



Protocol of the TOBO-Study: A prospective cohort study of patient satisfaction and quality of life after breast conserving therapy with and without oncoplastic reconstruction

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Keywords: Mammoplasty (Mesh); Breast conserving surgery; Breast neoplasm (Mesh); Oncoplastic reconstruction; Patient satisfaction (Mesh).

Ethics and dissemination

Approval for this study was obtained from the Medical Ethics Committee; the study has been registered at trialregister.nl. The results of this prospective study will be submitted to international science journals.

Abstract

Introduction: In the past, a mastectomy was the first approach to the treatment of breast cancer. Today, breast-conserving surgery combined with adjuvant radiotherapy has become the standard treatment for a large number of women with breast cancer. Even for resection of larger tumours, which previously could only be treated with a mastectomy, breast-conserving surgery in combination with oncoplastic reconstruction is possible with a good cosmetic result. The aim of this study is to evaluate the patient satisfaction with the cosmetic outcome after breast conserving therapy in patients treated with and without oncoplastic reconstruction.

Methods and analysis: In this prospective cohort study female breast cancer patients who are receiving breast conserving surgery (with or without oncoplastic reconstruction) for breast cancer are being asked to participate in this study. Both preoperatively and postoperatively, prospective data is collected concerning patient characteristics, tumour characteristics, treatment type and the occurrence of post-operative complications. Standardised photos of the breast are being made preoperatively, 2 weeks postoperatively, 3 months and one year postoperatively. At those same time points the quality of life and patient satisfaction are being measured using the BREAST-Q.



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Strengths and limitations of this study

- This is one of the first prospective studies, that focus on patient satisfaction and quality of life after oncoplastic breast reconstruction in breast conserving surgery with a validated questionnaire (Breast-Q).
- Randomization for breast conserving surgery with or without oncoplastic reconstruction is from an ethical and practical point considered to be not feasible. Therefore, we perform a prospective cohort study, thereby accepting the influence of possible confounding factors.
- The effect of adjuvant radiation on the cosmetic result and postoperative complications of the breast after breast conserving surgery (with or without oncoplastic reconstruction) are closely being monitored.
- All patients are being operated in the same hospital in the Netherlands and undergo conventional treatment.
- Photos of the breasts are being taken preoperatively, 2 weeks postoperatively and 3 months and 1 year postoperatively to score the cosmetic outcome by an independent panel of a layman, plastic surgeon, surgeon and nurse.

Introduction

Breast cancer represents 25% of all cancers in women, making it the most common cancer in women worldwide. In the past, a mastectomy was the first approach to the treatment of breast cancer [1,2]. Today, many patients are being treated with breast conserving surgery combined with adjuvant radiotherapy [3]. A combination of breast conserving surgery with oncoplastic reconstruction makes resection of larger tumours possible with a good cosmetic result, without the need of a mastectomy [4,5]. Several studies have shown that breast conserving surgery including oncoplastic reconstruction is a safe treatment regarding oncological aspects [6-12].

Combining breast conserving treatment with oncoplastic reconstruction was first described by Audretsch in 1998.⁶ Over time, several techniques have been developed to reconstruct a breast after breast conserving surgery. Which technique is performed depends on various factors, such as the location and size of the tumour, but also the surgeon's and patient's preference. In addition to the characteristics of the patient and the tumour, postoperative complications and adjuvant radiotherapy can also influence the final cosmetic result. Since adjuvant radiotherapy is almost always indicated after breast conserving surgery, it is very important to know what the effect of radiotherapy is on the appearance of the operated breast, especially in combination with oncoplastic surgery. A study of Lansu et al. suggested a poorer cosmetic result of oncoplastic breast reconstruction with breast conserving therapy compared to breast conserving therapy without oncoplastic reconstruction [13]. The hypothesis is that this could be caused by the fact that oncoplastic surgery may lead to both a larger wound area and a larger boost volume. However, this concerned a small study requiring further research. Therefore, the aim of the current study is to investigate whether there is a difference in the cosmetic outcome and quality of life as perceived by the patient, between patients treated with and without an oncoplastic reconstruction, as a part of breast conserving therapy for breast cancer.

