NeoRad Trial

Präoperative Radiotherapie versus postoperative Radiotherapie nach neoadjuvanter Chemotherapie („NeoRad“) beim Hochrisiko-Mammakarzinom: eine prospektiv randomisierte, internationale multizentrische Phase III-Studie

Preoperative radiotherapy versus postoperative radiotherapy after neoadjuvant chemotherapy (“NeoRad”) in high-risk breast cancer: a prospective, randomized, international multicenter Phase III trial

ClinicalTrails.gov Unique protocol Identifier: NCT04261244

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Study protocol

Grant	Deutsche Krebshilfe
Monitoring und Data Management	German Breast Group c/o GBG Forschungs GmbH
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PROTOCOL APPROVAL/ SIGNATURES NeoRad Breast Cancer

Neoadjuvant Chemotherapy followed by pre-operative radiotherapy in high-risk breast cancer:

A prospective randomized multicenter-phase III trial

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20.4.20
Date

Priv. Doz. Dr. med. C. Matuschek
(study chairman)

20.4.2020
Date

Prof. Dr. med. W. Budach
(deputy)

17. April 2020
Date

Prof. Dr. med. Tanja Fehm
(deputy)

The deputies and the study biostatistician have been informed about the Protocol Version 20 by the study chairman.

18.03.24dorf

Priv. Doz. Dr. med C. MatuschekPROTOCOL APPROVAL/ SIGNATURES NeoRad Breast Cancer

Neoadjuvant Chemotherapy followed by pre-operative radiotherapy in high-risk breast cancer:

A prospective, randomized multicenter phase III trial

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PROTOCOL APPROVAL/ SIGNATURES BY LOCAL INVESTIGATOR

By signing this page, I agree

- To conduct the trial described in this protocol in compliance with GCP, with applicable regulatory requirements and with the protocol given approval by the Ethics Committee and the regulatory authority
- To comply with procedures for data recording and reporting (including data protection)
- To retain the trail-related essential documents as described in the protocol
- To personally supervise the conduct of this study and to ensure its conduct in compliance with the protocol, informed consent, the Declaration of Helsinki, ICH Good Clinical Practice Guidelines, and European and national regulations governing the conduct of clinical studies.

_____	_____
Study site	Local investigator (Print Name)
_____	_____
Date	Local investigator (Signature)

STUDY SYNOPSIS

Title of study	**Preoperative radiotherapy versus postoperative radiotherapy after neoadjuvant chemotherapy ("NeoRad") in high-risk breast cancer: a prospective, randomized, international multicenter Phase III trial**
Grant	DKH – Deutsche Krebshilfe
Study Chairman	PD Dr. med. Christiane Matuschek, Study Principal Investigator, University Hospital Duesseldorf, Department of Radiotherapy and Radiooncology Deputies: Prof. Dr. med. Wilfried Budach Prof. Dr. med. Tanja Fehm
Rationale	The standard of care for high-risk breast cancer consists of neoadjuvant chemotherapy and surgery followed by postoperative whole breast/ chest wall irradiation+/- an additional boost (= irradiation restricted to the tumor bed in case of breast-conserving therapy). Adjuvant radiotherapy significantly reduces ipsilateral breast recurrences, breast cancer specific mortality and overall mortality. The optimal timing of radiotherapy in patients, who are candidates for neoadjuvant chemotherapy (NACT) has yet to be addressed in a randomized controlled trial. The NeoRad trial tests whether preoperative radiotherapy results in an improved DFS and less radiation-induced late effects compared to postoperative radiotherapy in higher risk breast cancer after NACT. The aim of postoperative radiotherapy is to eliminate residual locoregional microscopic disease in non-resected tissue. The overall treatment time for this residual microscopic disease from the first cycle of NACT to completion of radiotherapy is about 3 to 6 weeks shorter, if preoperative radiotherapy is administered. This should result in an improved locoregional control, which is of special interest in view of the higher locoregional recurrence rates that have been reported after NACT compared to adjuvant chemotherapy [1]. Furthermore, residual disease potentially resistant to NACT has less time for metastatic spread. In a Scandinavian 3 arm trial on stage I-III breast cancer, 960 patients were randomized between 1971-1976 to receive either mastectomy alone or mastectomy in combination with either preoperative radiotherapy (45 Gy in 30 fractions), or postoperative radiotherapy. No systemic treatment was given in this trial. In the first report of this trial a statistically significant advantage in overall survival (~7%) at 5 years follow up was observed in favour of the preoperative arm compared to both other arms [2]. However, this survival advantage gradually disappeared during longer follow up and was no longer detectable at 10 year follow up [3]. The causes of deaths were not well documented in this trial. Interestingly, a

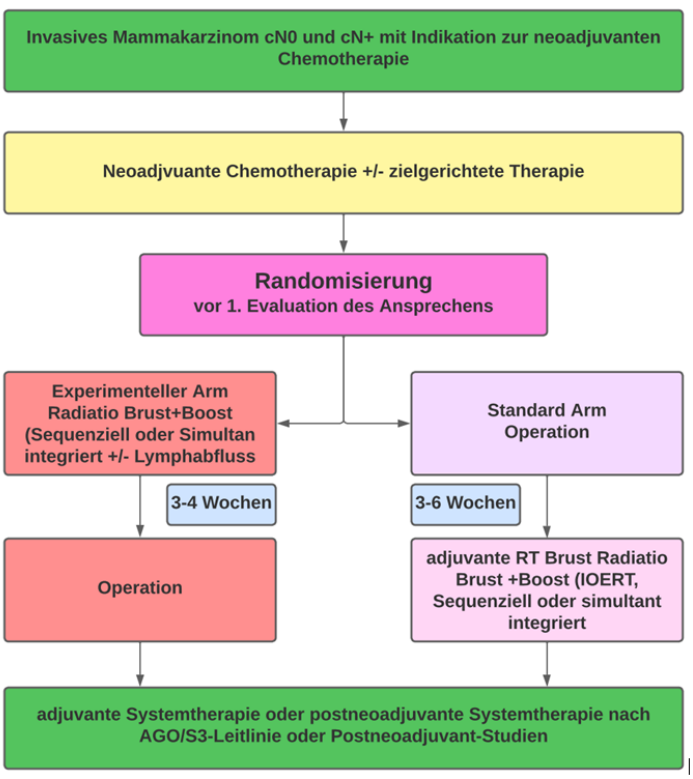
	higher rate of mortality from any cause was observed in the preoperative arm of the trial compared to the postoperative arm starting 4-5 years after treatment, which is unlikely to be caused by a higher breast cancer mortality. The used radiation techniques were substantially different between the pre- and postoperative arms in the trial. Whereas in the preoperative arm photons were used to irradiate the breast and the internal mammary chain lymph nodes, in the postoperative arm electrons were used to irradiate the chest wall and the internal mammary chain lymph nodes. The available radiation technique in the 1970s causes a large difference in the radiation dose to the heart in favour of the postoperative arm. The magnitude and time of occurrence of the higher mortality in the preoperative arm fits well to the documented higher cardiovascular mortality associated with this type of outdated radiotherapy in a large meta-analysis of the Early Breast Cancer Trialists Cooperative Group [4]. With modern radiation techniques, radiotherapy is no longer associated with a significantly increased cardiovascular mortality, even in left-sided breast cancer including internal mammary chain lymph nodes [5]. This indirectly indicates that with modern radiation techniques the survival benefit after 5 years could have persisted in long term. In a retrospective analysis based on the SEER database the outcome of 1123 breast cancer patients, who had received preoperative radiotherapy after NACT before surgery were compared to 155,077 patients who received surgery followed by postoperative radiotherapy [6]. They report a 12% absolute benefit in DFS at 20 years for the preoperatively irradiated patients. The corresponding overall survival benefit was only 3%, which could be explained by the fact that the majority of patients in the database were treated in the last century starting from 1972 to whom the same problems apply as described above. Brackstone et al. [7] published a matched pair analyses that compared a small cohort of high-risk breast cancer patients (n=108) preoperative radiotherapy after NACT to postoperative radiotherapy. In this cohort, modern chemotherapy regimens and modern radiation techniques were used. At 4 years an absolute advantage of 19% was observed for DFS and 14% for overall survival in favour of the preoperatively irradiated cohort. In summary, there is sufficient evidence to postulate that preoperative radiotherapy after NACT could improve DFS compared to postoperative radiotherapy, but data from a randomized trial using modern systemic treatment and radiation techniques is missing. Some investigators may argue that the observation of a pCR after preoperative radiotherapy after NACT could not have the same predictive value compared to a pCR after NACT alone, since a higher pCR rate is expected after additional radiotherapy. This could potentially be hazardous, since some patients, who would

	be candidates for postneoadjuvant chemotherapy or T-DM1 would not receive this treatment. However, the long term survival data (15 years) from a larger cohort of 315 patients treated with preoperative chemotherapy and radiotherapy at the University Hospital Duesseldorf [8] clearly indicate that pCR after preoperative radiotherapy and chemotherapy has the same impact on survival (no pCR 55% at 15 years, pCR 85% at 15 years) as typically observed in trials on NACT alone [9-11]. In addition, retrospective data have shown that higher pCR rates after additional radiotherapy after NACT compared to sole NACT can be expected especially in luminal B breast cancers, whereas a further increase of the already high pCR rates in Her2 positive and triple negative breast cancer will be less pronounced. The potential risk that less patients will receive postneoadjuvant treatment after preoperative radiotherapy is minimized in this trial, since an axillary sentinel node biopsy is mandatory before radiotherapy in the experimental arm and a biopsy of the residual breast lesion. For patients with triple negative or Her2 positive disease, who have residual invasive cancer in either of these biopsies, postneoadjuvant treatment is recommended also in case of a pCR after preoperative radiotherapy. Taken together, preoperative radiotherapy after NACT could significantly improve DFS (primary endpoint). In addition, preoperative radiotherapy will expectedly lead to less late complications and better cosmetic outcomes compared to postoperative radiotherapy. If preoperative radiotherapy is advantageous in these secondary endpoints, the trial has the potential to change clinical practice even if superiority of DFS is not achieved. We will perform a hierarchical test, starting with non-inferiority as the first primary analysis. If this is significant, then superiority as the second component of the main analysis will be tested. The most obvious advantage of preoperative radiotherapy regarding a potentially better cosmetic outcome does apply to patients who undergo partial mastectomy or mastectomy with immediate reconstruction with autologous flaps. Since the flab will not receive any radiotherapy, shrinkage and fibrosis of the flap can be expected to be significantly lower compared to flabs receiving postoperative radiotherapy. The best evidence in this regard comes from the long term cosmetic outcome (15 years) of 30 patients treated at the University Hospital Duesseldorf, who underwent immediate flab-based breast reconstruction after preoperative radiotherapy and had excellent or good cosmetic results in 60% and poor in 10% of cases [12] The theoretical advantage of preoperative radiotherapy in case of breast conserving surgery after preoperative radiotherapy is less obvious. According to their risk profile, some patients in the trial need boost radiotherapy. In the experimental arm, the center decides whether to administer a boost in the situation of complete

	remission in imaging after neoadjuvant chemotherapy (center's decision). Delineation of the boost volume is more accurate in the preoperative setting than postoperatively, since no change in anatomy has occurred due to the surgical procedure. This typically results in smaller target volumes being irradiated. Furthermore, a considerable part of the irradiated boost volume will be surgically removed in the preoperative arm. Both considerations should result in less late fibrosis and better cosmetic results. Wound healing problems and wound infections as well as postoperative seromas could potentially be more frequently observed after preoperative radiotherapy than after NACT alone. However, an unusually high rate of these complications was not observed in the large cohort (n=315) treated at the University Hospital Duesseldorf [13, 14]. Implant based immediate reconstructions were not or only rarely used in this cohort. Baltodano et al. [15] evaluated the database of the American College of Surgeons National Surgical Quality Improvement Program and found 75 patients, who had received preoperative radiotherapy before mastectomy and immediate implant based reconstruction versus 16,788, who had not received preoperative radiotherapy. Morbidities at the surgical site were observed at the same frequency in both cohorts (5.3 %). In the same database, 266 patients were registered for mastectomy alone after preoperative radiotherapy and 60,773 for mastectomy alone without preoperative radiotherapy. Morbidities at the surgical site were reported in 4.5% after preoperative radiotherapy and 2.7% without preoperative radiotherapy (n.s.). Reports on considerably higher surgical morbidities after preoperative radiotherapy [16-21] refer almost exclusively to delayed breast reconstruction several months or even years after mastectomy and postoperative radiotherapy. Unfortunately, many authors classified this postoperative radiotherapy after mastectomy as a “preoperative radiotherapy” setting, which is formally correct in the context of the delayed reconstructive surgery, but a misnomer in our view since these publications have raised concerns regarding the use of preoperative radiotherapy among breast surgeons. To allow for the highest degree of safety in view of the absence of randomized data, the current trial has implemented early safety checks concerning the surgical morbidity surveyed by an independent data safety monitoring committee.
Study type and study design	Prospective, randomized multicenter-phase III trial
Primary objective and endpoint	**Primary objective** is the superiority of preoperative radiotherapy (PRT) of the experimental treatment schedule in terms of disease-free survival (DFS). DFS as primary endpoint is defined as time from randomisation to any of the following events: local recurrence, regional recurrence, contralateral breast cancer, distant

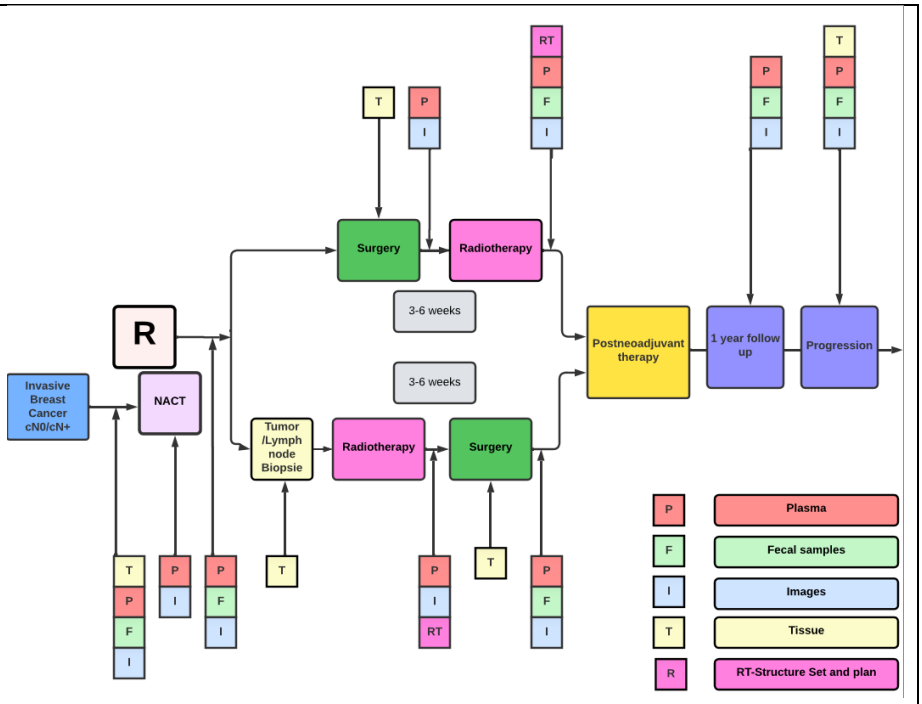
	recurrence, invasive second cancer or death due to any cause, whichever occurs first; patients without an event will be censored at the date of the last contact.
Secondary objective and endpoint	Assessment and comparison between treatment arms of • time to local recurrence [in affected breast] (LR) as a first site of recurrence • time to regional recurrence (RR) as a first site of recurrence • distant disease-free survival (DDFS) • overall survival (OS) •breast cancer specific survival (BCSS) • Pathological complete response (pCR) defined as ypT0/is, ypN0 • cosmetic results (5 Point Scoring System • breast retraction assessment=BRA • quality of life (EORTC C30, EORTC B23) •rate of arm lymphoedema >°I of the irradiated side • rate of plexopathy >°I of brachial plexus of the irradiated side • acute and late toxicity
Inclusion criteria	• Histologically proven invasive, unilateral breast cancer • Indication for radiotherapy • Indication for neoadjuvant chemotherapy (+/- antibody treatment or other targeted therapies) in accordance with national and international guidelines • Female • Informed consent for the trial signed by the patient • T2-T4a-d • T1 a-c, if G3, triple negative, HER2- positive, or cN+/pN+ • Hormone receptor and HER2 status: no restrictions • All grades G1-G3 • Age ≥18 years at the time of randomisation • Performance status ≤ 2 • No pre-existing conditions that forbid therapy • Signed consent form regarding registration, randomisation, collecting, and saving of personal data
Exclusion criteria	• Neoadjuvant treatment solely with endocrine therapy • Bilateral breast cancer • Pregnancy or lactation • Prior radiotherapy of the affected or contralateral breast • Connective tissue disease, including rheumatoid arthritis and thromboangiitis obliterans • Pre-existing symptomatic chronic lung disease (fibrosis, pneumoconiosis, adult-onset allergies, such as farmer's lung, severe lung emphysema,

	COPD ≥°III) • Cardiac comorbidities: symptomatic coronary heart disease, prior heart attack, heart failure NYHA ≥II or AHA ≥C, pacemaker, and/or implanted defibrillator • Malignoma except basalioma or in-situ-carcinomas in complete response • Distant metastasis • Plexopathies of the arm of the treated side • Stiffness of the shoulder of the arm of the side of the breast cancer of any origin (e.g. following a road accident) • Lymph edema ≥°II of the arm at the side of the breast cancer • Missing signature on consent form • Other medical conditions that prohibit the neoadjuvant radiotherapy (i.e. Expected non-compliance, etc.) • Male patients • Patients who have previously been assessed for chemotherapy response
Termination and interruption of the treatment	Termination and interruption of treatment should be decided by the responsible treating study site. For individual discussions the study chairmen should be involved NeoRad@med.uni-duesseldorf.de.
Treatment	All patients will receive NACT with or without combination with anti-Her2 therapy or other targeted therapies according to the latest S3/AGO guideline at the time of therapy. **In the standard arm** patients will undergo surgery, sentinel lymph node biopsy and eventually (targeted) axillary dissection according to the latest S3/AGO guideline at the time of therapy. After surgery patients will receive adjuvant radiotherapy and systemic treatment following S3/AGO guidelines. All patients will receive postneoadjuvant systemic therapy following S3/AGO guidelines **In the experimental arm** patients will receive whole breast irradiation (WBRT) with or without RNI following neoadjuvant chemotherapy. Approximately 3 weeks (3 - 6 weeks) after radiotherapy patients will undergo surgery and eventually (targeted) axillary dissection and then receive postneoadjuvant systemic therapy following S3/AGO guidelines. The trial treatment schedule is illustrated below:

	
Randomization procedure	Investigators will inform eligible patients about the NeoRad trial during the regular clinical consultation visits in the respective study site before or during NACT. The study permits inclusion of participants from the point of diagnosis until prior to the initial assessment of systemic therapy response. Informed consent will be obtained by the local radiation oncology department. A complementary translational study is planned to collect biomaterials. Patients can be enrolled in the translational study from the time of diagnosis until the first evaluation. In instances, where obtaining informed consent at the time of diagnosis is not feasible, the gynecologist may provide information regarding the trial and obtain informed consent for the translational study. Randomization is feasible from the point of enrollment in the study until prior to the initial evaluation of therapy response. All study related investigations and documentation of patients will be performed only after written informed consent was collected using the actual ethics committee approved patient information and consent form. Patients fulfilling the inclusion-/exclusion criteria will be registered online in the eCRF. For each patient, a unique patient number for pseudonymized identification throughout the study will be generated. Patients will be randomized at time of inclusion and before initial assessment of response to NACT 1:1 into one of the study arms, stratified by:

	1) biological subtype: Strata: HER2-type (HER2/neu positive), HR+/HER2- type (no HER2/neu overexpression), triple negative 2) cN-Status (before start of NACT): Strata: cN+, cN- 3) type of planned surgery: Strata: BCS vs Mastectomy (NSM, SSM or radical) The randomization plan will be generated by a validated SAS program and undergoes strict access control. Treatment groups will be allocated by the IWRS system integrated in the eCRF.
Sample size and justification	The primary endpoint of the NeoRad trial is DFS. For sample size calculations, we assumed a 10-year DFS of 70% in the control arm of the trial. This value is based on the experience of the GEPAR trials (GBG data on file, extrapolation from 5years), but takes into account that patients in the NeoRad trial may have a slightly lower risk of recurrence, since some high-risk patients will take part in trials testing novel neoadjuvant treatments and a substantial proportion will receive new postneoadjuvant systemic treatments. Accordingly, we hypothesise that preoperative radiotherapy after NACT will improve 10-year DFS from 70% in control arm to 76.5% in the experimental arm of the trial (HR=0.75), which we consider a clinically relevant improvement. In order to detect a difference of this magnitude at a power of 80%, a recruitment time of 4 years and an additional follow up of at least 6 years, 379 events and a sample size of 1826 patients, 913 in each arm using a 1:1 randomisation, are required to reject the null hypothesis of no improvement on a two-sided type I error level of 0.05. A cumulative drop-out rate of 10% in 10 years is included in these calculations. This calculation is based on an assumed exponential shape of the survival curves and this drop-out process.
Biostatistical methods	All primary efficacy analyses will follow the ITT principle, i.e. all randomized patients will be included in the analysis and the treatment groups they were randomized to. Time-to-event data, such as DFS and OS, will be displayed by treatment group as Kaplan-Maier curves and compared using the two-sided stratified log-rank test. The

	treatment effect will be additionally estimated as a hazard ratio in a proportional hazard's regression model with treatment and stratification characteristics. The hazard ratio will be reported with 95% confidence intervals. Drop-out will be dealt with as independent right censoring. We will perform a hierarchical test, starting with non-inferiority as the first primary analysis. If this is significant, then superiority as the second component of the main analysis will be tested. The non-inferiority margin is defined as 95% CI for HR<1.15 which corresponds to the absolute difference of 3.6% in 10 years DFS rate (from 70% to 66,4%) or 2.2% absolute difference in 5 years DFS rate. Time to LR and time to RR will be analyzed using competing risk models. Comparisons of the categorical data, e.g. response rates, dichotomized cosmetic results etc., will be performed using Fisher`s exact test, or a trend test according to Cochran/Armitage for ordinal scales, as suitable.
Planned interim analyses	While the pre-planned early safety assessment after n=100 patients is described in detail in section 4.6, no interim analyses of efficacy with early stopping option are planned. This is due to the fact that statistically significant differences in DFS and OS will first be measurable at a minimum of 5 years follow-up when the recruitment is completed, and an interim analysis would not allow for a reduction of patient numbers to be randomized.
Translational research (financial funding is applied separately)	Extensive translational research programs based on certified longitudinal biobanking of blood plasma, serum and stool will be implemented to further refine molecular prognostic and predictive profiling using Liquid Biopsy approaches, and eventually identifying subgroups for treatment stratification. The application for funding has been submitted. Once the German Cancer Aid has commited to the funding, the samples can be collected.

