labelling, PBMCs were stained with propidium iodide (PI) and Annexin V (Annexin V Apoptosis Detection Kit FITC, eBioscience™) according to the manufacturer's protocol. Finally, flow cytometric data acquisition of the cell samples was performed using a 5-laser Aurora system (Cytek® Biosciences) to detect radiation-induced lymphocyte apoptosis. Analysis of flow cytometric data was performed using the FlowJo 10.6 software package (Tree Star, Ashland, OR, USA). Apoptotic CD4+ and CD8+ T-lymphocytes were defined as cells staining positive for their cell type-specific antibodies, Annexin V and PI. The percentages of apoptosis of the CD4+ and CD8+ T-lymphocytes were calculated as (number of apoptotic CD4+ or CD8+ T-lymphocytes) / (total number of CD4+ or CD8+ T-lymphocytes) x 100. The frequency of radiation-induced apoptosis for each type of T-lymphocytes (RILA frequency) within each subject was calculated as 100% / (100% - % apoptotic cells at 0 Gy) x (% apoptotic cells at 0 Gy - % apoptotic cells at 8 Gy). For a detailed description of the RILA assay protocol see Supplementary Materials 1.

Analysis of the Risk Factors for RIF

Potential patient, treatment and tumour related risk factors were obtained from digital patient files, including patient characteristics, radiotherapy-related factors, information about systemic treatment, and surgery-related and tumour-related factors.

Statistical Analysis and Sample Size Calculation

The sample size was calculated by using the Fleis, statistical Methods for Rates and Proportions, formulas 3.18 & 3.19 (Open Epi, V3.0.). A sample size of 20 cases and 20 controls was required in order to have sufficient statistical power to detect an OR of 6.58 for a reasonable common exposure (25% underlying prevalence of a low RILA frequency in control group) with a two-tailed -error of 0.05 and a power of 0.80. The exposure rate and odds ratio (OR) were based on results of previous studies and the expected effect of our cohort.[22,23] Descriptive statistics using medians and percentages were calculated to present patient and treatment characteristics. The Pearson's correlation coefficient was used to test the correlation between the RILA frequencies (continuous) in fresh and frozen blood samples of healthy volunteers. The non-parametric Wilcoxon-Mann-Whitney test for continuous measures and the Fisher exact test for categorical measures were performed

to compare patient and treatment characteristics between cases and controls. If a continuous variable was normally distributed the two-sample t-test was performed. Associations between patient- and treatment-related factors and RIF were assessed with univariate unconditional logistic regression models, in which only promising patient- and treatment-related factors were used (defined as factors in which the p-value of the difference between cases and controls was below 0.4). The association between the RILA frequencies and RIF was assessed with an unconditional univariate logistic regression model in order to calculate ORs and their 95% confidence intervals. All statistical tests were two-sided and differences were considered significant if $p<0.05$. All statistical analyses were performed using SPSS (version 27.0) [24] and R (version 4.0.0). [25]

RESULTS

Study participants

Ten healthy volunteers were included to compare the RILA assay in fresh and frozen samples. In total, 60 patients were screened and 13 controls and 17 cases were enrolled in the study (see Figure 1). All included patients completed the one-time visit to the Erasmus Medical Centre. One control was excluded from the RILA assay analysis, because of difficulties in assigning the fibrosis score based on the LENT-SOMA scale.

There were no differences in patient, treatment or tumour characteristics between cases and controls at baseline (see Table 1a). The overall median age at inclusion was 55 (range 38-77). A total of 22 patients (73.3%) received lumpectomy with a sentinel node procedure, and six patients (20.0%) received lumpectomy with total axillary lymph node dissection. Two patients (6.7%) eventually underwent a mastectomy with radiotherapy instead of BCT, and were included because of grade 3 RIF. Systemic therapy was administered to nine controls (69.2%) and fourteen cases (82.4%).

The majority of the radiotherapy characteristics were well balanced between the cases and the controls (see Table 1b). Median boost volume, median total irradiated volume, and number of patients with acute radiation dermatitis (grade 2) were significantly higher in the cases ($p=0.03$, $p=0.03$, and $p=0.04$, respectively).

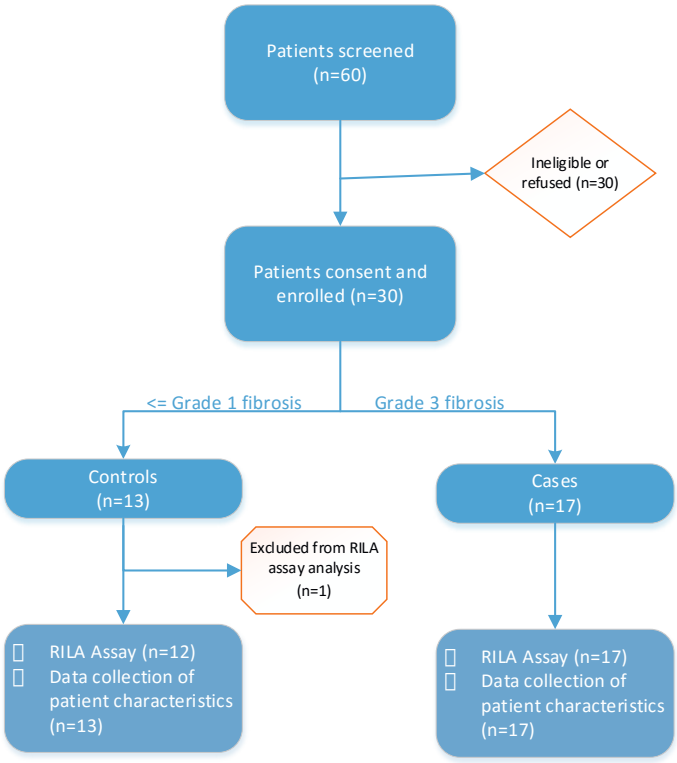


Figure 1. Flowchart of study procedures.

RILA Assay in Fresh and Frozen Samples

Percentages of (non)-irradiated CD4 and CD8 T-lymphocytes were similar between fresh and frozen samples in 8 of 10 volunteers (see Figure 2a and b). Overall, the RILA frequencies of freshly obtained and frozen PBMCs were highly comparable (see Figure 3a and b). Lower absolute RILA frequencies were observed in the RILA assay performed on frozen PBMCs compared to freshly obtained PBMCs for both the CD4 (mean 74.2% (SD 15,2) vs. 82.7 (SD 9.3), respectively) and CD8 T-lymphocytes (mean 76.8% (SD 14.0) vs. 82.5% (SD 11.0), respectively). The RILA frequency in frozen samples was positively and very strongly correlated to that of the fresh samples in CD4 (0.907, $p < 0.001$) and CD8 T-lymphocytes (0.921, $p < 0.001$).

Table 1a. Patient, tumour, and treatment characteristics.

	Controls grade 1 fibrosis	**Cases grade 3 fibrosis**	**P-value**
N	13	17	
Age at inclusion, median [IQR])	56 [52-62]	54 [49-67]	0.98
Age at diagnosis, median [IQR]	50 [46-51]	49 [42-56]	0.98
Malignancy History, Yes (%)	0 (0.0)	3 (17.6)	0.24
Medical history (%)			0.57
No	9 (69.2)	8 (47.1)	
Immunological disease	2 (15.4)	6 (35.3)	
Cardiovascular disease	2 (15.4)	3 (17.6)	
Allergies (%)			0.45
No	8 (61.5)	10 (58.8)	
Yes	4 (30.8)	7 (41.2)	
Unknown	1 (16.7)	0 (0.0)	
Smoke (%)			1.00
Ever	3 (23.1)	5 (29.4)	
Never	8 (61.5)	10 (58.8)	
Unknown	2 (15.4)	2 (11.8)	
Alcohol (%)			0.73
Ever	3 (23.1)	6 (35.3)	
Never	6 (46.2	8 (47.1)	
Unknown	4 (30.8)	3 (17.6)	
Hypertension, Yes (%)	1 (7.7)	4 (23.5)	0.36
Diabetes, Yes (%)	1 (7.7)	1 (5.9)	1.00
Side Malignancy, left (%)	7 (53.8)	10 (58.8)	
Operation type (%)			0.15
Lumpectomy + SN	12 (92.3)	10 (58.8)	
Lumpectomy + total axillary dissection	1 (7.7)	5 (29.4)	
Mastectomy + total axillary dissection	0 (0.0)	2 (11.8)	
Type carcinoma (%)			0.42
IDC	10 (76.9)	14 (82.4)	
ILC	5 (23.1)	5 (5.9)	
Micropapillary	0 (0.0)	1 (5.9)	
Unknown	0 (0.0)	1 (5.9)	
Oestrogen receptor (%)			0.64
Negative	2 (15.4)	4 (23.5)	
Positive	10 (76.9)	10 (58.8)	
Unknown	1 (7.7)	3 (17.6)	
Progesterone receptor (%)			0.66

Table 1a. Patient, tumour, and treatment characteristics.

	Controls grade 1 fibrosis	**Cases grade 3 fibrosis**	**P-value**
Negative	3 (23.1)	5 (29.4)	
Positive	9 (69.2)	9 (52.9)	
Unknown	1 (7.7)	3 (17.6)	
HER2 receptor (%)			0.23
Negative	8 (61.5)	13 (76.5)	
Positive	4 (30.8)	1 (5.9)	
Unknown	1 (7.7)	3 (17.6)	
Histological grade (SBR) (%)			0.19
Grade 1	5 (38.5)	2 (11.8)	
Grade 2	6 (46.2)	7 (41.2)	
Grade 3	2 (15.4)	5 (29.4)	
Unknown	0 (0.0)	3 (17.6)	
T-stage (%)			0.92
T1	6 (46.2)	9 (52.9)	
T2	6 (46.2)	6 (35.3)	
T3	1 (7.7)	1 (5.9)	
Unknown	0 (0.0)	1 (5.9)	
N-stage (%)			0.90
N0	8 (61.5)	12 (70.6)	
N1	4 (30.8)	3 (17.6)	
N2	1 (7.7)	1 (5.9)	
Unknown	0 (0.0)	1 (5.9)	
Systemic therapy, Yes (%)	9 (69.2)	14 (82.4)	0.67
Type systemic therapy (%)			0.13
No	4 (30.8)	3 (17.6)	
Endocrine therapy	3 (23.1)	1 (5.9)	
Chemotherapy	1 (7.7)	8 (47.1)	
Endocrine and chemotherapy	3 (23.1)	4 (23.5)	
Chemotherapy and Trastuzumab	1 (7.7)	1 (5.9)	
Endocrine, chemotherapy and Trastuzumab	1 (7.7)	1 (5.9)	

NA = not applicable. SBR = Scarff–Bloom–Richardson. IDC = Invasive ductal carcinoma. ILC = Invasive lobular carcinoma. SN= sentinel node procedure.

Medical history includes the presence or history of autoimmune, auto-inflammatory or cardiovascular disorders (no vs. yes). Allergy includes any kind of allergy (e.g. band-aids).

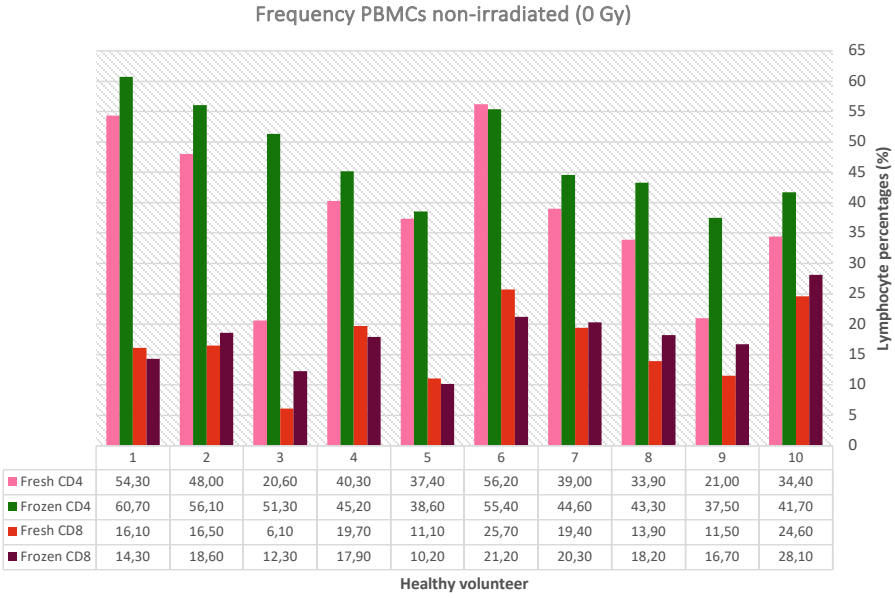
Table 1b. Radiotherapy characteristics

	Controls grade 1 fibrosis	**Cases grade 3 fibrosis**	**p-value**
N	13	17	
Radiation boost (%)			1.00
No	3 (23.1)	3 (17.6)	
Sequential Boost	6 (46.2)	8 (47.1)	
SIB	4 (30.8)	6 (35.3)	
Total Boost dose, median [IQR], Gy	15.00 [10.29, 15.00]	14.49 [13.35, 16.56]	0.64
Boost Volume, median [IQR], cc	65.40 [40.50, 78.00]	93.85 [81.75, 112.00]	**0.03**
Number of Fraction during radiotherapy, median [IQR]	25.00 [21.00- 25.00]	25.00 [16.00, 25.00]	0.95
Dose per fraction, median [IQR], Gy	2.00 [2.00, 2.17]	2.00 [2.00, 2.66]	0.85
Total radiation dose, median [IQR], Gy	55.86 [50.05, 67.00]	61.18 [53.40, 65.00]	0.83
Total Irradiated volume, median [IQR], cc	621.50 [314.30, 1097.25]	1183.00 [909.50, 1359.00]	**0.03**
Max dose during radiotherapy, median [IQR], Gy	68.05 [59.30, 71.30]	59.50 [56.55, 69.15]	0.26
Time between surgery and radiotherapy, median [IQR], days	47.00 [38.00, 127.00]	45.50 [34.25, 91.00]	0.76
Number of Acute radiation dermatitis (grade 2) (%)			**0.04**
No	12 (93.3)	9 (52.9)	
Yes	1 (7.7)	7 (42.1)	
Unknown	0 (0.0)	1 (5.9)	

SIB = simultaneous integrated boost.

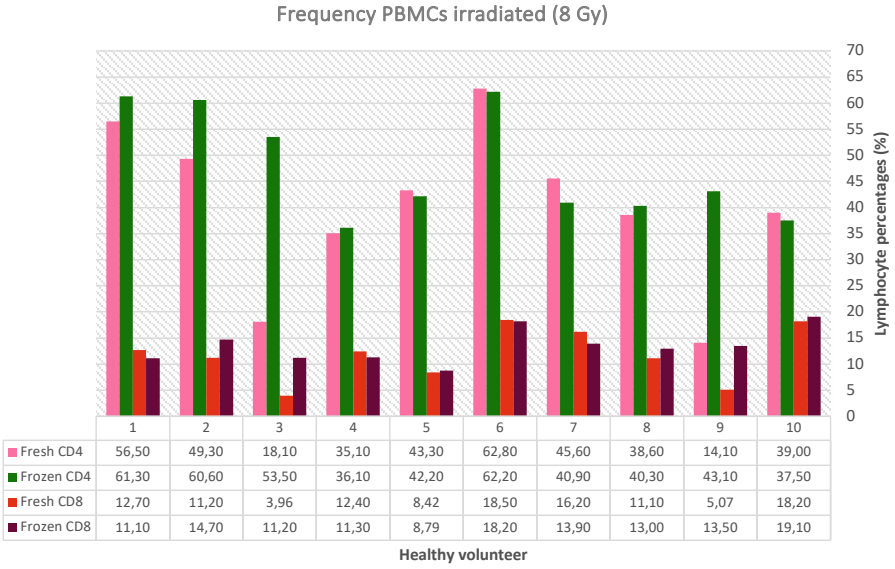
RILA Assay in Cases and Controls

RILA frequencies of CD4 and CD8 T-lymphocytes were calculated for all patients (see Figure 4a and b). In the CD4 T-lymphocyte group, the mean RILA frequency was 53.5% (SD 16.6) in the controls and 45.0% (SD 14.4) in the cases. In the CD8 T-lymphocyte group, the mean RILA frequency was 40.2% (SD 16.1) in the controls and 37.9% (SD 12.8) in the cases. There were no significant differences in mean RILA frequencies between the cases and controls in both lymphocyte groups (p=0.18 and p=0.69, respectively). The odds ratios for a 10% decrease in RILA frequency in the CD4 and CD8 T-lymphocyte groups were 1.58 (95% CI 0.85-3.33, p=0.16) and 1.13 (95% CI 0.62-2.10, p=0.68) respectively.



	1	2	3	4	5	6	7	8	9	10
Fresh CD4	54,30	48,00	20,60	40,30	37,40	56,20	39,00	33,90	21,00	34,40
Frozen CD4	60,70	56,10	51,30	45,20	38,60	55,40	44,60	43,30	37,50	41,70
Fresh CD8	16,10	16,50	6,10	19,70	11,10	25,70	19,40	13,90	11,50	24,60
Frozen CD8	14,30	18,60	12,30	17,90	10,20	21,20	20,30	18,20	16,70	28,10

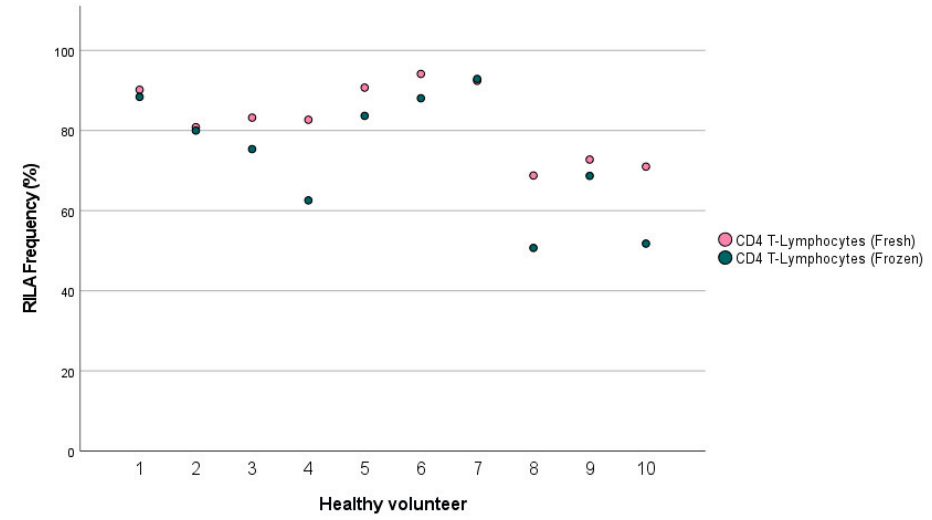
Healthy volunteer



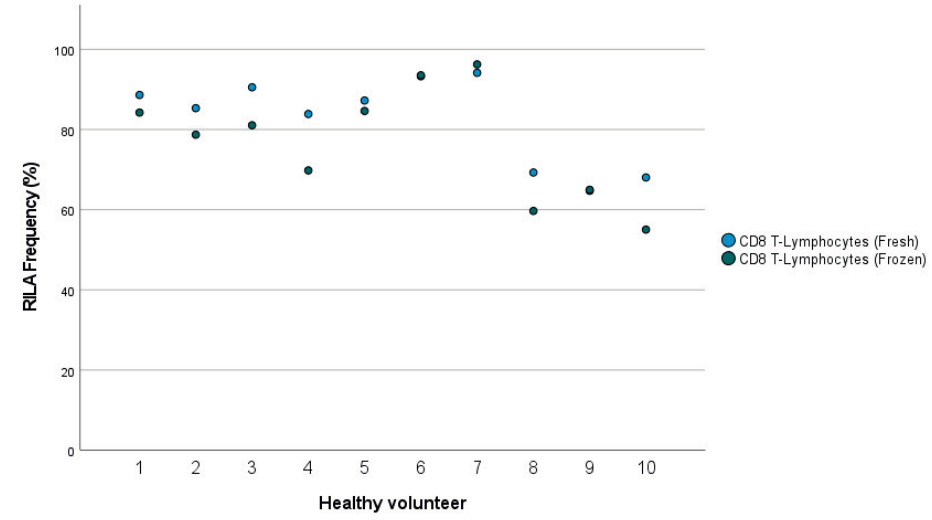
	1	2	3	4	5	6	7	8	9	10
Fresh CD4	56,50	49,30	18,10	35,10	43,30	62,80	45,60	38,60	14,10	39,00
Frozen CD4	61,30	60,60	53,50	36,10	42,20	62,20	40,90	40,30	43,10	37,50
Fresh CD8	12,70	11,20	3,96	12,40	8,42	18,50	16,20	11,10	5,07	18,20
Frozen CD8	11,10	14,70	11,20	11,30	8,79	18,20	13,90	13,00	13,50	19,10

Healthy volunteer

Figure 2a and b. Frequency PBMCs (CD4 and CD8 T-Lymphocytes) before and after irradiation using fresh and frozen samples of 10 healthy volunteers.



(a)



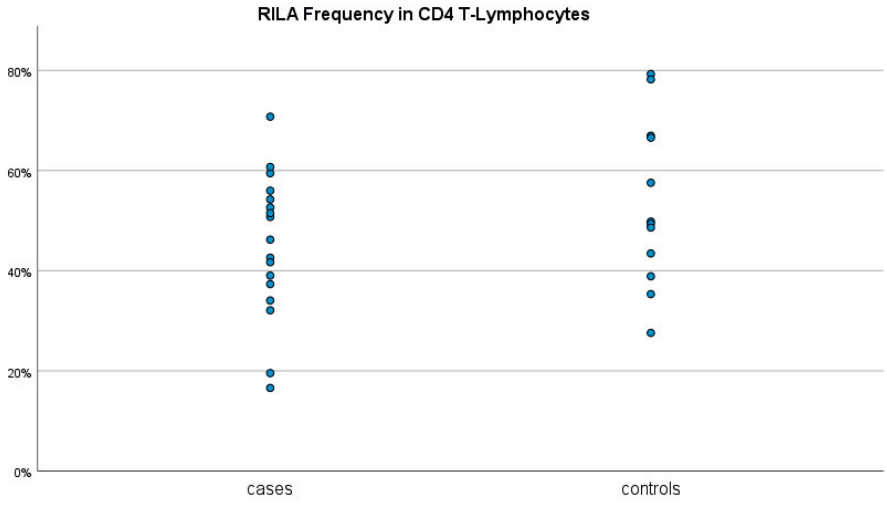
(b)

Figure 3a and b. RILA frequencies of CD4 and CD8 T-lymphocytes in fresh and frozen PBMC samples after 8 Gy irradiation of 10 healthy volunteers.

