STARLINGS Study Protocol

An integrated optimization of **s**urgery and radio**t**her**a**py techniques to imp**r**ove cosmetic outcome and qua**l**ity of l**i**fe in breast conserv**ing** therapy for brea**s**t cancer patients (STARLINGS) – Study ID: NCT05263362)

INTRODUCTION AND RATIONALE

Approximately one in seven women will be diagnosed with breast cancer during their lifetime in the Netherlands. In other words, the lifetime cumulative risk of developing breast cancer in the Netherlands is approximately 14.3 %. The majority of breast cancer patients (60-70%) can be treated with breast-conserving therapy (BCT) which consists of a lumpectomy (instead of mastectomy) combined with a sentinel node procedure or an axillary lymph node dissection, followed by irradiation of the breast and systemic therapy if indicated (1-3). In patients with a (relatively) large tumor and/or small breast, chemotherapy precedes surgery with the aim to reduce tumor volume, and thereby making it possible to perform BCT (4). Our group has shown that survival after breast-conserving therapy at least equals survival after mastectomy (5). Late adverse effects of the treatment affecting quality of life (QoL) have become increasingly important, due to the substantially longer life expectancy after BCT.

In oncoplastic reconstructive surgery, an oncological resection is combined with plastic reconstructive techniques with the aim of improving cosmetic outcome without compromising oncological safety (6). Breast conserving surgery techniques can be divided into four groups: (1) standard lumpectomy (removal of the tumor without reshaping the breast) without closure of the glandular tissue, (2) simple oncoplastic surgery techniques (tissue displacement over a small area in order to reshape the breast without nipple displacement and with closure of the glandular tissue) and two groups of complex oncoplastic surgery techniques, namely (3) tissue displacement with nipple repositioning or breast reduction techniques and (4) volume replacement using tissue from outside of the breast (6). In this study we will use three groups, where group 1 and 2 as mentioned above are combined (1) standard and/or simple oncoplastic lumpectomy (2) tissue displacement techniques (breast reduction techniques) and (3) tissue replacement techniques using tissue from outside of the breast. We choose to combine the first and second group, because nowadays in clinical practice a standard lumpectomy is not conducted anymore in the participating hospitals.

Adjuvant radiotherapy consists of partial or whole breast irradiation, which is dependent on patient and tumor-related factors as well as on the volume of the surgical area inside of the breast. Partial breast irradiation is an option in the case of favorable patient and tumor characteristics (i.e. age ≥ 50 years with completely removed pre-invasive breast cancer (i.e. ductal carcinoma in situ (DCIS)) or invasive non-lobular unicentric unifocal carcinoma, tumor grade 1 or 2, diameter ≤ 3 cm and without triple negative receptor status) in combination with a limited radiation target volume (i.e. a surgical area that encompasses less than one-third of the breast) (7). In all other breast conserving therapy patients, the whole breast needs to be irradiated to reduce the risk of breast tumor recurrence. In patients with certain (combinations of) high risk features, an indication for a radiation boost at the surgical area ('wound bed') exists. High risk features are age ≤ 40 years, grade 3 tumor, triple negative tumor (e.g. estrogen receptor, progesterone receptor and Her2neu receptor negative tumors), the presence of lymph vascular invasion, the presence of extensive DCIS, and focally non-complete tumor resection (8, 9). Unfortunately, breast fibrosis occurs as a late adverse event in a

substantial subset of patients (10-30%) after breast conserving therapy for DCIS or breast cancer (8, 10, 11). Fibrosis can be painful and may result in poor cosmetic outcome (Figure 1) (12). Fibrosis as well as poor cosmetic outcome can negatively affect QoL (13, 14). Well-known risk factors for the development of fibrosis are:

- Patient and tumor related: increasing age, larger breast volume and larger tumor size (15-18)
- Surgery related: larger excision volume and post-operative complications (e.g. seroma and hematoma) (10, 18)
- Radiotherapy related: boost treatment, larger boost volume and higher maximum radiation dose (10, 11, 15, 19)

In other words, besides patient and tumor related factors, both surgery and radiotherapy play a role in the risk of developing fibrosis. Of course, both surgical and radiation oncologists aim for the best cosmetic outcome and QoL of each breast cancer patient, without compromising oncological safety. However, especially in the light of current oncoplastic reconstructive surgery techniques, it has not yet been properly investigated how the different surgery and radiotherapy techniques interact. In order to avoid known risk factors for fibrosis, if possible, surgical techniques with the smallest chance of causing postoperative seroma and hematoma should be used. Furthermore, in patients who require a radiation boost or who are considered for partial breast irradiation, the surgical area should ideally be as small as possible, thereby reducing the radiotherapy target volume and the related risk of fibrosis on the long term (10). From a surgical perspective, a preference for oncoplastic reconstructive surgery may exist. However, if a radiation boost is indicated this approach might lead to an increased volume of the surgical area and thus may lead to a larger radiotherapy boost target volume and subsequently to a higher chance of fibrosis and a poorer cosmetic outcome than was initially aimed for by applying (complex) oncoplastic reconstructive surgery.

In our region in the Netherlands, the surgical approach and preferences for surgical (oncoplastic reconstructive) techniques differ within and between hospitals. All breast cancer patients are referred to the Erasmus MC for adjuvant radiotherapy. Due to our close regional collaboration, we can use surgical as well as radiotherapeutic variables to analyze their effect on fibrosis, cosmetic outcomes and QoL in order to unravel the impact of different (possible) surgical and radiotherapeutic risk factors contributing to the development of fibrosis and to assess their interaction, after breast-conserving therapy for (pre-invasive) breast cancer. The primary focus will be on the role of different combinations of surgery and radiotherapy techniques as risk factors for fibrosis. From a patient perspective however, not primarily fibrosis, but QoL is usually what matters most. In a substantial subset of patients not only breast fibrosis, but also cosmetic outcomes may influence QoL (20). Therefore, we will not only focus on fibrosis, but also on cosmetic outcomes and QoL.

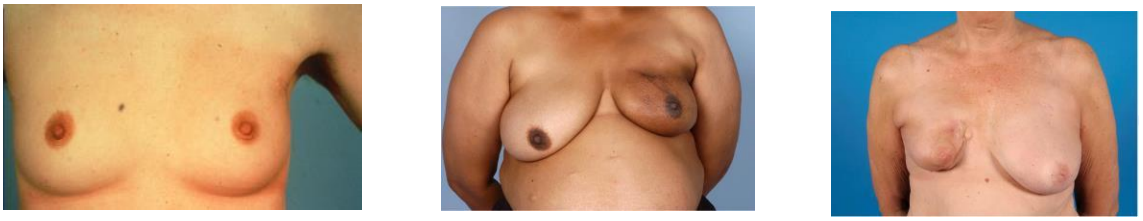


Figure 1: Three women after breast-conserving therapy. No fibrosis (picture left) and severe fibrosis (middle and right picture).

OBJECTIVES

The primary focus of this project will be to determine which different combinations of (oncoplastic reconstructive) surgery and radiotherapy techniques, in the context of BCT for (pre-invasive) breast cancer, contribute the most to the development of fibrosis as well as for moderate to poor cosmetic outcomes.

Based on this knowledge, predictive models for the development of moderate to severe fibrosis and unfavorable cosmetic outcomes will be developed that allow for patient tailored treatment decision making in future breast cancer patients.

The secondary endpoint will be to assess the relation between the presence and severity of fibrosis, cosmetic outcomes and different QoL domains and symptoms. With regard to QoL the specific focus will be on physical functioning, satisfaction with breast, psychosocial functioning, and breast symptoms. To this end health-related quality of life parameters will be captured.

METHODS

The STARLING study is a multi-center cross-sectional observational cohort study. Four Dutch hospitals will be participating (three large teaching hospitals: Albert Schweitzer hospital, Maasstad hospital and Franciscus hospital Gasthuis and Vlietland and one university hospital: Erasmus Medical Center). This study was prospectively registered February 21st 2022, at Clinical Trails.gov ID: NCT05263362.