	
Estimated number of sites	In total approximately 40 srudy sites in Germany are planned to recruiting patients.
Study duration	Start of preparation: Q3 2018 Start of recruitment: Q1 2024 Planned termination of recruitment: Q1 2028 Planned termination of follow-up: Q1 2034 Final study report: Q4 2034

ORGANISATION OF THE STUDY

This trial will be conducted by the study chairmen. The study is being conducted in Germany, but an outreach to Austria and Switzerland is conceivable. In case the study is transferred to other European countries, which is not planned at the time of the protocol, a corresponding amendment of the study protocol will be performed. In this case, national study leaders are appointed by the gynecology and radiotherapy departments to monitor the safety and

treatment of the enrolled patients on a national level and to ensure the compliance of the study with national laws and regulations. The national study leaders are also responsible for the quality assurance of the study.

Eligible patients should be treated with multimodal therapy according to standard guidelines for breast cancer (S3 and AGO-guidelines).

The study permits inclusion of participants from the point of diagnosis until prior to the initial assessment of systemic therapy response. Informed consent will be obtained by the local radiation oncology department. A complementary translational study is planned to collect biomaterials. Patients can be enrolled in the translational study from the time of diagnosis until the first evaluation. In instances where obtaining informed consent at the time of diagnosis is not feasible, the gynecologist may provide informations regarding the trial and obtain informed consent for the translational study. The samples can be collected, once the German Cancer Aid has committed the funding. Randomization is feasible from the point of enrollment in the study until prior to the initial evaluation of therapy response. Randomization is recommended at inclusion of the trial but can be performed until the first response assessment to neoadjuvant chemotherapy. The randomization of all patients will be performed by the treating study site. The randomization code will be created and hosted by the GBG. The study is open, blinding is not possible due to the different chronology of treatment modalities in the two arms.

The study group and the national study leaders will continue to run the protocols on a day-to-day basis and provide advisory services for trial patients (therapists and study coordinators with expertise in diagnosis and treatment of breast cancer).

Important note: This document describes a randomized trial for high-risk breast cancer and provides information regarding the patients entering procedures. It is not intended for use as an "aide-memoire" or guide for treating other patients. This draft has been carefully prepared, but corrections or amendments may be necessary. All participating study sites are asked to check the validity of their protocol version in regular intervals. According to current regulations, the responsible ethics committee (University of Duesseldorf, Germany) and the respective authorities (DEGRO expert panel) have been informed by the coordinating center. Participants are required to maintain confidentiality in regard to the content of this protocol. **No part of this protocol may be reproduced or circulated without prior**

authorisation by the study group center! NeoRad should only be used by persons and institutions participating in the study and should not be forwarded to anybody without written informed consent from the NeoRad study group.

Conduction of protocol therapy and supportive care requires a high level of medical and human competence and is only possible in specialized centers with adequate infrastructure. A state of emergency due to complications from the underlying disease or its treatment can develop in every patient at any time. It is, therefore, ethically and legally improper to treat patients, in accordance with this protocol, in institutions that are no participating study sites, have not signed the commitment form, or do not meet the minimum participation requirements.

Responsibility for the administration of the protocol treatments lies with the participants. An experienced team with multidisciplinary competences should thus treat breast cancer patients. Chemotherapeutic and other therapeutic substances needed for treatment are not part of the protocol and will not be paid for. Inclusion criteria must be met by any individual patient before the registration in the study site. Should questions arise regarding the treatment of registered patients, a consulting service is provided by the Study Group Center.

Every recommendation given in this protocol, particularly the drug doses, must be compared with commonly accepted guidance. Before accepting patients into the trial, the investigators must ensure the participation requirements are met. *NeoRad* was developed using the Master protocol of the Deutsche Krebshilfe e.V..

Each physician is responsible for the treatment of the patient and the application of the treatment recommended in the protocol!

Table of Content

List of Appendices

Abbreviations

AGO	Arbeitsgemeinschaft für Gynäkologische Onkologie
AND	Axillary Node Dissection
ARO	Arbeitsgemeinschaft für Radiologische Onkologie
BC	Breast Cancer
BCS	Breast Conserving Surgery
CT	Computer Tomography
CTV	Clinical Target Volume
DEGRO	Deutsche Gesellschaft für Radioonkologie
DFS	Disease Free Survival
DIBH	Deep Inspiration Breath-Hold
DMFS	Distant metastasis free survival
ECE	Extracapsular Extension
ER	Estrogen receptor
GBG	German Breast Group/ GBG Forschungs GmbH
GTV	Gross Tumor Volume
Gy	Gray
HER2/neu	Human epidermal growth factor receptor
HR	Hormon receptor
IMRT	Intensity-Modulated Radiation Therapy
IOERT	Intraoperative Radiotherapy with Electrons
ITT	Intention to treat
LAD	Left Descending Artery
LoE	Level of Evidence
LRR	Locoregional Recurrence
MRT	Magnetic Resonance Tomography
NACT	Neoadjuvant Chemotherapy
OGRO	Österreichische Gesellschaft für Radioonkologie
OS	Overall Survival

PR	Progesteron receptor
PRT	Preoperative radiotherapy
RNI	Regional Lymph Node Irradiation
RT	Radiotherapy
SD	Single Dose
SLN	Sentinel Lymph Node
T-DM1	Trastuzumab-Emtansin
VMAT	Volumentric Arc Therapy
WBRT	Whole-Breast Radiotherapy

1. GENERAL INFORMATION

NeoRad is a trial cooperating with ARO and GBG Forschungs GmbH.

NOTE: The ARO and the GBG Forschungs GmbH run several protocols for treatment of breast cancer

For further information, please refer to the www.gbg.de, https://www.krebsgesellschaft.de/arbeitsgemeinschaften/aro.html

2. INTRODUCTION

The standard of care for high-risk breast cancer consists of neoadjuvant chemotherapy and surgery followed by postoperative whole breast/chest wall irradiation +/- an additional boost (= irradiation restricted to the tumor bed in the case of breast-conserving therapy). In case of lymph node involvement, most patients require additional radiotherapy of the regional lymph nodes. Adjuvant radiotherapy significantly reduces ipsilateral breast recurrences, breast cancer specific mortality, and overall mortality. The optimal timing of radiotherapy in patients, who are candidates for neoadjuvant chemotherapy (NACT) has never been addressed in a randomized controlled trial.

2.1 Clinical rationale for preoperative radiotherapy in high-risk breast cancer

The NeoRad trial tests whether preoperative radiotherapy results in an improved DFS and less radiation induced late effects compared to postoperative radiotherapy in higher risk breast cancer after NACT. The aim of postoperative radiotherapy is to eliminate residual locoregional microscopic disease in non-resected tissues. The overall treatment time for this residual microscopic disease from the first cycle of NACT to completion of radiotherapy is about 3 to 6 weeks shorter, if preoperative radiotherapy is administered. This should result in an improved locoregional control, which is of special interest in view of the higher locoregional recurrence rates that have been reported after NACT compared to adjuvant chemotherapy [1]. Furthermore, residual disease potentially resistant to NACT has less time for metastatic spread. The advantage of preoperative radiotherapy has already been shown in randomized trials in other tumor entities like in rectal cancer and soft tissue sarcoma. In rectal cancer, neoadjuvant chemoradiation resulted in significantly better local control and functional outcome compared to postoperative chemoradiation [22]. Preoperative radiotherapy of 50 Gy in 25 fractions in soft tissue sarcoma has been shown to be equivalent in terms of local tumor control to a 32% higher dose (66 Gy in 33 fractions) postoperative radiotherapy. Late

radiation induced tissue fibrosis was less pronounced after preoperative radiotherapy and overall survival was significantly improved [23]. In localised NSCLC, preoperative chemoradiation (45 Gy, 1,5 Gy BID in 3 weeks) was equivalent to postoperative chemoradiation (54 Gy, 1,8 Gy in 6 weeks) in the intent to treat population. However, DFS and overall survival were better in the preoperative arm in patients who underwent surgical resection [24]. In a Scandinavian 3 arm trial on stage I-III breast cancer, 960 patients were randomized between 1971-1976 to receive either mastectomy alone or mastectomy in combination with either preoperative radiotherapy (45 Gy in 30 fractions) or postoperative radiotherapy. No systemic treatment was used in this trial. In the first report of this trial a statistically significant advantage in overall survival (~7%) at 5 years follow up was observed in favour of the preoperative arm of the trial compared to both other arms [2]. However, this survival advantage gradually disappeared during longer follow up and was no longer detectable at 10 year follow up [3]. Unfortunately, the causes of deaths were not well documented in this trial. Interestingly, a higher rate of mortality from any cause was observed in the preoperative arm of the trial compared to the postoperative arm starting 4-5 years after treatment, which is unlikely to be caused by a higher breast cancer mortality. The used radiation techniques were substantially different between the pre- and postoperative arms on the trial. While photons were used to irradiate the breast and the internal mammary chain lymph nodes in the preoperative arm, electrons were used to irradiate the chest wall and the internal mammary chain lymph nodes in the postoperative arm. With the available radiation technique of the 1970s, this resulted in a large difference in the radiation dose to the heart in favour of the postoperative arm. The extent and time of occurrence of the higher mortality in the preoperative arm fit well with the documented higher cardiovascular mortality associated with the type of outdated radiotherapy used in the preoperative arm of the trial in a large meta-analysis of the Early Breast Cancer Trialists Cooperative Group [4]. Using modern radiation techniques, radiotherapy is no longer associated with a significantly increased cardiovascular mortality, even in left sided breast cancer including internal mammary chain lymph nodes [8]. This indirectly indicates that when using modern radiation techniques, the survival benefit at 5 years could have persisted also in the long term. In a retrospective analysis based on the SEER database, the outcome of 1123 breast cancer patients who had received preoperative radiotherapy after NACT before surgery were compared to 155,077 patients who received surgery followed by postoperative radiotherapy [6]. They reported a 12% absolute

benefit in DFS at 20 years for the preoperatively irradiated patients. The corresponding overall survival benefit was only 3%, which could be explained by the fact that the majority of patients in the database were treated in the last century, starting from 1972. Therefore, the same problems apply as described above. Brackstone et al. [7] published a matched pair analysis that compared a small cohort of high-risk breast cancer patients (n=108) receiving preoperative radiotherapy after NACT to postoperative radiotherapy. In this cohort, modern chemotherapy regimens and modern radiation techniques were used. At 4 years follow-up, an absolute advantage of 19% was observed for DFS and 14% for overall survival in favour of the preoperatively irradiated cohort.

In summary, there is sufficient evidence to postulate that preoperative radiotherapy after NACT could improve DFS compared to postoperative radiotherapy, but data from a randomized trial using modern systemic treatment and radiation techniques is missing.

Some investigators may argue that the observation of a pCR after preoperative radiotherapy after NACT could not have the same predictive value compared to a pCR after NACT alone, since a higher pCR rate is expected after additional radiotherapy. This could potentially be hazardous, since some patients, who would be candidates for postneoadjuvant chemotherapy or TD-M1 would not receive this treatment. However, the long term survival data (15 years) from a larger cohort of 315 patients treated with preoperative chemotherapy and radiotherapy at the University Hospital Duesseldorf [8] clearly indicates that pCR after preoperative radiotherapy and chemotherapy has the same impact on survival (no pCR 55% at 15 years, pCR 85% at 15 years) as typically observed in trials on NACT alone [9-11]. In addition, retrospective data have shown that higher pCR rates after additional radiotherapy after NACT compared to sole NACT can be expected especially in luminal B breast cancers, whereas a further increase of the already high pCR rates in Her2 positive and triple negative breast cancer will be less pronounced. The potential risk that less patients will receive postneoadjuvant treatment after preoperative radiotherapy is minimized in the present trial, since an axillary sentinel node biopsy is highly recommended before radiotherapy in the experimental arm and a biopsy of the residual breast lesion is recommended.

For patients with triple negative or Her2 positive disease, who have residual invasive cancer in either of these biopsies, postneoadjuvant treatment is recommended also in case of a pCR after preoperative radiotherapy.

Taken together, we are convinced that the hypothesis of the NEORAD trial that preoperative radiotherapy after NACT could significantly improve DFS (primary endpoint) is scientifically sound. In addition, it is expected that preoperative radiotherapy will lead to less late complications and better cosmetic outcomes compared to postoperative radiotherapy. If preoperative radiotherapy is advantageous in these secondary endpoints, the trial has the potential to change clinical practice even if superiority of DFS cannot be shown. Therefore, the statistical design includes testing for non-inferiority of the preoperative arm before testing for statistically significant improvement of DFS.

The most obvious advantage of preoperative radiotherapy regarding a potentially better cosmetic outcome concerns patients who undergo partial mastectomy or mastectomy with immediate reconstruction with autologous flaps. Since the flap will not receive any radiation, shrinkage and fibrosis of the flap can be expected to be significantly lower compared to flaps receiving postoperative radiotherapy. The best evidence in this regard comes from the long term cosmetic outcome (15 years) of 30 patients treated at the University Hospital Duesseldorf, who underwent immediate flap-based breast reconstruction after preoperative radiotherapy and had excellent or good cosmetic results in 60% and poor in 10% of cases [12]. The theoretical advantage of preoperative radiotherapy in case of breast conserving surgery after preoperative radiotherapy is less striking. According to their risk profile, all patients in the trial will receive boost radiotherapy. The delineation of the boost volume is more accurate in the preoperative setting than postoperatively since no change in anatomy has occurred as a result of the surgical procedure. This typically results in smaller target volumes to be irradiated. Furthermore, in the preoperative arm a considerable part of the irradiated boost volume will be surgically removed. Both considerations should result in less late fibrosis and better cosmetic results. The long term cosmetic results after breast conserving surgery were favourable in 2 phase II trials using preoperative radiotherapy [25] [n=75] or preoperative chemoradiation [26] [n=41]. Data from randomized comparisons are not yet available.
Patients who undergo skin sparing or nipple sparing mastectomy with immediate implant based reconstruction have a high risk of developing capsular fibrosis and in long term require replacement of the implant, if postoperative radiotherapy is administered [27-29]. Most patients in these cohorts received conventionally fractionated radiotherapy (50 Gy in 25 fractions). In the current trial, hypofractionated radiotherapy (40.5 Gy in 15 fractions) is used

in both arms. According to the results of large, randomized trials, hypofractionated radiotherapy to 40 Gy was associated with less late effects and a better cosmetic outcome compared to conventionally fractionated radiotherapy to 50 Gy [30]. Therefore, it can be assumed that after hypofractionated radiotherapy less capsular fibrosis and better cosmetic outcome will be observed in both arms of the trial. In addition, preoperative radiotherapy may induce less capsular fibrosis compared to postoperative radiotherapy, because radiotherapy is not administered at a time when a proinflammatory microenvironment is already established at the boundary of the implant [31]. This concept is indirectly supported by retrospective comparisons in some uncontrolled cohorts indicating that capsular fibrosis is less severe and replacements of the implant are required less frequently, if preoperative radiotherapy is performed as compared to postoperative radiotherapy [28, 29]. The current trial is the first one to address this question in a randomized comparison and will hopefully be able to give an unequivocal answer.

Mastectomy without immediate reconstruction is also a treatment option in the trial. The lower dose of the implemented hypofractionated radiotherapy in both arm of the trial as compared to standard fractionation should result in less acute and late complications irrespective of the arm of the trial and whether a delayed reconstruction is performed or not. According to the available data from retrospective cohorts, we do not expect significant differences in late effect between the arms of the trial.

Acute side effects of radiotherapy are expected to be quite moderate and typically restricted to a mild erythema and edema of the irradiated breast. In a large, randomized trial (n=2215), moist skin reactions during or after hypofractionated postoperative radiotherapy to 40 Gy in 15 fractions occurred in 0.3% of patients compared to 1.3% with standard fractionation to 50 Gy in 25 fractions [32]. Adjuvant Chemotherapy before adjuvant radiotherapy did not significantly enhance skin toxicity. Thus, we expect that acute radiation related toxicity will be moderate in both arms of the trial.

2.1.1 Wound healing disorders

Wound healing problems and wound infections as well as postoperative seromas could be observed more frequently after preoperative radiotherapy than after NACT alone. However, no unusually high rate of these complications was observed in the large cohort (n=315) treated at the University Hospital Duesseldorf [13, 14]. Implant based immediate reconstructions were not or only rarely used in these cohort. Baltodano et al. [15] evaluated the database of the American College of Surgeons National Surgical Quality Improvement Program and found 75 patients, who had received preoperative radiotherapy before mastectomy and immediate implant based reconstruction versus 16,788 patients who had not received preoperative radiotherapy. Morbidities at the surgical site were observed at the same frequency in both cohorts (5.3 %). In the same database, 266 patients were registered for mastectomy alone after preoperative radiotherapy and 60,773 for mastectomy alone without preoperative radiotherapy. Morbidities at the surgical site were reported in 4.5% after preoperative radiotherapy and 2.7% without preoperative radiotherapy (n.s.). Reports on considerably higher surgical morbidities after preoperative radiotherapy [16-21] almost exclusively refer to delayed breast reconstruction several months or even years after mastectomy and postoperative radiotherapy. Unfortunately, many authors classified this postoperative radiotherapy after mastectomy as “preoperative radiotherapy” setting, which is formally correct in context to the delayed reconstructive surgery, but a misnomer in our view, since these publications have raised concerns regarding the use of preoperative radiotherapy among breast surgeons. To satisfy this scepticism and in view of the absence of randomized data, the current trial has implemented early safety checks concerning the surgical morbidity that will be surveyed by an independent data safety monitoring committee.

We have summarised all peer-reviewed published studies dealing with PRT in breast cancer in regards of side effects, in particular, wound healing disorders in Table 1.

2.2 Rationale for hypofractionated lymph node irradiation in breast cancer

In women with high-risk, node positive breast cancer, national and international guidelines recommend extending radiotherapy to the regional lymph nodes (apex axilla level III and/or supraclavicular region) after axillary dissection or sentinel lymph node biopsy to improve loco-regional control and survival [33], especially in the presence of additional clinical and biological risk factors. The standard dose for adjuvant radiotherapy after breast-conserving surgery is 50-50, 4 Gy in 1.8-2 Gy SD over 5 weeks. In high-risk patients, a boost to the tumor bed is recommended to further improve local control [34]. Several randomized trials proved that in low-risk patients, shorter treatment regimens (3 to 4 weeks) with a hypofractionated schedule may be safe and effective with comparable medical outcome and cosmesis [30, 35].
Based on data from other randomized trials, hypofractionated radiation is not associated with significant changes in breast toxicity, cosmesis, or cardiac toxicity. The addition of hypofractionated RNI is not expected to change the rates of breast or cardiac toxicity.
Hypofractionated radiotherapy of the breast is now standard of care and has been implemented in international guidelines.

RNI has been shown to increase rates of pulmonary dose even though toxicity has been low in randomized trials [36]. Hypofractionated RNI does not seem to be associated with more pulmonary complications than standard RNI [37-40]. However, confirmatory data regarding the lung toxicity of hypofractionated RNI is needed. Data from retrospective cohorts and randomized trials on hypofractionated WBRT did not show an increased rate in lymphedema [41]. Data from head and neck cancer as well as from hypofractionated breast radiation with RNI has not shown an increase in brachial plexopathy except for older trials that used large doses per fraction of >4 Gy. At this time, published data support the feasibility of hypofractionated RNI and the need for a prospective randomized trial addressing clinical outcomes and toxicity of hypofractionated RNI compared to standard fractionation RNI.