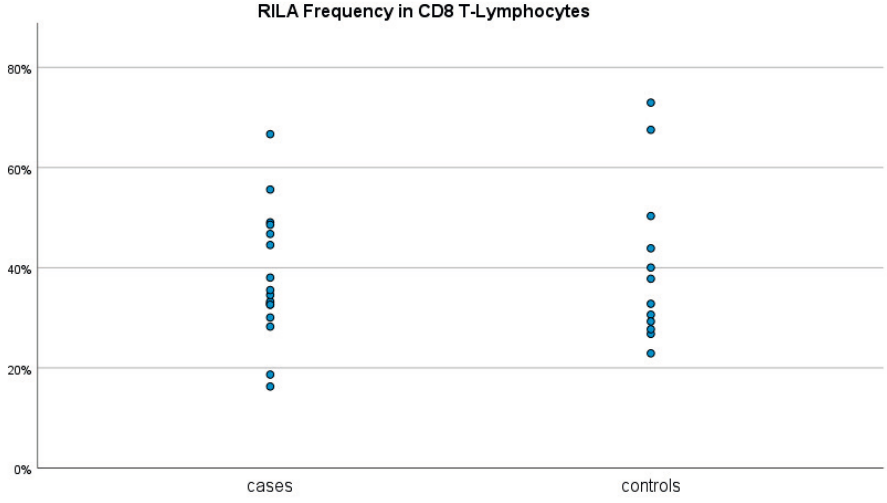
Percentages displayed in chart reflect the RILA-frequencies after irradiation with 8 Gy.

RILA frequency within each subject was calculated as 100% / (100% - % apoptotic cells at 0 Gy) x (% apoptotic cells at 0 Gy - % apoptotic cells at 8 Gy)

Volunteers are numbered from 1 to 10.



(a)



(b)

Figure 4a and b. RILA frequencies of CD4 and CD8 T-Lymphocytes in controls (n=12) and cases (n=17).

Risk Factors for RIF

The univariate logistic regression analysis revealed auto-immune disease (OR 8.40, p = 0.03), and total axillary dissection (OR 8.40, p = 0.03) as a significant risk factor of developing grade 3 fibrosis (see Table 2). According to the radiotherapy characteristics, boost volume (OR 1.53, p = 0.01), total irradiated volume (OR 1.12, p = 0.03), and acute radiation dermatitis (grade 2) (OR 13.71, p = 0.01) were significantly associated with an increased risk of developing grade 3 fibrosis.

Table 2a and b. Results of univariate logistic regression for RIF based on patient-, tumour- and treatment-related factors.

	OR	**p-value**
Histological grade (SBR)		0.26
Grade 1	ref	
Grade 2	2.92	
Grade 3	6.25	
Hypertension	3.69	0.23
Medical history	2.53	0.22
Auto-immune disease	8.40	**0.03***
Total axillary dissection	8.40	**0.03***
Chemotherapy	3.80	0.09
Hormonotherapy	0.60	0.49
Radiotherapy		
Total Boost dose, per 1 Gy increase	1.16	0.31
Boost Volume, per 10 cc increase	1.53	**0.01***
Total radiation dose, per 10 Gy increase	1.20	0.67
Total Irradiated volume, per 50 cc increase	1.12	**0.03***
Acute radiation dermatitis (grade 2)	13.71	**0.01***

SBR = Scarff–Bloom–Richardson, Medical history = presence or history of autoimmune, auto-inflammatory or cardiovascular disorders (no vs. yes).
Odds ratio >1 means that the factor increases the risk of developing RIF, <1 indicates that the factor reduces the risk of RIF.
*Significance at the level 0.05 (two-tailed).

DISCUSSION

In this study, the RILA assay was performed on both freshly isolated PBMCs versus frozen PBMCs from the same healthy volunteers to optimize the RILA assay to enhance clinical implementation and feasibility. An important outcome of our study is that the RILA assay is feasible using frozen PBMCs, suggesting an easier method to use in clinical practice. Previous studies used freshly obtained blood samples.[22,23,26,27] This procedure can be time-

consuming and impractical, due to the fact that the entire RILA procedure should be performed within 48 hours.[20] Our present study shows that performing RILA assay on frozen PBMCs yields very similar results as when performed on freshly obtained PBMCs or whole blood samples[22]. The absolute differences between the RILA frequencies of fresh and frozen samples were caused by a difference in the baseline (non-irradiated) apoptosis percentages. This baseline apoptosis was higher in the frozen PBMCs compared to freshly obtained samples. Using frozen PBMCs improves the feasibility of the RILA assay, as only the procedure of isolating PBMCs should be performed within 24 hours instead of the entire RILA procedure within 48 hours. This can stimulate the implementation of the RILA assay in clinical practice, but also increases the feasibility of this assay in studies with multiple research sites.

After applying the optimized RILA assay in cases and controls, no significant differences were observed. We were therefore unable to confirm the hypothesis that a decrease in RILA frequency is associated with an increased risk of developinggrade 3 RIF within our cohort. However, a trend towards a decreased RILA frequency and an increased risk of developing grade 3 RIF was observed in the CD4 T-lymphocyte group, but not in the CD8 T-lymphocyte group. This indicates that a larger patient sample is needed to investigate this association.

The association between RILA frequency and RIF in breast cancer patients was previously studied by large prospective and retrospective studies.[22,23,26,27] These studies showed that a low RILA frequency was associated with an increased risk of developing RIF. To illustrate, the study of Azria et al.[23] showed an increased risk of developing grade 2 fibrosis for patients with a low (12%) RILA frequency of CD8 T-lymphocytes after correction for tobacco smoking and adjuvant hormonotherapy. Also, the study of Veldwijk et al.[22] showed that a low CD4+ RILA frequency was significantly associated with an increased risk of grade 2 fibrosis after correction for some covariates (e.g. age at surgery, body mass index, hypertension, smoking status at 10 year follow-up, delivered radiotherapy dose (EQD2), and hormonal treatment). This result is in line with our observed trend between a decreased RILA frequency and an increased risk of developinggrade 3 RIF in the CD4 T-lymphocyte group. To note, we found overall higher RILA frequencies in both freshly obtained and frozen PBMCs of healthy volunteers and patients compared to previous studies.[22,23] The fact that we used a X-ray source with low energy X-rays may have resulted in slightly more or different DNA damage and consequently higher apoptosis frequencies.

Although we did not observe a significant association between RILA frequency and RIF, we were able to detect five risk factors for RIF. Previous studies assessing factors influencing the risk of RIF, likewise reported an increased risk of developing RIF with increasing boost volume, and breast size, which is correlated with the total irradiated volume.[9,15] Nevertheless, acute radiation dermatitis (grade 2) and presence of an autoimmune disease in patients emerged as a novel risk factor of RIF. Because information

about the latter is available prior to radiation of the breast, it could therefore be used in predictive modelling and counselling of breast cancer patients.

Limitations

The most prominent limitation of our study was the small sample size. As the RILA assay was never performed on frozen PBMCs, valuable information to calculate a proper sample size was missing. Furthermore, we expected to observe a large OR (6.58) for the association between RILA frequency and RIF, based on the results of previous studies and the expected effect of our cohort.[22,23] The effect of the cohort was probably overestimated, which means that according to an adjusted power calculation we should double our sample size to have sufficient power to detect an OR of 3.48 based on the results of previous studies.[22,23] However, the results of this study can be used for designing a full scale (prospective) study using frozen PBMCs to perform the RILA assay.

Clinical Implications

The RILA assay has already been used by other institutes as clinical routine after validation and CE-marking based on the study of Azria et al.[23] Our study emphasizes the importance of developing a comprehensive predictive model for RIF that can be used in treatment decision making, meaning a model that includes clinical risk factors that can be obtained before treatment. An example of such a risk factor, identified in the current study, is the presence of an auto-immune disease. To illustrate, if a patient is preoperatively identified as high-risk for developing RIF, an alternative treatment can be advised. In breast cancer treatment, the alternative for BCT is mastectomy with or without immediate implant based or autologous reconstruction. In this way a potential severe treatment complication, including additional invasive surgery can be prevented. Moreover, when an alternative treatment is not preferred, close monitoring and early treatment can potentially minimize the negative consequences of RIF.

CONCLUSIONS

This study provided an updated, clinically more feasible RILA assay method which can be used for preoperative decision making, and an overview of clinical risk factors of developing RIF. A large prospective study is needed to validate our updated RILA method based on frozen PBMCs. Results showed a trend in the association between a decreased RILA frequency of CD4 T-lymphocytes and an increased risk of developing grade 3 RIF after BCT in breast cancer patients. Further, the association between RILA frequency and RIF should be assessed and corrected for all potential clinical confounders, including those

suggested by this study. In this way, a promising novel predictive model can come forward to guide treatment decision making in breast cancer.

Acknowledgements: The authors wish to thank all patients and volunteers that participated in this research.

REFERENCES

1. Collins ED, Moore CP, Clay KF, et al. Can women with early-stage breast cancer make an informed decision for mastectomy? *J Clin Oncol.* 2009;27(4):519-525.
2. Agarwal S, Pappas L, Neumayer L, Kokeny K, Agarwal J. Effect of breast conservation therapy vs mastectomy on disease-specific survival for early-stage breast cancer. *JAMA Surg.* 2014;149(3):267-274.
3. Clarke M, Collins R, Darby S, et al. Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: an overview of the randomised trials. *Lancet.* 2005;366(9503):2087-2106.
4. Fisher B, Anderson S, Bryant J, et al. Twenty-year follow-up of a randomized trial comparing total mastectomy, lumpectomy, and lumpectomy plus irradiation for the treatment of invasive breast cancer. *N Engl J Med.* 2002;347(16):1233-1241.
5. Lagendijk M, van Maaren MC, Saadatmand S, et al. Breast conserving therapy and mastectomy revisited: Breast cancer-specific survival and the influence of prognostic factors in 129,692 patients. *Int J Cancer.* 2018;142(1):165-175.
6. Saadatmand S, Bretveld R, Siesling S, Tilanus-Linthorst MM. Influence of tumour stage at breast cancer detection on survival in modern times: population based study in 173,797 patients. *BMJ.* 2015;351:h4901.
7. Collette S, Collette L, Budiharto T, et al. Predictors of the risk of fibrosis at 10 years after breast conserving therapy for early breast cancer: a study based on the EORTC Trial 22881-10882 'boost versus no boost'. *Eur J Cancer.* 2008;44(17):2587-2599.
8. Bartelink H, Maingon P, Poortmans P, et al. Whole-breast irradiation with or without a boost for patients treated with breast-conserving surgery for early breast cancer: 20-year follow-up of a randomised phase 3 trial. *Lancet Oncol.* 2015;16(1):47-56.
9. Brouwers P, van Werkhoven E, Bartelink H, et al. Predictors for poor cosmetic outcome in patients with early stage breast cancer treated with breast conserving therapy: Results of the Young boost trial. *Radiother Oncol.* 2018;128(3):434-441.
10. Dorr W, Hendry JH. Consequential late effects in normal tissues. *Radiother Oncol.* 2001;61(3):223-231.
11. van Geel AN, Lans TE, Haen R, Tjong Joe Wai R, Menke-Pluijmers MB. Partial mastectomy and m. latissimus dorsi reconstruction for radiation-induced fibrosis after breast-conserving cancer therapy. *World J Surg.* 2011;35(3):568-572.
12. Immink JM, Putter H, Bartelink H, et al. Long-term cosmetic changes after breast-conserving treatment of patients with stage I-II breast cancer and included in the EORTC 'boost versus no boost' trial. *Ann Oncol.* 2012;23(10):2591-2598.
13. Mukesh MB, Harris E, Collette S, et al. Normal tissue complication probability (NTCP) parameters for breast fibrosis: pooled results from two randomised trials. *Radiother Oncol.* 2013;108(2):293-298.
14. Andreassen CN, Alsner J, Overgaard J. Does variability in normal tissue reactions after radiotherapy have a genetic basis--where and how to look for it? *Radiother Oncol.* 2002;64(2):131-140.

15. Lyngholm CD, Christiansen PM, Damsgaard TE, Overgaard J. Long-term follow-up of late morbidity, cosmetic outcome and body image after breast conserving therapy. A study from the Danish Breast Cancer Cooperative Group (DBCG). *Acta Oncol.* 2013;52(2):259-269.
16. Nguyen HQ, To NH, Zadigue P, et al. Ionizing radiation-induced cellular senescence promotes tissue fibrosis after radiotherapy. A review. *Crit Rev Oncol Hematol.* 2018;129:13-26.
17. Crompton NE, Ozsahin M. A versatile and rapid assay of radiosensitivity of peripheral blood leukocytes based on DNA and surface-marker assessment of cytotoxicity. *Radiat Res.* 1997;147(1):55-60.
18. Fhoghlu MN, Barrett S. A Review of Radiation-Induced Lymphocyte Apoptosis as a Predictor of Late Toxicity After Breast Radiotherapy. *J Med Imaging Radiat Sci.* 2019;50(2):337-344.
19. LENT SOMA tables. *Radiother Oncol.* 1995;35(1):17-60.
20. Crompton NE, Miralbell R, Rutz HP, et al. Altered apoptotic profiles in irradiated patients with increased toxicity. *Int J Radiat Oncol Biol Phys.* 1999;45(3):707-714.
21. Menz R, Andres R, Larsson B, Ozsahin M, Trott K, Crompton NE. Biological dosimetry: the potential use of radiation-induced apoptosis in human T-lymphocytes. *Radiat Environ Biophys.* 1997;36(3):175-181.
22. Veldwijk MR, Seibold P, Botma A, et al. Association of CD4(+) Radiation-Induced Lymphocyte Apoptosis with Fibrosis and Telangiectasia after Radiotherapy in 272 Breast Cancer Patients with >10-Year Follow-up. *Clin Cancer Res.* 2019;25(2):562-572.
23. Azria D, Riou O, Castan F, et al. Radiation-induced CD8 T-lymphocyte Apoptosis as a Predictor of Breast Fibrosis After Radiotherapy: Results of the Prospective Multicenter French Trial. *EBioMedicine.* 2015;2(12):1965-1973.
24. *IBM Corp. IBM SPSS Statistics for Macintosh* [computer program]. Version 27.0. Armon, NY: IBM Corp.Released 2020.
25. *R: A language and enviroment for statistical computing* [computer program]. Vienna, Austria: R Foundation for Statistical Computing; 2021.
26. Ozsahin M, Crompton NE, Gourgou S, et al. CD4 and CD8 T-lymphocyte apoptosis can predict radiation-induced late toxicity: a prospective study in 399 patients. *Clin Cancer Res.* 2005;11(20):7426-7433.
27. Bourgier C, Kerns S, Gourgou S, et al. Concurrent or sequential letrozole with adjuvant breast radiotherapy: final results of the CO-HO-RT phase II randomized trial. *Ann Oncol.* 2016;27(3):474-480.

SUPPLEMENTARY MATERIALS

Protocol RILA assay

Procedure day 1

1. Thaw PBMCs and preparation radiation PBMCs
   a. Thaw PBMCs in warm water
   i. move the frozen vial in water bath (37 until a small clump is left.
   b. Add PBMC suspension of each vial to 50 ml tube
   c. Flush each vial with 1 ml RPMI+20% FCS. add to 50 ml tube
   d. Add 9 ml RPMI+20% FCS to 50 ml tube. add drop by drop while stirring the tube.
   e. Centrifuge cells 380g. 10 min
   f. Pour off the 50 ml tube and remove remaining supernatant with a 1 ml pipet
   g. Resuspend thawed PBMCs in 1 ml RPMI/20%FCS/1%Penicillin-Streptomycin
   h. Count PBMCs
   i. Add 20 ul PBMCs and x ul trypan blue to a 96-well plate

1. Choose appropriate dilution factor
   a. To count approximately 150 cells
      ii. Add 20 ul from a 96-well plate to the counting chamber
      iii. Count 9 small boxes including two edges (e.g. top and right), count 1 small box in each big box (=N), repeat this for another small box
      iv. Total number of cells = N_{mean} * volume (ml) * dilution factor * 10.000
   i. Calculate volume of cell suspension needed (1.0 million cells/well)
   j. Dilute cell suspension in 50 ml tube (1.0 million cells/well)
   k. Add 2 ml RPMI/20%FCS/1%Penicillin-Streptomycin to each well of 6-wells culture plate

l. Add 1 ml of (1.0 million cells/1ml) diluted cell suspension to each well of 6-wells culture plate

2. Radiation of PBMCs
   a. Irradiate the PBMCs using 0- and 8-Gy X-rays RS320 (Xstrahl Live Sciences) following the machine's instructions.

3. Incubation of PBMCs
   a. Incubate PBMCs for 48 hours at 37 in a 5% CO_2/air atmosphere.
   b. Incubate remaining PBMCs in T25 culture flasks for control stainings

Procedure day 3

1. *Check cells of 6-wells culture plate under microscope*
   a. Check each condition (0 and 8 Gy)
      i. Check difference in medium colour
      ii. Check differences in cell amount
2. *Preparation of samples before staining*
   a. Pool duplicated wells from each patient in 15/50 ml tube
   b. Flush each well with 1 ml PBS and add to tubes, spin down (380g. 10 min)
   c. Pour off the tubes and remove remaining supernatant with a 1 ml pipet
   d. Resuspend cells in 100ul FACS buffer/well (PBS/0.5%BSA/0.05%SoAzide), transfer to FACS plate
3. *Staining with antibodies. Annexin V and Propidium Iodide (PI)*
   a. Spin down 280g. 2 min. remove supernatant
   b. Wash cells with 150 ul FACS buffer (280g, 2 min)
   c. Add 25 ul CD3, CD4 and CD8 antibody mix
   d. Incubate cell suspension 15 min at room temperature in the dark
   e. Add 150 ul PBS, spin down (280g. 2 min). remove supernatant
   f. Prepare 1x Binding Buffer, dilute 10 times with MilliQ
   g. Wash cells in 150 ul 1x Binding Buffer (280g. 2 min)
   h. Resuspend in 100 ul 1x Binding Buffer, add 5 ul Annexin V FITC
   i. Incubate cell suspension 10 min at room temperature in the dark, spin down (280g. 2 min)
   j. Wash cells in 150 ul 1x Binding Buffer (280g. 2 min)
   k. Resuspend in 200 ul 1x Binding Buffer
   l. Add 5 ul PI staining solution
   m. Analyse by flow cytometry within 4 h, cover plate in aluminium foil. store in fridge in meantime
4. *Flow cytometry*
   a. Measure the samples using the Cytek Aurora flow cytometer.
   b. Characterize CD4+ and CD8+ T-Lymphocytes based on their forward scatter fluorescence (cell size), side scatter fluorescence (cell 'granularity'), and specific conjugated-antibody fluorescence.
   c. Assess the apoptosis by measuring the fluorescence of the Annexin V and propidium iodide stained lymphocytes.
   d. Measure the level of apoptotic CD4+ and CD8+ T-lymphocytes.
      i. Note: Apoptotic CD4+ and CD8+ T-lymphocytes are defined as cells staining positively for their cell type-specific antibodies, Annexin V and propidium iodide.

FLOW CYTOMETRY DATA OF THE RILA ASSAY PERFORMED ON FRESHLY OBTAINED AND FROZEN PBMCS

Table 1a-d. Flow cytometry data of the RILA assay performed on 10 healthy volunteers.
(a)

	Fresh PBMCs. non-irradiated (0 Gy)					
Volunteer ID	**Total measured**	**Time gate**	**Lymphocytes**	**Single cells**	**CD3 CD4**	**CD3 CD8**
1	150000	98.2 %	36.0 %	97.2 %	54.3 %	16.1 %
2	150000	96.4 %	45.2 %	97.7 %	48.0 %	16.5 %
3	150000	97.8 %	75.6 %	88.0 %	20.6 %	6.10 %
4	150000	97.7 %	35.3 %	98.1 %	40.3 %	19.7 %
5	150000	97.8 %	43.5 %	96.2 %	37.4 %	11.1 %
6	129440	28.7 %	58.2 %	99.3 %	56.2 %	25.7 %
7	150000	96.6 %	60.2 %	98.0 %	39.0 %	19.4 %
8	150000	95.8 %	58.0 %	94.2 %	33.9 %	13.9 %
9	150000	96.3 %	38.4 %	90.7 %	21.0 %	11.5 %
10	150000	96.9 %	33.8 %	95.8 %	34.4 %	24.6 %
Mean	*147944*	*90.2 %*	*48.4 %*	*95.5 %*	*38.5 %*	*16.5 %*
SD	*6502*	*21.6 %*	*13.9 %*	*3.60 %*	*12.1 %*	*6.13 %*

(b)

	Fresh PBMCs. irradiated (8 Gy)					
Volunteer ID	**Total measured**	**Time gate**	**Lymphocytes**	**Single cells**	**CD3 CD4**	**CD3 CD8**
1	150000	97.0 %	27.7 %	98.1 %	56.5 %	12.7 %
2	150000	97.7 %	38.9 %	97.5 %	49.3 %	11.2 %
3	150000	96.8 %	73.3 %	83.9 %	18.1 %	3.96 %
4	150000	98.3 %	30.4 %	98.7 %	35.1 %	12.4 %
5	150000	98.3 %	31.0 %	98.3 %	43.3 %	8.42 %
6	150000	93.9 %	49.4 %	98.6 %	62.8 %	18.5 %
7	150000	98.2 %	41.8 %	98.6 %	45.6 %	16.2 %
8	150000	97.8 %	48.7 %	94.7 %	38.6 %	11.1 %
9	150000	97.2 %	33.2 %	87.6 %	14.1 %	5.07 %
10	150000	96.5 %	29.1 %	97.0 %	39.0 %	18.2 %
Mean	*150000*	*97.2 %*	*40.4 %*	*95.3 %*	*40.2 %*	*11.8 %*
SD	*0*	*1.32 %*	*14.0 %*	*5.24 %*	*15.3 %*	*5.00 %*

(c)

Frozen PBMCs. non-irradiated (0 Gy)						
Volunteer ID	**Total measured**	**Time gate**	**Lymphocytes**	**Single cells**	**CD3 CD4**	**CD3 CD8**
1	150000	97.1 %	49.4 %	98.3 %	60.7 %	14.3 %
2	150000	98.6 %	62.0 %	98.1 %	56.1 %	18.6 %
3	150000	97.8 %	77.1 %	98.2 %	51.3 %	12.3 %
4	150000	96.3 %	55.4 %	97.7 %	45.2 %	17.9 %
5	150000	97.7 %	53.6 %	98.8 %	38.6 %	10.2 %
6	150000	96.6 %	74.1 %	98.7 %	55.4 %	21.2 %
7	150000	97.7 %	64.8 %	98.7 %	44.6 %	20.3 %
8	150000	96.9 %	40.7 %	97.8 %	43.3 %	18.2 %
9	150000	93.7 %	39.2 %	98.0 %	37.5 %	16.7 %
10	150000	96.5 %	50.3 %	98.7 %	41.7 %	28.1 %
Mean	*150000*	*96.9 %*	*56.7 %*	*98.3 %*	*47.4 %*	*17.8 %*
SD	*0*	*1.33 %*	*12.8 %*	*0.41 %*	*7.95 %*	*5.01 %*

(d)

Frozen PBMCs. irradiated (8 Gy)						
Volunteer ID	**Total measured**	**Time gate**	**Lymphocytes**	**Single cells**	**CD3 CD4**	**CD3 CD8**
1	150000	97.8 %	46.2 %	99.0 %	61.3 %	11.1 %
2	150000	97.1 %	58.3 %	99.0 %	60.6 %	14.7 %
3	150000	97.5 %	71.2 %	98.9 %	53.5 %	11.2 %
4	150000	97.1 %	48.3 %	99.0 %	36.1 %	11.3 %
5	150000	97.0 %	48.7 %	99.3 %	42.2 %	8.79 %
6	150000	97.8 %	57.2 %	98.7 %	62.2 %	18.2 %
7	150000	96.5 %	49.7 %	99.2 %	40.9 %	13.9 %
8	150000	97.4 %	25.6 %	99.2 %	40.3 %	13.0 %
9	150000	97.4 %	32.0 %	98.3 %	43.1 %	13.5 %
10	150000	97.0 %	35.8 %	99.2 %	37.5 %	19.1 %
Mean	*150000*	*97.3 %*	*47.3 %*	*99.0 %*	*47.8 %*	*13.5 %*
SD	*0*	*0.40 %*	*13.5 %*	*0.30 %*	*10.5 %*	*3.22 %*

Table 2. Differences in RILA percentages in non-irradiated (0Gy) versus irradiated (8 Gy) CD4 T-lymphocytes in healthy volunteers (n=10).