Methods and analysis

Study design

This is a prospective cohort study, in breast cancer patients undergoing breast conserving therapy (with or without oncoplastic reconstruction) in the Zuyderland Medical Center. After giving informed consent to participate in the study, both preoperative and postoperative data are being collected prospectively, concerning patient characteristics, tumour characteristics, treatment types and the occurrence of postoperative complications. In addition, standardized photos of the breasts are taken at the various moments in time. At those time points, patients are also asked to complete the BREAST-Q questionnaire [14].

Patient and public involvement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination of our research.

Study population and treatment details

From August 2018 onwards, all consecutive breast cancer patients undergoing breast conserving therapy (BCT) with curative intent at the Zuyderland Medical Center (Sittard, the Netherlands) are screened for eligibility (see Table 1. for in and exclusion criteria). In short, all female patients > 18 years of age can be included as long as they are fluent in Dutch, did not receive previous radiotherapy to the affected breast, and have given informed consent to participate.

Both patients undergoing oncoplastic surgery as a part of their breast conserving therapy and patients without oncoplastic surgery are eligible. In this study, oncoplastic surgery is defined as every reconstruction of the breast performed by a plastic surgeon after breast conserving therapy.

Surgical treatment

Patients participating in the study receive the same standard breast cancer care that they would also receive without participation in the TOBO-study.

Whether or not patients are eligible for reconstruction after breast conserving surgery is first discussed during the multidisciplinary consultation on breast cancer patients. In this meeting, among others, the oncological surgeon is present as the plastic surgeon and imaging of the tumour and breasts are displayed. The final indication for an oncoplastic breast conserving surgery will be made during the consultation at the oncological surgeon preoperatively. If the surgeon expects that the shape of the breast will change too much after the lumpectomy, patients receive consultation at the plastic surgeon. Size of the breast, as well as size and location of the tumour play a pivotal role in this decision. Shared decision making is applied to choose the treatment for the individual patient.

All patients receive preoperative cefazoline intravenously; postoperatively no antibiotics are given.

Breast conserving surgery (without oncoplastic reconstruction)

In case of breast conserving therapy without oncoplastic reconstruction, the oncological surgeon removes the tumour from the breast with adequate margins. The resulting lumpectomy space is closed by undermining skin and mobilising glandular tissue, thereby approximating the breast tissue. This operation is done entirely by the oncological surgeon, without the interference of a plastic surgeon.

Breast conserving surgery with oncoplastic reconstruction

In case of breast conserving therapy with oncoplastic reconstruction, the plastic surgeon takes over the operation after the tumour has been removed with adequate margins by the oncological surgeon. The breast is reconstructed using one of the following techniques: wise-pattern, lateral intercostal artery perforator flap (licap), intercostal artery perforator flap (icap), latissimus dorsi flap, or grisotti flap in case of a retro areolar tumour. With these operation techniques, well vascularised tissue is placed in the lumpectomy space.

Postoperative care

A drain is placed according to surgeon's preference. When placed, the drain is removed after a production of less than 30cc/24 hours. All patients wear a postoperative bra from Emdaplast® day and night for 6 weeks. Postoperative pain is treated with oral analgesics, according to hospital protocol.

Adjuvant therapy

The indication for adjuvant systemic and radiation treatment is set according to national guidelines [15]. If chemotherapy is indicated, radiation therapy is given after chemotherapy if the patient is younger than 60, and if she will not be treated with trastuzumab, according to local protocols. In all other cases, adjuvant radiotherapy is planned to start within 3-5 weeks after surgery. The radiotherapy is being given in Maastricht (Maastricht, the Netherlands) and consists generally of 15x2.67 Gy to the whole breast with or without regional radiotherapy, dependent on nodal involvement. In addition, a simultaneous integrated boost may be given consisting of 20 - 22 x 2.67 Gy to the tumored, with an elective dose to the whole breast of 20 x 2.18 to 22x 2.03 Gy.