2.2.1 Published data referring to hypofractionated lymph node irradiation in breast cancer

Published data supporting hypofractionated schedules in breast cancer RNI are limited, and only few clinical trials are available on hypofractionated regional lymph node irradiation [42]. An update of the START A and START B trials [30] evaluated the locoregional RT in a limited group of patients, and neither the 5 week nor the 3 week treatment resulted in significantly adverse tissue impacts: the assessment of arm and shoulder effects yielded no radiation-induced brachial plexus toxicity after hypofractionated irradiation of the axilla and/or supraclavicular fossa. The authors stated that the START B regimen (40 Gy in 15 fractions/3 weeks) is equivalent to 47 Gy in 2 Gy fractions if the α/β value for brachial plexus is 2 Gy or to 49 Gy in 2-Gy fractions if α/β=1 Gy. Haffty and Buchholz commented on the absence of side effects in the small group of patients (n=116 of 2215 patients) enrolled in the START B trial and receiving regional hypofractionated RT. They confirmed that these results are consistent with modelling of normal tissue effects, which predicts that 40 Gy in 15 fractions should be as safe as the standard scheme for all normal tissue effects [43]. Badiyan et al reviewed prospective and randomized data to analyse the efficacy and toxicity of hypofractionated radiation schedules in breast cancer with RNI to the axilla and supraclavicular regions [42]. In total, 583 patients received hypofractionated RNI within randomized trials. Only one case of plexopathy was reported in these patients. They noted that RNI with standard fractionation is associated with increased toxicity compared to WBRT alone, but current data does not support an increased rate of toxicity with hypofractionated RT.

Guenzi et al investigated the impact of hypofractionated radiotherapy to the whole breast and infraclavicular lymph nodes after axillary dissection on late toxicity [44]. The patients received a moderate hypofractionation consisting of 46 Gy in 2.3 Gy SD 4 times a week plus an additional weekly dose of 1.2 Gy to the lumpectomy region.

From 2007 to 2012, n=100 female breast cancer patients (pT1-4, pN1-3, M0) were treated with conservative surgery, Axillary Node Dissection (AND), and locoregional radiotherapy (supra/infraclavicular fossa). After a median follow-up of 50 months (19-82), 6 (6%) patients died, 1 patient (1%) had local progressive disease, 2 patients (2%) developed distant metastases, and 1 patient (1%) presented both. The acute toxicity was mainly represented by

erythema and patchy moist desquamation in all patients. At the end of radiotherapy, n=27 patients (27%) presented arm lymphedema, but only n=10 cases (10%) seemed to be radiotherapy-related (n=4 mild, n=2, moderate, n=4, severe). These patients were treated with manual lymph drainage and compression therapy.

None of the patients showed a severe disorder of the brachial plexus, and the described cases of paraesthesia could not be attributed to RT definitely. No symptomatic pneumonitis was observed. The authors concluded that irradiation of the supra/infraclavicular lymph node regions using a mild hypofractionated schedule can be a safe and effective treatment without evidence of a significant increase in lymphedema.

Bellefqih et al retrospectively reviewed n=257 patients treated with 42 Gy in 15 fractions between 2009 and 2011 [45]. 19.8% of patients received breast-conserving surgery (BCS); 80.2% received radical surgery.

Patients treated with BCS also received a boost to the tumor bed.

The median follow-up was 64 months (range 11-88 months). The rates of 5-year OS, DFS, locoregional recurrence (LRR)-free survival, and distant metastasis (DM)-free survival were 8.,6%, 84.4%, 93.9% and 83.1%, respectively.

In multivariate analysis (MVA), lymph node ratio >65%, lymphovascular invasion, and negative hormone receptor status predicted for OS, DFS, and DM. T3 and T4 tumors were also associated with worse DFS and DM. For LRR, the independent prognostic factors on MVA were node positivity (N2, N3), and a high grading (grade 3). Regarding the side effects, hyperpigmentation was observed in 19.2% of patients, teleangiectasia, in 12.3% and fibrosis in 30.7%, accordingly. Grade ≥ 2 lymphedema was recorded in 5.8% of the cases. During the follow-up, no cardiac morbidity or symptomatic pneumonitis was observed, nor were plexopathy or rib fractures.

3. STUDY OBJECTIVES

3.1 Primary objective

Primary objective is the superiority of PRT of the experimental treatment schedule in terms of disease-free survival (DFS)* compared to the standard arm. We will perform a hierarchical test, starting with non-inferiority as the first primary analysis. If this is significant, then testing superiority as the second component of the main analysis will be performed.

If only non-inferiority but not superiority is confirmed, the cosmetic results (key secondary endpoint) need to be better in the preoperative radiotherapy arm for the study to be able to change clinical practice.

The investigated PRT-schedule consists of 5x 2.7 Gy per week to 40.5 Gy Standard-RT** prior to surgery. In case of planned breast-conserving surgery, a boost has to be administered in case of residual tumor after NACT. The boost can be administered percutaneously as simultaneous integrated boost (5x per week additional 0.5 Gy to 48 G) or after whole breast irradiation (3x 3.5 Gy to 10.5 Gy) or as an intraoperative boost. Intraoperative radiotherapy is administered with 10 Gy electrons of adequate energy.

**Standard RT is defined as radiotherapy of the breast +/- boost +/- lymph node regions.

*DFS is defined as the time in months between the breast cancer diagnosis and the disease recurrence (local or regional recurrence, contralateral breast cancer, distant metastases, second invasive cancer or death of any cause).

Table 1: Definition of disease-free survival

Event	**DFS**	**Time from randomisation until**
Locoregional recurrence	E	Date of locoregional recurrence
Lymph node recurrence	E	Date of lymph node recurrence (in the ipsilateral axillary, supra-/infraclavicular (including Rotter), and internal mammary chain lymph nodes)
Contralateral breast cancer	E	Date of contralateral breast cancer
Any distant metastatic disease	E	Date of distant metastases
Invasive non-breast cancer	E	Date of invasive non-breast cancer diagnosis
Treatment-related death	E	Date of death
Death of breast cancer	E	Date of death
Death of other cancer	E	Date of death
Non-cancer related death	E	Date of death
Death of unknown cause	E	Date of death
Under observation without event or lost to follow-up	C	Date last follow-up

3.2 Secondary objectives

Assessment and comparison between randomized arms of

1) time to local recurrence [in affected breast] (LR) as a first site of recurrence: recurrence in affected breast counts as an event; regional recurrence, distant recurrence, contralateral breast cancer, invasive non-breast cancer, death due to any cause are considered competing risks.

2) time to regional recurrence (RR) as a first site of recurrence: recurrence in the regional lymph nodes counts as an event, local recurrence, distant recurrence, contralateral breast cancer, invasive non-breast cancer, death due to any cause are considered competing risks.

3) distant disease-free survival (DDFS): distant recurrence, invasive non-breast cancer and death due to any cause are considered as events.

- overall survival (OS): death due to any cause is considered as an event.

5) breast cancer specific survival (BCSS): death due to breast cancer is considered as an event; in case of unknown death cause all effort will be made to determine the cause; if at the time of analysis there are still any deaths due to the unknown reason, they will be counted as tumor-related (worst case principle).

Time for all time-to-event endpoints will be computed starting from randomization after end of NACT.

6) pathological complete remission (pCR, defined as ypT0/is ypN0) rates.

7) cosmetic results (5 Point Scoring System, key secondary objective and subjective

8) breast retraction assessment=BRA)

9) quality of life (EORTC C30 and EORTC QLQ-BR23)

10) rate of arm lymph edema >°I of the irradiated side

11) plexopathy >°I of brachial plexus of the irradiated side

12) acute (up to 3 months after the end of radiotherapy) and late (after 3 months) toxicity (CTC 5.0, LENT-SOMA)

Definitions of outcome measures (clinical Trials.gov):

1. local recurrence rate [in affected breast] (LR) [Time Frame: 6 to 10 years]

   Rate of cancer that has recurred at the same location as the primary cancer. This is a way to measure how well the new treatment is working.

2. locoregional recurrence rate (LRR) [Time Frame: 6 to 10 years]

   Rate of new cancer at any locations (regional lymph nodes, chest wall/mastectomy site) on side which was previously affected by the primary cancer.

   This is a way to measure how well the new treatment is working.

3. disease metastases free survival (DMFS) [Time Frame: 6 to 10 years]

   Time interval beginning after randomisation in which the patient survives, and the cancer has not metastasized.

   This is a way to measure how well the new treatment is working.

4. overall survival (OS) [Time Frame: 6 to 10 years]

   Length of time beginning after randomisation in the study that the patient survives.

   This is a way to measure how well the new treatment is working.

5. disease specific survival (DSS) [Time Frame: 6 to 10 years]

   Length of time from the beginning of the study after randomisation in a study arm that the patient survives the specific cancer.

   This is a way to measure how well the new treatment is working.

6. pathological complete remission (pCR)

   defined as ypT0/is ypN0) rates.

7. Assessment of cosmetic results by the physicians and the patient using a 5-point Scoring System* [Time Frame: 6 to 10 years]

   A grading scale is provided for cosmetic results (5 Point Scoring System):

   E0 Excellent aesthetic result: At first sight no visible therapy sequalae. Both breasts have a similar appearance

   E1 Good: minimal changes in pigmentation, a visible scar, localized teleangieectasia.

   E2 Moderate: marked sequalae with a clear deformation of the breast contour, nipple displacement, or marked skin changes, but yet "acceptable".

   E3 Bad: severe retraction or fibrosis, severe teleangiectasia.

   E4 Complications: skin necrosis

   It will be analyzed as an ordinal scale and (key secondary objective) dichotomized as “Excellent/good vs moderate or worse”.

Assesment of cosmetic results by the physicians using breast retraction assessment-Score (BRA Score) * [Time Frame: 6 to 10 years]

*The BRA Score measures breast symmetry of the treated breast in comparison to the untreated breast. The average in the general population is 1.2 cm. A higher BRA score is worse. A BRA score of 0 cm is optimal.

8. Measurement of the quality of life (QOL): functional scale [Time Frame: 6 to 10 years]

   QoL will be assessed by EORTC (European Organisation for Research and Treatment of Cancer) QLQ-C30 questionnaires for overall QoL and EORTC QLQ-BR23 for breast-specific QoL. The QLQ-C30 consists of 30 questions categorized in functional and symptom-specific scales and provides a global score through two general questions concerning health and quality of life. QLQ-BR23 is a standard instrument for measuring QoL in patients with breast cancer. The questionnaire has 23 items with four possible answers each (not at all, a little, quite a bit, very much). Results are reported using functional scales (e.g., body image, sexual functioning) and symptom-related items (e.g. systemic therapy side effects, breast symptoms). It is also common practice to classify the summary scores into four distinct categories with functional scales (0-25 bad; 26-50 moderate; 51-75 good; 76-100 excellent) and symptom-related scales.

9. Measurement of the quality of life (QOL): symptom-related scale [Time Frame: 6 to 10 years]

QoL will be assessed by EORTC (European Organisation for Research and Treatment of Cancer) QLQ-C30 questionnaires for overall QoL and EORTC QLQ-BR23 for breast-specific QoL. The QLQ-C30 consists of 30 questions categorized in functional and symptom-specific scales and provides a global score through two general questions concerning health and quality of life. QLQ-BR23 is a standard instrument for measuring QoL in patients with breast cancer. The questionnaire has 23 items with four possible answers each (not at all, a little, quite a bit, very much). Results are reported using functional scales (e.g., body image, sexual functioning) and symptom-related items (e.g. systemic therapy side effects, breast symptoms). It is also common practice to classify the summary scores into four distinct categories with functional scales and symptom-related scales: (0-25 excellent; 26-50 good; 51-75 moderate, 76-100 bad)

10. Assessment of arm lymphedema rates by the physicians using common toxicity criteria for adverse events CTCAE, version 5.0 [Time Frame: 6 to 10 years]

    Lymphedema: 'A disorder characterized by excessive fluid collection in tissues that causes swelling.'

    A grading scale is provided for arm lymphoedema rates higher than Grade 1 of the irradiated side (0= "not present", 1= "Trace thickening or faint discoloration", 2= "Marked discoloration; leathery skin texture; papillary formation; limiting instrumental ADL*", 3= "Severe symptoms; limiting self-care ADL") using common toxicity criteria for adverse events CTCAE, version 5.0

    *ADL = activities of daily living

11. Assessment of plexopathia higher than Grade 1 of brachial plexus on irradiated side by the physicians using common toxicity criteria for adverse events CTCAE, version 5.0 [Time Frame: 6 to 10 years]

    Brachial plexopathia:'"A disorder characterized by regional paresthesia of the brachial plexus, marked discomfort and muscle weakness, and limited movement in the arm or hand.'

    A grading scale is provided for plexopathia of brachial plexus on the irradiated side higher than Grade 1 (0= "not present", 1= "Aysmptomatic; clinical or diagnostic observations only; intervention not indicated", 2= "Moderate symptoms; limiting instrumental ADL*", 3= "Severe symptoms, limiting self-care ADL") using common toxicity criteria for adverse events CTCAE, version 5.0

    Patients who have suffered from plexopathy grade 2 or higher will be subjected to special questions and possibly special neurological examinations. *ADL = activities of daily living

12. Assessment of treatment-related toxicity measured by the physicians using standardized common toxicity criteria for adverse events CTCAE, version 5.0.
[Time Frame: 6 to 10 years]

A grading scale is provided for each side effect (0= not present, 1=asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated, 3=moderate; minimal, local or noninvasive intervention indicated; -4=severe or medically significant but not immediately life-threatening)

4. STUDY DESIGN

4.1 Type of study

The NeoRad trial is a prospective, multicenter, randomized phase III trial. Patients with histologically confirmed invasive breast cancer having an indication for neoadjuvant chemotherapy will be screened for this trial. After signing informed consent all patients will be registered in the trial and prospectively randomized to either the experimental arm or the standard of care arm in a 1:1 ratio. About 80 sites throughout Germany are interested to take part (international study sites are invited). About 40 of these study sites will finally participate in this trial with an anticipated minimum recruitment of 6 patients per year and a maximum of 20 patients per year and study site. A sample size of 1826 patients (913 in each arm using a 1:1 randomisation; a cumulative withdrawal rate of 10% in 10 years included) is required for the primary endpoint with a power of 80% and 2-sided type I level of 0.05. The study procedure overview is shown in Figure 1. Until the initial assessment of response to neoadjuvant chemotherapy, patients may be enrolled in NeoRad.

4.2 Time schedule

Start of preparation: Q3 2018
Start of recruitment: Q1 2024
Planned termination of recruitment: Q1 2028
Planned termination of follow-up: Q1 2034
Final study report: Q4 2034

4.3 Study overview

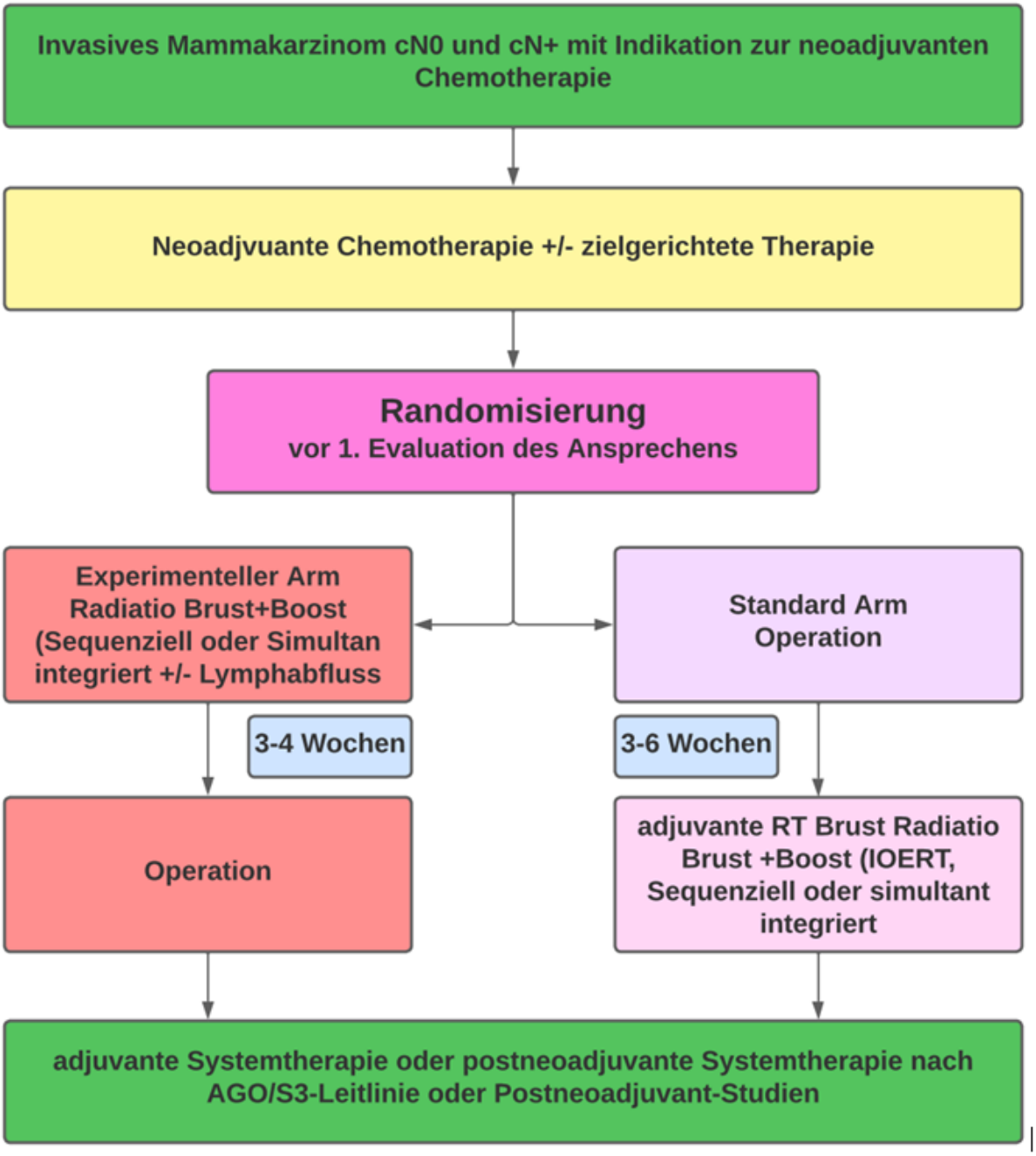


Fig. 1: Study overview

4.4 Standard of care arm

Patients randomized to the standard of care arm will receive surgery according to the national S3 and AGO-guidelines including targeted axillary dissection (TAD), sentinel lymph node biopsy (SLNB) +/- axilla dissection (AD).
3-6 weeks later, when wound healing is complete, the adjuvant radiotherapy to the whole breast/chestwall will be administered.

According to the S3/AGO guidelines postoperative radiotherapy of the breast/chest wall +/- regional lymph nodes (5x 2.7 Gy per week to 40.5 Gy) is recommended. If indicated according S3/AGO guidelines, a boost radiotherapy (optional intraoperative radiotherapy with electrons = IOERT) should be administered either as simultaneous integrated Boost or as sequential boost (see below).

After breast conserving surgery:
Whole breast radiotherapy with 5x2.7 Gy/week → 40.5 Gy in 3 weeks
+/- boost either as integrated boost (5x 3.2 Gy, totol dose 48 Gy) or as sequential boost (3x 3.5 Gy to 10.5Gy, total dose 51 Gy) or intraoperative boost with IOERT (electrons 1x10 Gy)
+/- + lymph node irradiation (5x2.7 Gy/week → 40.5 Gy in 3 weeks)

After mastectomy:
- chest wall irradiation: 5x2,7 Gy/week → 40,5 Gy in 3 weeks
+/- lymph node irradiation (5x2.7 Gy/week → 40.5 Gy in 3 weeks)

The standard of care arm presented here is a brief summary, which does not claim to be exhaustive. For a detailed summary of the radiotherapeutic treatment in this study, refer to Chapter 6

4.5 Experimental arm

Patients randomized into the experimental arm will receive the planned neoadjuvant systemic treatment as in the standard arm of the trial. Two weeks after completion of neoadjuvant

systemic therapy, a re-assessment of the axillary lymph nodes is highly recommended with core needle biopsy in case of suspected residual lymph node metastasis to assess the response to NACT and also for the indication for post-neoadjuvant chemotherapy. In addition, a core needle biopsy or the primary tumor/ tumor region is highly recommended in any situation irrespective of clinical response. The decision to perform these biopsies is the responsibility of the treating study physician.

Radiotherapy will start as soon as the patient recovers and can receive radiotherapy. The dose regime is similar to that prescribed for standard of care arm. If possible, preoperative radiotherapy should start approximately 3 weeks (2-4 weeks) after finalizing NACT.

Approximately 3 weeks (2.5 - 6 weeks) after completion of radiotherapy, surgery will be performed according to the S3/AGO-guidelines. The patient presents 2 weeks after the completion of radiation therapy for the evaluation of acute side effects. The radiation oncologist will authorize the patient for surgery. The management of the axilla is illustrated in figure 2.

The overarching consensus from the existing body of evidence supports the notion that a delay in surgical intervention due to preoperative radiotherapy does not have negative adverse effects on patient outcomes. Therefore, this trial proceeds under the assumption that a delay in surgery occasioned by preoperative radiotherapy is not a concern, and is in fact, a strategic part of the treatment protocol that could enhance patient outcomes. Neoadjuvant radiotherapy, aiming to sterilize tumor cells to curb their proliferation and metastatic potential.