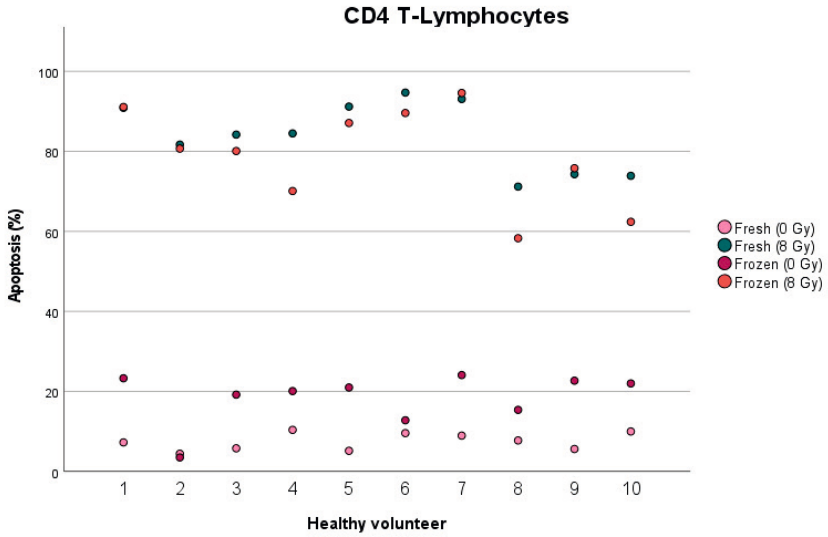
	Fresh PBMCs			Frozen PBMCs		
	CD3+CD4+			CD3+CD4+		
	Lymphocyte apoptosis (%)	Lymphocyte apoptosis (%)		Lymphocyte apoptosis (%)	Lymphocyte apoptosis (%)	
	Non-irradiated (0 Gy)	Irradiated (8Gy)	RILA frequency	Non-irradiated (0Gy)	Irradiated (8Gy)	RILA frequency
Volunteer ID						
1	7.3 %	90.9 %	90.2%	23.3 %	91.1 %	88.4%
2	4.4 %	81.7 %	80.9%	3.51 %	80.7 %	80.0%
3	5.8 %	84.2 %	83.2%	19.2 %	80.1 %	75.4%
4	10.4 %	84.5 %	82.7%	20.1 %	70.1 %	62.6%
5	5.2 %	91.2 %	90.7%	21.0 %	87.1 %	83.7%
6	9.6 %	94.7 %	94.1%	12.8 %	89.6 %	88.1%
7	9.0 %	93.1 %	92.4%	24.1 %	94.6 %	92.9%
8	7.8 %	71.2 %	68.8%	15.4 %	58.3 %	50.7%
9	5.6 %	74.3 %	72.8%	22.7 %	75.8 %	68.7%
10	10.0 %	73.9 %	71.0%	22.0 %	62.4 %	51.8%
Mean	*7.5 %*	*84.0 %*	*82.7%*	*18.4 %*	*79.0 %*	*74.2%*
SD	*2.2*	*8.6*	*9.3*	*6.3*	*12.3*	*15.2*

SD = standard deviation; PMBC = peripheral mononuclear blood cell; RILA = radiation-induced lymphocyte apoptosis. Results are based on positive Annexin V and propidium iodide staining. Details of RILA-assay protocol can be found in Supplementary Materials 1. RILA frequency is calculated by dividing 100% with 100% minus the percentages of apoptotic cells at 0 Gy (normalising) and multiply this value with the difference in percentage apoptotic cells at 0 vs 8 Gy.

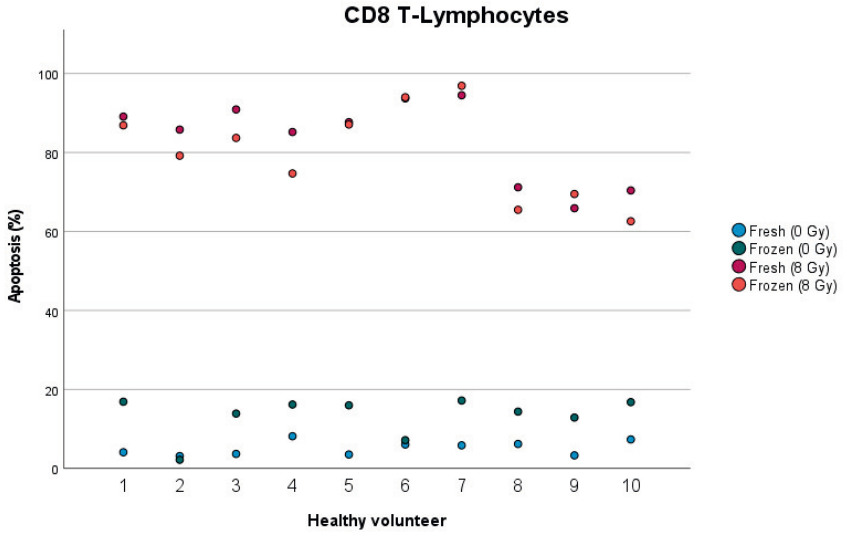
Table 3. Differences in RILA percentages in non-irradiated (0Gy) versus irradiated (8Gy) CD8 T-lymphocytes in healthy volunteers (n=10).

	Fresh PBMCs			Frozen PBMCs		
	CD3+CD8+			CD3+CD8+		
	Lymphocyte apoptosis (%)	Lymphocyte apoptosis (%)		Lymphocyte apoptosis (%)	Lymphocyte apoptosis (%)	
	Non-irradiated (0Gy)	Irradiated (8Gy)	RILA frequency	Non-irradiated (0Gy)	Irradiated (8Gy)	RILA frequency
Volunteer ID						
1	4.1 %	89.1 %	88.6%	16.9 %	86.9 %	84.2%
2	3.2 %	85.8 %	85.3%	2.2 %	79.2 %	78.7%
3	3.7 %	90.9 %	90.6%	13.9 %	83.7 %	81.1%
4	8.2 %	85.2 %	83.9%	16.2 %	74.7 %	69.8%
5	3.5 %	87.7 %	87.3%	16.0 %	87.1 %	84.6%
6	6.1 %	93.7 %	93.3%	7.2 %	94.0 %	93.5%
7	5.9 %	94.5 %	94.2%	17.2 %	96.9 %	96.3%
8	6.2 %	71.2 %	69.3%	14.4 %	65.5 %	59.7%
9	3.3 %	65.9 %	64.7%	12.9 %	69.5 %	65.0%
10	7.4 %	70.4 %	68.1%	16.8 %	62.6 %	55.1%
Mean	*5.15 %*	*83.4 %*	*82.5*	*13.4 %*	*80.0 %*	*76.8*
SD	*1.8*	*10.4*	*11.0*	*4.9*	*11.8*	*14.0*

SD = standard deviation; PMBC = peripheral mononuclear blood cell; RILA = radiation-induced lymphocyte apoptosis. Results are based on positive Annexine V and Propidium Iodide staining. Details of RILA-assay protocol can be found in Supplementary Materials 1. RILA frequency is calculated by dividing 100% with 100% minus the percentages of apoptotic cells at 0 Gy (normalising) and multiply this value with the difference in percentage apoptotic cells at 0 vs 8 Gy.



(a)



(b)

Figure 1a and b. Percentages apoptosis of CD4 and CD8 T-lymphocytes in non-irradiated (0Gy) versus irradiated (8Gy) fresh and frozen samples of healthy volunteers (n=10).

Chapter 9

Bilateral prophylactic mastectomy; should we preserve the pectoral fascia? Protocol of a Dutch double blinded, prospective, randomized controlled pilot study with a within-subject design (PROFAS)

Marloes E. Clarijs, Laurentine S.E. van Egdom, Cornelis Verhoef, Dalibor Vasilic, Linetta B. Koppert, PROFAS Collaborator Group

BMJ Open, Feb 2023

Introduction

Bilateral prophylactic mastectomy (BPM) in women with a high risk of developing breast cancer has shown to provide the greatest risk reduction. Many surgical guidelines recommend the removal of the pectoral fascia (PF) in mastectomies, however, there is no evidence to support this statement. Reported wound related complications following mastectomy include seroma, flap necrosis, infection, and hematoma. Seroma causes discomfort and may delay the reconstructive procedures. Whether removal or preservation of the PF influences drain volume, seroma formation, and other postoperative complications following BPM remains unclear. The aim of this study is to assess the impact of removal versus preservation of the PF on drain policy and seroma after BPM.

Methods and Analysis

This is a double blinded, prospective, randomized controlled pilot-study with a within-subject design. The inclusion criteria are women > 18 years, presenting in the Academic Breast Cancer Centre Rotterdam, who are opting for BPM. Patients with a history or diagnosis of breast cancer are excluded. According to the sample size calculation based on the difference in total drain volume, a number of 21 eligible patients will be included. Randomization will occur within the patient, which means PF preservation in one breast and PF removal in the contralateral breast. The primary study endpoint is total drainage volume. Secondary study outcomes include time to drain removal, number of needle aspirations, postoperative complications, and length of hospital stay.

Ethics and Dissemination

The study is approved by the Erasmus Medical Center Review Board (REC 2020-0431). Results will be presented during international conferences, and published in a peer-reviewed academic journal.

STRENGTHS AND WEAKNESS OF THIS STUDY

- PROFAS is the first surgical study that uses the within-patient randomization design to evaluate drain volume and seroma after PF preservation versus removal, and results will provide clear evidence for causality.
- According to the unique within-patient design, possible confounders are eliminated and this will strengthen the outcomes of our study.
- The primary limitation of this study is uncertainty of sample size calculation, as mean drain volume (primary outcome) after BPM in our institute is unknown. This may challenge the statistical analyses.

INTRODUCTION

Bilateral prophylactic mastectomy (BPM) involves removal of healthy breasts for breast cancer prevention. Indications include a BRCA 1 or 2 mutation or other genetic susceptibility, a strong family history with no demonstrable mutation, histological risk factors, and/or difficult surveillance. [1] The risk of developing breast cancer by the age of 70 years is 57- 65 % in woman with a BRCA 1 mutation and 45-47% in woman with a BRCA 2 mutation. [1,2] Importantly, BPM has been shown to reduce the risk of breast cancer by up to 95% in woman with BRCA 1 or 2 mutations. [3-6]

Halsted's radical mastectomy for invasive breast cancer included resection of the breast, overlying skin, pectoral major muscle, and an extensive lymph node dissection. [7] The radical mastectomy was abandoned in 1960 when more limited oncological breast surgery was introduced. Changes towards refined surgery are guided by similar oncologic outcomes and improved cosmetic results or quality of life. The simple and subsequently skin and nipple-sparing mastectomy was introduced in which the pectoral muscle was spared along with removal of the pectoral fascia (PF). [8] Ever since, many surgical guidelines recommend the removal of the PF to ensure tumor free margins. [9,10] However, there is no evidence to support this statement in early operable breast cancer, except for the minority of patients with tumor invasion in the PF. [11] The necessity of PF removal in prophylactic mastectomies is even more questionable.

It is known that the PF plays a role in lymph drainage, however, whether the removal or preservation of the PF influences seroma formation following mastectomy remains unclear. [12-14] The use of postoperative (suction) drains in breast cancer surgery have been shown to reduce the incidence and degree of seroma. [15,16] Nevertheless, the incidence of seroma is still 13-85%, and its sequelae forms the mainstay of complications in breast cancer surgery, varying from delayed wound healing, infection, skin flap necrosis, and patient discomfort. These complications will eventually delay the reconstructive procedures. [17-21] Preserving the PF may also have some advantages when a mastectomy is directly followed by submuscular implant reconstruction. The PF is a thin fibro-elastic layer, firmly attached to the pectoral muscle without a separating epimysium as found in other muscle fasciae, which prevents the disruption or detachment of the pectoral muscle during dissection and consequently exposure of the submuscular implant. [11,22] It is hypothesized that PF preservation may contribute to easier executable and more feasible reconstructive procedures, with superior cosmetic outcomes. Furthermore, as the PF is strongly adherent to the pectoral muscle, PF removal can result in muscle disruption. Most hematomas or postoperative bleedings originate in the pectoral muscle, and PF preservation may lead to less surgical muscle damage and hence reduced bleeding complications. [23]

To the best of our knowledge, there are no studies reporting on postoperative complications after PF preservation in women undergoing BPM. PROFAS is a pre-clinical study

that investigates the impact of removal versus preservation of the pectoral fascia on drain volume and complications after BPM followed by an immediate breast reconstruction using an within-subject randomization. We hypothesize that PF preservation decreases the total drain volume with subsequently seroma reduction and postoperative complications when compared to PF removal.

Main study objectives

The primary objectives are the impact of removal versus preservation of the PF on 1) the total drainage volume and 2) time to drain removal, and secondary objectives are the impact of removal versus preservation of the PF 1) seroma and number of needle aspirations, and 2) on postoperative pain, bleeding, wound related issues such as hematoma and infection, and hospitalization duration.

METHODS AND ANALYSIS

Study design

PROFAS is a Dutch prospective single center pilot-study, double blinded and randomized controlled with a within-subject design. The study includes high risk women above the age of 18 years presenting in the Erasmus MC Academic Breast Cancer Centre in Rotterdam, who are opting for BPM. Patients will be randomized after informed consent is given. Since the within-subject randomization design of the trial, preservation of the PF will be performed in one breast (intervention), while removal of the PF will be performed in the contralateral breast of the same patient (control). Consequently, the operation involves a total bilateral prophylactic mastectomy followed by an immediate reconstruction, with unilateral preservation of the PF. The surgery will be performed by three different experienced breast surgeons. The surgeon will operate both the right and left breast of an individual patient.

Patient and Public Involvement

There were no patients involved in the design of this study.

Intervention

A total mastectomy will be performed in the control breast: a procedure which includes removal of the breast glandular tissue including the PF and subcutaneously excision of the nipple-areolar complex, while the pectoralis muscle will be spared. As much of the healthy skin envelope will be preserved to enable the performance of an effective breast reconstruction afterwards. When a nipple-sparing mastectomy is performed, the skin envelope together with the nipple-areolar complex will be spared. The investigational part

of the operation is preservation of the PF. Dissection of cutaneous flaps and the breast with or without the PF will be performed with electrocautery. In the breast that is randomized to PF removal, the PF will be removed by electrocautery according to standard procedure. The procedure will be followed by an immediate reconstruction, either an autologous or implant-based reconstruction. In case of an implant-based reconstruction, the implants will be placed below the pectoral chest muscle (retropectoral). A closed suction drain will be placed bilaterally in the surgical wound bed at the end of the surgical procedure. The type of drain tube will be selected according to the attending surgeon's preference. For wound closure, one or two layers of (absorbable) sutures will be placed. No compression bandage will be used. The institution's guideline for drain removal will be followed post-surgery (see the section Outcome measurements).

Eligibility criteria

Women are eligible for this study if they are ≥ 18 years old, and scheduled for a BPM in the Erasmus MC Academic Breast Cancer Centre in Rotterdam. The ability to give written consent and adequate understanding of the Dutch language is a prerequisite. A subject will be excluded from participation in the study if they have a history or diagnosis of invasive breast cancer or ductal carcinoma in situ (DCIS), or other malignancies.

Randomization, blinding and allocation to intervention

Patients will be enrolled by the treating surgeon at the outpatient clinic. Randomization will be performed by computer-generated simple block randomization, with blocks of 4 and 6, which will be conducted by Castor Electronic Data Capture System. Per patient, each breast is allocated to the intervention- or control arm (i.e. preservation or removal of de PF, respectively). Allocation sequence is concealed until participants are enrolled. Randomization is revealed to the surgeon in the operating room shortly before start of the surgery. The patient and the outcome assessors (observer for drain volume) are both blinded for the assigned breast randomization. The surgeon(s) and coordinating researcher will not be blinded, and are, therefore, not allowed to measure the drain production. For this reason, the study is considered to be a double blind randomized controlled trial. The risk of exceptional circumstances that require unblinding is considered low, however, unblinding is permissible when necessary.

Outcome measurements

Each patient has the first scheduled clinical visit within postoperative week 1 or 2 and ad hoc thereafter, if needed. The drain production is observed by a nurse or ward doctor and is reported in the patients' medical file. When patients are discharged from the hospital with drains in situ, they will receive information from the ward nurse about drain care and drain amount measurements. The volume of 30 mL in 24 hours is established as a

guideline for timing of drain removal. When drain discharge is reduced to less than 30 mL per 24 hours the drain will be removed by a nurse in the hospital. The follow up time of each patient will be 6 weeks post=surgery.

The main endpoints are the impact of removal or preservation of the PF on the total drainage volume and the time to drain removal. Secondary endpoints are seroma and number of needle aspirations. The indication to perform a needle aspiration is the occurrence of seroma, which is defined as any clinically detected collection of fluid in the axilla or anywhere along the skin incisions requiring aspiration. Differences in drain policy will be measured according to the number of days the drain will be left in situ and the total drain volume. A volume of 30 mL in 24 hours is established as a guideline for timing of drain removal.

The definitions for the other secondary study endpoints are postoperative pain, measured with the Visual Analogue Scale (VAS); infection, defined as any wound appearance that is treated with antibiotics; hematoma, defined as collection of blood under the flaps that requires evacuation. Hospitalization is determined as duration of days in the hospital and/or readmissions.

Data collection

The patient's electronic health record will be viewed after removal of the drain for additional recorded variables, for example, hospital stay, the duration of drain use, the total drain volume of each breast, wound related issues such as hematoma and infection, the total volume of aspirated fluid and the number of needle aspirations (see Figure 1). Patient characteristics will be collected from the patient's electronic health record. These characteristics include 1) familial history of breast cancer, 2) BRCA1/2 mutation or other genetic susceptibility, 3) patient age at time of operation, 4) right/left dominance, 5) smoking-status, 6) time since start of surveillance if applicable (in case of gene mutation), 7) body mass index, and 8) co-morbidities.

Research data will be stored in a Castor database. Data is handled confidentially and will be coded (PROFAS 00 to 21). This record is filed at the investigational site and can only be accessed by the investigator and the supporting site staff. Data will be stored at the Erasmus Digital Research Archive. Study data will be stored for a maximum of 15 years after completion of the study.

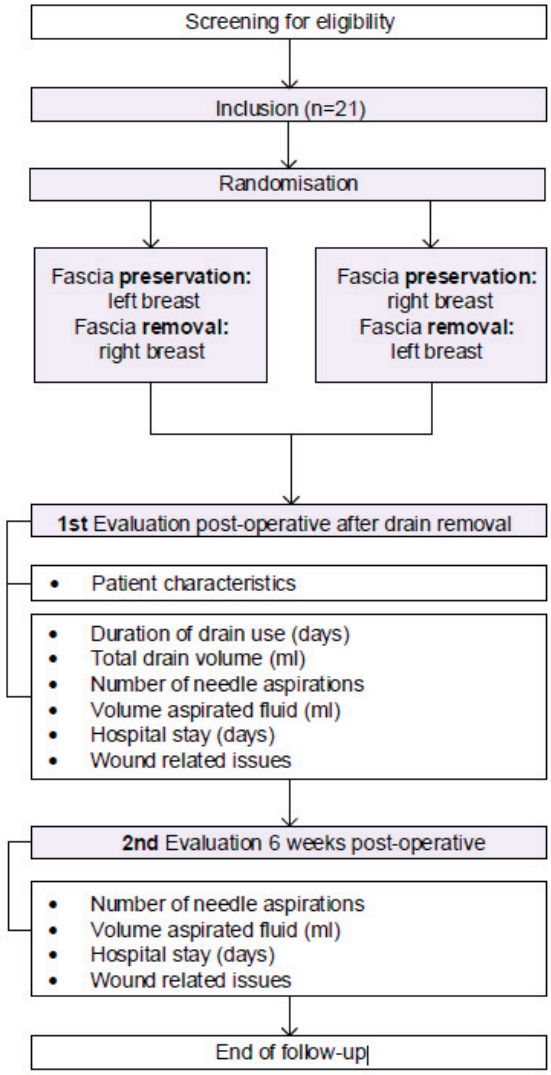


Figure 1. Study design

Ethics and dissemination

The study was approved by the local ethics committee of the Erasmus Medical Center (REC 2020-0431). The PROFAS study is registered at trialregister.nl (NTR7620) and Clinicaltrials.gov (NCT05391763). Written informed consent will be obtained from all participants prior to enrollment in the study. Results will be presented during international conferences, and published in a peer-reviewed academic journal.

Statistics

Sample Size

This is a pilot study assessing the effect of removal versus preservation of the pectoral fascia on seroma formation, and, thus, postoperative drain policy. There is no previous data of fascia preservation on drain volume in prophylactic bilateral mastectomies. According to the literature, a mean total drainage volume of approximately 545 mL is reported following mastectomy. In our institute, the total drainage volume in prophylactic mastectomies is lower, because no axillary dissection is performed. It is expected that fascia preservation will lower the drainage fluid with 100-150 mL of the total volume to be clinically relevant. In order to have sufficient statistic power to detect a difference of 100-150 mL in drainage volume between the intervention and control breast, with a power of 80% and a two-tailed alpha (error of 0.025), a number of 12 - 21 pairs is required. An SD of 165 mL for the control group and 135 mL for the intervention group was used. This means we aim to include 21 patients in this pilot study. This allows for using the results of this preliminary pilot study for an adequate power calculation of a full scale study.