Study population

The study population consists of breast cancer patients who were treated with breast-conserving therapy (BCT) at one of the four participating Dutch hospitals (Erasmus MC, Albert Schweitzer hospital, Maasstad hospital and Franciscus hospital Gasthuis and Vlietland), for non-metastatic, histological proven invasive breast cancer (pT1-3N0-2a) or DCIS between 2016 and 2020 (at time of inclusion in 2022 respectively 6, to 2 years after treatment), and subsequently received adjuvant radiotherapy at the Erasmus MC as part of their BCT.

In order to be eligible to participate in this study, a subject must meet all of the following criteria: female, aged ≥ 18 years, history of BCT with adjuvant radiation therapy for non-metastatic, histologically proven invasive breast cancer pT1-3N0-2a or DCIS. In light of BCT adjuvant systemic treatment (i.e. endocrine therapy, chemotherapy and immune therapy) is allowed. Furthermore, BCS between 1st of January 2016 and 31th of December 2020, and a patient must have been treated according to the currently applied dose fractionation schedules (START B trial), i.e. whole breast radiotherapy, with or without boost, and adequate understanding of the Dutch language and written informed consent

A potential subject who meets any of the following criteria will be excluded from participation in this study: any breast surgery or re-irradiation on the breast area after BCT, progression of disease (and additional treatment) since BCT, patients who received partial breast irradiation, pregnancy or breast feeding at the time of recruitment.

Subjects can leave the study at any time for any reason if they wish to do so without any consequences. The investigator can decide to withdraw a subject from the study for urgent medical reasons.

Recruitment and consent

At the participating hospitals a list of all patients who had breast-conserving surgery in the period 2016-2020 will be collected. These lists will be stored in a secure location at the hospital where the patient was treated, and only persons directly involved in subject recruitment, data collection, and data verification will have access to these lists. Also, a list of all irradiated patients in this period, meeting our inclusion criteria and operated on in the participating hospitals, will be collected at the Erasmus MC. In this way patients who are six years after surgery (and no longer have follow up appointments with their surgeon) will not be missed.

After this, the outpatient clinic schedule will be checked for eligible patients. If so, the surgeon or assistant will be informed by phone or email and will be asked to inform the patient about our study at the outpatient clinic. Preceding their regular follow up visit, after a short explanation of the study by the surgeon or nurse, eligible patients will be asked by their treating surgeon or nurse if they want to participate. They will receive written information regarding this study. Patients can consider participation as long as needed to make a well-considered decision. The researcher will contact patients (or vice versa) to explain more about the study and answer the remaining questions. Patients will be enrolled after all questions are answered satisfactorily and after written informed consent is given. After written informed consent is given, a visit to the outpatient clinic of their own hospital will be planned. If it is more convenient for the patient, it is also possible to plan the hospital visit at the Erasmus MC. At this appointment, the researcher (MD) will perform a physical examination (to grade fibrosis), score the predefined list of adverse events and cosmetic outcomes, and take photographs of the breasts. The physical examination will consist of palpation of the breasts, axillary, and peri-clavicular regions.

Patients will be informed at the outpatient clinic about the aim and the content of the study by the treating physician, but not all patients who are six years after surgery still have regular follow up anymore. In this case, the surgeon or radiotherapist (or colleague surgeon/radiotherapist, physician assistant, nurse practitioner from the team) who treated them will call these patients to notify them about the study. In the case of (permanent) absence of the primary treating physician, a colleague from the clinical team will call the patient. If the patient is open to this, they will be phoned by the researcher for more information. They will receive written information regarding this study and an informed consent form. Patients can consider participation as long as needed. The researcher will contact patients if necessary (or vice versa) to answer the remaining questions. Patients will be enrolled after written informed consent is given.

Study procedures and endpoints

Fibrosis

A summary of all study procedures is displayed in Figure 2. After inclusion of eligible patients, fibrosis will be graded by the researcher using the CTCAE v5 scale (see Appendix A) during the one time visit at the outpatient clinic (21). Cosmetic outcomes will be evaluated by means of a 9-item

cosmetic patient questionnaire (filled out by the patient) with scoring on a four-point scale (range from 'excellent' to 'poor' per item) (22). We will also be using a physical examination form (see Appendix B) as used for the PBSI (Permanent Breast Seed Implant) study including the assessment of adverse events (such as redness of the skin, pigmentation), which will be an addition to the fibrosis grading, because these are also important factors which play a role in cosmetic outcomes. This form will be filled out by the researcher.

Cosmetic outcomes

Furthermore, patients' photographs of the breasts (between collar bone and umbilicus) will be taken during this outpatient clinic visit, for asymmetry evaluations. Three color photographs of the breasts will be taken: two frontal views, one with arms along the body, one with arms lifted upwards and one profile view taken from the treated side with arms lifted upwards (19). With the use of the BCCT.core software from The Breast Research group (INESC TEC, the Faculdade de Medicina da Universidade do Porto) cosmetic outcomes will be assessed (23). With this software program, which we have been using and currently use in several studies (20, 22, 24, 25), various parameters can be extracted from the photographs. The three dimensionless asymmetry features known to be the most relevant variables that represent various aspects of breast fibrosis are Breast Retraction Assessment (BRA), Lower Breast Contour (LBC), and Breast Overlap Difference (BOD). These three parameters respectively represent nipple and breast retraction, 'lifting' of the breasts and contour and volume changes and will be used in our analyses (19).

Quality of life

Patient reported outcomes of QoL domains and symptoms will be assessed using the questionnaires that are proposed in the ICHOM breast cancer outcome set to evaluate breast cancer patients (26). The questionnaires we will be using are the Euro-QoL 5D- 5L (EQ 5D-5L version 2.0), the European Organization of Research and Treatment of Cancer QoL questionnaires (EORTC QLQ C30 version 3.0 and EORTC QLQ-B23) and BREAST-Q breast conserving therapy (postoperative module version 2.0) and 9-item cosmetic patient questionnaire (22, 27-30). These questionnaires consist of psychosocial, sexual and physical well-being items, symptoms and satisfaction with outcome and breasts.

A link to the electronic questionnaires will be sent to the participants by email after the patient has given explicit consent for transfer of personal data to the datacenter in coordinating institute (name, date of birth, email address and telephone number) and after inclusion in the trial. Some patients may already have completed some of the questionnaires that we are interested in (namely Breast-Q, EORTC QLQ-C30 and EORTC QLQ-B23), on behalf of the PROMs Citrien project (31). In the PROMs Citrien project, patients are asked to complete questionnaires after 6 months and then every year up until 5 years after treatment. If we include patients that filled in these questionnaires for the Citrien project already, we will ask the patient if we can use these questionnaires, in order to avoid having to fill in the same questionnaires twice. When filled out online, the questionnaires will automatically being transferred into our database. If the patient does not have an email address or cannot fill out the forms online for some reason, the questionnaires will be handed out on paper during the outpatient clinic visit at the referring site. Patients will then also receive a returning envelop, so that they are able to complete the questionnaires in their own time and space and send them to the Erasmus MC. All completed questionnaires will be stored by the Datacenter in the Erasmus MC and imported in the study database.

The site will be responsible for collection of questionnaires at the time point as defined in the study protocol. Every site may delegate the distribution and collection of online questionnaires to the Datacenter by sending a form containing the full name, date of birth, telephone number and email address of the patient and including a written consent for providing these data to the employees in Erasmus MC who are directly involved in the distribution and collection of digital questionnaires. Without this written consent form for digital collection of questionnaires, the distribution and collection of questionnaires cannot be delegated to the Datacenter in Erasmus MC and will remain a site responsibility.

All patient and tumor characteristics, as well as surgical techniques, will be collected (retrospectively) from (digital) records in the four hospitals. All radiation treatment data is available at the department of Radiotherapy at Erasmus MC and will be collected by the study staff in Erasmus MC. All technical radiation parameters can be retracted fully automated because of the extended information technology (IT) infrastructure at the department. Due to the excellent multidisciplinary collaboration, complete collection of clinical, surgical and radiotherapeutic data will be realistic.