In cases where patients have suspect lymph nodes (LK) that cannot be biopsied, the treatment approach should be based on the clinical stage as assessed by the examiner. This means that the treatment protocol for these patients should proceed as if they are either N+ or N-, depending on the examiner's evaluation.

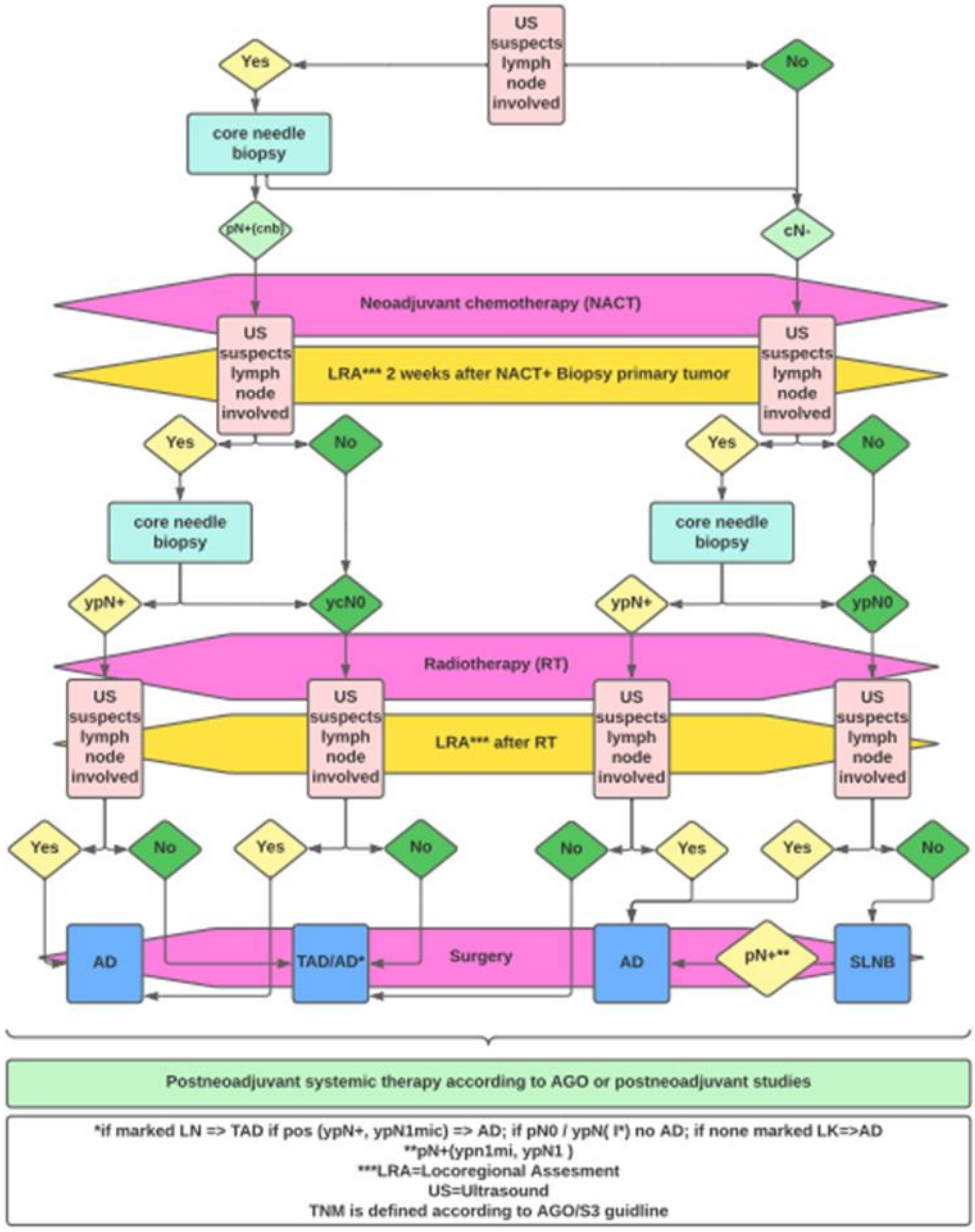


Figure 2: Axilla management within NeoRad Trial

Postneoadjuvant therapy should be performed in accordance with the recommendations provided by the AGO guideline. In cases where core needle biopsies from the axilla or primary tumor region reveal the presence of invasive tumors, the patients should receive postneoadjuvant therapy as patients without complete remission, even if a pathologic complete response (pCR) was detected in the surgical specimens after preoperative radiotherapy. Participation in studies focused on postneoadjuvant systemic therapy is allowed and encouraged.

4.6 Risk-benefit analysis

Preoperative radiotherapy after neoadjuvant chemotherapy +/- targeted therapy is expected to improve locoregional tumor control, progression free, distant metastasis free, and overall survival compared to postoperative standard radiotherapy. Results of randomized trials are not available. Results from the SEER Database indicate an improvement of progression free survival for breast cancer patients, who had received preoperative radiotherapy [6]. Indirect comparison suggests an approximately 20% higher rate of pathologically complete remission. A systemic effect of preoperative radiotherapy on subclinical distant metastases is presumed to be initiated by an immunogenic tumor cell death after radiotherapy. While in postoperative radiotherapy, little interaction with malignant cells in this regard can be expected, preoperative radiotherapy obviously has a higher potential. Another benefit for patients from preoperative radiotherapy is the expectation that cosmetic results and long-term toxicity are improved. In case of immediate breast reconstruction with autologous tissue, the transferred tissue will not receive radiotherapy and will show less shrinkage. The breast tissue in the region of the primary tumor receives the highest radiation dose (boost) and is responsible as a relevant risk factor for fibrosis and deformation of the irradiated breast. After preoperative radiotherapy, most tissue of this highly irradiated boost volume will be removed during surgery. Less fibrosis and deformation are therefore likely. Furthermore, a considerable part of the irradiated tissue will be removed at surgery and is no longer prone for the development of second cancers.

A small part of patients will have cT1/T2 cN0 M0 breast cancer with unfavorable biology. If these patients were surgically treated with mastectomy after neoadjuvant systemic therapy, postoperative radiotherapy is not indicated according to AGO guidelines, unless tumor progression is observed during neoadjuvant treatment. However, mastectomy in patients with cT1/T2 tumors is usually not indicated.

As mentioned above, it is likely that preoperative radiotherapy increases the rate of complete pathological remissions by about 20% compared to neoadjuvant systemic therapy alone. This sounds like a benefit, but might represent a potential risk, because the indication of some postneoadjuvant therapies is restricted to patients with no complete pathological remission in the surgical specimens after neoadjuvant systemic treatment. To minimize this potential

risk, in the experimental arm of the trial core needle biopsies from the primary tumor region and residual suspect axillary lymph nodes are taken 2 weeks after completion of neoadjuvant systemic treatment before preoperative radiotherapy. Available data indicate that these biopsies will predict non-pCR cases correctly in about 60% of the patients[46]. Hence, maximally 8% of patients who would qualify for neoadjuvant systemic treatment depending on pCR in the experimental arm would not receive the postneoadjuvant treatment. Based on the reported 5-10% improvement in overall survival[47] with postneoadjuvant therapy, a potential survival disadvantage of less than 0.8% cannot be calculated. However, the recently reported long term results [48] from a phase II trial (n=356) indicate that pCR after neoadjuvant chemotherapy and preoperative radiotherapy in breast cancer is highly predictive for long term survival (15 years overall survival: pCR: 74%, non-pCR: 56%, p=0.001) in all biological subgroups. This observation gives indirect evidence that the before mentioned risk is even lower.

Additionally, radiotherapy before surgery is not a common standard in breast surgery, which means that an increase in postoperative complications in particular wound healing disorders cannot be ruled out. However, previously published literature indicates that preoperative radiotherapy is safe[15]. Neoadjuvant radiotherapy is an established standard modality for other entities, such as in oesophageal-, rectal-, and lung cancers. In these entities preoperative radiotherapy leads to a small increase of wound healing complications, which is considered unproblematic in view of the proven benefits of preoperative radiotherapy in these cancers. To minimize the risk in the current trial wound healing complications will be closely monitored in the first 100 randomized patients after breast conserving therapy or autologous flap and implant reconstruction and reviewed by an independent expert panel.

4.7 Pre planned early safety assessment

The first safety analysis concerning wound healing disorders will be after n=100 patients, who received breast conserving surgery or an autologous flap. Patients who received (implant-based reconstruction will undergo the safety analysis after 40 and 100 patients. patients.
All safety parameters will be evaluated in an explorative or descriptive manner, providing proportions, means, medians, ranges, standard deviations and /or confidence intervals, as appropriate. The analysis will focus on the adverse events categorized and graded according to CTCAE v5.0. Adverse events will be summarised by treatment arm, body system and preferred term and intensity with frequencies and percentages reported, and eventually compared using chi test, Fishers' exact test or a trend according to Cochran/Armitage.
The results of the safety analyses will be reviewed by the independent safety monitoring board. The recommendations of the independent safety monitoring board will be taken into account.

4.8 Study oversight for safety evaluation

The study may be stopped if the Study Chairman concludes that patients are placed at undue risk because of clinically significant findings that meet any of the following criteria:

a) individual drop-out:

1) medical conditions of other diseases that jeopardise the patient if study treatment were continued. The follow up of these patients is planned to will continued.

2) new aspects regarding side effects (e.g., unexpectedly high rates of °III acute and/or chronic reactions)

5. PATIENT SELECTION

All patients enrolled must have breast cancer M0 and started/received chemotherapy. Each patient must meet all of the inclusion criteria and none of the exclusion criteria of this study.

5.1 Inclusion Criteria

1) Histologically proven invasive, unilateral breast cancer
2) Indication for neoadjuvant chemotherapy (+/- antibody treatment or other targeted therapies) in accordance with national and international guidelines
3) Indication for radiotherapy
4) Female
5) Informed consent for the trial signed by the patient
6) T2-T4a-d (d: max. 1 cm inflammation)
7) T1 a-c, if G3, triple negative, HER2- positive, or cN+/pN+
8) Hormone receptor and HER2 status: no restrictions
9) All grades G1-G3
10) Age ≥18 years at the time of randomisation
11) status ≤ 2
12) No pre-existing conditions that forbid therapy
13) Signed consent form regarding registration, randomisation, collecting, and saving of personal data.

5.2Exclusion criteria

1) Neoadjuvant treatment solely with endocrine therapy
2) Bilateral breast cancer
3) Pregnancy or lactation
4) Prior radiotherapy of the affected or contralateral breast
5) Connective tissue disease, including rheumatoid arthritis and

thromboangiitis obliterans

6) Pre-existing symptomatic chronic lung disease (fibrosis, pneumoconiosis, adult-onset allergies, such as farmer's lung, severe lung emphysema, COPD ≥°III)

7) Cardiac comorbidities: symptomatic coronary heart disease, prior heart attack, heart failure NYHA ≥II or AHA ≥C, pacemaker, and/or implanted defibrillator

8) Malignoma except basalioma or in-situ-carcinomas in complete response

9) Distant metastasis

10) Plexopathies of the arm of the treated side

11) Stiffness of the shoulder of the arm of the side of the breast cancer of any origin (e.g. following a road accident)

12) Lymph edema ≥°II of the arm at the side of the breast cancer

13) Missing signature on consent form

14) Other medical conditions that prohibit the neoadjuvant radiotherapy (i.e. expected non-compliance, etc.)

15) Male patients

16) Patients who have previously been assessed for chemotherapy response

5.3 Co-morbidities

If not listed under exclusion criteria, all severe co-morbidities must be controlled medicinally.

5.4 Co-medication

Any co-medication is allowed if not listed under exclusion criteria.

6. STUDY PROCEDURES

6.1 Diagnostics

Diagnostic procedures should follow the recommendations of the AGO guidelines. A biopsy of the primary tumor confirming an invasive breast cancer and an ultrasound assessment of the axilla including a core needle biopsy of tumor suspect lymph nodes +/- insertion of marker clips according to the AGO recommendations is required before initiating NACT. Mammography and breast sonography are obligatory for the documentation of tumor size. In addition, MRIs may be required according to the S3- or AGO-guidelines.

In the experimental arm, sonographic re-assessment of axillary lymph nodes is obligatory. A core needle biopsy of tumor suspect lymph nodes approximately 2 weeks after completion of NACT before preoperative radiotherapy is highly recommended. At the same time, a new biopsy of the primary tumor or, in case of complete remission, the region of the primary tumor is highly recommended.

Staging needs to be compliant with the current S3- and AGO-guidelines.

6.2 Surgery

All kinds of breast surgery in accordance with the S3- and AGO-guidelines are allowed, such as breast-conserving surgery, mastectomy, skin-sparing mastectomy, nipple-sparing mastectomy, as well as combined with expander, immediate or delayed reconstruction with implants or autologous flaps. Sufficient safety margins must be set according to the S3- and AGO-guidelines. Lymph node assessment needs to follow a sentinel node concept. Axillary dissection needs to be carried out according to S3-and AGO guidelines in patients treated within the standard arm and according to this protocol for patients within the experimental arm.

Surgery in the experimental arm (preoperative radiotherapy) is not allowed to be performed before radiation-induced acute skin toxicity has vastly disappeared. Surgery is recommended 2.5-4, latest 6 weeks after completion of preoperative radiotherapy. The patient presents 2 weeks after the completion of radiation therapy for the evaluation of acute side effects. The radiation oncologist will authorize the patient for surgery.

6.2.1 Systematic histopathologic analysis

Histopathologic work-up of excised breast tissues and (sentinel-) lymph nodes needs to follow the guidelines for gynaecologic oncology and/or equivalent national pathologic societies' guidelines of the respective participating study site.

6.3 Systemic Treatment

Neoadjuvant chemotherapy (NACT) is a prerequisite for inclusion in the study. The chemotherapy (CT) should be given according to the AGO- or S3-guidelines. There are no restrictions for different chemotherapeutic schedules. Additional systemic therapies like anti-Her2 therapy, immunotherapy should be administered as indicated in the current version of the AGO guideline. Termination of CT or change in substances used must be documented. Termination of CT is not a drop-out criterion. In the experimental arm, preoperative radiotherapy should be given according to the protocol.

Postneoadjuvant systemic therapy should be administered according to the current guidelines.

In the experimental arm, some patients will have a pathological complete remission (pCR) in the surgical specimen after preoperative radiotherapy but had residual invasive cancer after neoadjuvant systemic treatment in the core needle biopsies of the primary tumor region or the regional lymph nodes. If the indication for postneoadjuvant systemic treatment is restricted to non-pCR patients, postneoadjuvant treatment should also be offered to patients with a pCR in the surgical specimen, if residual invasive cancer after

neoadjuvant systemic treatment was detected in the core needle biopsies from the primary tumor region or the regional lymph nodes. The participation of patients from both arms of the NeoRad trial in clinical trials on postneoadjuvant systemic treatment is allowed.

Checkpoint Inhibitors: The co-administration of checkpoint inhibitors with radiotherapy is considered beneficial due to emerging evidence suggesting potential synergistic effects. The combination therapy aims to enhance the antitumor immune response and might potentially improve treatment outcomes. However, the precise mechanisms underlying the interaction between checkpoint inhibitors and radiotherapy require further investigation and has never been proven for breast cancer.

Trastuzumab/Pertuzumab: During the administration of Trastuzumab and/or Pertuzumab, caution is advised regarding the irradiation of unaffected left parasternal lymph nodes. However, if these lymph nodes are affected, targeted radiotherapy should be delivered to the affected lymph node with a safety margin (CTV) of 0.5 cm. In cases where right-sided irradiation of the parasternal lymph nodes is performed, their inclusion within the target volume is feasible. To optimize treatment precision, employing a deep inspiration breath-hold technique is recommended in this situation.

T-DM1: T-DM1 (trastuzumab emtansine) is an antibody-drug conjugate used in the treatment of HER2-positive breast cancer. It consists of trastuzumab, which targets HER2, and a chemotherapy drug (emtansine) that is attached to trastuzumab. T-DM1 administration in the experimental arm is planned after the completion of local radiotherapy. Aligning with the registration trial, the current protocol endorses the administration of T-DM1 after the completion of local therapy. Notably, the AGO guidelines permit concurrent administration of T-DM1 with radiotherapy in the standard arm.

CDK 4/6 inhibitors: CDK 4/6 inhibitors are a class of drugs that inhibit cyclin-dependent kinases 4 and 6, enzymes involved in cell cycle regulation. Due to concerns regarding potential increased lung toxicity, the initiation of CDK4/6 inhibitors is proposed after the completion of local therapy, consistent with the current AGO guidelines for the standard

treatment arm. The exact mechanism and impact of CDK4/6 inhibitors in combination with radiotherapy require further investigation and is not considered to be safe today.

Olaparib: Olaparib is a targeted therapy known as a PARP (poly ADP-ribose polymerase) inhibitor. By inhibiting PARP, olaparib disrupts DNA repair mechanisms in cancer cells with BRCA mutations. Consistent with the AGO guidelines, Olaparib therapy is intended to commence post-completion of local therapy. The specific timing and duration of Olaparib administration will be determined according to the trial protocol. Further research is needed to elucidate the potential interactions and synergistic effects of Olaparib and radiotherapy.

Endocrine therapy with aromatase inhibitors/Tamoxifen: Endocrine therapy is a standard treatment for hormone receptor-positive breast cancer. While concurrent administration of endocrine therapy and radiotherapy is theoretically feasible, it is not typically part of standard practice.

Sacituzumab Govitecan: Sacituzumab Govitecan is currently being investigated in the SASCIA study for HER2-negative patients. Available data suggest that simultaneous administration of Sacituzumab Govitecan with radiotherapy may pose potential safety concerns and, therefore, should be avoided. Further research is warranted to ascertain the optimal sequencing and potential interactions between Sacituzumab Govitecan and radiotherapy.

Capecitabine: Given the heightened risk of skin and mucosal toxicity, capecitabine administration is recommended after the completion of local therapy in the experimental arm. While the AGO guidelines generally permit concurrent administration of capecitabine with adjuvant radiotherapy in the standard arm, concerns regarding tolerability have limited its routine use in Germany. The potential for increased mucosal toxicity in the experimental arm, which could impact operability following neoadjuvant radiation, warrants caution and a sequential approach.

It is important to note that the NeoRad trial is primarily focused on investigating the optimal timing of radiotherapy. The recommendations for systemic agents within the trial are based on limited data, and the potential combined toxicity of radiotherapy and systemic therapy may not be readily predictable. Thus, patients should be thoroughly informed about the potential risks and uncertainties associated with combined treatment modalities. A comprehensive evaluation of current data, in conjunction with individual treatment plans and clinical considerations, is necessary to assess personalized benefits and risks, enabling the provision of tailored recommendations to patients.

Simultaneous Administration of Systemic Therapies with Adjuvant Locoregional Radiotherapy

Drug	**Standard-Arm**	**Experimental Arm**
Checkpoint Inhibitors	**+**	**+**
Trastuzumab/Pertuzumab	**+**	**+**
Endocrine therapy	**+**	**+**
Olaparib	**-**	**-**
CDK 4/6 inhibitors	**-**	**-**
Sacituzumab Govitecan	**-**	**-**
Capecitabine	**+**	**-**
T-DM1	**+**	**-**

“+”: allowed

“-“: prohibited

In case of early termination of NACT due to severe toxicity further treatment should follow the respective treatment arm (preoperative radiotherapy followed by surgery [exp. arm] or surgery followed by radiotherapy [standard arm]. In case of locoregional or distant progression during NACT further treatment is decided by local physicians.

6.4 Radiotherapy

For a comprehensive and step-by-step approach to the implementation of the preoperative radiotherapy procedure, trial participants are referred to the Radiotherapy Quality Assurance (RTQA) Guidelines. These guidelines provide a detailed explanation and practical instructions for each step of the process, ensuring standardized and quality-assured delivery of pre- and postoperative radiotherapy across all trial sites.

Patients in the experimental arm receive preoperative radiotherapy, starting with whole breast radiotherapy (5x 2.7 Gy to 40.5 Gy +/- Boost RT), preferably 2-3 weeks after the last application of neoadjuvant chemotherapy (NACT). Regional lymph node radiotherapy may be indicated depending on initial findings before NACT and targeted therapy (5x 2.7 Gy to 40.5 Gy). Specific conditions such as central or medial tumor location, ER/PR negative tumor, cT3 or cT4 tumor, cN2 status, inflammatory tumors, or enlarged lymph nodes in the internal mammary chain would necessitate internal mammary chain lymph node irradiation. However, this is not indicated for left-sided cancers treated with trastuzumab +/- pertuzumab or in the presence of relevant cardiac comorbidity. The technique for treatment involves using 3D, IMRT, and VMAT-Planning based on individual CT-slices, with a preference for deep inspiration breath-hold techniques in left-sided breast cancer. The dose planning must follow the ICRU 50, 62, and 83 guidelines.In terms of target volumes and safety margins, CTVs need to be adjusted for locally advanced disease (e.g., T4 or N2/3 disease) to ensure all macroscopic tumor tissue is covered with at least a 5mm safety margin. In cases where clinical complete remission is achieved during the initial therapy and no boost is applied, but histological evidence of tumor cells is subsequently detected following complete resection, the administration of boost after surgery becomes uncertain and is generally not recommended. The treatment protocol allows for the possible inclusion of axillary lymph node irradiation, though caution is advised to prevent lymphedema.