Planned Analysis

In the analyses of total drain volume, differences in means between the PF preservation and PF removal breast within one subject will be calculated using the paired T-test. The McNemar test will be used to analyze differences in proportions of needle aspirations. Time to drain removal will be analyzed with a paired T-test or Wilcoxon Signed Rank test if not normally distributed. For the secondary study parameters, differences in proportions will be analyzed using the McNemar test and differences in means with the paired T-test. All statistical analysis will be stratified for left or right dominance. Differences in means or proportions will be supplemented with corresponding 95% confidence intervals. A two-tailed alpha of 0.05 will be considered statistically significant. All standard statistical analysis will be performed using SPSS (current version 25.0, Chicago, IL, USA) or R (current version 4.1.0, R Foundation for statistical computing, Vienna, Austria).

DISCUSSION

As an alternative to intensive breast cancer screening, women with a high breast cancer risk (e.g. BRCA 1/2 mutation) may choose for a risk-reducing bilateral mastectomy mostly followed by an immediate breast reconstruction. In a multicenter cohort study with eight Dutch academic centers, 38% of BRCA 2 and 42% of BRCA 1 mutation carriers choose for BPM. [24] The rate of prophylactic surgery varies widely and is determined by several factors, such as cultural context, alternative screening options, or country-specific established

guidelines. [25,26] In the early 2000s, one of the highest reported incidences of prophylactic mastectomies in mutation carriers was in the Netherlands. [27] A trend towards prophylactic mastectomies may be very well supported by breast reconstruction availability. The reconstruction options after BPM are either autologous or implant-based, or a combination of both. Nowadays, de-escalating surgical procedures are becoming increasingly relevant. [28,29] From Halsted's radical mastectomy to the modified radical mastectomy, and more recently the introduction of skin- and nipple-sparing mastectomies; more and more breast components have been left intact. To note, some institutes are already preserving the PF as part of standard procedure. [12,14] In the light of this, we believe that PF preservation should be reconsidered, and results of this preliminary pilot trial will be helpful to gain knowledge about the role of the pectoral fascia in seroma formation.

Balancing the remaining oncological risk versus expected beneficial surgical outcomes (e.g. less complications, better cosmetic outcome etc.) remains however challenging. BPM has shown excellent survival rates in high risk women. [30] When PF preservation was introduced in mastectomy patients, a main concern was the oncologic safety of the procedure. The PF was thought to act as a tumor barrier and preserving the PF could potentially lead to more chest-wall recurrences. As BPM is an important part of cancer risk management, unnecessarily exposing this specific population of high risk women to oncological risks should be avoided. The oncologic safety of PF preservation in breast cancer patients has been previously studied. These results have been summarized and described in a recently published systematic review. [14] Of the five included articles, three studies investigated oncological outcomes after PF preservation. In conclusion, there were no significant differences in chest-wall and (loco)regional recurrences, or distant metastasis, along with similar mortality rates. [13,31,32] PF preservation seems safe, even in breast cancer patients with an indication or wish for a mastectomy. [33,34] A general remark is to recognize the importance of the tumor-to-PF distance when PF preservation is considered. A distance of less than 5 millimeters between the tumor and PF increases the risk of PF involvement; and could, therefore, be a contraindication for PF preservation.

The occurrence of seroma was compared between preservation or removal of the PF in two studies. [12,32] Dalberg *et al* found no differences between those two groups, although lower seroma rates appeared in the PF preservation group compared to the PF removal group (31/100 (31%) versus 39/98 (39.8%), $p = 0.2$). A statistically significant higher seroma rate was found in the short-term axillary drainage group compared to standard axillary drain removal (if drain discharge was less than 40 ml per 24 hours) (48/99 versus 22/99, $p < 0.001$). Because a 2x2 factorial design was used, patients were randomly assigned to four study groups based on short-term or standard axillary drainage, and PF preservation or removal. [12] However, the exact number of patients in each group was not presented and results were not analyzed according to the four randomization groups. As both axillary drainage and PF preservation may influence seroma, outcomes were prone to bias.

Abdelhamid *et al* found significant lower incidence of seroma in the PF preservation group (5.6% versus 24.3%, p = 0.025), however, a clear definition of seroma was not provided. [32]

A thorough search in the literature revealed no articles describing the effect of fascia preservation on cosmetic outcomes or quality of life. To evaluate the success of the breast reconstruction, both objective measurements as well as a patient's own evaluation are needed. Patient-reported outcomes (PROs) are direct assessments from patients that reflect a patient's quality of life, psychosocial or functional status, and they have become increasingly important in breast cancer research. BPM is associated with cancer-related distress in mutation carriers, however, it appears to be also inherent to lower physical wellbeing compared to active surveillance. [35,36] PROs are measured with validated questionnaires, of which nowadays the Breast-Q is the golden standard to evaluate cosmetic and reconstructive breast surgery. As the reconstruction module of the Breast-Q is not designed for a within-subject randomization, PROs were not included in our protocol.

An advantage of the within-subject design is omitting possible confounding factors (except for left or right dominance, or performing surgeon), resulting in sufficient statistical power with a relative small sample size. With a small sample size only the necessary number of patients will be given the intervention, and if PF preservation seems to be superior to removal, implementation in routine breast (cancer) care will not be delayed. Moreover, this method is time efficient and will provide important information for a prospective full scale study. Patient inclusion started at the end of 2021. Due to the COVID pandemic, prophylactic mastectomies were one of the many surgical procedures that were postponed because of other medical priorities. Despite this, six patients are included in the study and the first four procedures were successfully performed.

ACKNOWLEDGMENTS

The authors would like to thank all those involved in the PROFAS Collaborator Group: T. van Dalen; C. de Betue; J. Rothbarth; E.V.E. Madsen; L.M. Beelen; M.A.M. Mureau; E.M.L. Corten; A.J.M. Luijsterburg; M.J. Hop; H.M. Zuijdendorp; N.A.S. Posch; C.M.C.A. van Laarhoven; M. de Kraker.

REFERENCES

1. Antoniou A, Pharoah PD, Narod S, et al. Average risks of breast and ovarian cancer associated with BRCA1 or BRCA2 mutations detected in case Series unselected for family history: a combined analysis of 22 studies. *Am J Hum Genet*. May 2003;72(5):1117-30.
2. Chen S, Parmigiani G. Meta-analysis of BRCA1 and BRCA2 penetrance. *J Clin Oncol*. Apr 10 2007;25(11):1329-33.
3. Domchek SM, Friebel TM, Singer CF, et al. Association of risk-reducing surgery in BRCA1 or BRCA2 mutation carriers with cancer risk and mortality. *JAMA*. Sep 1 2010;304(9):967-75.
4. Hartmann LC, Schaid DJ, Woods JE, et al. Efficacy of bilateral prophylactic mastectomy in women with a family history of breast cancer. *N Engl J Med*. Jan 14 1999;340(2):77-84.
5. Meijers-Heijboer H, van Geel B, van Putten WL, et al. Breast cancer after prophylactic bilateral mastectomy in women with a BRCA1 or BRCA2 mutation. *N Engl J Med*. Jul 19 2001;345(3):159-64.
6. Rebbeck TR, Friebel T, Lynch HT, et al. Bilateral prophylactic mastectomy reduces breast cancer risk in BRCA1 and BRCA2 mutation carriers: the PROSE Study Group. *J Clin Oncol*. Mar 15 2004;22(6):1055-62.
7. WS H. The Results of Operations for the Cure of Cancer of the Breast Performed at the Johns Hopkins Hospital from June, 1889, to January, 1894. *Ann Surg Oncol*. 1894;50(5):497-555.
8. Patey DH, Dyson WH. The prognosis of carcinoma of the breast in relation to the type of operation performed. *Br J Cancer*. Mar 1948;2(1):7-13.
9. Kaidar-Person O, Offersen BV, Boersma LJ, et al. A multidisciplinary view of mastectomy and breast reconstruction: Understanding the challenges. *Breast*. Apr 2021;56:42-52.
10. National Comprehensive Cancer Network. Guidelines Invasive Breast Cancer (Version 2.2022). https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf
11. Vallejo da Silva A, Rodriguez FR, Loures CM, Lopes VG. Mastectomy in the era of implant-based reconstruction: should we be removing the pectoralis fascia? *Breast*. Dec 2012;21(6):779-80.
12. Dalberg K, Johansson H, Signomklao T, et al. A randomised study of axillary drainage and pectoral fascia preservation after mastectomy for breast cancer. *Eur J Surg Oncol*. Aug 2004;30(6):602-9.
13. Salgarello M, Barone-Adesi L, Terribile D, Masetti R. Update on one-stage immediate breast reconstruction with definitive prosthesis after sparing mastectomies. *Breast*. Feb 2011;20(1):7-14.
14. Suijker J, Blok YL, de Vries R, van den Tol MP, Krekel NMA. Pectoral Fascia Preservation in Oncological Mastectomy to Reduce Complications and Improve Reconstructions: A Systematic Review. *Plast Reconstr Surg Glob Open*. Mar 2020;8(3):e2700.
15. Somers RG, Jablon LK, Kaplan MJ, Sandler GL, Rosenblatt NK. The use of closed suction drainage after lumpectomy and axillary node dissection for breast cancer. A prospective randomized trial. *Annals of Surgery*. Feb 1992;215(2):146-9.
16. Cameron AE, Ebbs SR, Wylie F, Baum M. Suction drainage of the axilla: a prospective randomized trial. *Br J Surg*. Dec 1988;75(12):1211.
17. Budd DC, Cochran RC, Sturtz DL, Fouty WJ, Jr. Surgical morbidity after mastectomy operations. *Am J Surg*. Feb 1978;135(2):218-20.
18. Aitken DR, Hunsaker R, James AG. Prevention of seromas following mastectomy and axillary dissection. *Surg Gynecol Obstet*. Apr 1984;158(4):327-30.
19. Gupta R, Pate K, Varshney S, Goddard J, Royle GT. A comparison of 5-day and 8-day drainage following mastectomy and axillary clearance. *Eur J Surg Oncol*. Feb 2001;27(1):26-30.
20. Porter KA, O'Connor S, Rimm E, Lopez M. Electrocautery as a factor in seroma formation following mastectomy. *Am J Surg*. Jul 1998;176(1):8-11.

21. Tadych K, Donegan WL. Postmastectomy seromas and wound drainage. *Surg Gynecol Obstet*. Dec 1987;165(6):483-7.
22. Stecco C, Macchi V, Porzionato A, Duparc F, De Caro R. The fascia: the forgotten structure. *Ital J Anat Embryol*. 2011;116(3):127-38.
23. Seth AK, Hirsch EM, Kim JY, et al. Hematoma after mastectomy with immediate reconstruction: an analysis of risk factors in 883 patients. *Ann Plast Surg*. Jul 2013;71(1):20-3.
24. Heemskerk-Gerritsen BAM, Jager A, Koppert LB, et al. Survival after bilateral risk-reducing mastectomy in healthy BRCA1 and BRCA2 mutation carriers. *Breast Cancer Res Treat*. Oct 2019;177(3):723-733.
25. Henry DA, Lee MC, Almanza D, et al. Trends in use of bilateral prophylactic mastectomy vs high-risk surveillance in unaffected carriers of inherited breast cancer syndromes in the Inherited Cancer Registry (ICARE). *Breast Cancer Res Treat*. Feb 2019;174(1):39-45.
26. Julian-Reynier CM, Bouchard LJ, Evans DG, et al. Women's attitudes toward preventive strategies for hereditary breast or ovarian carcinoma differ from one country to another: differences among English, French, and Canadian women. *Cancer*. Aug 15 2001;92(4):959-68. 10.1002/1097-0142(20010815)92:4<959::aid-cncr1406>3.0.co;2-v
27. Metcalfe K, Eisen A, Senter L, et al. International trends in the uptake of cancer risk reduction strategies in women with a BRCA1 or BRCA2 mutation. *Br J Cancer*. Jul 2019;121(1):15-21.
28. Freeman MD, Gopman JM, Salzberg CA. The evolution of mastectomy surgical technique: from mutilation to medicine. *Gland Surg*. Jun 2018;7(3):308-315.
29. Ghossain A, Ghossain MA. History of mastectomy before and after Halsted. *J Med Liban*. Apr-Jun 2009;57(2):65-71.
30. Heemskerk-Gerritsen BA, Menke-Pluijmers MB, Jager A, et al. Substantial breast cancer risk reduction and potential survival benefit after bilateral mastectomy when compared with surveillance in healthy BRCA1 and BRCA2 mutation carriers: a prospective analysis. *Ann Oncol*. Aug 2013;24(8):2029-35.
31. Dalberg K, Krawiec K, Sandelin K. Eleven-year follow-up of a randomized study of pectoral fascia preservation after mastectomy for early breast cancer. *World J Surg*. Nov 2010;34(11):2539-44.
32. Abdelhamid MI, Alkilany MM, Lofty M. Pectoral fascia preservation during modified radical mastectomy: why and when. *Egypt J Surg*. 2017;36(4):333-335.
33. Kaidar-Person O, Poortmans P, Offersen BV, et al. Spatial location of local recurrences after mastectomy: a systematic review. *Breast Cancer Res Treat*. Sep 2020;183(2):263-273.
34. Pifer PM, Bice RP, Jacobson GM, et al. The Lack of Consensus of International Contouring Guidelines for the Dorsal Border of the Chest Wall Clinical Target Volume: What is the Impact on Organs at Risk and Relationships to Patterns of Recurrence in the Modern Era? *Adv Radiat Oncol*. Jan-Mar 2019;4(1):35-42.
35. Lodder LN, Frets PG, Trijsburg RW, et al. One year follow-up of women opting for presymptomatic testing for BRCA1 and BRCA2: emotional impact of the test outcome and decisions on risk management (surveillance or prophylactic surgery). *Breast Cancer Res Treat*. May 2002;73(2):97-112.
36. van Egdom LSE, de Kock MA, Apon I, et al. Patient-Reported Outcome Measures may optimize shared decision-making for cancer risk management in BRCA mutation carriers. *Breast Cancer*. May 2020;27(3):426-434.

PART III

Chapter 10

Summary

Against the background of good prognosis and limited local treatment associated morbidity for primary breast cancer patients who undergo curative treatment, attention shifts to maintaining quality of life (QoL) as an important goal of care. Value-based healthcare is an approach to medical care that prioritizes the improvement of patient outcomes and the overall quality of care, rather than the quantity of services provided. In breast cancer, value-based care would aim to provide patients with the most effective treatments, minimize unnecessary procedures, and improve patient experience and satisfaction. This thesis emphasizes that measuring and evaluating outcomes that matter most to patients should be an important focus of breast cancer care.

PART I focusses on the QoL and patient reported outcomes (PROs) in breast cancer patients. It emphasizes the need for a standardized approach for implementing and measuring PROs and the use of normative PRO data. The QoL between surgical mastectomy techniques and the QoL in caregivers of breast cancer patients were evaluated. **PART II** illustrates first developments towards the prediction of breast cancer treatment related outcomes. Firstly, the focus lies on a three-dimensional imaging tool used in the preoperative, neo-adjuvant setting to evaluate tumor size and volume with the potential to be used in predicting pathologic tumor response. Secondly, an optimized novel method to measure radiation-induced lymphocyte apoptosis was developed to improve the implementation in clinical practice and enhance predictive modelling in patients with radiation-induced fibrosis. To complete this section, a study protocol about pectoral fascia preservation and its relation to postoperative outcomes was described.

PART I PATIENT REPORTED OUTCOMES IN BREAST CANCER PATIENTS

As the use of patient-reported outcome measures (PROMs) in breast cancer clinical trials continues to rise, the availability of normative data can fill the knowledge gap in the interpretation of PROMs. Normative data describe outcomes of a defined population without the specific condition of interest. The Breast-Q, a patient reported outcome instrument for cosmetic and reconstructive breast surgery, is widely used in both clinical research and practice. In **Chapter 2**, normative data of the Breast-Q's Breast-Conserving Therapy module from a Dutch population sample was acquired and compared to existing normative Breast-Q values. The social media platforms of the Erasmus Medical Center were used to direct participants to anonymously self-complete an online version of four domains of the preoperative Breast-Q Breast-Conserving Therapy module. A total of 9 059 questionnaire responses of participants without a history of breast cancer were analyzed. Median Breast-Q domain scores were 64.0 ± SD 18.0 ("Satisfaction with Breasts"), 69.0 ± SD 21.0 ("Psychosocial Wellbeing"), 92.0 ± SD 20 ("Physical Wellbe-

ing") and 59.0 ± SD 15.0 ("Sexual Wellbeing"). Prior non-breast cancer-related surgery was a significant predictor for higher log-transformed "Satisfaction with Breasts" (β = 0.04, $p < 0.001$) and higher "Sexual Wellbeing" (β = –0.05, $p < 0.001$) scores. Compared to previously published normative data, small differences were found in mean Breast-Q domain scores (mean differences ranging between 2.45 – 6.24). These results show that normative Dutch Breast-Q scores follow similar patterns across domains in comparison to previously published normative data. Normative Dutch Breast-Q data enables future comparisons in breast-related satisfaction and QoL of Dutch breast cancer patients against their age-matched peers.

Age- and gender-specific normative values for the EQ-5D-5L of the aforementioned cohort of Dutch females were provided in **Chapter 3**. Respondents' health-related quality of life (HRQoL) outcomes gathered with the EQ-5D-5L were converted into a single utility score, that reflects an individual's health state at a particular point in time. Normative utility scores represent the HRQoL of the general population, are of utmost importance in cost-effectiveness studies and should reflect relevant sexes and age groups. The aim of this study was to estimate EQ-5D-5L normative utility scores in a population of Dutch females, stratified by age, and to compare these scores to those of female populations of three other countries. Mean normative utilities were computed using the Dutch EQ-5D-5L value set, stratified by age, and compared to normative utility scores of female populations elsewhere. Data of 9037 women were analyzed and the weighted mean utility score was 0.911 (SD 0.155, 95% CI 0.908–0.914). The mean normative utility scores differed between age groups, showing lower scores in older females. Compared to other normative utility scores of female populations, Dutch mean utilities were consistently higher except for age groups 18-24 and 25-34. Additionally, to support the use of the Dutch EQ-5D-5L data in other settings, normative utility scores were also calculated by applying the value sets of Germany, United Kingdom and United States.

While chapters 2 and 3 focused on normative values, the following chapters used real-world patient data to evaluate the QoL. **Chapter 4** describes the need for a standardized approach for measuring the QoL with PROs in real-world metastatic breast cancer (MBC) patients. MBC patients are almost always treated to minimize the symptom burden, and to prolong life without a curative intent. Although the prognosis of MBC patients has improved in recent years, the median survival after diagnosis is still only 3 years. Therefore, it is important to provide the best possible QoL weighted against treatment risks and adverse symptoms, and QoL should play a leading role in making treatment decisions. Heterogeneity in questionnaires used to evaluate the QoL in MBC patients complicates the interpretability and comparability of PROs globally. This review shares insights into the role of PROMs in MBC patients, and to discuss important issues in measuring QoL. Routinely collecting symptom information using PROs could enhance treatment evaluation and shared decision-making. An up-to-date standardized outcome set may improve

the implementation of PROs, and facilitates collecting and sharing data to establish valid comparisons in research. This is a prerequisite to learn about how they could impact the clinical care pathway. In addition, the prognostic value of intensified PRO collection throughout therapy on survival and disease progression is promising.

In **Chapter 5**, PROs and complication rates were compared between Nipple-Sparing Mastectomy (NSM) and Skin-Sparing Mastectomy (SSM) followed by immediate breast reconstruction, as oncological safety of both procedures appears to be similar. This systematic review and meta-analysis selected 13 comparative studies including 3895 patients from 1202 articles found. Meta-analyses of the Breast-Q domains showed a significant mean difference of 7.64 in the Sexual Well-being domain ($p = 0.01$) and 4.71 in the Psychosocial Well-being domain ($p = 0.03$), both in favor of NSM. Using the specifically designed questionnaires, no differences in overall satisfaction scores were found. In conclusion, patient satisfaction scores were high after both NSM and SSM, however, NSM led to a higher sexual and psychosocial well-being. There were no differences in overall complication rates between the two groups. In combination with other factors, such as oncological treatments, complication risk profile, and fear of cancer recurrence, the decision for NSM or SSM has to be made on an individual basis and only if NSM is considered to be oncologically safe.

Breast cancer patients face many difficulties during their cancer journey and often need the support of their caregivers. Despite the fact that successfully providing informal care can have positive effects on caregivers' wellbeing, it may also have a negative impact on their QoL. In **Chapter 6**, the care-related quality of life in caregivers of breast cancer patients was evaluated. The association with breast cancer patients' HRQoL was assed, and potential predictors were identified. The Care-related Quality of Life Instrument (CarerQoL) was used to obtain CarerQoL utility scores by applying a pre-existent set of Dutch tariffs and the CarerQoL VAS score, which represented the overall happiness of caregivers. A total of 116 completed CarerQoL questionnaires were analyzed. Most caregivers were male spouses or partners (81.4%) with a mean age of 55.7 ± 16.4. The median CarerQoL utility score was 92.4/100 and median CarerQoL VAS was 8.0/10. We found weak correlations between CarerQoL VAS scores and patients' EQ-5D-5L utility score (0.301, $p=0.002$) and EQ VAS score (0.251, $p = 0.009$), and between EORTC QLQ-C30 scores and CarerQol VAS (0.339, $p <0.001$) and utility score (0.236, $p = 0.015$). There was a negative association between chemotherapy and log-transformed CarerQoL utility score ($\beta = -0.063$, $p = 0.001$) and VAS score ($\beta = -0.044$, $p = 0.038$) at six months follow-up. This was the first study to provide an evaluation of the CarerQoL in caregivers of Dutch breast cancer patients. Our research underlines the importance to include caregivers of breast cancer patients in clinical practice, provides reference values for future research, and the results can be used to manage the caregivers' expectations prior to treatment.

PART II A WAY TOWARDS PREDICTING BREAST CANCER OUTCOMES

The Automated Breast Volume Scanner (ABVS, Siemens ACUSON S2000TM) is an operator-independent ultrasound technique, which provides standardized, automated, and reproducible whole breast ultrasounds with the ability to reconstruct 3-D images. We investigated the applicability of three-dimensional breast ultrasonography to improve diagnostic imaging techniques during neo-adjuvant chemotherapy (NAC). In **Chapter 7**, the continuation of the RESPONDER 1 study was performed to evaluate the accuracy of tumor response measurement using the ABVS, and to compare with the MRI and post-operative histopathology in breast cancer patients that underwent NAC. Additionally, volume measurements alongside longest diameter measurements were analyzed and compared. Analyses included 96 patients for pre- and mid-NAC evaluations, and 57 patients for post-NAC evaluation. MRI and ABVS showed absolute concordance in 66% for the mid-NAC and 63% for the post-NAC evaluation. A 'good' significant correlation between ABVS and MRI was found for the difference in longest diameter measurement for the first (ICC 0.64 (95%CI 0.51-0.75)) and second (ICC 0.68 (95%CI 0.50-0.80)) response evaluation. For volume measurements, 'good' and 'excellent' significant correlations for the first (ICC 0.69 (95% CI 0.57-0.78) and second (ICC 0.98 (95% CI 0.96-0.99)) response evaluation were found. Post-NAC ABVS and MRI showed absolute concordance with histopathologic response in 71% versus 50%, respectively. Patients' acceptability ratings were higher for the ABVS compared to MRI. Because the ABVS showed good to excellent correlations with MRI tumor diameter and volume response, and is advantageous over MRI in terms of costs, ease and acceptability, it should be considered as a sufficient alternative.