In case of a low risk of a local recurrence based on the definitive pathology, partial breast irradiation may also be considered, either in the context of the IRMA-Trial [16,17] (10 x 3.8 Gy, Bid) or as a regular scheme (15 x 2.67 Gy, according to the IMPORT LOW trial [18]). However, partial breast irradiation is only applied after breast conserving surgery without oncoplastic reconstruction.

Sample size

Our hypothesis is that patients with an oncoplastic reconstruction are more satisfied with the cosmetic results of their breast than patients who underwent breast conserving therapy without oncoplastic reconstruction. The primary endpoint is the score on the Breast-Q questionnaire. To our knowledge there is no literature on this subject for oncoplastic reconstruction as a part of breast conserving therapy that can be used to calculate sample sizes. However, there is a study that found a score of 60.33 (SD 19.18) on the Breast-Q questionnaire after mastectomy, and a score of 70.46 (SD 17.90) after mastectomy in combination with reconstruction [19]. In the absence of better data, we have used these figures to calculate our sample size. Assuming that patients without reconstruction have a score of 60.33 (SD 19.18) on the BREAST-Q, and those with a reconstruction of 70.46 (SD 17.90), we calculated to include 55 patients per group with a power of 80 % and $\alpha = 0.05$.

Outcome measures

Primary endpoint

Patient satisfaction on the cosmetic result of the breast,

measured at one year postoperatively, using the BREAST-Q questionnaire.

Secondary endpoints

- Patient satisfaction on the cosmetic result of the breast, measured at three months postoperatively, using the BREAST-Q questionnaire.
- Patient quality of life on the BREAST-Q immediately postoperatively compared to the quality of life on the BREAST-Q one year postoperatively.
- The frequency and type of postoperative complications that occur within 3 months.
- The effect of postoperative complications on the delay of adjuvant radiotherapy or chemotherapy.

Data collection

As shown in table 2, for all patients in the study various data will be collected prior to surgery (T0), 2 weeks after surgery, prior to radiotherapy (T1), 3 months after surgery (T2), 1 year after surgery (T3). These data include patient characteristics, diagnostics and treatment characteristics, patient questionnaires, photographs complications, according to the scheme in table 2. All data will be collected in an anonymous online database provided by the hospital (datamanagement zuyderland).

Table 1: Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
<ul style="list-style-type: none"> • Female • Age of at least 18 years • Planned to undergo breast conserving therapy with curative intent, because of breast cancer • Understanding of the Dutch language spoken and written • Signed informed consent to participate in the study 	<ul style="list-style-type: none"> • Intellectual disability to such an extent that it can be expected that the interpretation and/or answering of the questionnaires will be a problem • Previous radiotherapy on the affected breast

Table 2: Data collection

	T0 (preoperatively)	T1 (2 weeks after surgery)	T2 (3 months after surgery)	T3 (1 year after surgery)
Patient characteristics	x			
Tumour details	x	X		
Surgical details		X		
Radiation treatment details			x	
Breast Q	x	X	x	x
Photographs	x	X	x	x
Complications		X	x	x

Patient characteristics

The following patient characteristics will be collected: age, BMI, breast size, breast ptosis, asymmetry of the breast, diabetes mellitus, hypertension, active smoker, use of anticoagulation's or immunosuppressants, prior chemo- / immuno- / endocrine therapy for diseases other than the current breast cancer.

Diagnostics and treatment characteristics

Details of the operation

The following surgical details will be collected: duration of surgery, operated side, unilateral / bilateral operation, weight of the lumpectomy, technique of reconstruction (wise-pattern, lateral intercostal artery perforator flap (licap), intercostal artery perforator flap (icap), latissimus dorsi flap, grisotti flap, other), the number of placed drains, name of the surgeon, axillary surgery (sentinel node procedure, axillary lymph node dissection).

Tumour details

The following tumour characteristics will be collected: Tumour size measured on ultrasound preoperatively, localization of the tumour (quadrant of the breast), cTNM and pTNM classification, radicality of the breast conserving surgery.