For patients with initially negative clinical lymph node (cN0) and neoadjuvant therapy-induced negative pathologic lymph node (ycN0) status on biopsy but found to have histologically confirmed lymph node metastases at surgery, postoperative radiotherapy of the lymph node regions is recommended. Throughout all of this, cumulative toxicities and dose limits of organs

should be considered and adhered to, with efforts to minimize anatomical shifts between the two planning CTs. Patients should be adequately informed about potential for increased cumulative toxicity.

In the experimental arm, the center decides whether to administer a boost in the situation of complete remission in imaging after neoadjuvant chemotherapy (center's decision).

6.4.1 IOERT/IORT as boost irradiation

Intraoperative radiotherapy needs to be given according to the S3 or AGO guidelines.

Electrons with linear accelerator (IOERT 1x 10 Gy with electrons of adequate energy to cover the tumor bed) are for intraoperative Boost.

6.4.2 Whole Breast Radiotherapy (WBRT)

In the experimental arm, WBRT should preferably begin 2-4 weeks after the last application of NACT. In case of persistent toxicity that is regarded critical for radiotherapy, up to 6 weeks are allowed. Surgery should be performed after disappearance of the acute radiation induced erythema, preferably 3-6 weeks after completion of pre-operative radiotherapy. In the standard arm, post-operative WBRT should start 3-6 (up to 8) weeks after surgery.

6.4.3 Indication for breast/chest wall and regional lymph node irradiation:

Experimental arm (preoperative radiotherapy)

Preoperative radiotherapy Arm

- all patients receive whole breast radiotherapy (5x 2.7 Gy to 40.5 Gy +/- Boost RT)
- indication for regional lymph node radiotherapy depends on the initial findings before the start of the NACT +/ targeted therapy (5x 2.7 Gy to 40.5 Gy)

Lymph node region	**indicated, if initially**
Level I*- IV	cN+
Internal mammary chain LN**	**cN+ and >=1 of the following factors**

1) Central or medial tumor location

- 2) ER/PR negative tumor
- 3) cT3 tumor
- 4) cT4 tumor
- 5) cN2
- 6) inflammatory tumors
- 7) enlarged lymph nodes in the internal mammary chain

* Subtotal RT of Level I- II (see CTV definitions)
** No Internal mammary chain radiotherapy for left sided cancers treated with trastuzumab +/- pertuzumab and/or relevant cardiac comorbidity

Note: indications depend on the pretherapeutic findings irrespective of response to neoadjuvant systemic therapy

* Limited radiotherapy of Level I+II (see CTV definition)

** No IMC radiotherapy for left sided cancers treated in case of trastuzumab+/- pertuzumab or relevant cardiac comorbidity

Standard arm (postoperative radiotherapy):

The indication for whole breast / chest wall, for regional lymph nodes and boost radiotherapy should be administered according to the current recommendations of the AGO guideline.

6.4.4 Technical prerequisites

3D, IMRT, and VMAT-Planning have to be performed based on the individual CT-slices. Deep inspiration breath-hold techniques are strongly recommended in left-sided breast cancer. WBRT-treatment is delivered by photons 4-15 MV using linear accelerators. At least weekly verification imaging is required. Multileaf- and micro multi-leaf-collimators are required for proper treatment planning. Portal imaging or

cone beam CT are required for field verification. Photons (4-15 MV) and electrons (4-15 MeV) may be used.

6.4.5 Treatment technique

WBRT is usually performed using tangential wedged fields or IMRT/VMAT techniques with restricted angles to limit low-dose volumes in the lungs. IMRT and VMAT-techniques are preferred in case of regional lymph node irradiation, especially in internal mammary chain lymph node irradiation. In left-sided breast cancer, deep inspiration breath-hold is recommended if available at the study site.
In right-sided breast cancer, deep inspiration breath-hold is recommended in case of internal mammary chain lymph node irradiation.
The dose planning must follow the ICRU 50, 62 und 83.

6.4.6 Target volumes and safety margins (CTV and PTV)

CTV definition in both arms of the trial should follow the ESTRO guidelines for early breast cancer [49]; however, in case of locally advanced disease (e.g. T4 or N2/3 disease), CTVs need to be adjusted to ensure that all macroscopic tumor tissue is encompassed with at least a 5 mm safety margin.

Experimental arm (preoperative radiotherapy)

CTVb_low = total breast (excluding 5 mm below the skin) including the initial tumor volume + 5mm [+ 2cm skin in case of inflammatory cancer]
(Anatomically adjusted)

GTVp = primary tumor at the time of radiotherapy.
For CR = boost or no boost (GTVp) is indicated (as decided by the local institution)

Based on the presently available evidence, the clinical significance of administering a boost in the neoadjuvant radiotherapy setting subsequent to achieving complete remission via neoadjuvant chemotherapy remains uncertain. Consequently, a universal recommendation cannot be made, as it is contingent upon the cumulative experiences and expertise of the treating institution. In the context of this study, the participating study site will establish, at the outset, whether a boost will be implemented in this particular scenario. Following this determination, all patients within the given study site will receive treatment in accordance with the predetermined local decision.

In cases where clinical complete remission is achieved during the initial therapy and no boost is applied but histological evidence of tumor cells is subsequently detected following complete resection, the decision regarding boost administration after surgery becomes uncertain. The value of a boost in this specific situation, along with the radiobiological concerns associated with a prolonged treatment interruption, raises doubts about its role. Therefore, based on the available scientific evidence, it is not recommended to include boost administration in the protocol for these cases.

GTVn = marked + enlarged LK at time of radiotherapy

CTVp_high = GTVp + 0.5cm
(Anatomically adjusted)

CTVn = GTVn + 5mm + Level 1-2 (upper boarder 1 cm below V. axillares) + Level 3-4 + IMC (if indicated according to protocol)

PTVb_low = CTVb_low + 5-8 mm
PTVb_high = CTVp_high + 5-8 mm
PTVn = CTVn + 5-8 mm
No Gaps between **PTVb_low** and **PTVn** allowed

PTV concept in case of axillary lymph node irradiation

In axillary lymph node irradiation, the PTV should be limited below the level of the axillary vein at a distance of 0.5cm to prevent lymphedema, unless positive lymph nodes including a 0.5cm CTV margin, cross this virtual boundary. Positive lymph nodes should be contoured with a margin of 0.5 cm. If a lymph node including a safety margin extends outside the PTV this volume should be added to the CTV.

Patients with initially negative clinical lymph node (cN0) and neoadjuvant therapy-induced negative pathologic lymph node (ycN0) status on biopsy, but subsequently found to have histologically confirmed lymph node metastases at the time of surgery, who did not receive radiation to the axillary lymph node (ALN) region in the experimental arm are recommeded for for postoperative radiotherapy of the lymph node regions with field margin connection. It is important to note that cumulative toxicities should be considered in both treatment plans, and the cumulative dose limits of organs should be adhered to without accounting for potential recoveries (as significant recovery within such a short timeframe is unlikely). Efforts should be made to minimize anatomical shifts between the two planning CTs to minimize additional uncertainties. The patient should be adequately informed about the potential for increased cumulative toxicity. In these cases, it is advisable to involve the study leadership closely in the planning and implementation of the therapy.

Standard Arm (postoperative radiotherapy)

In case of breast conserving surgery:

CTVb_low = total breast (excluding 5 mm below the skin) including the initial tumor volume + 5mm [+ 2cm skin in case of inflammatory cancer]
(Anatomically adjusted)

GTVp = tumor bed of the primary tumor (best marked by clips)

CTVp_high = GTVp + 0.5cm (Indication according to AGO guidelines)
(Anatomically adjusted)

CTVn = Level 3-4 + IMC (Indication according to AGO guidelines). Level 1+2 in case of remaining macroscopic tumor and insufficient axillary surgery (see AGO guidelines)

In case of mastectomy:

CTVlow_chestwall (after mastectomy without reconstruction):
CTV definition regarding chest wall postmastectomy radiotherapy (standard arm only) in case of no reconstruction should follow the RTOG recommendations (https://www.srobf.cz/downloads/cilove-objemy/breastcanceratlas.pdf). However, the inclusion of the rips and the intercostal muscles into the CTV is only recommended in case of tumor infiltration before starting neoadjuvant systemic treatment and should be restricted to the initial area of infiltration +5 mm.

CTVlow_chestwall (after immediate breast reconstruction):

CTV definition regarding chest wall postmastectomy radiotherapy (standard arm only) in case of immediate reconstruction (implant or flab) should follow the ESTRO ACROP consensus guideline (Kaidar-Person et al. 2019, PMID: 31108277):

The implant and the contralateral breast should be delineated using a planning-CT. The transplanted tissues (skin; fat; muscle) and synthetic materials (implant, tissue expander, acellular dermal matrix [ADM]) are not part of the CTV. They should be contoured as organs at risk (OAR), without the aim of compromising the CTVlow_chestwall coverage. Other OARs that should be delineated for treatment planning purposes include heart, lungs, liver, thyroid and, in case of axillary lymph node irradiation with a regional boost, the brachial plexus.

CTVlow_chestwall after immediate breast reconstruction using retro-pectoral implant.

If the dorsal fascia of the breast is not involved by cancer, the CTVlow_chestwall for PMRT does not include the deep lymphatic plexus and therefore only includes the rim of tissue ventral to the major pectoral muscle and the implant, except at the medial, lateral and caudal borders where it may extend to the ventral side of the chest wall where it is not covered by the pre-surgical extension of the major pectoral muscle. Thus, the implant can be largely excluded from the CTVlow_chestwall, whilst the parts of the chest wall surrounding the pectoral muscle around which the lymphatics flow should still be included. As the pectoral muscle overlying the implant is very thin in some women, the muscle would inevitably be included at least partially in the CTV, meaning that the dorsal margin of the CTV would be at the ventral side of the implant.

For patients with adverse factors and/or where the tumor was localised in areas within the breast close to the dorsal fascia (tumor on ink at the dorsal fascia) that was not covered by the major pectoral muscle (mainly caudally located tumors that are often located adjacent to the intercostal muscles and ribs), only separated by the dorsal breast fascia, we recommend to delineate the tissue between the chest wall and the implant caudal from the pre-surgical position of the major pectoral muscle (ideally marked by surgical clips), which can be done as a separate dorsal CTV

CTVlow_chestwall after immediate breast reconstruction with pre-pectoral implant

After IBR-i using a pre-pectoral positioned implant, the CTVlow_chestwall is composed of 2 parts as the pre-pectoral volume is divided into 2 parts by the implant:

1. the ventral part between the skin and the implant, containing the subcutaneous lymphatic plexus and eventual residual glandular tissue
2. the dorsal part between the implant and the pectoral muscle/chest wall, containing eventual residual glandular tissue: only to be included in case of the presence of adverse tumor factors

Indications for including a volume posterior to the implant in the CTVlow_chestwall

Partial inclusion in retro-pectoral implant positioning: in case of the presence of adverse factors and/or if the tumor was localised in areas within the breast close to the dorsal fascia that was not covered by the initial position of the major pectoral muscle: separate volume.

Complete inclusion in pre-pectoral implant positioning: in case of the presence of adverse factors:

- Large primary breast cancer (pT3/pT4, inflammarory cancer)
- Locally advanced breast cancer (LABC) with non-pathological complete response to primary systemic therapy
- Invasion of the major pectoral muscle and/or the chest wall

CTVn (regional lymph nodes)

CTV definition of the regional lymph nodes in case of postmastectomy radiotherapy (with or without immediate reconstruction (standard arm only) should follow the ESTRO guidelines for early breast cancer [49]; however, the CTV for level IV needs to be adjusted to ensure that the region of initially involved lymph in the supraclavicular area is encompassed with at least a 5 mm safety margin. An additional boost radiotherapy after mastectomy is restricted to documented R1 or R2 resections. In the case of R1 resection the CTC_R1/R2 includes the suspect volume + 5 mm. A boost dose of 4x 2.7 Gy in case of R1- and 6x 2.7 Gy in case of R2-resection is recommended.

6.4.7 Radiotherapy Dose Prescription and Specification

The prescribed radiotherapy doses are based on the S3/AGO guidelines for breast cancer. The target volumes will receive following radiotherapy doses:

- PTV (breast): 40,5 Gy in 15 fractions (2,7 Gy daily)
- PTV (RNI): 40.5 Gy in 15 fractions (2.7 Gy daily)
- PTV boost (sequential): 10.5 Gy in 3 fractions (3.5Gy daily).

The radiotherapy dose will be defined ICRU-conform. 3D, IMRT (intensity modulated radiotherapy) and VMAT (volumetric modulated arc therapy) can be used. In left sided breast-cancer respiratory gating (deep inspiration breath hold) is strongly recommended.

Sequential			
Boost			
PTVb+n_low	15	2.7Gy	40.5Gy
PTVp_high	03	3.5Gy	10.5Gy
PTVn_high			
Total	18		51.0Gy
SIB			
PTVb+n_low	15	2.7Gy	40.5Gy
PTVp_high	15	3.2Gy	48Gy
PTVn_high			
IOERT			
IOERT	01	10Gy	10Gy
PTVb+n_low	15	2.7Gy	40.5Gy
PTVn_high	15	3.2Gy	
Total	16		50.5Gy

6.4.8 Documentation Requirements and Portal Films

Portal images of each field or orthogonal images that localise the isocenter placement must be obtained on the first day of therapy. Isodose plans, DVHs of the target volumes and critical normal structures are mandatory for planning. Weekly positioning verifications of the patients are required.

6.4.9 Diagnostics during WBRT

Weekly clinical examination of the breast (see 16.3 and Appendices).

6.4.10 Critical Normal Structures and Adverse Effects of Radiotherapy

Critical normal structures include the skin, lung, heart and brachial plexus. Acute side effects such as skin toxicity and breast oedema are common during treatment. These conditions are usually transient and resolve within a few weeks following the completion of radiotherapy. Pneumonitis requiring treatment as subacute side effect is rare. Heart toxicity and brachial plexus damage is expected to be rare.

6.4.11 Organs at risk

Single reference dose per fraction: 2.7 Gy (ICRU). Total dose is 40.5 Gy.

Dose constraints:

Please try to adhere to the following constraints. In case of conflict with the CTV/PTV dose prescription, priority has to be given to cover the CTV/PTV. The PTV to CTV margin may be compromised in select cases if deemed clinically acceptable. If the dose constrains to the lungs

and the heart are not kept, it is allowed to truncate the internal mammary chain CTV caudally to encompass just the region of the first 3 and not the first 4 intercostal spaces.
Please do not compromise the PTV in order to spare the LAD, caput humeri or thyroid.

Table 2: Recommended dose constraints for organs at risk

Organ at risk	**Accepted dose**	
	Breast/chest wall without lymph node irradiation	**Breast/chest wall with lymph node irradiation including IMC**
Heart	mean < 1 Gy (right side). mean < 3 Gy (left side)	mean <3 Gy (right side). mean <6 Gy (left side)
LAD	mean <1 Gy (right side) mean <8 Gy (left side)	mean < 6 Gy (right side) mean < 10 Gy (left side)
Lung ipsilateral	mean <10 Gy V20 <20 %	mean ≤ 14 Gy V20 ≤ 30%
Lung contralateral	mean <5 Gy V20 <10%	mean <6 Gy V20 <15 Gy
Lung Bilateral	mean < 9 Gy V20 < 10%	mean <10 Gy V20 <17%
Brachial plexus	max. 5 Gy	≤ 41 Gy
Contra-Lateral breast	mean < 2 Gy	mean < 4 Gy
Spinal cord	max. 2 Gy	max. 30 Gy
Esophagus	max. 2 Gy	max. 40.5 Gy mean 9 Gy
Caput humeri ipsilateral	Mean 3 Gy	Mean 10 Gy
Thyroid	Mean <1 Gy	Mean 15 Gy

The following organs at risks have to be delineated:

- ipsilateral lung
- contralateral lung
- heart
- LAD (if visible)
- contralateral breast
- spinal cord
- caput humeri

In case of indication for regional lymph node irradiation, additional delineation of the following structures is necessary:

- esophagus
- plexus brachialis
- thyroid

6.5. Procedures for registration and randomisation

Eligible patients will be informed about the NeoRad trial before or during NACT. If the patient is interested, the patient will sign an informed consent for the trial provided by the radiooncologist (see also chapter 10.3). Study inclusion must be completed until the evaluation of the first response to the neoadjuvant chemotherapy.

Screening failures have to be documented with reasons.

Definitive study entry is possible after the patient has signed written consent. After a patient has completed the necessary screening visit procedures, the corresponding baseline case report forms (CRFs) have to be completed by the site using the EDC system.

Randomisation and information to the study sites will be performed before first evaluation of response.

The patient insurance policy has to be provided by the participating study site.

In case of unavailability, other technical problems, or questions on the randomisation procedure, please contact

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and

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6.6 Procedures for handling patients incorrectly enrolled

Patients who are screened but are not randomized should be excluded from the study directly and documented as “screening failure” including the reason for exclusion from the trial.

Patients, who have been randomized in error, despite not meeting all inclusion/ exclusion criteria should be withdrawn from the trial after contacting the Study Chairperson and documentation of the reason for withdrawal (the inclusion/ exclusion criteria are not fulfilled); they will be still included in the ITT analysis up to the timepoint of withdrawal. Patients that fulfill all criteria, have been randomized and are then withdrawn will not be replaced, but the reason for withdrawal has to be documented.

6.7 Termination and interruption

Criteria for exclusion of subjects

Prior to preoperative radiotherapy (experimental arm) or surgery (standard arm), randomized subjects who experience distant metastasis or who wish to withdraw from the study will be excluded. In the present modified intention to treat analysis, all other patients are included in the analysis. The data of the excluded patients should not be obtained within the study. These patients are treated outside the study according to the currently valid guidelines and therapy recommendations and are not included in the analysis. For these patients, it is possible to enroll additional patients in the study. In all other situations, no patient can subsequently replace a patient. If a patient withdraws from the study during the trial or follow-up, survival

and oncological control data should still be gathered and included in the analysis, whenever possible.

Termination

Any decision to terminate an individual patient from a clinical trial must be made by the patient's healthcare team and with consideration of the patient's best interests. However, any discontinuation or interruption of therapy should be avoided whenever possible. The study center is available to the local study site for consultation. Nevertheless, data collection from these patients should continue (except the case when patient withdraws her consent to the study completely) since it can still provide valuable insights into the safety and efficacy of the treatment being studied. In general, patients who were enrolled in a clinical trial will be considered for analyses even if the study protocol including radiotherapy is terminated before completion. However, subgroup analyses are conceivable. Within the framework of this study, a retrospective quality assurance of all patients will be carried out. From the collected data, compliance with the study protocol can be checked at the end of the study. Regardless of compliance with the protocol, the patients are included in the analysis. Regardless of the quality of treatment, all patients will be included in the analysis. In a further analysis, the value of protocol compliance can be investigated.

6.8 Definition of predefined toxicity from radiotherapy and surgical treatment for safety analysis

Every adverse event (AE) after radiotherapy will be coded, categorized and graded in regards of its severity according to v5.0. If an event cannot be categorized it will be captured in a written form and grade as follows:

Grade 1 - low

Event is noticeable but tolerable

Grade 2 - moderate

Event limits everyday life activities

Grade 3 - severe

Event prohibits everyday life activities completely

Grade 4 – life-threatening

Grade 5 - deadly

Event leads to patient's death

Every adverse event has to be evaluated in terms of causalities:

Every adverse event has to be documented regardless of the examining doctor's opinion whether there is a causality to radiotherapy or not.

Adverse events are first recorded before the start of local therapy (after neoadjuvant chemotherapy), then during local therapy and as part of the follow-up examinations .

The following common toxicities are documented as AE of Special Interest as a Grade 3 toxicity or worse: skin reaction, pain and feeling of pressure. Complaints that appear during local examination are also documented as AE: edema of the breast, inflammation, haematoma, seroma and wound healing difficulties. Documentation includes the type of event: beginning, distinctness/ severity.

Signs of illness, symptoms and changes in laboratory values that are causally connected should be summarised to one single disease.

Documentation should be based on the given examination sheets (CRFs). AEs are identified by the doctor and coded by the GBG.

All adverse events that have a connection to the study therapy need to be observed until they disappear or stabilise.

Additional examinations that are deemed necessary by the examining doctor should be documented and marked as such in the CRFs.

°III-V Adverse events should be documented within 2 weeks after discovery into the database. The head of study in Duesseldorf will review the database periodically (minimum 4-week-interval).

A serious adverse event (SAE) in the context of the NeoRad trial refers to any unexpected or significant medical occurrence or outcome that results in one or more of the following:

1) Death of a participant

2) Life-threatening condition of a participant
3) Hospitalization or prolongation of existing hospitalization of a participant (exception: re-resection due to R1-status)
4) Disability or permanent damage to a participant

SAEs that have occurred from the initiation of radiotherapy and up to 3 months after radiotherapy should be reported to the GBG on the corresponding form. The GBG will inform the study chairmen.At regular intervals, the SAEs that have occurred will be discussed by the Safety Board of the study. In addition, the heads of study will consider preventive or corrective measures if necessary.

A patient that gets pregnant during study treatment will be withdrawn from the study and documented as drop-out. It is necessary to report to the study centre by sending in the case report. Local documents such as but not limited to hospitalization reports, autopsy reports, pathology report and lab sheets shall be provided in pseudonymized format when requested. Furthermore, the patient will be monitored during her pregnancy and after delivery. The constitutions of both mother and child need to be documented even if deemed normal and if no adverse events occurred.