The objectives of our non-matched case-control study as described in **Chapter 8** were to optimize the radiation-induced lymphocyte apoptosis (RILA) assay using frozen immune cells, to analyze the association between RILA frequencies in CD4 and CD8 T-lymphocytes and grade 3 radiation-induced fibrosis (RIF) after breast conserving therapy (BCT). RILA assay was performed on both freshly obtained and frozen peripheral blood mononuclear cells (PBMCs) that were isolated from blood samples of ten healthy volunteers. Similar RILA frequencies in frozen and freshly obtained PBMCs were found. Second, Dutch female breast cancer patients with ≤ grade 1 (controls, n = 13) or grade 3 (cases, n = 17) fibrosis on the LENT-SOMA scale were included. No statistically significant association was found between a decreased RILA frequency of CD4 or CD8 T-lymphocytes and an increased risk of developing grade 3 RIF in this relatively small clinical study (odds ratio 1.58 (95% CI 0.85-3.33, p=0.16) and 1.13 (95% CI 0.62-2.10, p=0.68). However, acute radiation dermatitis (≥ grade 2) and presence of an immunological disease in patients were identified as novel risk factors for RIF.

In **Chapter 9**, a study protocol to assess the impact of removal versus preservation of the pectoral fascia (PF) on drain policy and seroma after bilateral prophylactic mastectomy (BPM) was described. Many surgical guidelines recommend the removal of the PF in mastectomies, however, there is no evidence to support this statement. Reported wound related complications following mastectomy include seroma, flap necrosis, infection, and hematoma. Seroma causes physical discomfort and may delay the reconstructive procedures. The double blinded, prospective, randomized controlled pilot-study with a within-subject design is unique and will provide clear evidence. This means randomization will occur within the patient with PF preservation in one breast and surgical excision of the PF in the contralateral breast. The inclusion criteria are women > 18 years, presenting in the Academic Breast Cancer Centre Rotterdam, who are opting for BPM. A number of 21 eligible patients will be included. The primary study endpoint is total drainage volume. Secondary study outcomes include time to drain removal, number of needle aspirations, postoperative complications, and length of hospital stay. Patient inclusion started at the end of 2021, with currently eight inclusions and eight successful procedures, and results are expected in 2024.

SUMMARIZING

Due to the shift towards a value-based approach in breast cancer care, more attention is being paid to a patients' quality of life and shared decision-making during and after breast cancer treatment. The standardized measurement of outcomes, both PROs and clinical outcome measures, will lead to an improvement in the care delivered for the individual patient. The results of this thesis can aid in the implementation and interpretation of PROs, both in daily clinical care and in breast cancer-related research. An important next challenge lies the prediction of both clinical outcomes as well as quality of life related outcomes after breast cancer treatment.

Chapter 11

General discussion and future perspectives

MEASURING OUTCOMES: A STANDARDIZED APPROACH

To improve patients' health care experience in a value-based way, it's essential that clinicians actively involve patients in decision-making and capture their perspectives. Incorporating the patients' voice is ethically desirable, but also fundamental to improve overall patient outcomes. There are many processes that can be adapted within organizations to make them more value-based, both internally and externally. An internal example is the continuous improvement and learning by transparently comparing outcomes among healthcare providers. Externally, it refers to collaborations with health insurers to reimburse care based on outcome rather than service. [1] In other words, delivering good results by improving value for patients, defined as health outcomes achieved that matter most to patients, relative to the cost of achieving those outcomes. To realize this healthcare transformation, patient engagement and a comprehensive, standardized collection of health outcomes and patient reported outcomes (PROs) are mandatory.

PROs play an important role in providing a broader understanding of a patient's health status and treatment experience. It has been shown that patient level PRO data can be used in daily care settings to better involve patients in medical decisions and patient-provider communication[2-4], while data aggregated across providers can be used for quality improvement by benchmarking, shared learning, and information provision. [4-7] Aggregated PRO data may also be used to provide real-world evidence about treatment effectiveness and safety, and accountability to payers and the public. [8] A more universal and standardized approach to select patient reported outcome measures (PROMs) could enhance patient-centered care and increase the uptake of PROMs in clinical practice. Many initiatives worldwide have recognized the importance of collecting PROMs as part of standard care. The International Consortium for Health Outcomes Measurement (ICHOM) was founded with the aim to define a minimum standard set of outcomes for every major medical condition, including breast cancer. [9] ICHOM has played a prominent role in incorporating PROMs along with clinical outcomes in these standard sets. Although many health care providers and patients have a strong interest in measuring health outcomes, its implementation and engagement in health systems in Europe is slowly improving. Implementing a PRO system is known for barriers such as clarity of PROM questions, integration and synchronization of PRO data in the electronic health system, conflicting providers' opinions and the burden for patients, but above all requires a change in the culture of hospitals. [6,10,11] For successful implementation, it is important that all involved parties and stakeholders are aligned. The European Innovative Medicines Initiatives Funded Health Outcomes Observatory (H2O) is a strategic partnership between the public and private sectors to create a robust data governance and infrastructure model to collect and incorporate patient outcomes at scale into healthcare decision making at an individual and population level. [12] While ICHOM focuses on identifying what needs to

be measured to improve care and patient outcomes, H2O focuses on implementing these measurements in a way that is meaningful and relevant for patients to enhance communication between patients, healthcare providers and healthcare systems in routine clinical practice. Moreover, H2O strives for developing an efficient system for standardized health data collection and usage as part of the value-based healthcare approach, to ultimately drive better outcomes for patients. [13] A remarkable aspect of the initiative is that the H2O consortium brings together patients, patient advocates, clinicians, health care providers, researchers, and executives from the medical and pharmaceutical industry. In healthcare, a transition is required towards a proactive approach to help patients take control of the management of their health condition, and support self-care. This can be effective by improving quality of life en reducing outcomes such as side-effects or hospital admissions. In general, digital transformation and e-Health interventions are a fundamental tool to enhance patient-centered care, and will also increase the uptake of PROMS. H2O acknowledges this transformation by providing dashboards and digital tools for patients, and a data system that gives patients autonomy to control their data flows and allows for data sharing. The longitudinal PRO data in a real world setting and at population level can offer meaningful evidence for health policy and decision making, besides empowering patients at patient level. The H2O initiative will focus on diabetes, inflammatory bowel disease, and cancer amongst which (metastatic) breast cancer. In **Chapter 4**, we concluded that an important step in accelerating value-based health care for metastatic breast cancer patients is to implement an up-to-date standard outcome set as a prerequisite for clinical care improvement. As a result of a collaboration between H2O and ICHOM, a core outcome set containing PROMs and clinical variables for metastatic breast cancer patients was developed in 2022. [14] This outcome set is important for standardization of clinical research to develop a stronger theoretical foundation for future research, and will be first implemented in Austria, Germany, the Netherlands, Spain, and Denmark.

PATIENT REPORTED OUTCOME MEASUREMENT PROPERTIES

Other recent PROM developments have been focusing on better measurement properties, such as the application of common metrics and computer adaptive testing (CAT). [15] Common metrics are statistical models based on modern test theory (item response theory, IRT), that cover multiple questionnaires and, therefore, allow different questionnaires to be scored on a common scale. [16,17] Despite the great effort by ICHOM to develop standard sets, considerable overlap in PROs across these standard sets has been found, with large differences in terminology used, and the recommendation of different PROMs for the same PROs. [18] The Patient-Reported Outcomes Measurement Information System (PROMIS) is a conceptual framework of commonly relevant PROs across the physical,

mental and social functioning domains. In these domains, PROMs are not disease-specific but applicable across many patient populations. PROMIS also created standardized item banks (i.e. large sets of questions), offering the prospect of a less burdensome and more valid PRO assessment through tailored short forms and CAT. CAT describes an assessment of the respective construct (e.g. pain, fatigue) that uses specific algorithms to tailor questions deemed most informative for a patient based on currently available information. This results in greater precision without extending the questionnaire length, and decreases the effort and time for patients to answer questionnaires. Results have shown highly reliable and comparable scores if only a few relevant items were questioned. [15] In conclusion, an IRT-based standard set would only need to include the domains of interest, rather than specific questionnaires. Moreover, common metrics and construct-specific item banks would enable to compare data despite the fact that different items or instruments were used. The future perspective of PROMS is applying IRT and CAT where possible. [19] Especially in patients with a significant burden of disease, for example patients with metastatic breast cancer in a palliative phase, short questionnaires together with an adequate evaluation of their quality of life (QoL) is something important to strive for.

Even though PROM score differences between breast cancer treatment may exhibit statistical significance, this may not necessarily reflect a meaningful clinical change. One of the reasons clinicians are skeptical about PROMs, is the lack of clear instructions how to interpret PROM scores that would regard as meaningful. The interpretability and uptake of PROMs can be increased with normative scores (**Chapter 2)** and Minimal Clinically Important Differences (MCID), defined as the smallest difference in the score or domain of interest which patients perceive as beneficial and which would mandate, in the absence or troublesome side effects and excessive costs, a change in patients' management. More research focusing on establishing MCIDs for breast cancer specific PROMs is needed, however, no standard method for calculating MCIDS are currently available. [20] Fortunately, the usability of PROMs has increased with the development of an electronic PRO system and implementation in the patients' electronic health records. Electronically collecting PROMs instead of paper-based questionnaires provides a certain flexibility in completion time and location, allows for data collection on a larger scale, and enables the application of CAT. Patients' PROM results before, during, and after treatment can be viewed easily on dashboards to recall changes in their QoL or to compare patients' scores with age-, gender-, and country-specific normative and reference values. In **Chapter 3,** normative utility scores of the EQ-5D-5L were obtained in a Dutch female population. The reason to choose for the EQ-5D-5L questionnaire was the fact that the Academic Breast Cancer Centre has been using the EQ-5D-5L in its electronic PROM collection tool ("Zorgmonitor") as part of standard care over the last years. This would ease the comparisons between normative scores and EQ-5D-5L scores of breast cancer subgroups. Secondly, the normative scores can be used for cost-effectiveness studies to avoid making

assumptions about the health of the general population, as most cost-effectiveness models work with EQ-5D based utilities. The EQ-5D-5L can be used to calculate a utility score which represent the personal desirability of an individual's health state at a particular point in time and generally ranges between 1 (perfect health) and 0 (equal to death). [21] Subsequently, these utility scores can be used to calculate quality adjusted life years of a specific group of people over time, which can be applied to specific health states in cost-effectiveness analyses. Due to the variety of utility parameters (as a result of different HRQoL measures) for breast cancer health states, choices have to be made about which parameters to apply as this may influence in cost-effectiveness analyses outcomes. [22,23] Despite these arguments, there is currently an ongoing debate whether the 10 item PROMIS Global Health might be advantageous over the EQ-5D-5L in measuring generic QoL, as it is based on item banks. Given this, the Erasmus Medical Center has implemented hospital-wide generic PROMs for every patient who enters the out-patient clinic, in which the EQ-5D-5L has been replaced by the PROMS-10. Several studies have been performed to enable mapping between already existing EQ-5D scores and PROMIS. [24,25] Forthcoming mapping studies between de EQ-5D-5L and PROMIS-10 with data from our institute's breast cancer population are planned, as well as implementing CAT for the EORTC-QOL-C30 questionnaire.

PREDICTING BREAST CANCER RELATED OUTCOMES

The greater goal in the field of medicine is to individualize patients' management towards tailored-made treatments and patient-centered care, and to reduce the burden of disease along with avoiding overtreatment. Predictive modeling helps patients and clinicians in guiding shared-decision making and manage patient expectations prior treatment. Predicted outcomes are often specific events, such as death or complications, but they may also be quantities, such as disease progression, (changes in) pain, or quality of life. Breast cancer diagnosis and treatment can affect the QoL in different ways, therefore, prediction of long-term physical, psychosocial, and sexual outcomes is imperative. Interestingly, research has shown that PRO-supported care can have significant prognostic value in a variety of medical conditions, including cancer, and can provide predictive information on disease progression, treatment response, and overall survival. In particular, several studies have shown an increase in overall survival through intensified HRQoL monitoring using PROs. [26,27] Additionally, PROs can provide important information on symptom severity, patient's functional status and ability to perform daily activities, which can have implications for their long-term prognosis and survival. [28] A recent meta-analysis identified several PRO domains (e.g. fatigue, appetite loss, physical functioning) to be independent predictors for overall survival in metastatic breast cancer patients. [29] One can assume that PRO

monitoring might facilitate an early detection of symptoms associated with adverse events or disease progression, thus enabling timely countermeasures, which ultimately result in improved overall survival. The results underline the importance of baseline measurements and the systematic administration of PROs to capture this prognostic information.

PREDICTION MODELLING AND ARTIFICIAL INTELLIGENCE

Predicting outcomes with the application of machine learning techniques and artificial intelligence (AI) in oncological research is rapidly evolving. AI has the ability to generate risk-profiles of patients, for which large and complex datasets are processed. Such datasets include demographic, histologic, radiological and molecular characteristics. The central challenge is how to integrate diverse, multimodal information (clinical, imaging and molecular data) in a quantitative manner to provide specific clinical predictions that accurately and robustly estimate patient outcomes as a function of the possible decisions. [30] However, these methods have rarely been used on PROMs solely. The predictive capability of machine learning may optimize clinical treatment decision-making and thereby improve patient outcomes and patient empowerment. PROMs in predictive research can be used without any preconceived theoretical constructs (for example, predicting the risk of pain or hospital re-admission), and is therefore an important step towards patient-centered care with focus on the patient's perspective. [31,32] There are currently no existing machine learning tools available for breast cancer surgery, however, results of PRO machine learning concerning other medical diagnosis seem promising. [33,34] A previous study from our research group did try to apply machine learning methods to PROM datasets in order to predict QoL in breast cancer patients after breast surgery. [35] Learned from this experiment, the development of a prediction model needs baseline and prospectively collected PROs, a sufficiently large sample size and thorough external validation. Since PROM collection is considered standard of care at the Erasmus MC for several years now and with initiatives such as H2O, breast cancer datasets will progressively enlarge over time. Importantly, harmonized PRO data (standardized questionnaires, systematic time points, baseline measurements) is a prerequisite. In this way, utilizing machine learning and AI provide a promising avenue for enhancing the usefulness of PROMs.

The application of AI, and in particular deep learning algorithms, for the interpretation of medical images has also made significant advancements in breast cancer research. [36] Deep learning algorithms are being used to develop models that can identify disease, for example breast cancer detection on mammography. [37,38] Radiomics, the process of extracting quantitative properties, named features, from an image is based on the hypothesis that there is a relation between imaging features and biological information. Interestingly, a radiomics model can be developed, for example, to identify patients with partial or

complete pathologic response after neo-adjuvant treatment. Nowadays, the most accurate image modality to assess the response evaluation during NAC is by MRI. To eventually predict pathologic complete response (pCR), MRI is known for a high specificity but low sensitivity. [39,40] With increasing pCR rates during the last decade, more physicians are asking for possibilities to diagnose pCR with noninvasive methods. pCR prediction is of high interest because a valid prediction of residual tumor absence could strongly influence the extent of surgery. [41] Results of a recent systematic review focused on MRI-based radiomics for tumor response prediction to NAC in breast cancer patients showed promising results. [42] However, these radiomics models are only been applied to pre-NAC MRI images while images during routine response evaluation of the target lesion(s) after three to four chemotherapy doses may improve the results. The 3D ultrasound of the breast (ABVS) as described in **Chapter 7** of this thesis, is also available in addition to the MRI-scan at the same time points. Acknowledging the fact that the ABVS was more acceptable than MRI, achieved comparable results compared to MRI in tumor diameter and volume response evaluation, together with lower costs, the ABVS seems to be a good alternative for future response evaluations during NAC. It would be interesting to quantify pCR after NAC using radiomics features derived from 3-D ABVS ultrasound images and eventually predict pCR, specified for breast cancer subtypes. Although the response evaluation can currently not be based on the 3D ultrasound alone, as the axilla is not visualized, it may add value or even perform equal to the MRI based radiomics model. Another application of 3D imaging is tumor *volume* assessments to predict pCR. Current RECIST criteria used for tumor response evaluation depend on unidimensional size changes only, while tumor *volume* measurements might be a better discriminator for tumor response. However, consensus regarding response criteria for tumor volume are lacking. Results of the RESPONDER II trial (**Chapter 7**) can be used to determine cut-off values for tumor volume response evaluation and to assess its prognostic value with breast cancer survival. As neo-adjuvant endocrine therapy is more often indicated, the abovementioned 3-D ABVS and radiomics model could also be applied to this patient group.

While AI has shown great promise in the field of breast cancer, it is important to recognize that the technology is still in the early stages of development and must be validated through rigorous clinical trials. Reproducibility and external validation of models is of great importance. Additionally, AI should be used in combination with traditional medical methods and decision-making, not as a replacement, to ensure the best outcomes for patients.

COSMETIC OUTCOME PREDCITION AFTER BREAST CONSERVING TREATMENT

The surge of automated prediction and data mining has created new possibilities. A first step towards predicting cosmetic outcome after breast conserving surgery using large datasets with imaging features has shown encouraging results. [43] Predicting cosmetic outcome can be of great value, as unfavorable cosmetic outcome is reported up to 25% of patients that underwent breast conserving therapy (BCT). [44,45] A previous study used breast photographs representing different surgeries and cosmetic outcome (BCT 3 scenarios, mastectomy with or without reconstruction 3 scenarios) that were showed to the general population and breast cancer patients. In both groups, BCT with good cosmetic outcome was preferred and BCT with poor cosmetic outcome was rated the lowest, underlining the importance of predicting cosmetic outcome pre-operatively (data not published). With at least equal survival rates for BCT together with favorable QoL, more patients opt for BCT, however, the balance between a clean resection and aesthetic outcome is a key issue and difficult to predict. A definition of aesthetics is very broad and it is difficult to comprise cosmetic outcome in one evaluation. Cosmetic outcome relies on various factors, often subjectively measured by visual inspection based on breast shape, colour, or irregularity. Taking this into account, the evaluation of cosmetic outcome performed by observers is questionable and poorly reproducible. This does not mean that visual assessment using pre- and post-operative photographs is useless; but combining this with objective measures, such as the frequently used BCCT.core, may provide a more complete cosmetic evaluation. [46-48] Interestingly, the BCCT.core in combination with extracting predesigned features from a patients photograph could be applied to machine learning models. Vos et al. developed a decision model that can predict the cosmetic outcome by generating a tumor volume and breast volume ratio to improve treatment decision making, e.g. choice between mastectomy or BCT. [49,50] Parameters used in this model include breast volume, tumor volume, localization of tumor in terms of the quadrant of the breast. Breast volume and tumor volume can be measured by the 3-D ABVS, in a similar way as described in **Chapter 7**, as the 3-D ABVS showed high association with the histopathological measurement of tumor volume. [51] To investigate whether this prediction model works, results of the ongoing TURACOS trial must be awaited. [52] The TURACOS trial is a multicenter, single-blinded, randomized controlled trial comparing standard preoperative work-up to a work-up with the additional prediction model. It is expected that a superior cosmetic result in breast cancer patients opting for BCT is seen in the group randomized to the pre-operative prediction tool. This prediction tool can be especially usefully in patients with small breast but large breast tumor, to advocate for BCT or mastectomy depending on the tumor quadrant localization. Photographs prior to surgery and 1 year post-surgery are also obtained, resulting in a large database of breast photographs and

BCCT.core outcomes that will enable the development, testing and validation of machine learning models to improve cosmetic outcome prediction. In the end, predicting cosmetic outcome after BCT might also improve QoL, therefore, the (long-term) QoL of patients included in the TURACOS trial will be evaluated at multiple time points. A critical point is that conventional BCT has advanced onto oncoplastic surgery techniques with ranging complexity. This means that the appearance of the breast will be altered during surgery, and knowledge on QoL and cosmetic outcome after these procedures is not known. [53] Besides oncoplastic techniques, the cosmetic result after BCT depends largely on the way the operation is performed in terms of total excision volume, tumor localization, and scars. Moreover, BCT is almost always followed by radiation therapy. Radiation therapy can cause severe side effects, among which fibrosis is a late complication with various clinical symptoms, e.g. pain, skin induration and thickening, limited joint mobility, and lymphedema. Although radiation induced fibrosis is rare, the consequences can have a major impact on quality of life, cosmetic outcome and costs. The RILA assay (**Chapter 8**) to predict radiation induced fibrosis has already been used by other institutes as clinical routine after validation and CE-marking based on a previous study. [54,55] Future research should be investigating in radiation induced fibrosis prediction, in terms of a prognostic model including clinical risk factors (presence of an auto-immune disease, boost yes/no) that are known before start of treatment and the RILA-assay. To illustrate, if a patient is preoperatively identified as high-risk for developing RIF, an mastectomy (with or without immediate implant based or autologous reconstruction) that not necessarily requires radiotherapy can be optional. In this way a potential severe treatment complication, including additional invasive surgery, can be prevented. Moreover, when an alternative treatment is not preferred, close monitoring and early treatment can potentially minimize the negative consequences of RIF. Also PROs should be further investigated to determine its role in prediction modeling for patients at high risk of developing radiation induced fibrosis.

DE-ESCALATING BREAST CANCER RELATED SURGERY

In oncologic surgery, the vision is changing more and more into de-escalating surgery, active surveillance, and combining surgery with radiation or oncologic treatment modalities. A number of trials have shown equivalent survival outcomes following different de-escalating treatments, for example omitting axillary dissection, re-excision or radiotherapy in certain subgroups. [56,57] Breast cancer is common, often discovered in early-stages due to screening programs, and highly curable with great survival rates, which makes it an interesting group to investigate. Consequently, patients might be at risk for overtreatment. Thus, it seems important to continuously ask ourselves why certain guidelines are followed.

The PROFAS study (**Chapter 9**), in which the role of fascia removal in bilateral prophylactic mastectomies was questioned, has presently completed nine successful procedures. Another possible benefit of pectoral fascia preservation that was not discussed in **Chapter 9**, is its effect on cosmetic outcome. Cosmetic outcome was not included as an objective in this study, as it may implied that a cosmetic difference could be found between the operated breast due to the within-subject design. This would not be ethically justified in patients seeking for risk-reducing surgery. We do not believe that fascia preservation can lead to major aesthetic changes, but when the placing of a submuscular implant is planned at the same time of a mastectomy, the preservation of the pectoralis fascia may be of great help. The pectoral fascia aids the medial and inferior aspects of the muscle to remain firmly attached to the thoracic wall, greatly reducing the risk of its accidental detachment, which may jeopardize implant coverage. In the same way, it helps with the cohesions of the pectoralis fibres, preventing its disruption during dissection, which may cause exposure of the implant. [58,59] Although PROFAS is a pilot study, results can be used to determine the sample size for a full scale study. If we succeed in demonstrating that fascia preservation results in less drain production, earlier removal of the drain, and therefore less seroma formation, this could become the gold standard in bilateral prophylactic mastectomies. However, translating these results to the group of breast cancer patients undergoing unilateral mastectomy requires additional research. While studies have shown pectoral fascia preservation to be oncologically safe if certain criteria's are met, and already occurs in a substantial part of Dutch medical centers[60], there is still insufficient evidence to support PF preservation as standard care in national guidelines. Future studies should therefore provide insights into all aspects of pectoral fascia preservation.