The study ends when the last included patient has her photographs taken and has completed the questionnaires. There will be no follow-up of patients in the context of this study. Patients will continue with their regular follow-up.

If patients are withdrawn from the study, the standard care and follow-up will be continued. We do not expect a reason to terminate the study prematurely since only minimal to no risks are associated with participating in the study.

Data collection

The main goal of this project is to determine risk factors and their interaction contributing to the development of fibrosis and cosmetic outcome, after breast-conserving therapy for (pre-invasive) breast cancer. The primary focus will be on the role of different combinations of (oncoplastic reconstructive) surgery and radiotherapy techniques as risk factors for the development of fibrosis, as well as for moderate to poor cosmetic outcome and QoL. To be more specific:

1. To determine prognostic risk factors for moderate to severe fibrosis, moderate to poor cosmetic outcome and QoL, especially in the light of current oncoplastic surgery techniques.

2. To develop prediction models for the risk of moderate to severe fibrosis stratified for (oncoplastic) surgery and radiotherapy parameters

3. To develop prediction models for cosmetic outcome stratified for (oncoplastic) surgery and radiotherapy parameters

To this end clinical, surgical and radiotherapeutic related parameters will be captured:

Patient characteristics such as age at time of inclusion; age at time of diagnosis of breast cancer; length, weight, body mass index (BMI; kg/m^2); diabetes; menopausal status, smoking; allergies; hypertension; presence of connective tissue disorders; presence or history of autoimmune or auto-

inflammatory disorders; history of malignancies and received treatments, previous operations of the breast(s).

Tumor characteristics: clinical tumor size (cm) on X-mamma/echo/MRI, tumor location (lateral upper quadrant, lateral lower quadrant, medial upper quadrant, medial lower quadrant, central), macroscopic size (cm) of the tumor (in the pathology report), tumor to breast volume ratio, tumor histology, ER, PR and Her2neu expression, tumor grade, presence of complementary DCIS (in the case of invasive breast cancer), size and location of DCIS, lymphovascular space invasion (LVSI).

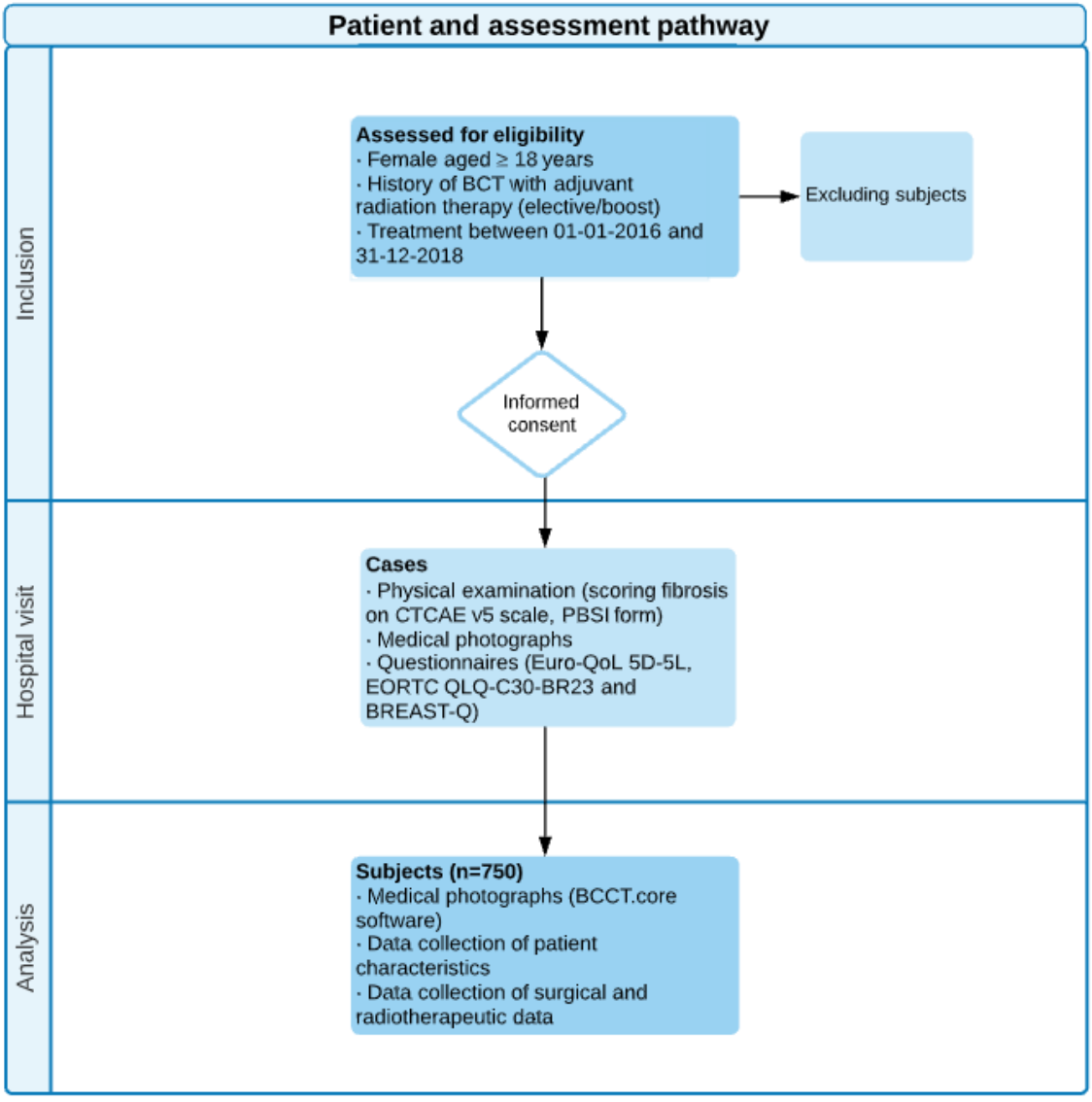


Figure 2: Study Flowchart

Surgery characteristics: weight of tissue of specimen (pathology report) or macroscopic size (cm) of the tissue specimen (if available in the pathology report), post-operative complications, type of

surgery (1. standard/simple lumpectomy, 2. tissue displacement techniques 3. tissue replacement techniques), re-resection (yes/no), axillary dissection (yes/no).

Radiotherapy characteristics: Technical, volumetric and dosimetric data will be collected. On this basis the relevant parameters can be extracted.

In case of systemic therapy: use of Aromatase inhibitor and Chemotherapy (type, timing: neo-adjuvant or adjuvant); use of antimicrobial, anti-inflammatory, biological and cardiovascular agents; duration of Aromatase inhibitor therapy and Chemotherapy, use of Hormonal therapy, use of Trastuzumab; use of Hyperbaric Oxygen Therapy.

The secondary endpoint will be to assess the relation between the presence and severity of fibrosis, cosmetic outcome and different QoL domains and symptoms. With regard to QoL the specific focus will be on physical functioning, satisfaction with breast, psychosocial functioning and breast symptoms. To this end health related quality of life parameters will be captured:

- Health Related Quality of Life: pain (NRS scale 0-10), use of medication for pain (yes/no). Patient reported outcomes will be used to evaluate the health-related quality of life, which are measured by different questionnaires about quality of life and symptoms. This includes:
    - European Organization for Research and Treatment of Cancer QoL Questionnaire–Core 30 (EORTC QLQ-C30, version 3) (28)
    - Postoperative BCT of the BREAST-Q (version 2)(only postoperative items) (27)
    - EuroQol Group 5-level EQ-5D (EQ 5D-5L) (29)
    - European Organization for Research and Treatment of Cancer QoL
    - Questionnaire BR23 (EORTC QLQ-BR23 version 1.0) (30)
    - 9-item cosmetic patient questionnaire (22)

These questionnaires (in Dutch) consist of psychosocial, sexual and physical well-being items, as well as symptoms, and satisfaction with breasts. All scales and single item measures range in a score of 0-100 after transformation. A higher score means better functioning and QoL, whereas for the symptom domains higher scores represent more symptoms. The results of these questionnaires of our participants will be used to measure the impact of cosmetic outcomes and fibrosis on the HRQoL.

