Breast reconstruction and neoadjuvant radiotherapy, a changing algorithm.

Published: 20-12-2022
Last updated: 19-08-2024

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Ethical review	Approved WMO
Status	Recruiting
Health condition type	Breast neoplasms malignant and unspecified (incl nipple)
Study type	Interventional

Summary

ID

NL-OMON51819

Source
ToetsingOnline

Brief title
Breast Reconstruction and Neoadjuvant Radioterapy (BRENAR)

Condition

- Breast neoplasms malignant and unspecified (incl nipple)
- Breast therapeutic procedures

Synonym
breast cancer, malignant neoplasm of the breast

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Utrecht
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: breast cancer, breast reconstruction, neoadjuvant radiotherapy, surgical complications

Outcome measures

Primary outcome

Primary endpoint: Acute post-surgical complications at 3 months following mastectomy and immediate breast reconstruction after NART in the treatment of breast cancer.

Secondary outcome

1. Other adverse events following NART or surgery other than described in the primary outcome measure. Number of participants with treatment-related adverse events as assessed by CTCAE v5.0. Time Frame: Within 3 months after both breast reconstruction and radiotherapy.

2. Patient-reported Satisfaction with Breasts, Physical, emotional and sexual well-being (as measured using BREAST-Q). Time Frame: At baseline and 3 months after definitive treatment (definitive breast reconstruction).
The BREAST-Q is a multiscale, multimodule, patient-reported outcome instrument measuring important aspects of health-related quality of life and patient satisfaction in women who undergo breast surgery.The BREAST-Q has multiple domains, and each domain score is obtained by transforming the raw scale item responses with the Q-Score software program. Each domain results in an independent score from 0 to 100 (higher scores indicate greater satisfaction or quality of life).

3. Physician-reported cosmetic results (as assesses by a panel of experts on breast photos obtained as part of standard of care). Time Frame: at basline and 3 months after definitive breast reconstruction surgery.

The clinical investigators will assess the physician-reported aesthetic outcome from photographs using the Aesthetic Items Scale,12 which is a standardised method. Five standardised photographs (frontal, oblique, and lateral) will be taken before and at 3 months after placement of the breast implant. The photos will be evaluated independently by five plastic surgeons. All photographs will be compiled into a slideshow presentation. They will be shown in a random order without any additional information (eg, on preoperative or postoperative status, reconstruction method used, complications). To minimise bias, blank slides will be shown between photographs and the random order of the photographs was different for each observer. The surgeons will rate the aesthetic outcome on five items with a five-point Likert scale12.

4. Timely initiation of (possible) adjuvant therapy

5. Pathological response assessed in mastectomy specimen

6. Oncologic follow-up < 3 months locoregional recurrence, breast-cancer free survival, distant-metastasis-free survival, overall survival.

Study description

Background summary

Treatment of patients with breast cancer requires a multimodality approach with often systemic therapy, radiotherapy (RT) and surgery. Postmastectomy radiotherapy (PMRT) reduces locoregional recurrences and improves survival, especially in patients with involved axillary nodes. However, PMRT is known to substantially increase the complication rate when combined with a breast reconstruction. Breast reconstructions can be performed within the same surgery as the mastectomy (i.e. immediate) or in a later stage where patients remain without a breast contour for several months to years before the reconstruction is completed (i.e. delayed).
In the Netherlands, most patients are being withheld an immediate breast reconstruction if there is the slightest risk of PMRT, because PMRT in combination with immediate breast reconstruction is associated with a severe increase in postoperative complications, especially in case of an implant-based reconstruction: complication rates up to 40% have been reported, in comparison to less than 10% without PMRT. Short-term complications include infection and loss of implant, while long-term complications include pain, capsular contracture and fibrosis. Such complications have been shown to negatively affect quality of life, perceived body image and sexual well-being. Furthermore, PMRT after an immediate reconstruction is associated with impaired cosmetic results and lower patient satisfaction, even when no complications have occurred.
If patients aim for an autologous reconstruction (i.e. use of own tissue), usually PMRT is performed first, followed by a delayed autologous reconstruction to avoid radiotherapy on the flap, thereby subjecting patients to a second major surgical procedure and a long period of living without a breast contour.
The unsatisfying cosmetic results and high complication rate have led to controversy and a wide practice variation in reconstruction approaches that are being offered to this specific group of patients. Since immediate breast reconstructions have proven to yield better cosmetic outcomes, psychosocial results and reduced overall costs, solutions that would allow for an immediate breast reconstruction in combination with radiation therapy (RT), without an increase in complications, are highly needed. Previous studies in breast cancer patients indicated that neoadjuvant RT (NART) is a safe approach from an oncological perspective, and does not increase the overall post-operative complication rate. However, limited data are available on NART in combination with an immediate breast reconstruction, and no data are available on patient-reported cosmetic outcomes.