Concerning de-escalating surgery, PROMs will continue to have an important role in this discussion. As mentioned above, pCR after neoadjuvant treatment results in better survival rates. Trials are currently even investigating the safety of omitting surgery in case of pCR for invasive cancer, although high rates of recurrent disease have been found. [61,62] Similarly, node positive breast cancer patients with an axillary pCR after NAC do not benefit from axillary lymph node dissection. Therefore, less invasive axillary staging procedures have been introduced to establish response-guided treatment, but their impact on QoL is unknown. [63,64] As PROs are routinely collected within the Erasmus MC Academic Breast Cancer Center, QoL data after different axillary treatments is available and will be used for mixed modelling analysis. The cohort involves women diagnosed with breast cancer who received either axilla preserving surgery with or without axillary radiotherapy or full axillary lymph node dissection with or without axillary radiotherapy. Using this QoL data, shared-decision making for axillary treatment in the consultation room can be strengthened. It would also be beneficial to conduct a validation study with other databases, such as the Dutch registry MINIMAX

study that investigates the impact of less invasive axillary staging procedures on QoL. [64] Results of this multicenter study must be awaited to state proper conclusions.

SUMMARIZED

In a constantly improving and changing health care system, where patient-centered care is being more prioritized, measuring PROs should be a routine clinical assessment. Particularly in the field of breast cancer, with major developments in PROMs over de last years, the necessity for comparable outcome data is apparent. Research should focus on increasing the uptake of PROMs in routine clinical care, by showing its clinical applicability and interpretability. The uptake of PROMS can be improved by the arrival of digital transformation and e-Health interventions. By using such instruments, patients can take active control in their own health journey. Real world data can be of great value in breast cancer patients to evaluate, compare, and visualize their quality of life with the normal population and peers. First steps towards predicting breast cancer related outcomes are promising, with upcoming prediction models, AI and machine learning techniques providing a new era of medical innovation. By this, outcome driven care with a value-based approach in breast cancer care will continue to evolve.

REFERENCES

1. Porter ME, Lee TH. *The Strategy That Will Fix Health Care.* Vol 91:24: Harvard Business Review; 2013.
2. Chen J, Ou L, Hollis SJ. A systematic review of the impact of routine collection of patient reported outcome measures on patients, providers and health organisations in an oncologic setting. *BMC Health Serv Res.* 2013;13:211.
3. Velikova G, Booth L, Smith AB, et al. Measuring quality of life in routine oncology practice improves communication and patient well-being: a randomized controlled trial. *J Clin Oncol.* 2004;22(4):714-724.
4. Kotronoulas G, Kearney N, Maguire R, et al. What is the value of the routine use of patient-reported outcome measures toward improvement of patient outcomes, processes of care, and health service outcomes in cancer care? A systematic review of controlled trials. *J Clin Oncol.* 2014;32(14):1480-1501.
5. Kool M, van der Sijp JR, Kroep JR, et al. Importance of patient reported outcome measures versus clinical outcomes for breast cancer patients evaluation on quality of care. *Breast.* 2016;27:62-68.
6. van Egdom LSE, Oemrawsingh A, Verweij LM, et al. Implementing Patient-Reported Outcome Measures in Clinical Breast Cancer Care: A Systematic Review. *Value Health.* 2019;22(10):1197-1226.
7. Prodinger B, Taylor P. Improving quality of care through patient-reported outcome measures (PROMs): expert interviews using the NHS PROMs Programme and the Swedish quality registers for knee and hip arthroplasty as examples. *BMC Health Serv Res.* 2018;18(1):87.
8. Porter ME, Teisber EO. *Redefining health care: creating value-based competition on results.* Harvard Business Press; 2006.
9. International Consortium for Health Outcomes Measurement (ICHOM). www.ichom.org.
10. Basch E, Snyder C. Overcoming barriers to integrating patient-reported outcomes in clinical practice and electronic health records. *Ann Oncol.* 2017;28(10):2332-2333.
11. Nguyen H, Butow P, Dhillon H, Sundaresan P. A review of the barriers to using Patient-Reported Outcomes (PROs) and Patient-Reported Outcome Measures (PROMs) in routine cancer care. *J Med Radiat Sci.* 2021;68(2):186-195.
12. Stamm T, Andrews M, Benard AHM, et al. Strengthening the Patient Voice in Health Outcome Measurement in Real-World Data in Europe - the Health Outcomes Observatory. *Value in Health.* 2022;25(12):S472-S472.
13. Stamm T, Bott N, Thwaites R, et al. Building a Value-Based Care Infrastructure in Europe: The Health Outcomes Observatory. *N Engl J Med Catalyst Innovations in Care Delivery.* 2021.
14. de Ligt KM, de Rooij BH, Hedayati E, et al. International development of a patient-centered core outcome set for assessing health-related quality of life in metastatic breast cancer patients. *Breast Cancer Res Treat.* 2023.
15. Thomas ML. Advances in applications of item response theory to clinical assessment. *Psychol Assess.* 2019;31(12):1442-1455.
16. Friedrich M, Hinz A, Kuhnt S, Schulte T, Rose M, Fischer F. Measuring fatigue in cancer patients: a common metric for six fatigue instruments. *Qual Life Res.* 2019;28(6):1615-1626.
17. Choi SW, Schalet B, Cook KF, Cella D. Establishing a common metric for depressive symptoms: linking the BDI-II, CES-D, and PHQ-9 to PROMIS depression. *Psychol Assess.* 2014;26(2):513-527.
18. Terwee CB, Zuidgeest M, Vonkeman HE, Cella D, Haverman L, Roorda LD. Common patient-reported outcomes across ICHOM Standard Sets: the potential contribution of PROMIS(R). *BMC Med Inform Decis Mak.* 2021;21(1):259.
19. Cella D, Gershon R, Lai JS, Choi S. The future of outcomes measurement: item banking, tailored short-forms, and computerized adaptive assessment. *Qual Life Res.* 2007;16 Suppl 1:133-141.

20. Wells G, Beaton D, Shea B, et al. Minimal clinically important differences: review of methods. *J Rheumatol.* 2001;28(2):406-412.
21. Torrance GW. Utility approach to measuring health-related quality of life. *J Chronic Dis.* 1987;40(6):593-603.
22. de Kok I, Korfage IJ, van den Hout WB, et al. Quality of life assumptions determine which cervical cancer screening strategies are cost-effective. *Int J Cancer.* 2018;142(11):2383-2393.
23. Omidvari AH, Lansdorp-Vogelaar I, de Koning HJ, Meester RGS. Impact of assumptions on future costs, disutility and mortality in cost-effectiveness analysis; a model exploration. *PLoS One.* 2021;16(7):e0253893.
24. Hartman JD, Craig BM. Comparing and transforming PROMIS utility values to the EQ-5D. *Qual Life Res.* 2018;27(3):725-733.
25. Pan T, Mulhern B, Viney R, et al. Evidence on the relationship between PROMIS-29 and EQ-5D: a literature review. *Qual Life Res.* 2022;31(1):79-89.
26. Denis F, Basch E, Septans AL, et al. Two-Year Survival Comparing Web-Based Symptom Monitoring vs Routine Surveillance Following Treatment for Lung Cancer. *JAMA.* 2019;321(3):306-307.
27. Basch E, Deal AM, Dueck AC, et al. Overall Survival Results of a Trial Assessing Patient-Reported Outcomes for Symptom Monitoring During Routine Cancer Treatment. *JAMA.* 2017;318(2):197-198.
28. Efficace F, Collins GS, Cottone F, et al. Patient-Reported Outcomes as Independent Prognostic Factors for Survival in Oncology: Systematic Review and Meta-Analysis. *Value Health.* 2021;24(2):250-267.
29. Efficace F, Biganzoli L, Piccart M, et al. Baseline health-related quality-of-life data as prognostic factors in a phase III multicentre study of women with metastatic breast cancer. *Eur J Cancer.* 2004;40(7):1021-1030.
30. Lambin P, van Stiphout RG, Starmans MH, et al. Predicting outcomes in radiation oncology--multifactorial decision support systems. *Nat Rev Clin Oncol.* 2013;10(1):27-40.
31. Arkin FS, Aras G, Dogu E. Comparison of Artificial Neural Networks and Logistic Regression for 30-days Survival Prediction of Cancer Patients. *Acta Inform Med.* 2020;28(2):108-113.
32. Chekroud AM, Zotti RJ, Shehzad Z, et al. Cross-trial prediction of treatment outcome in depression: a machine learning approach. *Lancet Psychiatry.* 2016;3(3):243-250.
33. Verma D, Jansen D, Bach K, Poel M, Mork PJ, d'Hollosy WON. Exploratory application of machine learning methods on patient reported data in the development of supervised models for predicting outcomes. *BMC Med Inform Decis Mak.* 2022;22(1):227.
34. Verma D, Bach K, Mork PJ. Application of Machine Learning Methods on Patient Reported Outcome Measurements for Predicting Outcomes: A Literature Review. *Informatics-Basel.* 2021;8(3).
35. van Egdom LSE, Pusic A, Verhoef C, Hazelzet JA, Koppert LB. Machine learning with PROs in breast cancer surgery; caution: Collecting PROs at baseline is crucial. *Breast J.* 2020;26(6):1213-1215.
36. Crivelli P, Ledda RE, Parascandolo N, Fara A, Soro D, Conti M. A New Challenge for Radiologists: Radiomics in Breast Cancer. *Biomed Res Int.* 2018;2018:6120703.
37. Rodriguez-Ruiz A, Lang K, Gubern-Merida A, et al. Stand-Alone Artificial Intelligence for Breast Cancer Detection in Mammography: Comparison With 101 Radiologists. *J Natl Cancer Inst.* 2019;111(9):916-922.
38. Tagliafico AS, Piana M, Schenone D, Lai R, Massone AM, Houssami N. Overview of radiomics in breast cancer diagnosis and prognostication. *Breast.* 2020;49:74-80.
39. Schott AF, Roubidoux MA, Helvie MA, et al. Clinical and radiologic assessments to predict breast cancer pathologic complete response to neoadjuvant chemotherapy. *Breast Cancer Res Treat.* 2005;92(3):231-238.

40. Marinovich ML, Houssami N, Macaskill P, et al. Meta-analysis of magnetic resonance imaging in detecting residual breast cancer after neoadjuvant therapy. *J Natl Cancer Inst.* 2013;105(5):321-333.
41. Tadros AB, Yang WT, Krishnamurthy S, et al. Identification of Patients With Documented Pathologic Complete Response in the Breast After Neoadjuvant Chemotherapy for Omission of Axillary Surgery. *JAMA Surg.* 2017;152(7):665-670.
42. Granzier RWY, van Nijnatten TJA, Woodruff HC, Smidt ML, Lobbes MBI. Exploring breast cancer response prediction to neoadjuvant systemic therapy using MRI-based radiomics: A systematic review. *Eur J Radiol.* 2019;121:108736.
43. Cardoso JS, Cardoso MJ. Towards an intelligent medical system for the aesthetic evaluation of breast cancer conservative treatment. *Artif Intell Med.* 2007;40(2):115-126.
44. Lyngholm CD, Christiansen PM, Damsgaard TE, Overgaard J. Long-term follow-up of late morbidity, cosmetic outcome and body image after breast conserving therapy. A study from the Danish Breast Cancer Cooperative Group (DBCG). *Acta Oncol.* 2013;52(2):259-269.
45. Zwakman M, Tan A, Boersma C, et al. Long-term quality of life and aesthetic outcomes after breast conserving surgery in patients with breast cancer. *Eur J Surg Oncol.* 2022;48(8):1692-1698.
46. Cardoso MJ, Cardoso J, Amaral N, et al. Turning subjective into objective: the BCCT.core software for evaluation of cosmetic results in breast cancer conservative treatment. *Breast.* 2007;16(5):456-461.
47. Cardoso MJ, Cardoso JS, Oliveira HP, Gouveia P. The breast cancer conservative treatment. Cosmetic results - BCCT.core - Software for objective assessment of esthetic outcome in breast cancer conservative treatment: A narrative review. *Comput Methods Programs Biomed.* 2016;126:154-159.
48. Lagendijk M, Vos EL, Nieboer D, Verhoef C, Corten EML, Koppert LB. Evaluation of cosmetic outcome following breast-conserving therapy in trials: panel versus digitalized analysis and the role of PROMs. *Breast J.* 2018;24(4):519-525.
49. Vos EL, Koning AH, Obdeijn IM, et al. Preoperative prediction of cosmetic results in breast conserving surgery. *J Surg Oncol.* 2015;111(2):178-184.
50. Vos E, Koppert L, van Lankeren W, Verhoef C, Koerkamp BG, Hunink M. A preliminary prediction model for potentially guiding patient choices between breast conserving surgery and mastectomy in early breast cancer patients; a Dutch experience. *Qual Life Res.* 2018;27(2):545-553.
51. Lagendijk M, Vos EL, Ramlakhan KP, et al. Breast and Tumour Volume Measurements in Breast Cancer Patients Using 3-D Automated Breast Volume Scanner Images. *World J Surg.* 2018;42(7):2087-2093.
52. Lagendijk M, Vos EL, Koning AHJ, et al. TUmor-volume to breast-volume RAtio for improving COSmetic results in breast cancer patients (TURACOS); a randomized controlled trial. *BMC Cancer.* 2017;17(1):336.
53. Bonci EA, Anacleto JC, Cardoso MJ. Sometimes it is better to just make it simple. De-escalation of oncoplastic and reconstructive procedures. *Breast.* 2023;69:265-273.
54. Azria D, Riou O, Castan F, et al. Radiation-induced CD8 T-lymphocyte Apoptosis as a Predictor of Breast Fibrosis After Radiotherapy: Results of the Prospective Multicenter French Trial. *EBioMedicine.* 2015;2(12):1965-1973.
55. Fhoghlu MN, Barrett S. A Review of Radiation-Induced Lymphocyte Apoptosis as a Predictor of Late Toxicity After Breast Radiotherapy. *J Med Imaging Radiat Sci.* 2019;50(2):337-344.
56. Shubeck SP, Morrow M, Dossett LA. De-escalation in breast cancer surgery. *NPJ Breast Cancer.* 2022;8(1):25.
57. Vos EL, Siesling S, Baaijens MHA, et al. Omitting re-excision for focally positive margins after breast-conserving surgery does not impair disease-free and overall survival. *Breast Cancer Res Treat.* 2017;164(1):157-167.

58. Vallejo da Silva A, Rodriguez FR, Loures CM, Lopes VG. Mastectomy in the era of implant-based reconstruction: should we be removing the pectoralis fascia? *Breast.* 2012;21(6):779-780.
59. Suijker J, Blok YL, de Vries R, van den Tol MP, Krekel NMA. Pectoral Fascia Preservation in Oncological Mastectomy to Reduce Complications and Improve Reconstructions: A Systematic Review. *Plast Reconstr Surg Glob Open.* 2020;8(3):e2700.
60. Blok YL, Suijker J, van den Tol MP, et al. Preservation of the Pectoral Fascia in Mastectomy With Immediate Reconstruction: A Nationwide Survey. *J Surg Res.* 2023;284:101-105.
61. Heil J, Kuerer HM, Pfob A, et al. Eliminating the breast cancer surgery paradigm after neoadjuvant systemic therapy: current evidence and future challenges. *Ann Oncol.* 2020;31(1):61-71.
62. van Loevezijn AA, van der Noordaa MEM, van Werkhoven ED, et al. Minimally Invasive Complete Response Assessment of the Breast After Neoadjuvant Systemic Therapy for Early Breast Cancer (MICRA trial): Interim Analysis of a Multicenter Observational Cohort Study. *Ann Surg Oncol.* 2021;28(6):3243-3253.
63. van Nijnatten TJA, Simons JM, Smidt ML, et al. A Novel Less-invasive Approach for Axillary Staging After Neoadjuvant Chemotherapy in Patients With Axillary Node-positive Breast Cancer by Combining Radioactive Iodine Seed Localization in the Axilla With the Sentinel Node Procedure (RISAS): A Dutch Prospective Multicenter Validation Study. *Clin Breast Cancer.* 2017;17(5):399-402.
64. de Wild SR, Simons JM, Vrancken Peeters M, Smidt ML, Koppert LB, Group M. MINImal vs. MAXimal Invasive Axillary Staging and Treatment After Neoadjuvant Systemic Therapy in Node Positive Breast Cancer: Protocol of a Dutch Multicenter Registry Study (MINIMAX). *Clin Breast Cancer.* 2022;22(1):e59-e64.

Chapter 12

Dutch Summary / Nederlandse samenvatting

BORSTKANKER

Borstkanker is de meest voorkomende vorm van kanker bij vrouwen, met een jaarlijkse incidentie van 47.8 per 100.000 vrouwen wereldwijd. In Nederland krijgen jaarlijks ongeveer 17.000 vrouwen de diagnose borstkanker. Gemetastaseerde borstkanker omvat 5-10% van de borstkankerpatiënten op het moment van diagnose, en hoewel er een trend is naar minimale overlevingsverbeteringen, blijft de 10% 10-jaarsoverleving helaas slecht. Genetische aanleg, zoals een BRCA 1- of BRCA 2-genmutatie, en een familiegeschiedenis van borst- en/of eierstokkanker verhogen het risico op het ontwikkelen van borstkanker. Het risico op het ontwikkelen van borstkanker op de leeftijd van 70 jaar is 57-65% bij vrouwen met een BRCA 1-mutatie en 45-47% bij vrouwen met een BRCA 2-mutatie.

BEHANDELING

De hoeksteen van de behandeling van vroeg-stadium borstkanker is de chirurgische verwijdering van de tumormassa. Mogelijkheden voor borstchirurgie zijn borstsparende therapie, bestaande uit een lumpectomie met schildwachtklierbiopsie in combinatie met adjuvante radiotherapie van de borst, of een borstamputatie al dan niet gevolgd door borstreconstructie. Langetermijnresultaten van gerandomiseerde onderzoeken hebben ten minste gelijke algemene en ziektevrije overlevingspercentages aangetoond voor BCT en mastectomie bij borstkanker in een vroeg stadium. Een Nederlandse populatie-gebaseerde studie heeft zelfs superieure overlevingspercentages aangetoond voor BCT in vergelijking met mastectomie bij T1-2N0-2M0 borstkankerpatiënten, na correctie voor mogelijke confounders. (neo-)Adjuvante systemische behandeling, zoals chemotherapie, endocriene therapie en immuuntherapie, en radiotherapie zijn belangrijke aanvullende behandelmodaliteiten in geval van niet-gemetastaseerde borstkanker. De behandeling van mutatiedraagsters omvat intensieve surveillance gericht op vroege detectie, of een bilaterale profylactische mastectomie (BPM). Het landschap van borstreconstructies is de laatste jaren aanzienlijk veranderd. Een borstreconstructie, directe of uitgestelde autologe of prothese reconstructie, kan het lichaamsbeeld van een vrouw, de tevredenheid met borsten en haar kwaliteit van leven verbeteren.

PATIENT GERAPPORTEERDE UITKOMSTEN

De diagnose borstkanker heeft een onvoorstelbaar grote impact op het leven van een vrouw en dat van haar familie. Borstkankerpatiënten komen tijdens hun oncologische en chirurgische behandeling voor veel uitdagingen te staan, wat vraagt om keuzes. Hoewel overlev-

ings- en recidiefpercentages vergelijkbaar zijn, heeft elke behandeling een ander niveau van impact op cosmetisch resultaat, fysiek en psychosociaal welzijn en seksueel functioneren. Deze uitkomsten, vaak de kwaliteit van leven van een patiënt genoemd, kunnen leidend zijn bij het nemen van (chirurgische) behandelbeslissingen. Tegen de achtergrond van een goede prognose en beperkte lokale behandeling-gerelateerde morbiditeit voor primaire borstkankerpatiënten die curatieve behandeling ondergaan, verschuift de aandacht naar het handhaven van de kwaliteit van leven als een belangrijk zorgdoel. Waardegedreven zorg is een benadering van medische zorg die de verbetering van patiëntresultaten en de algehele kwaliteit van zorg voorrang geeft boven de hoeveelheid geleverde diensten. Voor borstkanker specifiek is het waardegedreven aspect erop gericht haar patiënten de meest effectieve behandelingen te bieden, onnodige procedures te minimaliseren en de ervaring en tevredenheid van de patiënt te verbeteren. Terwijl de evolutie van de gezondheidszorg naar een waardegedreven zorg voortduurt, ligt de uitdaging in het identificeren, meten en verbeteren van uitkomsten. Uitkomsten die er het meest toe doen voor borstkankerpatiënten, gemeten vanuit het eigen perspectief van de patiënt.

Dit proefschrift richt zich in **DEEL I** op de gezondheid gerelateerde kwaliteit van leven en door de patiënt gerapporteerde uitkomsten (PRO's) in borstkankerpatiënten. Het benadrukt de behoefte aan een gestandaardiseerde aanpak voor het implementeren en meten van PRO's en het gebruik van normatieve PRO data. **DEEL II** illustreert de eerste ontwikkelingen naar het voorspellen van uitkomsten van verschillende borstkankerbehandelingen. Allereerst ligt de focus op de 3D borst echografie om in de neo-adjuvante setting de tumorresponse te evalueren, met de potentie om te worden gebruikt bij het voorspellen van pathologische tumorrespons. Ten tweede wordt een geoptimaliseerde nieuwe methode ontwikkeld om radiotherapie-geïnduceerde lymfocytenapoptose te meten, om zo de implementatie in de klinische praktijk te verbeteren. Tevens kunnen deze resultaten gebruikt worden om een predictiemodel te ontwikkelen voor radiotherapie-geïnduceerde fibrose. Tot slot werd een onderzoeksprotocol over het behoud van de pectorale fascie en de associatie met postoperatieve uitkomsten beschreven.