To this end the participants will be asked to fill out the questionnaires during their one-time study visit. Fibrosis will be prospectively graded using the CTCAE v5 scale (see appendix A) (21) together with a predefined list of adverse events / cosmetic outcomes (see appendix B), and patients' breast photographs will be made to assess objective cosmetic outcomes.

Sample size calculation

Between 2016-2020 approximately 1600 patients underwent simple or complex oncoplastic lumpectomy (6) (Figure 1) at one of the four hospitals and subsequently received adjuvant radiotherapy at the Erasmus MC as part of their BCT. Considering data of 2016, we can conclude that approximately 50% was treated with a simultaneously integrated boost (SIB), roughly 15% got a sequential boost and the rest only received the elective dose. A radiation boost dose to the surgical area was delivered as a SIB in 49% of the patients and directly after the elective radiation dose (sequentially) in 17%. The 1600 eligible patients will be asked to participate in this study at their

planned standard follow-up appointment during the 1 to 1.5 years of patient inclusion at their follow-up appointment 2-, 3-, 4-, 5- or 6-years after treatment. However, not all patients who are six years after surgery still have regular follow up anymore. In this case the surgeon or radiotherapist who treated them will call to notify about the study. Earlier studies showed that an inclusion rate of 70% is feasible (21). In our experience, at least 50% of the patients agrees to participate in the study. This means that approaching 1600 patients should be sufficient to result in a cohort of at least 750 patients. It is expected that approximately 20% (11) of these patients will have moderate or severe fibrosis in the breast, including the boost area. That means that the sample size of 750 will provide sufficient information to develop a model with approximately 7-15 degrees of freedom (DF) (using the rule of thumb of the effective sample size of 10-20 per DF). It is expected that the percentage of patients with unsatisfactory cosmetic outcomes will be approximately 30%, so according to the same reasoning as above, there will also be sufficient information to develop a model to predict cosmetic outcomes.

Statistical analysis

All statistical analyses will be performed using SPSS (current version 25.0, Statistical Package for Social Sciences, Chicago, IL, USA) and the latest R version. Statistical tests will be two-sided and differences are considered significant if $p<0.05$.

Primary study parameter(s)

The primary aim of this study is to develop prediction models for fibrosis and moderate to poor cosmetic outcome after treatment with different combinations of (oncoplastic) surgery and radiotherapy techniques. It will be investigated whether the type of surgical technique (standard / simple oncoplastic lumpectomy; complex oncoplastic technique with tissue displacement, or complex oncoplastic technique with tissue replacement) is associated most with cosmetic outcome and the risk of fibrosis, or whether it is one or more radiotherapeutic parameter(s), or both. These analyses will be adjusted for other patient and tumor characteristics (e.g., age, breast volume, tumor size), and factors related to radiotherapy (e.g., boost treatment, boost volume, maximum radiation dose).

The surgical techniques with tissue displacement and replacement will be compared to determine whether they should be analysed separately or could be considered as one treatment. The analysis will be supported by a comparison of the post-operative complications (e.g., seroma and hematoma), because these are known to be associated with fibrosis.

If there are differences between the surgical techniques, then it will be useful to develop models that predict their outcome for individual patients. The treatment options actually consist of combinations of surgical techniques and radiotherapy. Therefore, the interaction will be tested between surgical technique and whether a radiation boost dose was given (and volume of the boost). The interaction will be included in the model if it is found to be relevant. Patient and tumor characteristics and factors related to radiotherapy treatment will be considered as candidate variables to be included in the model. But factors will not be considered candidate variables if they are related to the success of the surgery procedure itself (e.g., excision volume, post-operative complications seroma and

hematoma), because it is expected that any differences between the surgical techniques on outcome may be caused *via* these factors. However, whether this is the case will be investigated.

If no clinically relevant differences are found between the surgical techniques, then it may be more worthwhile to focus the research on the role of radiotherapy techniques. In that case, it will be important to investigate correlations between the candidate predictor variables, and resolve multicollinearity issues if possible, when developing a model. The model may then be used to identify radiotherapy parameters that can be taken into consideration during radiotherapy treatment planning. These parameters could then be investigated in a future planning study, with the aim of optimizing radiotherapy treatment plans. For such a model, factors related to surgery are candidate covariates (along with patient and tumor characteristics, and radiotherapy parameters), because in practice the results of the surgery will be known at the time of radiotherapy planning.

The endpoints will be modeled as follows:

- Fibrosis will be dichotomized into no/mild and moderate/severe fibrosis and modeled using logistic regression.
- Overall cosmetic outcome derived from patient questionnaires will be dichotomized into excellent/good outcome ("satisfactory cosmetic outcome") and moderate/poor ("unsatisfactory cosmetic outcome") and modeled using logistic regression.

Prediction models will be developed by means of a multivariable logistic regression using variable selection criteria and supported by univariable analysis.

Furthermore, the parameters that will be found in our literature search for the review will also be added. Internal validation of the models will be investigated using a bootstrap or cross-validation procedure. External validation will not be part of this study but can be done in the future by means of a validation study or a replication cohort (for example Breastcenter ZuidHollandZuid or Umbrella cohort, University Medical Center Utrecht). Details of the methods will be described in a statistical analysis plan.

Secondary study parameter(s)

The secondary objectives are to describe the presence and severity of fibrosis, cosmetic outcomes, and QoL according to the different patient and tumor characteristics and the different surgery and radiotherapy techniques. Second, to assess the relation between the presence and severity of fibrosis, cosmetic outcome and the different QoL domains and symptoms. With regard to QoL, the specific focus will be on physical functioning, satisfaction with breast, psychosocial functioning and breast symptoms.

Summary statistics and tables of patient characteristics will be produced. Participants will be asked to fill out five questionnaires. The results of each domain from the EORTC QLQC30, EORTC QLQ-B23, Breast-Q, 9-item questionnaire and EQ 5D-5L questionnaires, will be converted to a numeric score (range 0-100) by the use of manual scoring tables. All statistical tests will be two-sided and differences are considered significant if $p<0.05$.

Univariate logistic regression analysis will be used to assess whether there is a relation between fibrosis and BCCT.core. parameters (treated as continuous variables), and whether fibrosis or the BCCT.core parameters were associated with patient reported unsatisfactory cosmetic outcome. In

order to evaluate whether fibrosis or unsatisfactory cosmetic outcome lead to a worse QoL, linear regression will be used. A separate model will be built for each of the QoL scales/single items.

Future plans

If the findings of this project lead to changes in shared decision-making, it will be important to explore which risk factors and specific (sub)domains of cosmetic outcomes and QoL are most relevant to patients during treatment decision-making, and how these aspects relate to one another. This may also include consideration of lifestyle interventions, such as quit smoking, aimed at reducing the risk of postoperative complications and subsequent fibrosis.

If our study demonstrates that certain patients have a choice regarding the type of (oncoplastic) lumpectomy, a patient decision aid (PDA) will be developed. This will be carried out in close collaboration with Dutch breast cancer patient advocates (Borstkankervereniging Nederland) and with the use of the International Patient Decision Aid Standards (IPDAS) checklist (32).

The next step will be to assess its effect on quality of care and QoL of our breast cancer patients. Our prospective registration of patient-reported outcome measures (PROMs) within the Citrien project will be of great value to evaluate this in a prospective manner (31). If future research demonstrates that such a decision aid improves quality of care, it will become more widely available.

Acknowledgements
The authors would like to thank the INESC Porto Breast Research Group for the use of the BCCT.core software.

Funding
This study was partially funded by Stichting BeterKeten (Dutch: Stichting BeterKeten).

Ethics approval and consent to participate
The study is in compliance with the Helsinki declaration. Ethical approval has been granted by the Institutional Review Board of the Erasmus University Medical Centre, Rotterdam, the Netherlands (reference-number: MEC-2021-0829) and of the institutional Review Board of all participating hospitals. This trial is registered before the start of the inclusion. Upon inclusion, a written informed consent is obtained from all participants.