7. QUALITY ASSURANCE

Only study sites with a distinct expertise in multimodality breast cancer therapy will be approved to treat patients within the NeoRad study. The study center will request the dose plans from the first 10 Patients of each study site by means of DICOM/FFP-Server and give feedback to the physicians/physicists retrospectively. To ensure optimal treatment coverage, regular training on treatment planning and typical inhomogeneities will be provided. Following completion of the planning, treatment plans are to be sent to the study chairmen. For research the dose plans from all study sites will be collected.

8. VISITS AND FOLLOW-UP DIAGNOSTICS

8.1 Visits

Study visits after WBRT begin in week 2after completion of WBRT. Additionally, in the standard treatment arm a visit 3 months after surgery is performed and a visit 6 months after WBRT. In the experimental arm a visit 2 weeks after WBRT/110 days prior to surgery is performed followed by a visit 3 months after surgery and 6 months after surgery. Afterwards, the visits will be repeated annually until year 10. For the schedule of study procedures see table 3 and 4.

8.2 Gynaecologic examinations, Mammography/breast sonography

The above should be performed according to German S3 and AGO guidelines.

8.3 Toxicity assessment

Assessment of acute toxicity of WBRT according to CTC toxicity-scoring systems:

- Every week during RT.
- At every visit up to 3 months after surgery in both arms

Assessment of late toxicity according to LENT-SOMA scoring-systems at every further follow-up (i.e. once a year)

8.4 Cosmetic evaluation

Assessment of cosmetic outcome (objective and subjective) will be done according to a 5-point-scoring system (van Limbergen) **before WBRT** and after 1, 3,5,7 and 9 years. Breast retraction assessment (BRA) will be performed before WBRT and after 3,7, and 9 years.

8.5 Study schedule

Overview in Table 3/4

Table 3: Schedule of study procedures in the standard of care arm

	after biopsy or latest before first response evaluation after the 1.cycle of NACT	prior to first response assessment	end of NACT	1-14 days before surgery	surgery	day 21 (+/-5)	1-2 weeks before start of WBRT (WBRT start: 4-8 weeks after surgery)	WBRT week 1, 2, 3	2 weeks after WBRT (+/- 3 days)	3 months after surgery (+/-1 month)	6 months after WBRT	every year (+/-2 months) until 9 years after WBRT or end of study
screening for study	x											
in-/exclusion criteria	x											
written consent	x	x										
registration	x											
randomization		x										
biopsy or surgery of primary breast cancer	histology reports (including FNB in case of susp. LN				x							
sentinel node biopsy					x (or AD according to guidelines)							
breast/LN sonography	x		x	x						x	x	x (according to guidelines)
Staging according to guidelines (CT chest/abdomen, bone scan)	x											
medical history documentation	x											
medication log	x											
response assessment according to guidelines			x									
mammography	x										x	x (according to guidelines)
surgery report including pathology report?					x							
radiotherapy								x				
quality of life questionnaire				x								at year 1, 3,5,7,9
report of (planned) surgery technique	x				x							
clinical assessment	x		x	x	x	x	x	x	x	x	x	x
cosmetic scoring				x								year 1,3,5,7,9
BRA				x								year 3,7,9

Table 4: Schedule of study procedures in the experimental arm

	after biopsy or latest before first response evaluation after the 1.cycle of NACT	orior to first response assessment	1-14 days before WBRT	WBRT wk. 1, 2, 3	2 weeks after WBRT (+/- 3 days)	4-6 weeks after WBRT (+/- 10 days) before surgery	surgery	day 21 after surgery (+/- 5 days))	3 months after surgery (+/-10 days)	6 months after surgery (+/- 1 month)	every year (+/-2 months) until 9 years after surgery or end of study
Screening for study	x										
In-/exclusion criteria	x										
written consent	x	x									
registration	x										
randomization		x									
biopsy or surgery of primary breast cancer	histology reports (including FNB in case of susp. LN		re-biopsy								
sentinel node biopsy			x								
breast/LN sonography	x		x						x	x	x (according to guidelines)
Staging according to guidelines (CT chest/abdomen, bone scan)	x										
medical history documentation	x										
medication log	x										
response assessment according to guidelines			x								
mammography	x									x	x (according to guidelines)
Surgery report including pathology report?							x				
radiotherapy				x							
quality of life questionnaire			x							x	at year 1, 3,5,7,9
report of (planned) surgery technique	x						x				
clinical assessment	x		x	x	x	x	x	x	x	x	x
cosmetic scoring			x								year 1,3,5,7,9
BRA			x								year 3,7,9

9. STATISTICAL METHODS AND SAMPLE SIZE DETERMINATION

NeoRad is a multicenter, open, randomized phase III study aiming to estimate the efficacy of changing the sequence of surgery and radiotherapy in high-risk breast cancer by comparing DFS as the primary endpoint and secondary endpoints between the treatment arms.

9.1 Randomization and stratification

Patients will be randomized to either the experimental arm or the standard of care arm in a 1:1 ratio, stratified by the following parameters:

1) biological subtype: Strata: Her2-type (HER2/neu positive), HR + type (no HER2/neu overexpression), triple negative
2) cN-Status (before start of NACT): Strata: cN+, cN-

- type of planned surgery: Strata: type of planned surgery: Strata: BCS vs Mastectomy (NSM, SSM or radical)

9.2 Description of analysis sets

9.2.1. Efficacy analysis set

The full analysis set or ITT (intention to treat or “treatment policy”) set will be the primary population for efficacy endpoints, notably for the primary endpoint DFS. For the ITT analysis, all randomized patients will be included as randomized, regardless of possible errors after randomisation.

Patients who have received protocol treatment unless they experience unequivocally documented earlier disease progression and have no major protocol deviations thought to impact the efficacy conclusions of the trial will be included in the per protocol set for the sensitivity analysis of non-inferiority; the final list of the major protocol violations leading to

the exclusion from the per protocol set will be defined in the statistical analysis plan (SAP); patients who were enrolled although they unequivocally did not fulfil the selection criteria of the trial a priori ("non-eligible") will be excluded from the per protocol set.

9.2.2 Safety analysis set

All patients who have received breast surgery or at least one fraction of radiotherapy will be included in the safety analysis set. For this analysis, patients will be grouped according to the treatment they actually received, accounting for errors after randomization; patients who only received surgery and no radiotherapy will be included together with the post-surgery radiotherapy.
Toxicity, quality of life endpoints as well as the cosmetic results will be analysed based on the safety set.

9.3 Methods of statistical analysis

9.3.1 Efficacy analysis

The primary endpoint of the trial is DFS. DFS as primary endpoint is defined as time from randomisation to any of the following events: local recurrence, regional recurrence, contralateral breast cancer, distant recurrence, invasive second cancer or death from any cause, whichever occurs first; patients without an event will be censored at the date of the last contact.

The primary hypothesis is that preoperative radiotherapy improves DFS compared to postoperative radiotherapy.

The primary efficacy analysis will follow the ITT ("treatment policy") principle. DFS will be displayed by treatment group as Kaplan-Maier curves with 5 year and 8-year rates with the respective 95% confidence intervals and compared using the 2-sided stratified log-rank-test to the significance level of α=0.05; all stratification factors for randomization will be used in the stratified test. Drop-out will be dealt with as independent right censoring. In addition, the

treatment effect will be estimated as a hazard ratio in a Cox proportional hazard regression model including treatment and stratification characteristics, the Wald p-value from the Cox regression will be the primary analysis to the significance level of α=0.05. The hazard ratio will be reported with 95% confidence interval.

We will perform a hierarchical test, starting with non-inferiority as the first primary analysis (in both ITT and (as a sensitivity analysis) in per protocol sets). If this is significant in ITT set, then superiority as the second component of the main analysis will be tested [50].

The margin for the non-inferiority will be defined as 95% CI for HR <1.15, which corresponds to the absolute difference of 3.6% in 10 years DFS rate (from 70% to 66.4%) or 2.2% absolute difference in 5 years DFS rate. This difference implies that the survival curve for DFS in the experimental arm will not run below that of the standard arm at most parts of the curve. Combined with the relatively narrow confidence limits, we expect that most clinicals would consider this result as clinically acceptable to recommend the experimental treatment, if the cosmetic results would be favourable.

Further explorative multivariate analysis, including other factors (e.g. grading, menopausal status, tumor size; the final list will be defined in the SAP) will be performed if deemed useful.

Regarding the primary endpoint the following predefined subgroups will be analysed in the similar way (stratified by the remaining stratification factors in case of a subgroup defined by a stratification factor): subgroups by biological subtype (HER2+ vs HER2-negative/HR-positive vs TNBC); ME, BET, Implant+/- Mesh. An interaction test will be performed for treatment against biological subtype. No adjustment for multiplicity is planned, the results should be considered as exploratory.

All secondary endpoints are defined in section 3.2.

The following secondary time-to-event endpoints will be analysed in a similar way (except for the non-inferiority): DDFS, OS, DSS.

LR (as a first site of recurrence) and RR (as a first site of recurrence) will be analysed using competing risk models: cumulative incidence function will be plotted and compared between treatment arms using (stratified) Gray's test; 5 year and 8-year cumulative incidence rates will be reported with the respective 95% CI; multivariate Fine-Gray model including treatment and stratification will be used to estimate hazard ratios with 95% CI.

Rates will be reported with 95% CI. Comparisons of the categorical data will be performed using Fisher's exact test (for pCR rates), or a trend test according to Cochran/Armitage (e.g. for cosmetic results), as suitable; further explorative multivariate analyses, including other relevant models (e.g. logistic regression) will be performed if deemed useful. Subgroups analyses in the same predefined subgroups as for the primary analysis will be performed if deemed useful.

If only non-inferiority but not superiority is confirmed, the cosmetic results (dichotomized as excellent/good vs moderate or worse, key secondary endpoint) must be better in the preoperative radiotherapy arm for the study to be able to change clinical practice. With the sample size of the study, the exact test of Fisher will have over 90% power to detect a clinically relevant improvement by 15% irrespective of the rate of excellent/good cosmetic results in the control arm.

9.3.2 Safety analysis

All safety parameters will be evaluated in an explorative or descriptive manner, providing proportions as applicable. The analyses will focus on the adverse events categorized and graded according to CTCAE v5.0. Adverse events will be summarised by treatment arm, body system and preferred term, intensity, and causal relationship to radiotherapy (in the experimental arm). Frequencies and percentages of any grade AE and grade 3-4 AE will be reported and eventually compared using Fishers' exact test.

Quality of life data will be analysed according to the corresponding scoring manuals; the details will be defined in the SAP.

The first safety analysis concerning wound healing disorders will be performed after n=100 patients, who received breast conserving surgery or an autologeous flap (n=100 both together), as well as in patients, who received implant-based reconstruction after n=40 and n=100 patients. The Independent Safety Monitoring Board will perform a review and give recommendations for the study accordingly.

9.4 Determination of sample size

The primary endpoint of the NeoRad trial is DFS. To determine the sample size, we assumed that DFS is an exponential parameter and amounts to a 5-year rate of approximately 80% for high-risk breast cancer. This value matches the risk detected in the Gepar trials. NeoRad will also include patients with a slightly lower risk (nodal-negative luminal B tumors and triple negative, Her2 positive cases receiving new postneoadjuvant therapy). Therefore, we expect less events and calculate a higher sample size. We further expect to include less high-risk patients because of competing trials that include only high-risk breast cancer patients. That is why we calculate a marginally increased number to treat.

Therefore, we hypothesise that the 10-year DFS rate will show an improvement from 70% in the control arm to 76.5% in the experimental arm (HR=0.75), which would be considered clinically relevant. In order to detect a difference of this magnitude with a power of 80%, 379 events and a sample size of 1826 patients, 913 in each arm using a 1:1 randomisation, are required to reject the null hypothesis of no improvement on a two-sided type I error level of 0.05. A cumulative drop-out rate of 10% in 10 years is included in these calculations. This calculation is based on an assumed exponential shape of the survival curves and the drop-out process, 4 years of recruitment as well as a minimum follow-up period of six years for all patients and was performed with nQuery Advisor 7.0.

Test of exponential survival (n large) and exponential dropout (*statistics by German breast Group*):

Test significance level,	0.050
1 or 2 sided test?	2
Length of accrual period	4.00
Maximum length of followup	10.00
Common exponential dropout rate, d	0.0105

Group 1 exponential parameter, λ_1	0.0268
Group 2 exponential parameter, λ_2	0.0357
Hazard ratio, h=λ_1 / λ_2	0.750
Power (%)	80
n per group	913
Total number of events required, E	379

Conversion to alternate rates for exponential survival curves

	DFS rates	D/o rate
Time t	10.0	10.0
Group 1 proportion π_1 at time t	0.765	0.900
median survival	25.911	65.788
exponential parameter, λ_1	0.0268	0.0105
Group 2 proportion π_2 at time t	0.700	
median survival	19.434	
exponential parameter, λ_2	0.0357	

9.5 Interim analysis

The pre-planned early safety assessment after n=100 patients is described in detail in section 4.6. No interim analyses of efficacy with early stopping option are planned due to the fact that statistically significant differences in DFS and OS will first be measurable at a minimum of 5 years follow-up when the recruitment is completed and an interim analysis would not allow for a reduction of patient numbers to be randomized.

9.6 Additional procedures

Further details of the statistical analysis will be outlined in a Statistical Analysis Plan (SAP), which will be finalised prior to performing any efficacy analyses within the framework of the study. Questionable cases, notably with regard to allocation to the analysis sets, as well as severe protocol violations and event categories, will likewise be decided in a blinded way at the pre-analysis meeting.

10. ETHICAL AND REGULATORY REQUIREMENTS

10.1 Ethical conduct of the study

The study will be performed in accordance with (the) ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH/Good Clinical Practice/applicable regulatory requirements for patient data protection.

10.2 Ethics and regulatory review

The study will be performed according to current legal standards. The ICH E6 harmonised Tripartite Guideline for Good Clinical Practise, dating to 1997 and including Revision 2 from June 2017, will be taken into account. In Germany, the requirements according to the following documents will be fulfilled: Good clinical practice (GCP), all in their current versions. The coordinating investigator has at least fifteen years of experience in clinical trials for medical products.

As the radiation therapy is performed according to current established standards (approved by the DEGRO-Expertengremium, 20/11/2019), involvement of theBundesamt für Strahlenschutz‘ (BfS) or reference to the ‘Atomgesetz’ are not required.

10.3. Informed consent

Each patient will be informed that participation in the study is completely voluntary, and that they may withdraw their participation in the trial at any time without having to declare any reasons. This will not lead to any disadvantage for the respective patient. If during the study procedure an adverse side effect occurs, the patient must inform the treating physician about this. The treating physician will inform the patient about the combined modality treatment used and its possible adverse events. At the same time, they will be informed about the nature and objectives of the study, expected advantages of the participation, possible risks of the study, and alternatives to the treatment.

The patient shall also receive the necessary information on the trial-specific insurance and their obligations with this respect. The patient will have sufficient time to decide and will be provided an opportunity to ask additional questions. Moreover, the patient will receive a written "patient information" *(*see Appendix *2)* containing all relevant information for the patient's decision and the course of the study. The consent of the patient to participate must be obtained in writing before recruitment to the study. The informed consent form must be dated and signed by the patient.

Thereby, they declare their voluntary consent to participate in the study and the willingness to comply with the requirements of the trial and the instructions of the treating investigator (medical doctor) for the duration of the study. The investigator has to sign the informed consent form after the patient. There are two copies of the informed consent form: one for the patient and one to be kept by the investigator in his study documents. The informed consent is only valid after receiving the patient's and the investigator's signature. Thereafter, the patients can be entered into the study if they fulfil the selection criteria. With the declaration of consent, the patient agrees that the data on his disease are recorded within the framework of the clinical trial, and that they are transferred to the coordinating center in a pseudonymized way. Furthermore, the patient agrees that delegates from the responsible authorities or the coordinating center may have direct access to their original medical records for trial-related monitoring, audit, review, and regulatory inspection.

Data protection

Each patient is assigned a number code by the central data collection point (GBG). There is no personal data collected allowing conclusions to be drawn about a person. The confidentiality obligation applies to the practitioners and the central data collection organisation. Patient data are collected at the treating centres and passed on to the central data collection group (GBG). Here, the names of the patients are pseudonymized. The study centre has pseudonymized data at the time of the analysis. The randomisation table is held by the GBG.

10.4 Changes to the protocol and informed consent form

Any modifications of the protocol, which may impact the conduct or potential benefits of the study, including changes of study objectives, procedures, or its design, as well as patient population, sample sizes, or significant administrative aspects (cf. § 10, Abs. 1 GCP-V for the decision criteria) will require a formal amendment to the protocol. Such amendment needs to be agreed upon by the coordinating center and the study chairmen. It requires a new application to the responsible ethics committee prior to implementation, according to § 10, Abs. 2 to 4 GCP-V. Administrative or technical changes to the protocol, such as minor corrections and/or clarifications that have no effect on conduction of the study nor the risk-benefit-ratio, will be agreed upon by the coordinating center and the study chairmen, and will be documented in a memorandum to the protocol. The competent ethics committee may be notified of such changes at the discretion of the coordinating investigator. The coordinating investigator need to assure that all amendments have been added to the study documents at any site involved in the trial.

10.5 Audits

In case of an audit by the coordinating center or an appropriate authority, the investigator will make all relevant documents available. If an audit visit by a regional authority is announced, the respective study site should inform the coordinating center and the study chairmen as well as the monitoring center (GBG Forschungs GmbH) as early as possible in order to allow for an appropriate preparation and support. The sponsor and the coordinating inspected

investigator or organisational institution of the study shall be informed about the result of the audit.

Internal quality reviews will take place at the meetings of the study participants. Therefore, the coordinating investigator reference board will instruct the participating study sites to present their primary documentations of the study procedures. The results will be discussed at the meetings to improve the quality of the procedures and documentation.

11. STUDY MANAGEMENT

11.1 Training of study site personnel or per online meeting

Study personnel will be informed about the trial and the conduction of the study by in-house training by the investigator. The study protocol and other information regarding the IP and the study itself will be provided. Forms for collecting source data will be provided during the patients' visits. Standard Operating Procedures will be established and made available to all study personnel.

11.2 Monitoring of the study

Source data

The study will be monitored externally by site visits, written queries, and telephone calls to the investigator by personnel that is authorized by the coordinating center and the study chairmen. Queries or monitoring visits may take place before, during and after recruitment of patients into the study. The number of contacts will depend on the characteristics of the respective study site, e.g. the number of recruited patients. According to the investigator's agreement and the patients' informed consent, the monitor is allowed to access the trial documentation and the patients' personal medical records in the participating study site.
In order to assure the quality of the data, all entries into the CRFs are formally inspected for completeness and plausibility. During site visits, an additional control with respect to identity of the data recorded in the personal patient records and in the CRF (Source Data Verification) may be performed. The monitor should observe study procedure and will discuss any problems with the investigator.

12. DATA MANAGEMENT

All patient-related data is recorded in a pseudonymized way. Each patient is uniquely identified by a trial subject number that is assigned prior to randomisation into the study. The investigator must keep a patient identification log, including the full name and address of the subject and, eventually, additional relevant personal data, such as the hospital record number, home physician, etc. All patients, including those who were screened but not be recruited for whatever reason, e.g. inclusion criteria not fulfilled, etc.), are recorded in the patient screening log.

Data management will be performed by GBG for the GBG sites. GBG will provide the investigator site with a web base electronic data capture (EDC) system that is fully validated and conforms to 21 CFR Part 11 requirements. Investigator site staff will not be given access to EDC system until they have been trained on the EDC system.

Adverse events and medical history will be classified according to the terminology of CTCAE v5.0.

Data Entry and Queries:

All CRF data will be entered into the trial database using the MedCODES® application, which will perform automated plausibility and value range checks before accepting the data into the database. All CRF data will be reviewed by a data entry clerk, who will create queries for data fields that do not match the trial guidelines. These queries are stored and forwarded (within MedCODES®) to the study site for resolution. The resolved queries will be checked again by a data entry clerk and either closed or re-queried.

Data Validation GBG Sites

Visual and computerized methods of data validation are applied in order to ensure accurate, consistent and reliable data.

Database Close and Lock

At the end of recruitment, new patient randomisation or registration is stopped. As soon as all data is entered in the trial database and all queries are closed, new data entry or change of existing data in MedCODES® is stopped; all patients (CRF) are set to “Final Status”.

Privacy Protection and Data Safety GBG Sites

Data Transfer and Network Access: All Communication between the MedCODES® server and the client computers is conducted via 256 Bit encrypted HTTPS (Secure HTTP) connections.

Pseudonymisation: In order to protect patient data confidentiality and for safeguarding the privileged doctor patient relationship, each participating patient is assigned a unique GBG reference number. This reference number consists of a trial specific prefix and a unique randomization number from a prepared block of numbers. Instead of the true patient identity the pseudonym is used in all communication between the trial site and the GBG Forschungs GmbH.

User Access Control: Every user is provided with a personal username and password. Every user is assigned to a user group, which represents their role in the CRF workflow. Access control is based on username, group and place of work (e.g. study site or the GBG Headquarters). Therefore, users can only access those datasets necessary for them to fulfill their role in the CRF workflow ("need to know basis").