Postoperative details

We will record the number of days of admission, number of days after which the drain was removed, postoperative complications (see further), treatment of postoperative complications, number of days between surgery and postoperative complication, number of days between surgery and the start of the first adjuvant radiotherapy or the first adjuvant chemotherapy, occurrence of complications after or before adjuvant radiothe-

rapy, performed secondary surgical adjustments to the breast for a better cosmetic result.

Details of (neo)adjuvant therapy

(Neo)adjuvant chemotherapy or radiotherapy, total dose of radiotherapy, number of fractions of radiotherapy, date of last radiotherapy, volume of the delineated mammary gland tissue (CTVbreast [20]) in cc, volume of the irradiated boost volume (in case of boost) in cc, type and timing of adjuvant chemotherapy and /or hormone therapy, maximum acute skin toxicity during or in the first four weeks after radiotherapy scored according to the CTCAE 4.0 criteria.

Patient questionnaires

The validated BREAST-Q [14] questionnaires will be completed by the participating patients for 2 modules: The general domain (quality of life) and the breast conserving surgery module.

Photographs of the breast

Photos of the breasts (in front and side view) will be taken in a standardized way, on all four time points, with a digital camera. At the end of the study the photos will be assessed by an independent panel. Cosmetic result of each breast at the different time points is assessed by the Harris-scale [21].

Complications

The following complications will be noted if they occur: Fat necrosis, seroma, postoperative bleeding, infection, skin necrosis, wound problems. These complications will be subdivided by the Clavien-Dindo classification as shown in table 3 [22].

Table 3: Clavien-Dindo Classification of surgical complications

Grades	Definition
Grade I	Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic and radiological interventions. Allowed therapeutic regimens are: drugs as antiemetics, antipyretics, analgetics, diuretics and electrolytes and physiotherapy. This grade also includes wound infections opened at the bedside.
Grade II	Requiring pharmacological treatment with drugs other than such allowed for grade I complications. Blood transfusions and total parenteral nutrition are also included.
Grade III	Requiring surgical, endoscopic or radiological intervention
- IIIa	Intervention not under general anesthesia
- IIIb	Intervention under general anesthesia
Grade IV	Life-threatening complication (including CNS complications)* requiring IC/ICU-management
- IVa	single organ dysfunction (including dialysis)
- IVb	multiorgan dysfunction
Grade V	Death of a patient

Data analyses

Descriptive statistics will be performed for patient and treatment characteristics. Differences in complications, time between surgery and start of radiotherapy will be analysed using T-tests or the Mann-Whitney U-test.

Using linear mixed models test, differences between the groups regarding the BREAST-Q score at the different time points will be examined. The differences between T0 and T1, T1 and T2, T1 and T3, T2 and T3 will be analysed.

With the chi-squared test the difference in cosmetic outcome measurement scored by the panel as well as by the patient herself will be analysed.

Finally, the influence of certain variables on the four different endpoints will first be tested using univariate analysis. Subsequently, a multivariable logistic regression analysis will be performed. All statistical analysis will be performed with SPSS from IBM Software.

Adverse events

There are no adverse events expected as a result of this study, because patients do not undergo any additional interventions. If any adverse events occur, it will be reported to the medical ethical commission and hospital board.

Ethics and dissemination

This study is being conducted according to the principles of the Declaration of Helsinki (64th WMA General Assembly, Fortaleza, Brazil, October 2013).

The described study was approved by the Medical Ethics Committee of Maastricht University Medical Centre/Maastricht University. All amendments made to the protocol will be first proposed to the Medical Ethics Committee. After approval they will be communicated to all involved parties.

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Disclaimer

The funder will not have any authority over any of the study-related activities, consisting of data collection, data management, data analysis, interpretation of results, writing the report, nor submission for publication.

Ethics approval

Approval for this study was obtained from the Medical Ethics Committee Zuyderland Medical Center with the following protocol ID: Z2017135/ METC 17-N-162. This protocol is version 1 from 13.11.2017.

Author Contributions

NH, YV, KV, LB conceptualised the project, NH drafted the manuscript. YV, KV, LB, RH reviewed and edited the manuscript. All authors read and approved the final manuscript.

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