Appendices

Appendix A: CTCAE v5

CTCEA Term	Superficial soft tissue fibrosis / Fibrosis deep connective tissue
Grade 0	Not applicable
Grade 1	Mild induration, able to move skin parallel to plane (sliding) and perpendicular to skin (pinching up)
Grade 2	Moderate induration, able to slide skin, unable to pinch skin; limiting instrumental ADL
Grade 3	Severe induration; unable to slide or pinch skin; limiting joint or orifice movement (e.g., mouth, anus); limiting self-care ADL
Grade 4	Generalized; associated with signs or symptoms of impaired breathing or feeding
Grade 5	Death

Appendix B: Physical examination form STARLINGS study

Physical Examination Form STARLING STUDY

formulier ten behoeve van medisch dossier

Patiënt name _____ PID nr_____

Date of assessment primary endpoint _____

Physician who scored primary endpoint _____

Teleangiectasia score (Bentzen) |___| 0 = none

1 = grade I – less than 1cm^2

2 = grade II – 1 to 4 cm^2

3 = grade III – over 4cm^2

Distance of teleangiectasia from

reference point (nipple lowerinner) _____ mm

Angle of teleangiectasia from

reference point (nipple lowerinner) _____ degree

Teleangiectasia in which

skin projection location? |___| 0 = none

1 = central

2 = mediocranial quadrant

3 = mediocaudal quadrant

4 = laterocaudal quadrant

5 = laterocranial quadrant

Primary endpoint evaluable |___| 0 = no
1 = yes

If non-evaluable, reason: |___| 1 = re-irradiation on ipsilateral breast/chestwall <

2yrs post-treatment

2 = re-surgery on ipsilateral breast/chestwall
< 2 yrs post-treatment

5 = other, specify below

Comments: _____

_____

_____

Naam + Handtekening: _____

Physical Examination Form STARLING STUDY

formulier ten behoeve van medisch dossier

Patient name _____ PID nr _____

Date of AE assessment _____

Pain in breast |___| 0 = none
1 = occasional and minimal – hypersensation – pruritus
2 = intermittent and tolerable
3 = persistent and intense
4 = refractory and excruciating

Redness |___| 0 = no
1 = yes, but no effect on ADL
2 = yes and effect on ADL

Pigmentation |___| 0 = none
1 = transitory – slight;
2 = permanent marked

Skin induration |___| 0 = none
1 = mild induration / able to move skin parallel to plane
(sliding) and perpendicular to skin (pinching up)
2 = moderate induration / able to slide skin / unable to pinch skin / limiting instrumental ADL
3 = Severe induration / unable to slide or pinch skin / limiting self-care ADL
4 = generalized

Subcutaneous induration |___| 0 = none
1 = slight induration and loss of subcutaneous fat
2 = moderate fibrosis but asymptomatic
3 = severe induration and loss of subcutaneous tissue / field contracture
4 = necrosis

Distance of clinical max skintoxicity from reference point (nipple lowerinner)
_____mm Angle of clinical max skintoxicity from

reference point (nipple lowerinner) _____degree Max skin toxicity in wich skin
projection location: |_____| 0=none

1=central
2=mediocanial
quadrant

3=medialcaudal
quadrant
4=laterocaudal
quadrant
5=laterocranial
quadrant

Any other radiotherapy induced adverse events? |____| 0 = no; 1 = yes

If yes, specify: _____

_____

Naam + Handtekening: _____

Appendix C: **Dutch questionnaires**

9-item cosmetische vragenlijst:

Beoordeel het uiterlijk van uw behandelde borst met betrekking tot:

Operatie-litteken				
	uitstekend	goed	matig	slecht
Grootte van de borst	uitstekend	goed	matig	slecht
Vorm van de borst	uitstekend	goed	matig	slecht
Positie van de tepel	uitstekend	goed	matig	slecht
Kleur van de huid	uitstekend	goed	matig	slecht
Hoe de borst er als geheel uitziet	uitstekend	goed	matig	slecht
Asymmetrie / verschil tussen de behandelde en onbehandelde borst	helemaal niet	een beetje	nogal	heel erg
Tevredenheid met hoe de borst er als geheel uitziet	uitstekend	goed	matig	slecht
Tevredenheid met de keuze voor borstsparende operatie ten opzichte van niet-borstsparende operatie	uitstekend	goed	matig	slecht

Memorial Sloan Kettering Cancer Center

BREAST-Q Version 2.0©

Breast Conserving Therapy Module

Pre- and Postoperative Scales

Dutch (NL) Version

THE UNIVERSITY OF BRITISH COLUMBIA

Translated by a local academic.

BREAST-Q™ – BREAST CANCER CORE SCALE (PRE- AND POSTOPERATIVE) VERSION 2.0: PSYCHOSOCIAL WELL-BEING

Als u aan uw borstgebied denkt, hoe vaak voelde u zich de afgelopen zeven dagen:

	Nooit	Zelden	Soms	Vaak	Altijd
a. Vol zelfvertrouwen in een sociale situatie?	1	2	3	4	5
b. Emotioneel in staat om de dingen te doen die u wilde doen?	1	2	3	4	5
c. Emotioneel gezond?	1	2	3	4	5
d. Gelijkwaardig aan andere vrouwen?	1	2	3	4	5
e. Zelfverzekerd?	1	2	3	4	5
f. Vrouwelijk in uw kleding?	1	2	3	4	5
g. In staat uw lichaam te accepteren?	1	2	3	4	5
h. Normaal?	1	2	3	4	5
i. Net als andere vrouwen?	1	2	3	4	5
j. Aantrekkelijk?	1	2	3	4	5

Uitleg voor onderzoekers: Deze schaal kan los van de andere schalen gebruikt worden. Deze schaal is exact hetzelfde voor de drie pre-operatieve en post-operatieve borstkanker modules (i.e. mastectomie, reconstructie en borstsparende therapie).

BREAST-Q™ - BREAST CANCER CORE SCALE (PRE- AND POSTOPERATIVE) VERSION 2.0: PSYCHOSOCIAL WELL-BEING CONVERSION TABLE

Instructions: If missing data is less than 50% of the scale's items, insert the mean of the completed items. Use the Conversion Table below to convert the raw scale summed score into a score from 0 (worst) to 100 (best). Higher scores reflect a better outcome.

SUM SCORE	EQUIVALENT RASCH TRANSFORMED SCORE (0-100)
10	0
11	13
12	18
13	21
14	24
15	27
16	29
17	31
18	32
19	34
20	35
21	37
22	38
23	39
24	41
25	42
26	43
27	44
28	45
29	47
30	48
31	49
32	50
33	52
34	53
35	55
36	56
37	58
38	60
39	62
40	64
41	66
42	69
43	71
44	74
45	77
46	80
47	83
48	87
49	93
50	100

BREAST-Q™ - BREAST CANCER CORE SCALE (PRE- AND POSTOPERATIVE) VERSION 2.0: SEXUAL WELL-BEING

Denkend aan uw seksualiteit hoe vaak voelde u zich in het algemeen:

	Nooit	Zelden	Soms	Vaak	Altijd
a. Seksueel aantrekkelijk met uw kleding aan?	1	2	3	4	5
b. Op uw gemak tijdens seksuele handelingen?	1	2	3	4	5
c. Zelfverzekerd op seksueel gebied?	1	2	3	4	5
d. Tevreden met uw seksleven?	1	2	3	4	5
e. Zelfverzekerd op seksueel gebied over hoe uw borstgebied eruit ziet zonder kleding aan?	1	2	3	4	5
f. Seksueel aantrekkelijk zonder kleding aan?	1	2	3	4	5

Uitleg voor onderzoekers: Deze schaal kan los van de andere schalen gebruikt worden. Deze schaal is exact hetzelfde voor de drie pre-operatieve en post-operatieve borstkanker modules (i.e. mastectomie, reconstructie en borstsparende therapie).

The following statement can be added to the stem to provide an opportunity for the patient to decline completing this scale. 'The following questions ask about your sexual well-being. If you are uncomfortable answering these questions or do not feel that they apply to you, please check the box and skip the questions that follow.'