DEEL I PATIËNTGERAPPORTEERDE UITKOMSTEN IN BORSTKANKERPATIËNTEN

Aangezien het gebruik van patiënt-gerapporteerde uitkomstmaten (PROM's) in klinische onderzoeken naar borstkanker blijft toenemen, kan normatieve PRO data nuttig zijn bij de interpretatie van PROM's. Normatieve data beschrijft de uitkomsten van een gedefinieerde populatie zonder een specifieke aandoening of ziekte. De Breast-Q is het meest gebruikte instrument om PROs na cosmetische en reconstructieve mammachirurgie te meten. In **Hoofdstuk 2** werd normatieve data van de Borstsparende therapie module

van de Breast-Q van een Nederlandse vrouwelijke populatie verkregen en vergeleken met bestaande normatieve Breast-Q waarden. De social media platforms van het Erasmus Medisch Centrum werden gebruikt om deelnemers te werven en te verwijzen naar een online vragenlijst. Deze anonieme vragenlijst bestond uit vier domeinen van de preoperatieve Breast-Q Borstsparende therapie module. In totaal werden 9059 vragenlijsten van deelnemers zonder voorgeschiedenis van borstkanker geanalyseerd. De mediane Breast-Q domeinscores waren 64.0 ± SD 18.0 ("Tevredenheid met Borsten"), 69.0 ± SD 21.0 ("Psychosociaal Welzijn"), 92.0 ± SD 20 ("Fysiek Welzijn") en 59.0 ± SD 15.0 ("Seksueel Welzijn"). Eerdere niet-borstkanker gerelateerde chirurgie was een significante voorspeller voor hogere "Tevredenheid met Borsten" ($\beta = 0.04$, $p < 0.001$) en hogere "Seksueel Welzijn" ($\beta = -0.05$, $p < 0.001$) scores. In vergelijking met eerder gepubliceerde normatieve data werden kleine verschillen gevonden in de gemiddelde Breast-Q domeinscores (gemiddelde verschillen variërend tussen 2.45 – 6.24). Deze resultaten tonen aan dat normatieve Nederlandse Breast-Q scores vergelijkbare patronen volgen in vergelijking met eerder gepubliceerde normatieve gegevens. Deze normatieve Nederlandse Breast-Q data kunnen gebruikt worden in toekomstige analyses naar de kwaliteit van leven en tevredenheid van borstkanker patiënten gedurende hun behandeling.

Leeftijd-specifieke normatieve waarden voor de EQ-5D-5L van het eerder genoemde cohort Nederlandse vrouwen werden geanalyseerd in **Hoofdstuk 3**. De antwoorden van de respondenten op de verschillende vragen van de EQ-5D-5L kunnen worden omgezet in een enkele utiliteitsscore, die de gezondheidstoestand van een individu op een bepaald moment weergeeft. Normatieve utiliteitsscores vertegenwoordigen de gezondheid gerelateerde kwaliteit van leven van de algemene bevolking, zijn van het belang in kosteneffectiviteitsonderzoeken en weerspiegelen idealiter een relevant geslacht en leeftijdsgroep. Het doel van deze studie was om EQ-5D-5L normatieve utiliteitsscores te schatten in een populatie van Nederlandse vrouwen, gestratificeerd naar leeftijd, en om deze scores te vergelijken met die van vrouwelijke populaties in drie andere landen. Gemiddelde normatieve utiliteitscores werden berekend met behulp van vooraf gedefinieerde Nederlandse EQ-5D-5L 'valuesets', gestratificeerd naar leeftijd, en vergeleken met normatieve utiliteitsscores van vrouwelijke populaties elders. Gegevens van 9037 vrouwen werden geanalyseerd en de gewogen gemiddelde utiliteitsscore was 0,911 (SD 0.155, 95% CI 0.908-0.914). De gemiddelde normatieve utiliteitsscores verschilden tussen leeftijdsgroepen en lieten lagere scores zien bij oudere vrouwen. Vergeleken met andere normatieve utiliteitsscores van vrouwelijke populaties, waren de Nederlandse gemiddelde utiliteitsscores consistent hoger, behalve voor de leeftijdsgroepen 18-24 en 25-34 jaar. Om het gebruik van de Nederlandse EQ-5D-5L data in andere landen te ondersteunen, werden normatieve utiliteitsscores berekend door de 'valuesets' van Duitsland, het Verenigd Koninkrijk en de Verenigde Staten toe te passen.

Terwijl hoofdstuk 2 en 3 zich richten op normatieve waarden, worden in de volgende hoofdstukken 'real-world' patiëntdata gebruikt om de kwaliteit van leven te evalueren. **Hoofdstuk 4** beschrijft de behoefte aan een gestandaardiseerde aanpak voor het meten van de kwaliteit van leven met PRO's bij patiënten met gemetastaseerde borstkanker (MBC). MBC-patiënten worden vrijwel altijd behandeld om symptomen te minimaliseren en om het leven te verlengen zonder curatieve intentie. Hoewel de prognose van MBC-patiënten de afgelopen jaren is verbeterd, is de mediane overleving na diagnose nog steeds slechts 3 jaar. Daarom is het belangrijk om de best mogelijke kwaliteit van leven te bieden, afgewogen tegen behandelingsrisico's en nadelige symptomen. Kwaliteit van leven zou leidend moeten zijn bij het nemen van behandelbeslissingen. Heterogeniteit in vragenlijsten die worden gebruikt om de kwaliteit van leven bij MBC-patiënten te evalueren, bemoeilijkt de interpretatie van en vergelijking met PRO's wereldwijd. Dit review deelt inzichten in de rol van PROM's bij MBC-patiënten en bespreekt belangrijke kwesties bij het meten van kwaliteit van leven. Het routinematig verzamelen van bijwerkingen en symptomen met behulp van PRO's kan mogelijk de behandeling en gedeelde besluitvorming verbeteren. Een up-to-date gestandaardiseerde set van uitkomsten kan de implementatie van PRO's verbeteren, maar ook het verzamelen en delen van data vergemakkelijken om zo beter onderzoek te kunnen doen. Dit is een vereiste om te leren hoe PROs het klinische zorgtraject kunnen beïnvloeden. Bovendien is de prognostische waarde van het monitoren van PROs tijdens de behandeling op overleving en ziekteprogressie veelbelovend.

In **Hoofdstuk 5** werden PRO's en complicaties vergeleken tussen tepelsparende mastectomie (NSM) en huidsparende mastectomie (SSM) met directe reconstructie, aangezien de oncologische veiligheid van beide procedures vergelijkbaar lijkt te zijn. In deze systematische review en meta-analyse werden 13 van de 1202 studies geselecteerd, resulterend in totaal 3895 patiënten. De meta-analyses van de Breast-Q domeinen toonden een significant verschil van 7.64 in het domein Seksueel Welzijn ($p = 0.01$) en 4.71 in het domein Psychosociaal Welzijn ($p = 0.03$), beide in het voordeel van NSM. In de artikelen die specifiek ontworpen vragenlijsten gebruikte, werden geen verschillen in scores gevonden. Concluderend waren de patiënttevredenheidsscores na zowel NSM als SSM hoog, maar leidt NSM tot een hoger seksueel en psychosociaal welzijn. Er waren geen verschillen in complicaties tussen de twee groepen. In combinatie met andere factoren, zoals oncologische behandelingen, het risicoprofiel van complicaties en de angst voor terugkeer van kanker, moet de beslissing voor NSM of SSM op individuele basis worden genomen en alleen wanneer NSM als oncologisch veilig kan worden beschouwd.

Borstkankerpatiënten worden geconfronteerd met veel moeilijkheden tijdens hun oncologisch traject en hebben vaak de support van hun omgeving nodig. Ondanks het feit dat het verlenen van mantelzorg positieve effecten kan hebben op iemands welzijn, kan het de kwaliteit van leven ook negatief beïnvloeden. In **Hoofdstuk 6** werd de kwaliteit van leven van mantelzorgers van borstkankerpatiënten geëvalueerd. De associatie met de

HRQoL van borstkankerpatiënten werd beoordeeld en mogelijke voorspellers werden geïdentificeerd. De Care-related Quality of Life Instrument (CarerQoL) werd gebruikt om CarerQoL-utiliteitsscores te berekenen met reeds bestaande Nederlandse 'valuesets'. Daarnaast reflecteert de CarerQoL VAS-score het algehele geluk van de mantelzorger. In totaal werden 116 CarerQoL-vragenlijsten geanalyseerd. De mantelzorgers waren grotendeels mannelijke echtgenoten of partners (81.4%) met een gemiddelde leeftijd van 55.7 ± 16.4 jaar. De mediane CarerQoL-utiliteitsscore was 92.4/100 en de mediane CarerQoL VAS was 8.0/10. We vonden zwakke correlaties tussen CarerQoL VAS-scores en de EQ-5D-5L-utiliteitsscore (0.301, p = 0,002) en EQ VAS-score (0.251, p = 0.009) van de patiënt, en tussen EORTC QLQ-C30-scores en CarerQol VAS (0.339, p <0.001) en utiliteitsscore (0.236, p = 0.015). Er was een negatief verband tussen chemotherapie en CarerQoL-utiliteitsscore (β = –0.063, p = 0.001) en VAS-score (β = –0.044, p = 0.038) na zes maanden follow-up. Dit is de eerste studie die de CarerQoL bij mantelzorgers van Nederlandse borstkankerpatiënten heeft geëvalueerd. Ons onderzoek benadrukt het belang om mantelzorgers van borstkankerpatiënten in de klinische praktijk te betrekken, biedt referentiewaarden voor toekomstig onderzoek en de resultaten kunnen worden gebruikt om verwachtingen van de mantelzorgers voorafgaand aan de behandeling te bespreken.

DEEL II RICHTING HET VOORSPELLEN VAN BORSTKANKER UITKOMSTEN

De Automated Breast Volume Scanner (ABVS, Siemens ACUSON S2000TM) is een echografietechniek die gestandaardiseerde, geautomatiseerde en reproduceerbare echobeelden van de hele borst bewerkstelligd en geeft de mogelijkheid om 3D-beelden te reconstrueren. We onderzochten de toepasbaarheid van driedimensionale echografie van de borst tijdens neo-adjuvante chemotherapie (NAC). In **Hoofdstuk 7** werd het vervolg van de RESPONDER 1 studie uitgevoerd om de nauwkeurigheid van tumorresponsmetingen met behulp van de ABVS te evalueren en om deze te vergelijken met de MRI en postoperatieve histopathologie bij borstkankerpatiënten die NAC ondergingen. Naast de langste diameter werden ook tumorvolume metingen verricht. Er werden 96 patiënten voor pre- en mid-NAC-evaluaties en 57 patiënten voor post-NAC-evaluatie geanalyseerd. De MRI en ABVS toonden absolute concordantie in 66% voor de mid-NAC en 63% voor de post-NAC-evaluatie. Een 'goede' significante correlatie tussen ABVS en MRI werd gevonden voor het verschil in langste diametermeting voor de eerste (ICC 0,64 (95%CI 0,51-0,75)) en tweede (ICC 0,68 (95%CI 0,50-0,80)) responsevaluatie. Voor volumemetingen werden 'goede' en 'uitstekende' significante correlaties gevonden voor de eerste (ICC 0,69 (95% BI 0,57-0,78) en tweede (ICC 0,98 (95% BI 0,96-0,99)) responsevaluatie. Post-NAC ABVS en MRI toonden absolute overeenstemming met de histopathologische

respons in respectievelijk 71% versus 50%. De acceptatiescores van patiënten waren hoger voor de ABVS in vergelijking met MRI. Omdat de ABVS goede tot uitstekende correlaties vertoonde met MRI-tumordiameter en volumerespons, en goedkoper, gemakkelijker en minder invasief dan de MRI is, moet de ABVS als een goed alternatief voor response evaluatie worden beschouwd.

Het doel van deze non-matched case-controle studie, zoals beschreven in **Hoofdstuk 8,** was het optimaliseren van de bestraling-geïnduceerde lymfocyten apoptose (RILA) assay met behulp van bevroren immuuncellen, het analyseren van de associatie tussen RILA frequenties in CD4 en CD8 T-lymfocyten en graad 3 bestraling-geïnduceerde fibrose (RIF) na borstsparende therapie. De RILA-assay werd uitgevoerd op zowel vers verkregen als ingevroren perifere mononucleaire bloedcellen (PBMC's) die werden geïsoleerd uit bloedmonsters van tien gezonde vrijwilligers. Vergelijkbare RILA-frequenties werden gevonden in bevroren en vers verkregen PBMC's. Ten tweede werden Nederlandse vrouwelijke borstkankerpatiënten met ≤ graad 1 (controles, n = 13) of graad 3 (gevallen, n = 17) fibrose op de LENT-SOMA-schaal geïncludeerd. Er werd geen statistisch significant verband gevonden tussen een verlaagde RILA-frequentie van CD4- of CD8-T-lymfocyten en een verhoogd risico op het ontwikkelen van graad 3 RIF in dit relatief kleine cohort (odds ratio 1,58 (95% BI 0,85-3,33, p=0,16) en 1,13 (95% BI 0,62-2,10, p=0,68). Acute dermatitis (≥ graad 2) en de aanwezigheid van een immunologische ziekte bij patiënten werden echter geïdentificeerd als nieuwe risicofactoren voor RIF.

In **Hoofdstuk 9** wordt een studieprotocol beschreven die de impact van verwijdering versus behoud van de pectorale fascie (PF) op drainbeleid en seroom na een bilaterale profylactische mastectomie (BPM) onderzoekt. Veel chirurgische richtlijnen bevelen de verwijdering van de PF aan bij een mastectomie, maar bewijs om deze bewering te ondersteunen ontbreekt. Gerapporteerde wond gerelateerde complicaties na een mastectomie zijn seroom, lapnecrose, infectie en hematoom. Seroom veroorzaakt lichamelijk ongemak en kan leiden tot een delay in borstreconstructie. Deze studie is een dubbelblinde, prospectieve, gerandomiseerde, gecontroleerde pilot met een 'within-subject design'. Randomisatie vindt dus plaats binnen de patiënt, wat betekent PF behoud in één borst en chirurgische excisie van de PF in de contralaterale borst. De inclusiecriteria zijn vrouwen ouder dan 18 jaar, die kiezen voor BPM in het Academisch Borstkankercentrum Rotterdam. In totaal zullen 21 patiënten worden geïncludeerd. Het primaire eindpunt van de studie is het totale drainvolume. Secundaire uitkomsten zijn het aantal dagen dat de drains in situ zijn, het aantal naaldaspiraties, eventuele postoperatieve complicaties en de opnameduur. De inclusie van patiënten is eind 2021 gestart, met momenteel acht inclusies en acht succesvolle procedures, en de resultaten worden in 2024 verwacht.

SAMENVATTEND

Mede dankzij de shift naar een value-based approach in de borstkankerzorg, wordt er veel aandacht besteed aan de kwaliteit van leven van patiënten en gedeelde besluitvorming tijdens en na de behandeling van borstkanker. Het gestandaardiseerd meten van uitkomsten, zowel PROs als klinische uitkomstmaten, zal leiden tot een verbetering van de zorg voor de individuele patiënt. De resultaten van dit proefschrift kunnen helpen bij de implementatie en interpretatie van PROs, zowel in de dagelijkse klinische zorg als in borstkanker-gerelateerd onderzoek. Een belangrijke volgende uitdaging ligt in de predictie van zowel harde klinische eindpunten als kwaliteit van leven gerelateerde uitkomsten na een borstkanker behandeling.

12

APPENDICES

LIST OF PUBLICATIONS

This thesis

Oemrawsingh A*, **Clarijs ME***, Pusic AL, Lingsma HF, Verhoef C, Hazelzet JA, Koppert LB. BREAST-Q Breast-Conserving Therapy Module: Normative Data from a Dutch Sample of 9059 Women. Plast Reconstr Surg. 2022 Nov 1;150(5):985-993. doi: 10.1097/PRS.0000000000009607. 2022 Aug 22. PMID: 35994350; PMCID: PMC9586822.

Clarijs ME, Oemrawsingh A, Bröker MEE, Verhoef C, Lingsma H, Koppert LB. Quality of life of caregivers of breast cancer patients: a cross-sectional evaluation. Health Qual Life Outcomes. 2022 Feb 19;20(1):29. doi: 10.1186/s12955-022-01930-0. Erratum in: Health Qual Life Outcomes. 2022 Jul 26;20(1):114. PMID: 35183212; PMCID: PMC8858558.

Clarijs ME, Thurell J, Kühn F, Uyl-de Groot CA, Hedayati E, Karsten MM, Jager A, Koppert LB. Measuring Quality of Life Using Patient-Reported Outcomes in Real-World Metastatic Breast Cancer Patients: The Need for a Standardized Approach. Cancers (Basel). 2021 May 12;13(10):2308. doi: 10.3390/cancers13102308. PMID: 34065805; PMCID: PMC8151772.

Clarijs ME, Kregting LM, van Ravesteyn NT, Koppert LB, Korfage IJ. Health-related Quality of Life using the EQ-5D-5L: normative utility scores in a Dutch female population. Qual Life Res. 2022 Oct 20:1–9. doi: 10.1007/s11136-022-03271-3. Epub ahead of print. PMID: 36264532; PMCID: PMC9584237.

Clarijs ME, Peeters NJMCV, van Dongen SAF, Koppert LB, Pusic AL, Mureau MAM, Rijken BFM. Quality of life, patient satisfaction, and complications after nipple-sparing versus skin-sparing mastectomy followed by immediate breast reconstruction. A systematic review and meta-analysis. Plast Reconstr Surg. 2023 Jan 10. doi: 10.1097/PRS.0000000000010155. PMID: 36728484.

Clarijs ME, van Egdom LSE, Verhoef C, Vasilic D, Koppert LB; PROFAS Collaborator Group. Bilateral prophylactic mastectomy: should we preserve the pectoral fascia? Protocol of a Dutch double blinded, prospective, randomised controlled pilot study with a within-subject design (PROFAS). BMJ Open. 2023 Feb 17;13(2):e066728. doi: 10.1136/bmjopen-2022-066728. PMID: 36806067; PMCID: PMC9944307.

Other

Huberts AS, **Clarijs ME**, Pastoor H, van Rosmalen M, Koppert LB. Sexual well-being in patients with early-stage breast cancer at 1- and 2-year follow-up. J Sex Med. 2023 Feb 15:qdad007. doi: 10.1093/jsxmed/qdad007. PMID: 36790026.

van Bekkum S, **Clarijs ME**, van der Veen FJC, van Rosmalen J, Koppert LB, Menke-Pluijmers MBE. What affects women's decision-making on breast reconstruction after mastectomy for breast cancer? Breast Cancer. 2023 Jun 12. doi: 10.1007/s12282-023-01471-4. Epub ahead of print. PMID: 37303033.

Vrancken Peeters NJMC, Kaplan ZLR, **Clarijs ME**, Mureau MAM, Verhoef C, van Dalen T, Husson O, Koppert LB. Health-related quality of life (HRQoL) after different axillary treatments in women with breast cancer: a 1-year longitudinal cohort study. Qual Life Res. 2023 Oct 27. doi: 10.1007/s11136-023-03538-3. Epub ahead of print. PMID: 37889384.

CONTRIBUTING AUTHORS

A. Jager
Department of Medical Oncology – Erasmus MC University Medical Center, Rotterdam, the Netherlands

A.L. Pusic
Division of Plastic and Reconstructive Surgery, Patient-Reported Outcomes, Value and Experience (PROVE) Center, Brigham and Women's Hospital

A.H.J. Koning
Department of Bioinformatics – Erasmus MC University Medical Center, Rotterdam, the Netherlands

A. Oemrawsingh
Center for Medical Decision Making, Department of Public Health – Erasmus MC University Medical Center, Rotterdam, the Netherlands

B.F.M. Rijken
Department of Plastic and Reconstructive Surgery – Erasmus MC University Medical Center, Rotterdam, the Netherlands

C.A. Uyl-de Groot
Department of Health Technology Assessment, Erasmus School of Health Policy & Management, Erasmus University Rotterdam, the Netherlands

C.H.M. van Deurzen
Department of Pathology – Erasmus MC University Medical Center, Rotterdam, the Netherlands

C. de Monye
Department of Radiology - Erasmus MC University Medical Center, Rotterdam, the Netherlands

C. Verhoef
Department of Surgical Oncology – Erasmus MC University Medical Center, Rotterdam, the Netherlands

D. Vasilic
Department of Plastic and Reconstructive Surgery – Erasmus MC University Medical Center, Rotterdam, the Netherlands

D.C. van Gent
Department of Molecular Genetics – Erasmus MC University Medical Center, Rotterdam, the Netherlands

E. Lubberts
Department of Rheumatology – Erasmus MC University Medical Center, Rotterdam, the Netherlands

E. Hedayati
Department of Oncology-Pathology, Karolinska Institute and Karolinska University Hospital, Sweden.

F. Kühn
Department of Gynecology with Breast Center, Charité-Universitätsmedizin Berlin, Corporate Member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Germany

H. Lingsma
Center for Medical Decision Making, Department of Public Health – Erasmus MC University Medical Center, Rotterdam, the Netherlands

I.J. Korfage
Department of Public Health– Erasmus MC University Medical Center, Rotterdam, the Netherlands

J.A. Hazelzet
Department of Public Health– Erasmus MC University Medical Center, Rotterdam, the Netherlands

J. Turell
Department of Oncology-Pathology, Karolinska Institute and Karolinska University Hospital, Sweden.

L.S.E. van Egdom
Department of Plastic and Reconstructive Surgery – Erasmus MC University Medical Center, Rotterdam, the Netherlands

L.M. Kregting
Department of Public Health – Erasmus MC University Medical Center, Rotterdam, the Netherlands

L.B. Koppert
Department of Surgical Oncology – Erasmus MC University Medical Center, Rotterdam, the Netherlands

M.A.M. Mureau
Department of Plastic and Reconstructive Surgery – Erasmus MC University Medical Center, Rotterdam, the Netherlands

M.M. Karsten
Department of Gynecology with Breast Center, Charité-Universitätsmedizin Berlin, Corporate Member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Berlin, Germany

M.C. Capala
Department of Radiation Oncology – Erasmus MC University Medical Center, Rotterdam, the Netherlands

M. Bröker
Department of Surgical Oncology – Franciscus Gasthuis and Vlietland, Rotterdam the Netherlands

N. Davelaar
Department of Rheumatology – Erasmus MC University Medical Center, Rotterdam, the Netherlands

N.T. van Ravesteyn
Department of Public Health – Erasmus MC University Medical Center, Rotterdam, the Netherlands

N.J.M.C. Vrancken Peeters
Erasmus University Rotterdam – Erasmus MC University Medical Center, Rotterdam, the Netherlands

PROFAS Collaboration Group

T. van Dalen
Department of Surgical Oncology – Erasmus MC University Medical Center, Rotterdam, the Netherlands

C. de Betue
Department of Surgical Oncology – Isala, Zwolle, the Netherlands

J. Rothbarth
Department of Surgical Oncology – Erasmus MC University Medical Center, Rotterdam, the Netherlands

E.V.E. Madsen
Department of Surgical Oncology – Erasmus MC University Medical Center, Rotterdam, the Netherlands

L.M. Beelen
Department of Plastic and Reconstructive Surgery – Erasmus MC University Medical Center, Rotterdam, the Netherlands

E.M.L. Corten
Department of Plastic and Reconstructive Surgery – Erasmus MC University Medical Center, Rotterdam, the Netherlands

A J.M. Luijsterburg
Department of Plastic and Reconstructive Surgery – Erasmus MC University Medical Center, Rotterdam, the Netherlands