Monitoring and Source Data Verification GBG Sites

All source data verification (SDV) is conducted according to GBG Trial Monitoring plan (TMP).
The investigator must permit the monitor, the sponsor's internal auditors and representatives from the regulatory authorities to inspect all study-related documents and pertinent hospital or medical records for confirmation of data contained within the CRFs.
After logging in to the MedCODES® application, the monitor chooses a trial site (their current location) and a trial. Source data verification is then performed by consulting the patient file. In case of discrepancies the monitor creates queries, which must be solved by the study site.

Computer Systems GBG Sites

All data are collected and stored using the MedCODES® application. Due to the nature of the MedCODES® application, the trial sites must be equipped with computer terminals with online access and current versions of Microsoft Internet Explorer or Mozilla Firefox. JavaScript execution must be enabled within the web browser.

Data archiving

All relevant study documents, including the eCRFs, are stored at the office of the coordinating center and the coordinating investigator for at least 15 years after the completion of the final study report. The investigators have to archive major administrative documents, such *as* the correspondence with the authorities, the

coordinating center, or the ethics committee. The same applies to the patient identification log, signed informed consent forms, main study documents such *as* the protocol and the amendments, which should be kept for the same period of time. The original patient records must be archived in accordance with standard procedure as per standard procedure of the respective institution but kept for a minimum of 15 years.

13. REPORTING GUIDELINES

The trial will be reported according to CONSORT criteria.

Publication Policy

The results of this trial will be submitted for publication in a peer-reviewed, international English-language journal of appropriate aim and scope. Accordingly, the clinical trial will be registered at clinicaltrials.gov and in the ISRCTN register before recruitment starts. According to the results of main and concomitant scientific projects, the results will be submitted in separate or combined manuscripts; decisions about the form and scope of individual manuscripts will be discussed among all persons participating in the design, conduct and analysis of the study who qualify for authorship. The coordinating investigator together with the biometrician(s) is responsible for drafting and circulating manuscripts and for discussing and handling requests by co-authors or/and coordinating center to edit the text.

The authorship will follow the criteria for authorship developed by the International Committee of Medical Journal Editors (ICMJE), including those that distinguish authors from other contributors.

The ICMJE recommends that authorship be based on the following 4 criteria:

- Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND
- Drafting the work or revising it critically for important intellectual content; AND
- Final approval of the version to be published; AND
- Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

All those designated as authors should meet all four criteria for authorship, and all who meet the four criteria should be identified as authors. Those who do not meet all four criteria will be acknowledged in the manuscript.

The scientific use of data resulting from this trial bay local trial sites is ruled by the site contracts between the coordinating center and the local trial sites. Generally, sites might use

data for own scientific questions (independent from the questions discussed in this trial protocol) and publication after consultation with the coordinating center.

14. PRT IN BREAST CANCER

Table 5: Overview of all peer-reviewed published studies dealing with PRT in breast cancer. We searched these studies for side effects, in particular, wound healing disorders

Author, Year of publication, Journal	Number of patients	Inclusion criteria	RT Technique/ dose/ fractions	Surgical procedure	Chemotherapy	Time interval between end of neoadjuvant therapy and surgery	Acute toxicity (up to three months after surgery) + Subacute toxicity (three months until one year after surgery)	Late toxicity (from one year after surgery)
Reish et al. [21], 2015, Plastic and Reconstructive Surgery	n=605: immediate breast reconstructions, n=517 no RT, n=88 treated with RT: n=43 PRT, n= 45 adjuvant RT	NR	irradiation of tissue expander (n = 10) or final silicone implant (n = 35)	nipple-sparing mastectomy and immediate reconstruction	adjuvant RT: neoadjuvant CT n= 10 adjuvant CT: n=35 PRT: NR	NR	Breast Reconstructions with PRT vs. no Radiation Therapy: Infection: n=3 (7.0%) vs. n=15 (2.9%) p=0,153 Hematoma: n=1 (2.3%) vs. n= 9 (1.7%), p=0,533 Seroma: n=0 (0.0%) vs. n=9 (1.7%), p=1 PRT or adjuvant RT vs. no RT Infection : n=6 (6,8%) vs. n=15 (2,0%), p=0,064 Hematoma: n=1 (1,1%) vs. n=9 (1,7%), p=1 Seroma: n=1 (1,1%) vs. n=9 (1,7%), p=1	Breast Reconstructions with PRT vs.no Radiation Therapy: Nipple-areola complex necrosis: n=3 (7.0%) vs.n= 20 (3.9%), p=0,409 Mastectomy skin flap necrosis: n=4 (9.3%) vs. n=28 (5.4%), p=0,296 Explant secondary to complications: n=2 (4.7%) vs. n=5 (1.0%), p=0,095 Malposition : n=1 (2.3%) vs. n=7 (1.4%), p=0,475 Oncologic margins: n=1 (2.3%) vs. n=15 (2.9%), P=1 Capsular contracture: n=4 (9.3%) vs. n=12 (2.3%), p=0,028 Fat grafting n=11 (25.6%) vs. n=20 (3.9%), p<0,001 PRT or adjuvant RT vs. no RT Nipple-areola complex necrosis: n=4 (4.6%) vs. n= 20 (3.9%), p=0,767 Mastectomy skin flap necrosis: n=7 (8%) vs. n=28 (5.4%), p=0,346 Explant secondary to complications: n=6 (6,8%) vs. n=5 (1.0%), p=0,001 Nipple removal/Malposition : n=1 (1,1,%) vs. n=7 (1.4%), p=1 Oncologic margins: n=4 (4,6%) vs. n=15 (2.9%), P=0,503 Capsular contracture: n=11 (12,5%) vs. n=12 (2.3%), p<0,001 Fat grafting n=12 (13.6%) vs. n=20 (3.9%), p<0,001
Gerlach et al. [14], 2003, Strahlentherapie und Onkologie	CT (chemotherapy)-PRT (preoperative radiotherapy) n=134: n=194 with 198 biopsy-proven invasive breast tumors, n=64 (CT)-	nonmetastatic tumors (except postsurgically defined supraclavicular or subscapular lymph node metastasis), <77 years of age,	PRT: 50 Gy/ Gy SD whole breast external irradiation, boost of 6-11 Gy, all but n=5 electron boost, ipsilateral internal mammary lymph nodes	toumorectomy, toumorectomy+LAT flap, MRM, MRM+TRAM flap LAT=latissimus dorsi myocutaneous flap TRAM=trans-rectus abdominis	Simultaneous preoperative chemo-and radiotherapy n=2	PRT group: 3 to 38 weeks (median 16 weeks) CT and adjuvant radiotherapy group: 4 to 24	n=1 necrosis of a myocutaneous flap after preoperative chemo-and radiotherapy	NR

Author, Year of publication, Journal	Number of patients	Inclusion criteria	RT Technique/ dose/ fractions	Surgical procedure	Chemotherapy	Time interval between end of neoadjuvant therapy and surgery	Acute toxicity (up to three months after surgery) + Subacute toxicity (three months until one year after surgery)	Late toxicity (from one year after surgery)
	group and adjuvant radiotherapy	tumor diameter >3 cm, <3 cm if unfavorable ratio of tumor/breast volume or anatomic difficulties that prohibit initial breast - preserving approach, ECOG performance status 0-1, white blood cell count > 4,000/µl, platelet count >100,000/µl	irradiated in n = 9, supraclavicular fossa irradiated: 50 Gy in n=137	myocutaneous flap MRM=modified radical mastectomy		weeks (median 8 weeks)		
Chang et al. [71], 2007, Ann Plast Surg	N = 41 patients, follow-up of 8-year period, primary autologenous breast reconstruction (both immediate and delayed), n= 37 breast reconstructions in 34 patients	patients with failed reconstruction attempts (n=2), exposed to postoperative radiation therapy (n=5) or with radiation damage to skin (n=0) excluded from study population; nonsmokers, otherwise healthy, without any confounding comorbidities (e.g. diabetes mellitus)	4500-5000 cGy to primary intact breast, additional boost to tumor bed, bringing total to 6000 cGy over course of 6 weeks	Skin-sparing mastectomy (SSM) or conventional mastectomy (CM) and reconstructed with either TRAM flap or latissimus dorsi flap with supplemental implant preoperative radiotherapy prior to SSM (n=8), CM after preoperative radiation therapy (n=9) no chest wall irradiation prior to SSM (n=20)	NR	Breast reconstruction performed 3-6 months after conclusion of radiation treatment	Native skin flap complications (necrosis, dehiscence, delayed wound healing): Preop Radiation SSM (n=8, 75%), Preop Radiation CM (n=9, 0%), No Radiation SSM (n=20, 20%) Flap viability all groups (100%) Donor-site complications (seroma, laxity, delayed wound healing) Preop Radiation SSM 0%, Preop Radiation CM 11%, No Radiation SSM 0% Delay in chemotherapy in all groups 0% Complications requiring surgery Preop Radiation SSM 13%, Preop Radiation CM 0%, No Radiation SSM 0% Asymmetry requiring surgery Preop Radiation SSM 38%, Preop Radiation CM 22%, No Radiation SSM 0%	Capsular contracture Preop Radiation SSM 63% Preop Radiation CM 11%, No Radiation SSM 0% Capsular Contracture Formation in Latissimus Flap With Implant Reconstruction: Preop Radiation SSM 100% Preop Radiation CM 20% No Radiation SSM 0%
Grinsell et al. [72], 2018, ANZ J Surg	N = 29 patients, n = 30 breast tumors, n = 8 inflammatory cancer, n = 1 bone metastasis	core biopsy-proven invasive disease, radiological tumor size >4cm or tumor size >3 cm if more than one-third of breast and positive axillary lymph nodes, patients	NR	autologous reconstruction where appropriate, latissimus dorsi and tissue expander if autologous tissue not available, skin sparing or partial skin-sparing mastectomy, deep inferior epigastric perforator (DIEP) or	N = 29 chemotherapy regime of approximately 3-6 months with reference to biological and hormonal status of each tumor, patients with >25% reduction in tumor size neoadjuvant radiotherapy followed by mastectomy and immediate reconstruction with a DIEP flap 6 weeks after final radiotherapy,	mastectomy and immediate reconstruction 6 weeks after end of radiotherapy	N = 1 moderate mastectomy flap necrosis, n = 15 delayed inset of skin, n = 7 conservative debridement of skin edges only, no major mastectomy skin flap complications, n = 1 reoperation on first post-operative day due to haematoma superficial to flap Total flap loss: n = 0 (0%) Partial flap loss: n = 0 (0%) Breast skin necrosis: n = 1 (3%) first case, Unplanned take-backs: n = 1 (3%) diffuse flap haematomaUnplanned anastomosis take-backs:	NR

Author, Year of publication, Journal	Number of patients	Inclusion criteria	RT Technique/ dose/ fractions	Surgical procedure	Chemotherapy	Time interval between end of neoadjuvant therapy and surgery	Acute toxicity (up to three months after surgery) + Subacute toxicity (three months until one year after surgery)	Late toxicity (from one year after surgery)
		with bilateral disease, inflammatory cancer, skin involvement or bony metastases included		transverse rectus abdominus myocutaneous flaps; no nipple sparing mastectomies, n = 27 free abdominal tissue transfer, n= 30 flaps (n = 4 bilateral), n = 1 pedicled latissimus dorsi flap for chest wall, n = 1 bilateral breast cancer reconstructed with bilateral latissimus dorsi flaps and implants, n = 2 excluded from flap analysis	chemotherapeutic non-responders: mastectomy with axillary clearance and insertion of tissue expander, followed by post-operative adjuvant radiotherapy and delayed reconstruction with DIEP flap		n = 0 Donor site morbidity : n = 0 Delayed skin inset: n = 15 Planned operation	
Hartmann et al. [73], 1997, Strahlentherapie und Onkologie	n = 158	IIA-IV breast cancers	interstitial boost of 10 Gy and course of external beam radiotherapy of 50 Gy, using 5 x 2 Gy/week, local hyperthermia with 43.5-44.5 °C for 60 minutes immediately before interstitial radiotherapy, median time of radiotherapy treatment: 44 days (37-63 days)	n =142 patients salvage surgery, n = 74 (52%) breast-conserving approach, n = 53 (37%) flap-supported surgery Operations: Breast conserving surgery, Breast conserving surgery with Latissimus dorsi myocutaneous flap, Mastectomy, mastectomy with latissimus dorsi myocutaneous flap, mastectomy with rectus abdominis myocutaneous flap, mastectomy with thoracoepigastric myocutaneous flap	n = 154 chemotherapy	NR	No loss of a myocutaneous flap was reported	NR
Hultman et al. [74], 2003, Ann Plast Surg	N=37 SSM and immediate breast reconstruction	clinical stage: benign disease, n=3 (8.1%), stage 0, n=11 (29.7%), stage 1, n=6 (16.2%), stage 2 a, n=11 (29.7%),	NR	SSM and immediate breast reconstruction, n = 20 unilateral reconstruction, n = 17 bilateral reconstruction: TRAM flap n=18 (48.6%); extended	NR	NR	loss of SSM flaps (9/37 patients - 24,3% or 9/53 performed SSM - 17%), dehiscence, infection, haematoma, need for reoperation, failure of breast reconstruction, and delay in initiation of adjuvant therapies General Postoperative Complications: n = 4 (10,8%) n = 1 hospital-acquired pneumonia n = 2 uncomplicated urinary tract infections	NR

Author, Year of publication, Journal	Number of patients	Inclusion criteria	RT Technique/ dose/ fractions	Surgical procedure	Chemotherapy	Time interval between end of neoadjuvant therapy and surgery	Acute toxicity (up to three months after surgery) + Subacute toxicity (three months until one year after surgery)	Late toxicity (from one year after surgery)
		stage 2 b, n=6 (16.2%) stage 0 disease had ductal carcinoma in situ (DCIS) or lobular carcinoma in situ (LCIS) no patient with stage 3 or stage 4 breast cancer underwent SSM or immediate reconstruction		latissimus flap without implant n=3 (8.1%); latissimus flap with implant n=9 (24.3%); latissimus flap and expander n=1 (2.7%); expander/implant n=5 (13.5%); implant alone n=1 (2.7%)			n = 1 deep venous thrombosis (2 weeks postoperatively) Wound Complications: n = 9 SSM flap loss Other infrequent wound complications: n = 4 dehiscence (10.8%) n = 3 infection (8.1%) n = 2 hematoma (5.4%) Donor site morbidity: 30% seroma after latissimus reconstructions n = 2 abdominal wall laxity/bulge after TRAM flap reconstruction n = 7 (18.9%) reoperations	
Krueger et al.[75] , 2001, Int. J. Radiation Oncology Biol. Phys.	N = 81 included n = 66 completed satisfaction survey	candidates for either autologous tissue or implant reconstruction	N =19 RT, n =62 without RT, either before or after reconstruction, treatment portal included chest wall, breast or reconstructed breast in all patients, either expander or permanent prosthesis was irradiated, tangent treatment alone n = 8 (42%), tangents and supraclavicular field n = 8 (42%), tangents, supraclavicular, posterior axillary boost n = 3 (16%), n = 14 boost dose of 12.25 Gy (range, 9.7-16.2 Gy), n = 17 (90%) four - or 6-MV n = 1 (5%) cobalt electrons (8MeV), n = 8 tissue equivalent bolus, 3/5 delayed reconstructions had radiation before E/I reconstruction for high-risk disease (Stage III and node-	mastectomy and tissue expander/implant (E/I) reconstruction, n = 24 (30%) bilateral reconstruction, n = 57 (70%) unilateral reconstructions no RT group: n = 19 (31%) bilateral and n = 43 (69%) unilateral reconstructions, RT group: n = 5 (26%) bilateral, n = 14 (74%) unilateral reconstruction, n = 14 immediate reconstruction, n = 5 delayed reconstruction	more patients in the RT group had chemotherapy; 74% of the RT patients and 42 % of no RT patients received chemotherapy	NR	NR	median follow-up was 31 months from date of surgery, complications in 68% (13/19) with RTvs. 31% (19/62) without RT, 12/ 81 (15%) breast reconstruction failure (2 months - 11 years after reconstruction), associated with use of radiotherapy, observed reconstruction failure rates were 37% (7/19) and 8% (5/62) for patients treated with and without radiotherapy; Complications: infection, contracture, wound dehiscence, deflation, rupture, haematoma, seroma, lymphoedema and back pain: 68% (13/19) of RT patients vs. 31% (19/62) without RT, most common complications: infections in 37% (7/19) with RT vs. 19% (12/62) without RT (<1 month - 13 months after surgery) Capsular contracture in 26% (5/19) and 10% (6/62), with and without RT (4 months - 11 years after surgery)

Author, Year of publication, Journal	Number of patients	Inclusion criteria	RT Technique/ dose/ fractions	Surgical procedure	Chemotherapy	Time interval between end of neoadjuvant therapy and surgery	Acute toxicity (up to three months after surgery) + Subacute toxicity (three months until one year after surgery)	Late toxicity (from one year after surgery)
			positive disease) and 2/5 after reconstruction for local recurrence, median dose breast/chest wall, including boost 60.4 Gy (range, 50.0-66.0 Gy) in 1.8- to 2.0-Gy fractions n = 7: Mastectomy + Immediate Recon + XRT n = 7: Lumpectomy + XRT + Mast for recurrence + Immediate Recon n = 3: Mastecomy + XRT + Delayed Recon n = 2: Mastectomy + Delayed Recon + XRT					
Lerouge et al. [76], 2004, Int. J. Radiation Oncology Biol. Phys.	n = 120	n = 75 Stage IIIA, n = 41 Stage IIIB, n = 4 Stage IIIC, Locally advanced breast cancer (LABC) without metastases , Karnofsky performance status ≥90, no history of prior malignant tumor, adequate hematologic, renal, hepatic functions (white blood cell count ≥ 3000/μL and platelet count ≥ 100,000/μL, serum creatinine <1.5mg/dL, serum bilirubin <1.5 mg/dL), less than 75 years, no history of myocardial infarction, congestive cardiac failure, or	preoperative radiotherapy: external RT using Cobalt 60, irradiation of whole breast, chest wall, ipsilateral regional lymph nodes (supraclavicular, axillary, and internal mammary nodes) irradiated with total dose of 45 Gy in 23 fractions over 31 days, breast and thoracic wall medial and lateral tangential fields	n = 49 mastectomy and axillary dissection, n = 71 conservative treatment surgical excision and axillary dissection and radiation therapy, brachytherapy	4 cycles of induction CT, n = 94 doxorubicin, vincristine, 5-fluorouracil, cyclophosphamide, n = 16 theprubicin, vindestine, 5-fluorouracil, cyclosphosphamide, n = 10: epirubicin, 5-fluorouracil, cyclophosphamide	decisions about local therapy were made 8 weeks after irradiation	Arm lymphedema in 17% (14/ 81) after axillary dissection and in 2.5 % (1/ 39) without axillary dissection, painful limitations of shoulder movements in 28.5% (14/ 49) with mastectomy and axillary dissection, 6% (2/ 32) and 2.5% (1/ 39) after tumorectomy and axillary dissection, or RT without surgery, no patient had congestive heart failure, extended pulmonary fibrosis, brachial plexopathy or rib fracture	NR

Author, Year of publication, Journal	Number of patients	Inclusion criteria	RT Technique/ dose/ fractions	Surgical procedure	Chemotherapy	Time interval between end of neoadjuvant therapy and surgery	Acute toxicity (up to three months after surgery) + Subacute toxicity (three months until one year after surgery)	Late toxicity (from one year after surgery)
		cardiac arrhythmia and no uncontrolled hypertension or uncontrolled infectious disease n = 98 infiltrating ductal carcinomas, n = 14 lobular carcinomas, n = 2 medullary carcinomas, n = 5 mucosecreting carcinomas, n = 1 nonclassified adenocarcinoma						
Mukai et al. [77], 2013, Oncology	n=108	n=104 T2 tumors (96%), n= 3 T3 tumors, n=1 T1 tumor; core needle biopsy-proven invasive breast cancer (female only), clinical stage I-IIIA (UICC/TNM system 1997), tumor diameter 2-5 cm confirmed by breast ultrasound sonography. existence of all tumors within planning target volume of the boost radiation, if multifocal lesions exist in same breast, no bilateral breast cancer (metachronous contralateral breast cancer allowed), aged between 20 and 70, ECOG	preoperative radiotherapy: after completion of chemotherapy: radiation therapy with dose of 45 Gy in 25 fractions over 5 weeks, tangential fields to whole breast followed by 10-Gy boost with 5 fractions over 1 week to the original tumor region,n= 89 radiation therapy as the protocol treatment evaluated	n =106 surgery, mastectomy or lumpectomy, breast conservation rate 88.9%	four courses of doxorubicin, cyclophosphamide followed by paclitaxel prior to radiation therapy and surgery	mastectomy or lumpectomy 12 to16 weeks after completion of radiation therapy to maximize effect of radiation therapy	n = 8 reapportion 0-49 days after initial surgery, n = 2 surgical wound dehiscence	NR