BREAST-Q™ - BREAST CANCER CORE SCALE (PRE- AND POSTOPERATIVE) VERSION 2.0: SEXUAL WELL-BEING CONVERSION TABLE

Instructions: If missing data is less than 50% of the scale's items, insert the mean of the completed items. Use the Conversion Table below to convert the raw scale summed score into a score from 0 (worst) to 100 (best). Higher scores reflect a better outcome.

SUM SCORE	EQUIVALENT RASCH TRANSFORMED SCORE (0-100)
6	0
7	14
8	20
9	24
10	27
11	31
12	34
13	36
14	39
15	41
16	43
17	46
18	48
19	50
20	53
21	56
22	59
23	62
24	66
25	70
26	74
27	79
28	84
29	91
30	100

BREAST-Q™ – BCT MODULE (POSTOPERATIVE) VERSION 2.0:
SATISFACTION WITH BREASTS

De volgende vragen gaan over uw borsten en de behandeling van uw borstkanker (met behandeling bedoelen we een borstsparende operatie met of zonder bestraling). Als u een operatie en bestraling van beide borsten heeft ondergaan, beantwoord deze vragen dan terwijl u denkt aan de borst waar u het minst tevreden over bent.

Als u aan uw borsten denkt, hoe tevreden of ontevreden bent u de afgelopen zeven dagen geweest met:

	Zeer ontevreden	Enigszins ontevreden	Enigszins tevreden	Zeer tevreden
a. Hoe u er in de spiegel uitziet met uw kleding aan?	1	2	3	4
b. De vorm van uw geopereerde borst als u een bh aan hebt?	1	2	3	4
c. Hoe normaal u zich voelt in uw kleding?	1	2	3	4
d. Het kunnen dragen van strakkere kleding?	1	2	3	4
e. Hoe uw geopereerde borst zit/hangt?	1	2	3	4
f. Hoe glad gevormd uw geopereerde borst eruit ziet?	1	2	3	4
g. Het profiel (silhouet) van uw geopereerde borst?	1	2	3	4
h. Hoe gelijk van grootte uw borsten zijn?	1	2	3	4
i. Hoe normaal uw borstsparend geopereerde borst eruit ziet?	1	2	3	4
j. Hoeveel uw borsten op elkaar lijken?	1	2	3	4
k. Hoe u er in de spiegel uitziet zonder kleding aan?	1	2	3	4

Uitleg voor onderzoekers: Deze schaal kan los van de andere schalen gebruikt worden.

BREAST-Q™ - BCT MODULE (POSTOPERATIVE) VERSION 2.0: SATISFACTION WITH BREASTS CONVERSION TABLE

Instructions: If missing data is less than 50% of the scale's items, insert the mean of the completed items. Use the Conversion Table below to convert the raw scale summed score into a score from 0 (worst) to 100 (best). Higher scores reflect a better outcome.

SUM SCORE	EQUIVALENT RASCH TRANSFORMED SCORE (0-100)
11	0
12	15
13	20
14	24
15	26
16	29
17	31
18	33
19	35
20	36
21	38
22	40
23	42
24	43
25	45
26	46
27	48
28	50
29	51
30	53
31	55
32	57
33	59
34	61
35	63
36	65
37	67
38	69
39	72
40	75
41	78
42	82
43	88
44	100

BREAST-Q™ - BCT MODULE (POSTOPERATIVE) VERSION 2.0: PHYSICAL WELL-BEING: CHEST

Hoe vaak hebt u in de afgelopen zeven dagen last gehad van:

	Nooit	Soms	Altijd
a. Moeite om uw armen op te tillen of te bewegen?	1	2	3
b. Moeite met slapen doordat uw borstgebied ongemakkelijk aanvoelde?	1	2	3
c. Een strak gevoel in uw borstgebied?	1	2	3
d. Een trekkend gevoel in uw borstgebied?	1	2	3
e. Gevoeligheid in uw borstgebied?	1	2	3
f. Scherpe pijn in uw geopereerde borst?	1	2	3
g. Zeurende pijn in uw geopereerde borst?	1	2	3
h. Moeite om op de kant van uw geopereerde borst te liggen?	1	2	3
i. Zwelling (lymfoedeem) van uw arm aan de kant van uw geopereerde borst?	1	2	3

Uitleg voor onderzoekers: Deze schaal kan los van de andere schalen gebruikt worden.

BREAST-Q™ - BCT MODULE (POSTOPERATIVE) VERSION 2.0: PHYSICAL WELL-BEING: CHEST CONVERSION TABLE

Instructions: Items 'h' and 'i' are stand-alone items that are not included in the scale score. Recode items a, b, c, d, e, f, and g as follows: "None of the time" = 3; "Some of the time" = 2; "All of the time" = 1. If missing data is less than 50% of the scale's items, insert the mean of the completed items. Use the Conversion Table below to convert the raw scale summed score into a score from 0 (worst) to 100 (best). Higher scores reflect a better outcome.

SUM SCORE	EQUIVALENT RASCH TRANSFORMED SCORE (0-100)
7	0
8	13
9	21
10	27
11	33
12	38
13	45
14	52
15	60
16	66
17	71
18	76
19	82
20	89
21	100

BREAST-Q™ – BREAST CANCER CORE SCALE (POSTOPERATIVE) VERSION 2.0: ADVERSE EFFECTS OF RADIATION

Als u bestraling van beide borsten heeft ondergaan, beantwoord deze vragen dan terwijl u denkt aan de borst waar u het minst tevreden over bent. Als u aan uw bestraalde borst(en) denkt, hoe vaak hebt u in de afgelopen zeven dagen last gehad van:

	Nooit	Soms	Altijd
a. Bestraalde huid van de borst die er anders uitzag (bijv. te donker of te licht)?	1	2	3
b. Markeringen op de huid van de borst door de bestraling (bijv. kleine zichtbare bloedvaten)?	1	2	3
c. Bestraalde huid van de borst die droog aanvoelde?	1	2	3
d. Bestraalde huid van de borst die gevoelig is bij aanraking (bijv. bij temperatuursveranderingen van het water tijdens het douchen)?	1	2	3
e. Bestraalde huid van de borst die onnatuurlijk dik (ruw, hard) aanvoelt als u het aanraakt?	1	2	3
f. Bestraalde huid van de borst die geïrriteerd aanvoelt bij het dragen van kleding?	1	2	3

Note to Investigators: This scale can be used independently of the other scales and should only be completed by patients who have had radiation. The following statement can be added to the stem to provide an opportunity for the patient to decline completing this scale. 'If you have not had radiation, please check the box and skip the questions that follow.' This scale is exactly the same across the three Breast Cancer Postoperative Modules (i.e. Mastectomy, Reconstruction, and Breast Conserving Therapy).

BREAST-Q™ – BREAST CANCER CORE SCALE (POSTOPERATIVE) VERSION 2.0: ADVERSE EFFECTS OF RADIATION CONVERSION TABLE

Instructions: Rescore items a, b, c, d, e and f as follows: "Not at all" = 3; "A little" = 2; "A lot" = 1. If missing data is less than 50% of the scale's items, insert the mean of the completed items. Use the Conversion Table below to convert the raw scale summed score into a score from 0 (worst) to 100 (best). Higher scores reflect a better outcome.

SUM SCORE	EQUIVALENT RASCH TRANSFORMED SCORE (0-100)
6	0
7	11
8	21
9	29
10	36
11	44
12	51
13	58
14	65
15	71
16	78
17	87
18	100

DUTCH

Studienummer:

EORTC QLQ-C30 (version 3)

Wij zijn geïnteresseerd in bepaalde dingen over u en uw gezondheid. Wilt u alle vragen zelf beantwoorden door het getal te omcirkelen dat het meest op u van toepassing is. Er zijn geen "juiste" of "onjuiste" antwoorden. De informatie die u geeft zal strikt vertrouwelijk worden behandeld.