M.J. Hop
Department of Plastic and Reconstructive Surgery – Erasmus MC University Medical Center, Rotterdam, the Netherlands

H.M. Zuijdendorp
Department of Plastic and Reconstructive Surgery – Erasmus MC University Medical Center, Rotterdam, the Netherlands

N.A.S. Posch
Department of Plastic and Reconstructive Surgery – Erasmus MC University Medical Center, Rotterdam, the Netherlands

C.M.C.A van Laarhoven
Department of Plastic and Reconstructive Surgery – Erasmus MC University Medical Center, Rotterdam, the Netherlands

M. de Kraker
Department of Plastic and Reconstructive Surgery – Erasmus MC University Medical Center, Rotterdam, the Netherlands

R. van der Groef
Erasmus University Rotterdam – Erasmus MC University Medical Center, Rotterdam, the Netherlands

S.A. van Dongen
Erasmus University Rotterdam – Erasmus MC University Medical Center, Rotterdam, the Netherlands

PHD PORTFOLIO

PhD Candidate: Marloes Elisabeth Clarijs
PhD period: October 2019 – May 2023
Erasmus MC Department: Surgical Oncology
Promotor: Prof. dr. C. Verhoef, MD PhD
Copromotor: Dr. L.B. Koppert, MD PhD MHS

PhD Training	Year	ECTS
General academic skills		
Scientific Integrity	2020	0.3
BROK (Good Clinical Practice)	2020	1.5
Research skills		
Basic Introduction SPSS, Molmed	2019	1.0
Biostatistical Methods I: Basic Principles, NIHES	2020	5.7
Basis course on R, Molmed	2021	2.0
PROMs Summer school, Harvard Medical School	2020	1.0
Biomedical English Writing Course	2021	2.0
Presentations		
Borstkanker Behandeling Beter Symposium, Rotterdam, the Netherlands (x2)	2020-21	1.0
Research Meeting Breast Clinic, Rotterdam, the Netherlands	2021	0.5
EBCC-12 Congress, virtual event (poster)	2020	0.5
ESSO-40 Congress, Lisbon, Portugal (poster x2)	2021	0.5
PROVE Center monthly meeting, Boston, United States of America	2021	0.5
The Cancer Research Retreat Erasmus MC, Rotterdam, the Netherlands (poster)	2023	0.5
Attendance at (inter)national Conferences and Seminars		
Borstkanker Behandeling Beter Symposium, Rotterdam, the Netherlands	2019-21	1.5
12th European Breast Cancer Conference (virtual event)	2020	1.0
ICHOM Patient-Centered Healthcare and the Value-Based approach (virtual event)	2020	0.5
Value Based Health Care Summer Course, Erasmus MC	2020	1.0
NVPC Scholingsdag en Wetenschapsdag, Amsterdam, the Netherlands	2021	0.5
40th Congres of the European Society of Surgical Oncology, Lisbon, Portugal	2021	1.0
Breast Cancer Research Meeting, Academic Breast Cancer Center, Rotterdam, the Netherlands	2019 - 22	0.3
Organizational skills		
Value Based Healthcare Summer Course – Erasmus MC	2020-22	1.5
Value Based Healthcare Ambassador Courses – Healthcare Transformation Academy	2021-22	1.5
Train the Facilitator Course – Healthcare Transformation Academy	2022	1.0

PhD Training	Year	ECTS
Teaching skills		
Supervising NIHES master thesis		
Romy van der Groef (Erasmus MC)	2020	2.0
Noelle Vrancken Peeters (Erasmus MC)	2021	2.0
Community project – 'Dutch normative Breast-Q scores'	2019	1.0
Community project – 'Ervaringen van borstkankerpatiënten in het zorgkeuzeproces'	2020	0.5
Nascholingen		
ICHOM Breast Cancer Standard Set implementation example	2021	0.1
EORTC Webinar: Metastatic Breast Cancer	2021	0.1
Driving a brighter future in healthcare through PROs: The H2O approach	2021	0.1
Refereeravond plastische chirurgie (oral presentation)	2022	0.1
Innovation for Leaders Course	2022	1.0
PiPPi Webinar: How to get started – 3 steps into the PiPPi joint innovation platform	2022	0.1

ACKNOWLEDGEMENTS / DANKWOORD

De afgelopen jaren heb ik met ontzettend veel plezier onderzoek gedaan, iets dat mijn verwachtingen overtroffen heeft. Gedurende deze periode ben ik gegroeid als arts en onderzoeker, maar ook op persoonlijk vlak. Tegen veel mensen heb ik gezegd dat ik dit nog wel 3 jaar met genoegen had vol kunnen houden, en dat komt door alle mensen die ik heb leren kennen gedurende mijn promotietijd. Zonder jullie was dit proefschrift niet tot stand gekomen, en daarom wil ik graag diegene bedanken die op een manier, direct of indirect, betrokken zijn geweest bij mijn onderzoek.

Geachte promotor, **prof. dr. C. Verhoef**, beste Kees, dank voor je enthousiasme, kritische blik en interesse gedurende mijn promotie. Het moment dat jij en Linetta op de afdeling naar me toe kwamen (om te vragen of ik interesse had in onderzoek), dacht ik dat ik iets grandioos fout gedaan had. Wat een eer om als opvolger voor het mammaonderzoek benaderd te worden. Ook al waren het niet veel meetings, ik liep wél altijd met veel nieuwe ideeën en visies het kantoor uit. Het is bijzonder om te zien hoe jij je inzet voor alle OGC onderzoekers. Ik heb met veel plezier samengewerkt, zowel als ANIOS op de afdeling als in de onderzoekstoren. En later af en toe een schouderklop op OK als we elkaar tegenkwamen. Dank voor je vertrouwen en de mogelijkheden die je hebt gegeven.

Geachte co-promotor, **dr. L.B. Koppert**, lieve Linetta, het einde is nu dan écht in zicht. Ik wil je bedanken voor je begeleiding, lieve appjes, interesse (in werk en privé), waardevolle tijd en adviezen tijdens mijn promotie. Ik kan veel leren van je onverminderde positiviteit en bevlogenheid en heb veel bewondering voor jou als arts, onderzoeker en mens. De dinsdagmiddag was ons vaste onderzoeksmomentje waar ik altijd naar uit keek, om natuurlijk knopen door te hakken maar vooral ook om bij te kletsen. Door jouw prettige manier van de druk opvoeren hebben we in korte tijd zoveel moois bereikt. We hebben nota bene een pandemie overleefd! Tevens hebben we een gezellig diner bij jou thuis gehad, waar ik ook je prachtige gezin kon ontmoeten. Maar hoe zit het eigenlijk met dat strijkijzer… Overal waar ik kwam heb je me ontzettend welkom laten voelen, en was je trots. Je bent als een mentor voor me, en ik vond het een enorm voorrecht om met je samen te werken.

Geachte leden van de leescommissie, **prof. dr. Leebeek, prof. dr. Klazinga en prof. dr. van der Poll,** dank voor de uw tijd en interesse om mijn proefschrift te beoordelen. Ook wil ik de overige leden van de promotiecommissie, **prof. dr. M. Mureau, dr. D. Vasilic, dr. D. van Gent, prof. Lingsma,** graag bedanken voor het deelnemen in mijn promotiecommissie.

Beste **Marc en Dalibor**, dank voor de altijd leuke samenwerking, het kritisch beoordelen van manuscripten, en jullie participatie in de promotiecommissie. Met wat obstakels is de PROFAS dan toch écht van start gegaan. Jullie inzet en passie voor onderzoek is bewonderingswaardig en werkt aanstekelijk. Een voorbeeld voor later. Dank voor de fijne samenwerking tijdens mijn ANIOS periode bij jullie op de afdeling, tot snel!

Dik en Marta, jullie hebben me veel geleerd op het gebied van radiatiefibrose. De RILARIF is een mooi project dat hopelijk in de toekomst voortgezet wordt. Dank voor jullie geduld, scherpe inzichten en de energie die jullie in dit project gestopt hebben.

De publicaties waren niet tot stand gekomen zonder hulp van alle coauteurs. Dank voor jullie kritische blik, suggesties, feedback en input. In het bijzonder **Arvind**, mijn allereerste publicatie was met jou. En wat gingen we snel! Ik ben enorm trots op onze studie met 10 000 vrouwen (!) en de soepele samenwerking. Staat de publicatie nu dan echt online? **Lindy**, elkaar ontmoeten in een pandemie met alleen maar online meetings was gek. Gelukkig heeft ons dat niet weerhouden van een mooie publicatie! **Romy**, een studie van begin tot eind opzetten was niet altijd makkelijk; dank voor al jouw kostbare uren in het lab. Succes met je verdere carrière! Veel dank ook voor de collega's in centra die deelnamen aan de Turacos en Responder studies, zonder jullie hulp was het niet gelukt. Daarnaast bijzonder veel dank aan de patiënten die deel hebben genomen in deze studies.

Prof. A. Pusic, Dear Andrea, thank you for our collaboration the past three years. Your work in the field of Patient Reported Outcome Measurements and breast surgery is inspiring. You were always supportive when we came up with new research ideas. I hope we can meet each other in person one day!

Dear **Elham Hedayati** and **Maria Karsten**, thank you for our pleasing collaboration. It was nice to see a different point of view on the implementation of PROs in your institutes, and I have learned a lot from your experiences. Your dedication for breast cancer patients and research is inspiring. Also many thanks to **Friedrich** and **Jacob** for helping me out!

Anton Koning, dank voor al jouw hulp als ik er weer eens niet uitkwam met de V-Scope.

Beste **fotografen** van het Erasmus MC, dank voor het maken van de honderden foto's voor de TURACOS studie. Ik hoefde maar te bellen en jullie kwamen!

Lieve dames van het **Internationale Waardegedreven zorg** team; An, Nouk en Anouk, Nadia en Angela, wat hebben wij veel mooie dingen op internationaal vlak bereikt met elkaar. Het ontzettend leuke teamuitje ga ik niet vergeten; met jullie durf ik elk onbe-

woond eiland aan. An, dank voor de altijd fijne samenwerking met veel positiviteit; ik ben ontzettend trots op onze High Value Care cursussen.

Mammacare en **verpleegkundig specialisten** van het Academisch Borstkanker Centrum, Joyce, Mandy, Sjane, Johanna en Angelieke, wat zouden wij maar vooral de borstkanker-patiënten zonder jullie moeten. Jullie inzet wordt enorm gewaardeerd. **Ada,** dank voor je hulp!

Chirurgen van de **OGC**; Carlijn, Eva, Joost en Thijs; jullie passie voor het vak is inspirerend. Fijn dat jullie af en toe de pectorale fascie voor me wilde laten staan. Hopelijk zien we elkaar snel weer op OK!

Chirurgen uit het **Franciscus Gasthuis & Vlietland**; Ingeborg, Mirelle, en Taco, leuk dat de studies ook hier zo goed lopen. Dank voor alle inclusies van de afgelopen jaren!

Lieve **Sandra en Esmee**, maar natuurlijk wil ik ook jullie bedanken. Na de ontelbare keren mijn contract verlengen, kwam er dan toch echt een einde aan. Jullie inzet voor de OGC onderzoekers is bewonderingswaardig. Altijd behulpzaam, altijd vrolijk en altijd in voor een praatje; jullie zijn toppers!

Collega's van de **afdeling Heelkunde** in het Erasmus MC; ik heb een geweldige tijd gehad als ANIOS bij jullie, en wat heb ik mezelf kunnen ontwikkelen. Vers uit de schoolbanken hebben jullie me geleerd om een dokter te worden. Dank voor de begeleiding hierin.

Chirurgen en assistenten van de **afdeling Plastische Chirurgie** in het Erasmus MC, zo lang naar uitgekeken en daarom zo blij dat ik aangenomen werd. De 6 maanden als ANIOS waren fantastisch en leerzaam, en bevestigde dat ik écht plastisch chirurg wil worden. Dank voor de kans die jullie me gegeven hebben; ik kan niet wachten om als AIOS dit mooie vak te leren.

Collega's van de **afdeling Heelkunde** in het Amphia Ziekenhuis; dank voor het warme welkom in het altijd mooie Brabant! Bij een teambuilding dag denk ik normaliter niet gelijk aan geblinddoekt, in 30 graden met een veel te grote overall, door het water geëscorteerd worden, maar het was al met al een topdag! Ik kijk er naar uit om mijn vooropleiding bij jullie te doen.

Pien, dank voor het vertrouwen dat je had om de mamma onderzoekslijn aan mij door te geven. Als we het dan over kopietjes hebben, volg ik ook je voetstappen in de richting

van de plastische chirurgie en blijven we collega's. Zoals jij jouw voorbeeld had, ben jij die van mij!

Noelle, het 6e mamma-meisje, welkom! Dank voor het overnemen van de 3d-echo, zonder jou was het niet gelukt om de studies voort te zetten en af te ronden. Ik wil je veel succes wensen, zet hem op!

Louise, al een aantal jaar weten wij elkaar te vinden op het gebied van de plastische chirurgie en hebben we altijd veel te bespreken tijdens onze koffie-momentjes. Dank voor het (tijdelijk) overnemen van de PROFAS; en leuk dat we ook samen wat gaan publiceren! Succes en veel plezier bij de derma, je bent een topper!

In de afgelopen 2,5 jaar heb ik er niet alleen nieuwe collega's bij gekregen, maar ook vrienden. Allerliefste collega-vriendinnen van NA21, de 'meidenkamer'; jullie hebben mijn PhD tijd zo ontzettend leuk en memorabel gemaakt. **Evalyn**, Ev, bedankt voor je altijd aanwezige humor, inclusief slechte en goede grappen, noedels pindakaas, maar vooral je openheid en eerlijkheid. Zo leuk dat we elkaar de aankomende 2 jaar nog regelmatig bij chirurgie onderwijs zullen zien. **Kelly** en **Michelle**, met zijn drieën de enige echte spandoekencommissie; dank voor alle juice, discrete mailtjes, SJINGO, lager dan knieniveau gaan, bommetjes, snapchats en stickers: het is echt altijd feest met jullie. Mies, mega veel plezier en succes in Australië! Kel, helaas dunt de meidenkamer uit, maar ik bel binnenkort nog eens een keertje aan. **Elisabeth** en **Charlotte**; team Hazes verkleed als bierflesje en het bafscheidsfeestje in de achtertuin; ik heb gelachen met jullie! **Christianne**, ondanks dat onze onderzoekstijd niet echt overlap had, ben ik blij dat we toch een aantal borreltjes samen meepakken. En ik hoop dat we in de toekomst collega's blijven bij de plastische! Maidon, duizendmaal dank voor alle koffies, klaagkwartiertjes, feestjes, hulp en luisterend oor gedurende onze tijd op de meidenkamer.

Lieve mannen van de mannenmeidenbende; **Hidde**, toen nog buurman! Altijd gezellig de wandelingen met koffie (en Fred) tijdens het thuiswerken, dank voor je aanstekelijke enthousiasme tijdens het stunten. **Robert** en **Sam**, jullie maken elke borrel gezellig, dank voor jullie hulp waar nodig en de vele potjes darten. **Job**, zelfs met 3 uur vertraging in een vliegtuig zitten was gezellig! Op naar het volgende huisfeestje. **Ben**, dank voor het organiseren van mijn eerste onvergetelijke skireis. Laten we die borrel met bacardi en goocheltrucs nog eens herhalen. **Berend**, wat hebben we gelachen met en zonder plezierspoortjes in Lissabon. Ons business plan voor de botox-bus is bijna klaar, beloofd.

Collega NA21-onderzoekers, **Jan, Hakan, Jonne, Boris, Diederik, Florian, Wills, Stijn, Chris, Yannick, Roos, Birgit, Stefanie, Lissa, Maartje, Josephine, Charlene en Ibtissam**; bedankt voor de gezelligheid en als hoogtepunt natuurlijk friet Friday!

Lieve vrienden en vriendinnen, jullie maken mijn leven een heel stuk leuker!

Lieve Eekhoorns, **Britte, Nino, Kelly, Charlotte, Martijn, Daan, Trevor, Raoul en Max**, al zó lang vrienden. Dank voor jullie support en afleiding. Het jaarlijkse weekendje weg is iets waar ik altijd weer naar uit kijk, op naar de 11e editie!

Lieve oud huisgenootjes, **Eva, Marjolein en Charlotte;** soms konden we niet anders dan over de medische wereld praten, sorry Char! Onze (studenten)tijd in het poppenhuisje op de Nolensstraat 12B2 was fantastisch (inclusief gaskachel en fleecedekens, mosselavonden, studiesessies, middagdutjes, brakke ochtenden en wijntjes op het balkon) en had ik met niemand anders willen doorbrengen. Dank voor jullie lieve woorden, het meeleven bij spannende momenten, en de vele huisavondjes die we gelukkig nu nog steeds doorzetten. Ik ben mega trots op jullie. Lieve **Monique**, dank voor het tijdelijk bivakeren in jouw kamer, de ontelbare keren dat ik de auto mocht lenen, alle goede gesprekken maar vooral de gezellige tijd!

Lieve **Sanne,** blij dat ik je nog zo vaak zie tijdens onze etentjes, met een glas wijn en genoeg stof om over te kletsen; dank voor al je support!

Lieve club, **JC Touché**, we zijn wat verder uit elkaar gaan wonen, maar maken nog altijd tijd vrij voor een bootfeestje, padel wedstrijd, zondag middag borrel of tegenwoordig prachtige bruiloften. Dank voor jullie interesse en steun. Niet aan te tippen!

Lieve **Annabelle** en **Juliette**, wat waren we uit in Ibiza! Dank voor de nodige afleiding tijdens het maken van dit proefschrift. Jullie hebben mijn hele carrière op de voet gevolgd en waren er op belangrijke momenten. Ik ben ontzettend dankbaar voor onze vriendschap en weet dat we altijd bij elkaar terecht kunnen in leuke of minder leuke tijden. Als bijna buurvrouwen hoop ik nog heel lang bij elkaar in Rotterdam-Noord te wonen. Maar vooral kijk ik uit naar alle herinneringen die we nog gaan maken. Wanneer is de volgende girlstrip?!

Lieve **Ivona** en **Anne-Rose**, wat ben ik ontzettend blij dat jullie als paranimfen naast me willen staan. Lieve Ivona, Ivo, je hebt me met open armen op NA21 ontvangen, en na ons eerste avondje stappen in de Vibes klikte het direct; al had ik natuurlijk niet anders verwacht gezien onze Brabantse roots! Ik heb van je genoten op de skireis en vele feestjes

die we samen hebben gevierd. Als je wenkies maar goed zitten! Ik ben supertrots op hoe jij de afgelopen jaren ook keihard gewerkt hebt. Op naar een mooie opleidingsplek voor jou! Lieve Anne-Rose, AR, bijna tegelijkertijd begonnen en dus onze gehele promotie met elkaar doorgebracht. Wat was ik blij dat wij team Lissabon waren; daar hebben we toch wel even de bloemetjes buiten gezet. Ik kijk uit naar Festiven 3.0! Dank voor de altijd goede gesprekken en het sparren over de toekomst, ik waardeer je openheid enorm. Ik vind het superknap dat je voor jezelf gekozen hebt, en je nu zo aan het shinen bent bij de derma. Het gaat je zeker lukken. Lieverds, successen tijdens onze promotietijd hebben we altijd goed gevierd dus laten we dat in de toekomst ook voor altijd blijven doen! Jullie zijn toppers.

Lieve **Meraux**, ondanks dat je een heel ander vak beoefend en je bij het vertellen over een ledemaat of operatie al niet lekker wordt, ben je echt altijd geïnteresseerd geweest en vroeg je hoe het met het onderzoek ging. "Dus deze publicatie is nummer…?" Ik bewonder je positieve instelling, gedrevenheid, openheid en eerlijkheid (of was het kwetsbaarheid?) en je ambitie en inzet voor je eigen succesvolle bedrijf. Duizendmaal dank voor je luisterend oor, je humor, adviezen en oppeppers als de zon niet scheen en het gordijntje weer dicht ging. Ik heb van je genoten op vakantie in Barcelona (wat zullen we het hier nog lang over hebben), de feestjes en decadente diners, friet met prosecco als vaste prik op de vrijdagavond en rocycle mét koffie. Ik kan me geen betere vriendin voorstellen. Op naar nog zoveel mooie dingen samen!

Lieve familie, **Laura**, **Coen**, **Pieter**, **Rosy** en kleine **Maud** en **Andrea**; wat ben ik trots op jullie mooie gezinnen. Jullie hebben de afgelopen jaren vele verhalen uit het ziekenhuis moeten aanhoren, soms inclusief geluiden en wilde gebaren. Maar ik wil jullie bedanken voor jullie altijd oprechte interesse, steun en adviezen. Wat een geluk dat FaceTime bestaat! En wat heerlijk om een adresje in Eindhoven én Italië te hebben waar ik als kleine zusje altijd welkom ben. *Grazie mille*!

Lieve **papa** en **mama**, zonder jullie had ik hier nu niet gestaan. Mogelijk zegt iedereen dit, maar ik kan me geen betere ouders wensen! En eindelijk ook opa en oma, die rol staat jullie fantastisch. Dank voor jullie onvoorwaardelijke liefde en bemoedigende woorden; jullie hebben me altijd gesteund en nooit getwijfeld. Thuiskomen voelt nog steeds als echt thuiskomen, met of zonder appelflap of glaasje rosé. Ik hou van jullie!

ABOUT THE AUTHOR

Marloes Elisabeth Clarijs was born on the 18th of March 1994 in Klundert, the Netherlands. She graduated from pre-university education in 2012 at Markland College in Oudenbosch, the Netherlands. Hereafter, she studied Medicine at the Erasmus University Medical Center in Rotterdam, where she received her medical degree in spring 2019. From start studying Medicine, but especially after her internship and master thesis at the Department of Plastic, Reconstructive and Hand Surgery of the Erasmus University Medical Center, her interest in plastic surgery grew more and more. Marloes started as a surgical resident (ANIOS) at the Department of Surgery at the Erasmus Medical Center Rotterdam, the Netherlands (prof. dr. J. Hendriks). By working at the Surgical Oncology department of the Erasmus MC Cancer Institute and her interest in the oncological breast surgery, she had the opportunity to start as a PhD-Candidate in October 2019 (prof. dr. C. Verhoef, dr. L.B. Koppert). During this period, she also worked part-time at the Department of Quality and Patient care of the Erasmus Medical Center, Rotterdam, the Netherlands, in which she was involved in various international high value care projects and courses as part of the Healthcare Transformation Academy (prof. dr. M. Hazes, dr. L.B. Koppert). Marloes stayed interested and enthusiastic about plastic and reconstructive surgery throughout all her activities, with the growing ambition to become a plastic surgeon. From July until December 2022, Marloes was employed as a plastic surgery resident (ANIOS) at the Department of Plastic, Reconstructive and Hand Surgery of the Erasmus University Medical Center, Rotterdam, the Netherlands (dr. A.J.M. Luijsterburg). Marloes started her plastic surgery residency (VAIOS) in the Amphia hospital, Breda, the Netherlands, by May 2023.