Study objective

The purpose of the pilot study is to assess acute post-surgical complications following mastectomy and immediate breast reconstruction after NART. We hypothesize that NART will avoid the negative effects of PMRT on the capsule of

an implant, or on the skin and underlying tissue of an autologous flap, and would therefore lead to better cosmetic results, better quality of life and less complications compared to PMRT. If this hypothesis is confirmed, NART would allow more patients to undergo an immediate reconstruction resulting in superior cosmetic results and quality of life. Furthermore, the use of RT in a neoadjuvant setting could potentially result in a shorter overall loco-regional treatment time from diagnosis to receiving the last locoregional treatment. However, this pilot study will mainly assess whether or not the post-surgical complications of breast reconstruction with NART are acceptable. Further study to investigate long term quality of life and oncologic follow-up results will be conducted after this pilot study, if complication rates are acceptable.

Study design

The study will be conducted as a prospective multicenter single arm interventional pilot study. The primary endpoint is post-surgical complications at three months after the latest patient has received the final reconstructive surgery.

Intervention

The intervention consists of NART followed by mastectomy with immediate reconstruction, where the standard treatment is mastectomy and PMRT, with an immediate or delayed reconstruction.

Study burden and risks

Burden:
Currently, in certain hospitals, the indication for RT is based upon the pathological nodal status of the sentinel or previously involved nodes, removed during mastectomy. Since patients in this study will receive NART, the indication for RT is not always clear prior to surgery. In those cases, an axillary staging procedure has to be performed prior to the breast surgery, to determine whether there is an indication for RT at all. This requires two separate surgical procedures, which is nowadays already common practice in several hospitals, to determine whether an immediate breast reconstruction is possible. Currently, for cT1-3N0 patients, it is known that about 25% has a positive axillary node after neoadjuvant chemotherapy and thus still requires PMRT; for patients with cT1-3N+ breast cancer, about 55-70% still have positive nodes after neoadjuvant chemotherapy requiring PMRT. Consequently, some patients that have given their informed consent for NART but will be excluded from this study if the sentinel node appears to be free of tumor cells.
Another additional burden can be an additional biopsy of the tumor after neoadjuvant chemotherapy, to determine whether residual disease is present. If residual disease is present, there is also an indication for adjuvant systemic treatment in triple negative patients or her2- positive patients. Since a

biopsy is not sufficiently accurate to determine pCR status, patients are excluded from the study if the biopsy does not contain tumors cells, since NART can influence the final pathological tumor status.
Finally, from a patient*s perspective, additional time is required for filling in questionnaires with regard to cosmetic results and quality of life (approximately 15-30 minutes).

Risk: Data from current pilot studies indicates that NART is at least as effective as PMRT with regard to oncologic safety. A risk that is associated with participation is the possibility of decreased vascularization of the skin (nipple) flap of the breast after a sparing mastectomy leading to early complications, especially in the implant group. However, we anticipate that this risk of necrosis and loss of tissue expander/implant is low, since previous pilot studies showed that overall short and long-term complications were similar between PMRT and NART.

Benefit and group relatedness:
NART will allow patients to always receive an immediate breast reconstruction (both implant-based and autologous), even is RT is indicated. It is hypothesized that this will result in a better QoL and cosmetic outcome.
Finally total treatment time will be shorter with NART.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

Women >= 18 years with:
- breast cancer
- an indication for mastectomy
- an indication for radiotherapy
- wish for a breast reconstruction

Exclusion criteria

- Legal incapacity
- Not able to understand and sign Dutch written informed consent
- Previous history of breast cancer or another malignancy for which radiotherapy of the breast or axilla
- Pregnant or lactating.
- Smoking
- BMI > 35 kg/m2
- cT4 tumour (and skin sparing mastectomy not possible)

Study design

Design

Study type: Interventional

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	03-10-2023

Enrollment:	20
Type:	Actual

Ethics review

Approved WMO Date:	20-12-2022
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	19-07-2024
Application type:	Amendment
Review commission:	METC NedMec

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
Other	80252
CCMO	NL80349.041.22