Wilt u uw initialen invullen: _____

Uw geboortedatum (Dag, Maand, Jaar): __ __ / __ __ / __ __

De datum van vandaag (Dag, Maand, Jaar): 31 / __ __ / __ __

		Helemaal niet	Een beetje	Nogal	Heel erg
1.	Heeft u moeite met het doen van inspannende activiteiten zoals het dragen van een zware boodschappentas of een koffer?	1	2	3	4
2.	Heeft u moeite met het maken van een lange wandeling?	1	2	3	4
3.	Heeft u moeite met het maken van een korte wandeling buitenshuis?	1	2	3	4
4..	Moet u overdag in bed of op een stoel blijven?	1	2	3	4
5.	Heeft u hulp nodig met eten, aankleden, uzelf wassen of naar het toilet gaan?	1	2	3	4

Gedurende de afgelopen week:

		Helemaal niet	Een beetje	Nogal	Heel erg
6.	Was u beperkt bij het doen van uw werk of andere dagelijkse bezigheden?	1	2	3	4
7.	Was u beperkt in het uitoefenen van uw hobby's of bij andere bezigheden die u in uw vrije tijd doet?	1	2	3	4
8.	Was u kortademig?	1	2	3	4
9.	Heeft u pijn gehad?	1	2	3	4
10.	Had u behoefte om te rusten?	1	2	3	4
11.	Heeft u moeite met slapen gehad?	1	2	3	4
12.	Heeft u zich slap gevoeld?	1	2	3	4
13.	Heeft u gebrek aan eetlust gehad?	1	2	3	4
14.	Heeft u zich misselijk gevoeld?	1	2	3	4

Wilt u a.u.b. naar de volgende bladzijde gaan

Gedurende de afgelopen week:	Helemaal niet	Een beetje	Nogal	Heel erg
15. Heeft u overgegeven?	1	2	3	4
16. Had u last van obstipatie? (was u verstopt?)	1	2	3	4
17. Had u diarree?	1	2	3	4
18. Was u moe?	1	2	3	4
19. Heeft pijn u gehinderd in uw dagelijkse bezigheden?	1	2	3	4
20. Heeft u moeite gehad met het concentreren op dingen, zoals een krant lezen of televisie kijken?	1	2	3	4
21. Voelde u zich gespannen?	1	2	3	4
22. Maakte u zich zorgen?	1	2	3	4
23. Voelde u zich prikkelbaar?	1	2	3	4
24. Voelde u zich neerslachtig?	1	2	3	4
25. Heeft u moeite gehad met het herinneren van dingen?	1	2	3	4
26. Heeft uw lichamelijke toestand of medische behandeling uw familieleven in de weg gestaan?	1	2	3	4
27. Heeft uw lichamelijke toestand of medische behandeling u belemmerd in uw sociale bezigheden?	1	2	3	4
28. Heeft uw lichamelijke toestand of medische behandeling financiële moeilijkheden met zich meegebracht?	1	2	3	4

Wilt u voor de volgende vragen het getal tussen 1 en 7 omcirkelen dat het meest op u van toepassing is

29. Hoe zou u uw algehele gezondheid gedurende de afgelopen week beoordelen?

1 2 3 4 5 6 7

Erg slecht Uitstekend

30. Hoe zou u uw algehele "kwaliteit van het leven" gedurende de afgelopen week beoordelen?

1 2 3 4 5 6 7

Erg slecht Uitstekend

Studienummer:

EORTC QLQ - BR23

Soms zeggen patiënten dat ze de volgende klachten of problemen hebben. Wilt u aangeven in welke mate u deze klachten of problemen gedurende de afgelopen week heeft ervaren

Gedurende de afgelopen week:	**Helemaal niet**	**Een beetje**	**Nogal**	**Heel erg**
31. Had u een droge mond?	1	2	3	4
32. Was de smaak van voedsel en drank anders dan u gewend was?	1	2	3	4
33. Had u pijnlijke, geïrriteerde of tranende ogen?	1	2	3	4
34. Heeft u haaruitval gehad?	1	2	3	4
35. Deze vraag alleen invullen indien u haaruitval heeft gehad: Was u door het verlies van uw haar van streek?	1	2	3	4
36. Voelde u zich ziek of onwel?	1	2	3	4
37. Heeft u opvliegers gehad?	1	2	3	4
38. Heeft u hoofdpijn gehad?	1	2	3	4
39. Voelde u zich lichamelijk minder aantrekkelijk ten gevolge van uw ziekte of behandeling?	1	2	3	4
40. Voelde u zich minder vrouwelijk ten gevolge van uw ziekte of behandeling?	1	2	3	4
41. Vond u het moeilijk om u zelf naakt te zien?	1	2	3	4
42. Was u ontevreden met uw lichaam?	1	2	3	4
43. Maakte u zich zorgen over uw gezondheid in de toekomst?	1	2	3	4

Gedurende de afgelopen <u>vier</u> weken:	**Helemaal niet**	**Een beetje**	**Nogal**	**Heel erg**
44. In hoeverre had u zin in seks?	1	2	3	4
45. In hoeverre was u seksueel actief? (met of zonder geslachtsgemeenschap)	1	2	3	4
46. Deze vraag alleen invullen indien u seksueel actief was: In hoeverre was seks plezierig voor u?	1	2	3	4

<u>Wilt u a.u.b. naar de volgende bladzijde gaan</u>

Studienummer:

Gedurende de afgelopen week:	Helemaal niet	Een beetje	Nogal	Heel erg
47. Had u pijn in uw arm of schouder?	1	2	3	4
48. Heeft u een gezwollen arm of hand gehad?	1	2	3	4
49. Was het moeilijk om uw arm naar omhoog of opzij te bewegen?	1	2	3	4
50. Heeft u pijn gehad in het gebied van uw aangedane borst?	1	2	3	4
51. Was het gebied van uw aangedane borst gezwollen?	1	2	3	4
52. Was het gebied van uw aangedane borst overgevoelig?	1	2	3	4
53. Heeft u huidproblemen gehad in het gebied van uw aangedane borst (bijv. jeukerig, droog of schilferachtig)?	1	2	3	4

Studienummer:

EQ-5D-5L:

Zet bij iedere groep in de lijst hieronder een kruisje in het hokje dat het best past bij uw gezondheid VANDAAG.

MOBILITEIT

Ik heb geen problemen met lopen ❑
Ik heb een beetje problemen met lopen ❑
Ik heb matige problemen met lopen ❑
Ik heb ernstige problemen met lopen ❑
Ik ben niet in staat om te lopen ❑

ZELFZORG

Ik heb geen problemen met mijzelf wassen of aankleden ❑
Ik heb een beetje problemen met mijzelf wassen of aankleden ❑
Ik heb matige problemen met mijzelf wassen of aankleden ❑
Ik heb ernstige problemen met mijzelf wassen of aankleden ❑
Ik ben niet in staat mijzelf te wassen of aan te kleden ❑

DAGELIJKSE ACTIVITEITEN *(bijv. werk, studie, huishouden, gezins- en vrijetijdsactiviteiten)*

Ik heb geen problemen met mijn dagelijkse activiteiten ❑
Ik heb een beetje problemen met mijn dagelijkse activiteiten ❑
Ik heb matige problemen met mijn dagelijkse activiteiten ❑
Ik heb ernstige problemen met mijn dagelijkse activiteiten ❑
Ik ben niet in staat mijn dagelijkse activiteiten uit te voeren ❑

PIJN / ONGEMAK

Ik heb geen pijn of ongemak ❑
Ik heb een beetje pijn of ongemak ❑
Ik heb matige pijn of ongemak ❑
Ik heb ernstige pijn of ongemak ❑
Ik heb extreme pijn of ongemak ❑

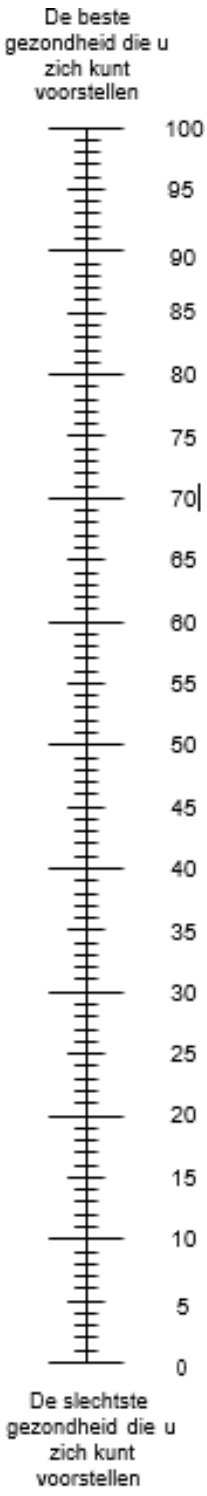
ANGST / SOMBERHEID

Ik ben niet angstig of somber ❑
Ik ben een beetje angstig of somber ❑
Ik ben matig angstig of somber ❑
Ik ben erg angstig of somber ❑
Ik ben extreem angstig of somber ❑

Studienummer:

- We willen weten hoe goed of slecht uw gezondheid VANDAAG is.
- Deze meetschaal loopt van 0 tot 100.
- 100 staat voor de beste gezondheid die u zich kunt voorstellen.
  0 staat voor de slechtste gezondheid die u zich kunt voorstellen.
- Markeer een X op de meetschaal om aan te geven hoe uw gezondheid VANDAAG is.
- Noteer het getal waarbij u de X heeft geplaatst in onderstaand vakje.

UW GEZONDHEID VANDAAG = ☐



Studienummer:

References

1. Fisher B, Anderson S, Bryant J, Margolese RG, Deutsch M, Fisher ER, 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):1233-41.
2. Litiere S, Werutsky G, Fentiman IS, Rutgers E, Christiaens MR, Van Limbergen E, et al. Breast conserving therapy versus mastectomy for stage I-II breast cancer: 20 year follow-up of the EORTC 10801 phase 3 randomised trial. Lancet Oncol. 2012;13(4):412-9.
3. Veronesi U, Cascinelli N, Mariani L, Greco M, Saccozzi R, Luini A, et al. Twenty-year follow-up of a randomized study comparing breast-conserving surgery with radical mastectomy for early breast cancer. N Engl J Med. 2002;347(16):1227-32.
4. Alberro JA, Ballester B, Deulofeu P, Fabregas R, Fraile M, Gubern JM, et al. Long-term outcomes for neoadjuvant versus adjuvant chemotherapy in early breast cancer: meta-analysis of individual patient data from ten randomised trials. Lancet Oncology. 2018;19(1):27-39.
5. Lagendijk M, van Maaren MC, Saadatmand S, Strobbe LJA, Poortmans PMP, Koppert LB, 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):165-75.
6. De La Cruz L, Blankenship SA, Chatterjee A, Geha R, Nocera N, Czerniecki BJ, et al. Outcomes After Oncoplastic Breast-Conserving Surgery in Breast Cancer Patients: A Systematic Literature Review. Ann Surg Oncol. 2016;23(10):3247-58.
7. Correa C, Harris EE, Leonardi MC, Smith BD, Taghian AG, Thompson AM, et al. Accelerated Partial Breast Irradiation: Executive summary for the update of an ASTRO Evidence-Based Consensus Statement. Pract Radiat Oncol. 2017;7(2):73-9.
8. Bartelink H, Maingon P, Poortmans P, Weltens C, Fourquet A, Jager J, 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. Vrieling C, van Werkhoven E, Maingon P, Poortmans P, Weltens C, Fourquet A, et al. Prognostic Factors for Local Control in Breast Cancer After Long-term Follow-up in the EORTC Boost vs No Boost Trial: A Randomized Clinical Trial. JAMA Oncol. 2017;3(1):42-8.
10. Collette S, Collette L, Budiharto T, Horiot JC, Poortmans PM, Struikmans H, 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):2587-99.
11. Brouwers P, van Werkhoven E, Bartelink H, Fourquet A, Lemanski C, van Loon J, 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):434-41.
12. Brouwers PJ, van Werkhoven E, Bartelink H, Fourquet A, Lemanski C, van Loon J, et al. Factors associated with patient-reported cosmetic outcome in the Young Boost Breast Trial. Radiother Oncol. 2016;120(1):107-13.
13. Hau E, Browne L, Capp A, Delaney GP, Fox C, Kearsley JH, et al. The impact of breast cosmetic and functional outcomes on quality of life: long-term results from the St. George and Wollongong randomized breast boost trial. Breast Cancer Res Treat. 2013;139(1):115-23.
14. Waljee JF, Hu ES, Ubel PA, Smith DM, Newman LA, Alderman AK. Effect of esthetic outcome after breast-conserving surgery on psychosocial functioning and quality of life. J Clin Oncol. 2008;26(20):3331-7.
15. Hammer C, Maduro JH, Bantema-Joppe EJ, van der Schaaf A, van der Laan HP, Langendijk JA, Crijns AP. Radiation-induced fibrosis in the boost area after three-dimensional

conformal radiotherapy with a simultaneous integrated boost technique for early-stage breast cancer: A multivariable prediction model. Radiother Oncol. 2017;122(1):45-9.
16. Lilla C, Ambrosone CB, Kropp S, Helmbold I, Schmezer P, von Fournier D, et al. Predictive factors for late normal tissue complications following radiotherapy for breast cancer. Breast Cancer Res Treat. 2007;106(1):143-50.
17. Murphy C, Anderson PR, Li T, Bleicher RJ, Sigurdson ER, Goldstein LJ, et al. Impact of the radiation boost on outcomes after breast-conserving surgery and radiation. Int J Radiat Oncol Biol Phys. 2011;81(1):69-76.
18. Vrieling C, Collette L, Fourquet A, Hoogenraad WJ, Horiot JH, Jager JJ, et al. The influence of patient, tumor and treatment factors on the cosmetic results after breast-conserving therapy in the EORTC 'boost vs. no boost' trial. EORTC Radiotherapy and Breast Cancer Cooperative Groups. Radiother Oncol. 2000;55(3):219-32.
19. Immink JM, Putter H, Bartelink H, Cardoso JS, Cardoso MJ, van der Hulst-Vijgen MHV, 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):2591-8.
20. 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):519-25.
21. Available at: National Cancer Institute. Common terminology criteria for adverse events, v5.0. 2017. 2017.
22. Vos EL, Koning AHJ, Obdeijn IM, van Verschuer VMT, Verhoef C, van der Spek PJ, et al. Preoperative Prediction of Cosmetic Results in Breast Conserving Surgery. J Surg Oncol. 2015;111(2):178-84.
23. Cardoso JS, Cardoso MJ. Towards an intelligent medical system for the aesthetic evaluation of breast cancer conservative treatment. Artif Intell Med. 2007;40(2):115-26.
24. Lagendijk M, Vos EL, Koning AHJ, Hunink MGM, Pignol JP, Corten EML, 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.
25. 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):545-53.
26. Ong WL, Schouwenburg MG, van Bommel ACM, Stowell C, Allison KH, Benn KE, 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):677-85.
27. 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):345-53.
28. Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst. 1993;85(5):365-76.
29. Herdman M, Gudex C, Lloyd A, Janssen M, Kind P, Parkin D, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). Qual Life Res. 2011;20(10):1727-36.
30. Tan ML, Idris DB, Teo LW, Loh SY, Seow GC, Chia YY, Tin AS. Validation of EORTC QLQ-C30 and QLQ-BR23 questionnaires in the measurement of quality of life of breast cancer patients in Singapore. Asia Pac J Oncol Nurs. 2014;1(1):22-32.

31. Organisatie van kwaliteitsindicatoren Waardegedreven zorg: Ontwikkeling regionaal platform en dashboard Borstkanker. Available at: https://www.oncologienetwerken.nl/nieuws/artikel/project-de-organisatie-van-kwaliteitsindicatoren-pilot-borstkanker.
32. Vromans R, Tenfelde K, Pauws S, van Eenbergen M, Mares-Engelberts I, Velikova G, et al. Assessing the quality and communicative aspects of patient decision aids for early-stage breast cancer treatment: a systematic review. Breast Cancer Res Treat. 2019;178(1):1-15.