Author, Year of publication, Journal	Number of patients	Inclusion criteria	RT Technique/ dose/ fractions	Surgical procedure	Chemotherapy	Time interval between end of neoadjuvant therapy and surgery	Acute toxicity (up to three months after surgery) + Subacute toxicity (three months until one year after surgery)	Late toxicity (from one year after surgery)
		performance status of 0 or 1, no previous treatment with chemotherapy or radiotherapy, adequate organ function (absolute neutrophil count (ANC) ≥1,500/mm^3, platelet count ≥100,000/mm^3, serum creatinine ≤1.5 mg/100 ml, GPT (ALT)≤ 60 IU/l, total bilirubin ≤1.5 mg/100ml), written consent						
Ogunleye et al. [78], 2012, Journal of Plastic, Reconstructive & Aesthetic Surgery	n = 645	NR	Radiotherapy (for malignancy, within 90 days prior to surgery) n = 5 (0.8%)	Distribution of procedures: Implant alone, Tissue expander insertion, TRAM flap, Latissimus Dorsi flap, Free flap, Other	Chemotherapy (for malignancy, within 30 days prior to surgery n = 28 (4.3%)	NR	overall 30-day morbidity 5.7% General complications: myocardial infarction, pulmonary embolism, deep venous thrombosis, severe bleeding) Superficial surgical site infection n = 16 (2.4%) (within 30 days after operation), Deep SSI n = 11 (1.7%), Wound disruption n = 7 (1.1%), DVT n = 2 (0.3%), Severe bleeding n = 1 (0.15%); complications no CT: n = 29 (4.7%) complications with CT: n = 3 (10.7%) complications no RT: 30 (4.7%) complications with RT: 2 (40%) Radiotherapy within 90 days: Odds Ratio Estimate (95% CI) 11.87 (1.60-88.11) radiotherapy is an independent risk factor for wound infections	NR
Paillocher et al. [79], 2016, Eur J Surg Oncol	n = 111	operable invasive breast cancer, breast reconstruction by autologous latissimus dorsi flap with (LDI) or without (ALD) implant	pre-operative radiotherapy: 50 Gy in 25 sessions without boosts	94.6% (n=105) SSM (Skin-sparing mastectomy), mastectomy with immediate breast reconstruction (IBR), mastectomy after RT, breast reconstruction by autologous latissimus dorsi flap	median interval between end of chemotherapy (CT) and beginning of RT 30 days	median interval between the end of RT and surgery 41 days =correlation between time of RT and surgery: if surgery was performed 7 weeks after completing RT,	rate of primary complications 66.6% (n=74) including seroma secretion (reduced to 10.8% without serum secretion), necrosis 5.4%, RT-related complications (e.g. radiodermatitis) in 92% of patients (n=102) primary complications: within first month of surgery in 66.6% including seroma; excluding seroma: complications rate 10.8% primary complications (<1 month): seroma: n = 60 (54%), necrosis (skin, muscular flap): n=6 (5.4%), Haematoma: n=4 (3.6%), infection: n=2	NR

Author, Year of publication, Journal	Number of patients	Inclusion criteria	RT Technique/ dose/ fractions	Surgical procedure	Chemotherapy	Time interval between end of neoadjuvant therapy and surgery	Acute toxicity (up to three months after surgery) + Subacute toxicity (three months until one year after surgery)	Late toxicity (from one year after surgery)
				with (LDI) or without (ALD) implant		the rate of complications increased	(1.8%) secondary complications >1 month: n= 48 (43.2%) after the first month of post-operative surgery, shoulder adhesive capsulitis: n= 26 (23.4%), neurogenic pain: n=12 (9%), dorsal adherence pain: n=3 (2.7%), capsular contracture: n=3 (2.7%), fat necrosis: n=2 (1.8%), displacement of prothesis: n=1 (0.9%), scar disunity: n=1 (0.9%); major secondary complication: limitation of up to 45° of scapulo-humeral joint abduction n=26 (23.4%), neurological pain n=10 (9%); minor secondary complications: implant hernias, capsular contracture, painful dorsal scar adherence, nine surgical procedures had to be performed in order to treat primary or secondary complications, n =35 corrective reconstruction procedures	
Riet et al. [80], 2017, European Journal of Cancer	n =202 PreopRT, n=15 excluded, n=187 analysed	non-inflammatory and non-metastasized BC T2-T4 or N2 tumors n = 166 centrally reviewed tumor biopsy specimens: 22% triple-negative (TN) phenotype, 17% HER2 3+ or amplified and 61% ER+	RT with Cobalt-60 unit, slightly hypofractionated RT to whole breast, ipsilateral supraclavicular fossa and axilla ± internal mammary chain (45-55 Gy/18 fractions of 2.5 Gy/34 days) followed by modified radical mastectomy with axillary dissection	mastectomy	no preoperative chemotherapy, postoperative chemotherapy (CMF or anthracycline-based regimens) prescribed according to institutional guidelines n= 58 (31%)	modified radical mastectomy (MRM) with axillary dissection (AD) at least 4 weeks after the completion of radiotherapy, whatever tumor response	postoperative complication rate (grade>2) 19% with 4.3 % of localized skin necrosis; 30-day postoperative complication rate 19% (n=36); Grade ≥ 2 dehiscence of suture n= 7 (4%), Grade ≥ 3 skin necrosis n=8 (4%), n=9 patients (5%) second surgical procedure for grade 3 infection or haematoma, n=10 (5%) grade ≥ 2 lymphocele during early postoperative period, n=1 (0.5%) myocardial infarction, n=1 (0.5%) death 3 days after surgery due to a pulmonary embolism	NR
Semiglazov et al. [81], 1994, Annals of Oncology	n=271	stage IIb-IIIa breast cancer (TNM classification) group I (n=137): Neoadjuvant chemotherapy in combination with preoperative radiotherapy group II (n=134): preoperative radiation therapy alone	preoperative radiotherapy Cobalt-60, mammary gland was irradiated daily through tangential fields, foci single dose 2 Gy, total dose 60 Gy, axillary area irradiated (total dose 40 Gy), supraclavicular and subclavicular areas irradiated with single daily doses of 2 Gy (total dose 40 Gy)	modified radical mastectomy including complete axillary clearance	chemotherapy started before and continued during radiation therapy, after surgery adjuvant chemotherapy, TMF	modified radical mastectomy (including complete axillary dissection) in all patients 3-4 weeks after completion of radiation therapy	Postoperative Lymphorrea: Group 1:n=25 (18.2%) Group 2:n=22 (16.4%) Suppuration: Group 1: n=6 (4.3%) Group 2: n 8 (6.7%) Pneumonia: Group 1: n=4 (2.9%) Group 2: n= 5 (3.7%) Nausea, vomiting: Group 1: n=86(62.7%) Group 2: n=79(58.9%) Stomatitis, gastroenterocolitis: Group 1: n=8 (5.8%) Group 2: n=7 (5.2%)	NR

Author, Year of publication, Journal	Number of patients	Inclusion criteria	RT Technique/ dose/ fractions	Surgical procedure	Chemotherapy	Time interval between end of neoadjuvant therapy and surgery	Acute toxicity (up to three months after surgery) + Subacute toxicity (three months until one year after surgery)	Late toxicity (from one year after surgery)
							Skin allergic reaction and moist epidermitis: Group 1: n=9 (6.5%) Group 2: n=12 (8.9%)	
Selber et al. [20], 2006, Annals of Plastic Surgery	n=500 n=100 adjuvant RT PRT: NR	NR	NR	n= 500 TRAM flap reconstruction, n=69 had bilateral free flap reconstructions	NR	NR	-overall complication rate 20.9% (n=119) -fat necrosis in 3.3% (n=19) -neuroma in 1.9% (n=11 patients) -partial flap loss in 1.6% (n=9) -abdominal hernia in 1.9% (n=11) -total flap loss in 0.3% (n=2) -wound infection in 3.5% (n=20) -abdominal flap necrosis in 3.3% (n=19) -mastectomy flap necrosis in 3.0% (n=17) -seroma in 1.2% (n=7) -hematoma in 0.5% (n=3) -arterial thrombosis in 0.2% (n=1) Frequency of Flap Complications by Risk Factor Preoperative Radiation: -Fat necrosis: n=2 (0.4%) -Neuroma: n=2 (0.4%) -Lymphedema: n=0 (0%) -Hernia: n=2 (0.4%) -Free-flap necrosis: n=0 (0%) -Wound infection: n=1 (0.2%) -Abdominal-flap necrosis: n=3 (0.6%) -Mastectomy-flap necrosis: n=3 (0.6%) -Hematoma: n=0 (0%) -Seroma: n=2 (0.4%) -Arterial thrombosis: n=0 (0%)	NR
Unukovych et al. [82], 2016, Plast Reconstr. Surg Glob Open	n=436 breast reconstructions with free flap procedure n=433 patients included in study	NR	58.8% patients received preoperative radiotherapy (n=254)	Deep inferior epigastric perforator (DIEP) = autologous breast reconstruction, n=503 free flaps in 433 patients, n=363 (83.8%) unilateral and n=70 (16.2%) bilateral procedures 503 flaps: -484 (96.2%) DIEPs -19 (3.8%) superficial inferior epigastric artery (SIEA)	NR	NR	All Flaps (n=503) flap failure: 2.0% (n=10), partial flap loss 1.2% (n=66), arterial thrombosis 2.0% (N=10), venous thrombosis: 0.8% (n=4) , venous congestion: 1.2% (n=6), vein kinking: 0.6% (n=3), bleeding: 2.2% (n=11) hematoma: 3.0% (n=15) , fat necrosis 2.8% (n=14), infection 0.2% (n=1) Demographic and Patient Characteristics Stratified for Reoperation Preoperative radiation: All flaps (n=503) No 222 (44.7%) Yes 275 (55.3%) No Reoperation Group (n=423) No 186 (44.5%) Yes 232 (55.5%) Reoperation Group (n=80) No 36 (45.6%) Yes 43 (54.4%)	NR

Author, Year of publication, Journal	Number of patients	Inclusion criteria	RT Technique/ dose/ fractions	Surgical procedure	Chemotherapy	Time interval between end of neoadjuvant therapy and surgery	Acute toxicity (up to three months after surgery) + Subacute toxicity (three months until one year after surgery)	Late toxicity (from one year after surgery)
Shanta et al. [83], 2008, Int. J. Radiation Oncology Biol. Phys.	n=1117 completed treatment protocol, including surgery	locally advanced breast cancer (LABC), stage IIB, IIIA and IIIB	preoperative radiotherapy: Cobalt 60, total tumor dose of 4,000 cGy delivered in 20 fractions of 5/wk -additional dose given by the posterior axillary fields to deliver a total tumor dose of 4,000 cGy in 20 fractions	NR	regime 1: (n=954) cyclophosphamide, methotrexate, 5-fluorouracil, regime 2: (n=163) anthracycline-based regimen, cyclophosphamide, 5-fluorouracil, and adriamycin or epirubicin, Cemotherapy cycles given at 3-week intervals -administered on Day 1, RT started next day, fourth chemotherapy cycle 8-12 days postoperative	surgery scheduled for 3 weeks after end of RT, depending on patient`s skin condition, but not later than 4-6 weeks after RT completion	-morbidity during preoperative RT and chemotherapy: occasional break in <5% of cases because of neutropenia or vomiting but did not last for >1 or 2 days, skin morbidity consisted of deep pigmentation and mild to servere dry epidermis, moist reaction only in large pendulous breasts postoperative morbidity: surgery performed after patient recovered from radiation epidermitis (usually 4 weeks after RT for most patients) no significant postoperative morbidity was noted -seroma collection for about 7-10 days in about 15% of cases -no major skin morbidity such as skin necrosis or breakdown of incisions related to chemotherapy - wound infection rate 5.8% (n=10)	NR
Touboul et al. [84], 1997, Radiotherapy and Oncology	n=147 patients treated by CT followed by preoperative RT	locally advanced non-inflammatory breast cancer (LABC) and stage II>3 cm in diameter, Karnofsky perfomance status at least 90, no history of prior malignant tumor, adequate hematologic, renal, hepatic functions (WBC count ≥ 300/µl and platelet count ≥ 100000/µl, serum creatinin< 1.5 mg/dl, serum bilirubin< 1.5 mg/dl) and less than 75 years of age, no history of myocardial infarction, congestive cardiac failure or cardiac arrythmia and no uncontrolled hypertension, or uncontrolled infectious disease no distant metastases	preoperative RT: -Cobalt 60 in 147 patients and 6 MV n=6 -whole breast, chest wall, ipsilateral regional lymph nodes (supraclavicular, axillary, and internal mammary nodes) irradiated with a total dose of 45 Gy in 23 fractions over 31 days -4 weeks after completion of irradiation, fifth cycle of chemotherapy was given	mastectomy and axillary dissection n=52, conservative treatment n=95	Primary Chemotherapy followed by external preoperative irradiation (RT), CT (doxorubicin, vincristine, cyclophosphamide, 5-fluorouracil)	-4 weeks after fifth cycle (29 weeks after beginning of treatment) 3 different loco-regional therapeutic approaches =decision about local therapy 8 weeks after irradiation	-arm lymphedema in 11% (11/ 99) of patients with axillary dissection and in 4% (2/ 48) of patients treated without axillary dissection -limitation of shoulder movements 7.5% (4/ 52) patients with mastectomy and axillary dissection but in 2% (1/ 47) and 0% (0/ 48) of patients following tumorectomy and axillary dissection or radiotherapy without surgery -no patient showed congestive heart, failure extended pulmonary fibrosis, brachial plexopathy, or rib fracture	NR

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		Histological examination: -120 infiltrating ductal carcinomas -21 lobular carcinomas -4 medullary carcinomas -2 mucosecreting carcinomas n=4 staged M1 with isolated clavicular or subclavicular node involvement						
Aryus et al. [85], 2000, Strahlentherapie und Onkologie	n=73 with n=74 biopsy-proven invasive breast cancers	-non-metastatic tumors, <75 years of age, largest tumor diameter >3 cm -ECOG performance status 0 to 1 -white blood cell count > 4000/µl and platelet count > 100000/µl -all but one patient with planned flap-supported surgery were subjected to preoperative chemotherapy and radiation	n=55 patients and n=56 tumors treated with combined neoadjuvant chemo-radiotherapy, followed by surgery (chemo-radiotherapy group preoperative radiotherapy: 2 Gy fractions up to a total dose of 50 Gy, followed by tumor boost of 6 to 11 Gy 5 fractions per week using megavoltage or 60 Colbalt - all patients received electron boost to primary tumor -n=3 tumors in central or inner part of breast additional internal mammary node irradiation -supraclavicular fossa irradiated in n=55	n=45 (61%) breast-preserving procedures with or without latissimus dorsi mycutaneous flaps (LAT), n=8 cases (11%) immediate breast reconstruction with rectus myocutaneous flaps (TRAM) after mastectomy, n= 21 (28%) modified radical mastectomies (MRM) without reconstruction, n=1 in chemotherapy group and n=36 in chemo-radiotherapy group flap-supported surgery	n=18 neoadjuvant chemotherapy followed by surgery and adjuvant irradiation (chemotherapy group), most patients of both treatment groups received 4 cycles of EC chemotherapy, -median time interval between end of chemotherapy and beginning of irradiation between 2 and 8 weeks (median 4 weeks) in chemo-radiotherapy group	-median overall treatment time 41 days (35 - 55 days) median time interval between end of neoadjuvant therapy and surgery was 11 weeks (10-22 weeks) and 27 weeks (11- 41 weeks) for the chemotherapy and chemo-radiotherapy group - extended time interval in chemo-radiotherapy group to guarantee full recovery from acute radiation side-effects before surgery	-wound complication rates not increased when acute radiation side-effects have subsided at time of surgical intervention -wound healing is not delayed after flap-supported surgery -no toxic deaths -side-effects radiotherapy and chemotherapy were manageable, generally mild or moderate and reversible	-over last years no myocutaneous flap was lost after preoperative chemotherapy and radiation
Calitchi et al. [25], 2001, Int. J. Cancer	n=74	NR	external beam irradiation with cobalt or 4 MV accelerator, 45 Gy in 5 weeks to -chest wall	n=72 (96%): secondary tumorectomy, n=3 (4%): reduction mammaplasty, secondary	n=0 patients received neoadjuvant CT	NR	none	Late complications: -n= 2 (3%) of lymphoedema -n=2 fibrosis (3%)

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			-lower axillary lymph nodes and internal mammay nodes - boost of 15 Gy to internal mammary nodes, using direct 10 MeV electron beam -after tumorectomy postoperative boost of 20 Gy using iridium-192 low dose rate (LDR) -afterloading interstitial techniques	tumorectomy followed by postoperative boost of 20 Gy (range 15 to 25 Gy), n=50 axillary lymph node dissection (67%)				-no radiation-induced malignancy -no cardiac complications
Baltodano et al. [15], 2017, Plast Reconstr Surg Glob Open	n=77.902	NR	n=341 (data from the American College of Surgeons National Surgical Quality Improvement Program (ACS-NSQUP) 2005-2011 containing n=77,902 data sets	PRT: ME-only: n=266 ME+immediate breast reconstruction: n=75 No PRT: ME-only: n=61039 (78,4%) ME+immediate breast reconstruction: n=16863 (21,6%)	NR	NR	surgical site morbidity: ME-only group: PRT: n= 12 (4.5%) vs. n= 1.637 (2.7%) not receiving PRT Immediate Reconstruction Group (Mastectomy with Concurrent Reconstruction): PRT: n=4 (5.3%) vs. n=895 (5,3%) with no PRT Systemic Morbidity Mastectomy-only Group (No Reconstruction) PRT: n=17 (6.4%) vs. n=5.469 (9.0%) with no PRT Immediate Reconstruction Group (Mastectomy with Concurrent Reconstruction): PRT: n= 8 (10.7%) vs. n=1.463 (8.7%) with no PRT Overall morbidity: Mastectomy-only Group: PRT: n= 25 (9.4%) vs. n=6711 (11,1%) with no PRT Immediate Reconstruction Group (Mastectomy with concurrent Reconstruction): PRT: n=11 (14.7%) vs. 1.873 (11.2%) with no PRT Conclusion: PRT is not significantly correlated with higher postoperative 30-day morbidity	NR
Ascherman et al. [86], 2006, Plast. Reconstr. Surg.	n=104 patients	NR	n=27 premastectomy or postmastectomy radiation therapy n=8 radiation before mastectomy n=19 radiation after mastectomy	tissue expansion and implant breast reconstruction after mastectomy, n=123 breast reconstructions with implants (n=85 unilateral and n=19 bilateral)	in patients undergoing chemotherapy, expansion was performed within 3 days before and 3 days after chemotherapy	NR	complications requiring removal or replacement of tissue expander more frequent in breasts that received radiation than breasts that did radiated (n=27) not radiated (n=96) Complications resulting in removal or replacement radiated: n=5 (18.5%) not radiated: n=4 (4.2%) Infection: radiated: n=1 (4%) not radiated: n=0 (0%) Extrusion: radiated: n=4 (14.8%)	NR

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							not radiated: n=0 (0%) Port malfunction: radiated: n=0 (0%) not radiated: n=1 (1.0%) Capsular contracure radiated: n=0 (0%) not radiated: n=1 (1.0%) Pain: radiated: n=0 (0%) not radiated: n=1 (1.0%) Rippling: radiated: n=0 (0%) not radiated: n=1 (1.0%) Complications not resulting in removal or replacement radiated: n=6 (22.2%) not radiated: n=12 (12.5%) Pulmonary embolism: radiated: n=0 (0%) not radiated: n=2 (2.1%) Seroma: radiated: n=4 (14.8%) not radiated: n=7 (7.3%) Skin necrosis: radiated: n=1 (3.7%) not radiated: n=2 (2.1%) Cellulitis: radiated: n=1 (3.7%) not radiated: n=0 (0%) Pain: radiated: n=0 (0%) not radiated: n=1 (1.0%) Total complications: radiated: n=11 (40.7%) not radiated: n=16 (16.7%) timing of radiation therapy: no statistically significant difference in number of complications	
Weintraub et al. [87], 2008, Eplasty	n=112 with breast cancer, including 140 breasts, who underwent postmastectomy tissue expander placement	NR	-16% (n=23) radiation therapy during reconstruction -17% (n=4) radiation therapy more than 5 years prior to placement of tissue expander -17% (n=4) radiation therapy within 5 years after tissue expander was placed -65% (n=15)	-postmastectomy tissue expander placement -all patients underwent replacement of tissue expander placement with permanent prosthesis, silicone implants in 46%, saline implants in 54% median time interval	NR	NR	NR	-risk of developing capsular contracture unchanged by application of radiotherapy at any point -radiation exposure independent risk factor for complications leading to reoperation (e.g. wound dehiscence, infection, implant rupture) -no significant difference in rate of complications whether RT was applied or not -average follow-up 29 months (12-84 months) after placement of permanent prosthesis -10% (n=14) complications that necessitated reapportion after placement of tissue expander Complications included: -hematoma (n=2)

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			radiation therapy during tissue expansion	for all patients between completion of tissue expansion and placement of permanent implant 2.5 months (0.5-16 months)				-leak/ rupture of the tissue expander (n=4) -partial necrosis of mastectomy flap with threatened exposure (n=4) -seroma (n=1) -wound dehiscence with tissue expander exposure (n=2) -infection, including cellulits (n=1) -time interval between completion of tissue expansion and placement of permanent implant had no effect on capsular contracture -14% (n=19) of complications (other than capsular contracture) needed reoperation after placement of permanent implant: included: infection/cellulitis (n=5), wound dehiscence with implant exposure (n=12) and implant rupture (n=4) -18% (n=25) capsular contracture Amount of patients who underwent radiation therapy at some point during reconstruction: 16% F25
Skinner et al. [88], 2000, Annals of Surgical Oncology	n=29 enrolled, n=28 assessable for clinical response and toxicity, n=27 assessable for pathological response	locally advanced breast cancer stage IIB (T3N0) or IIIA (T0N2, T1N2, T2N2, or T3N1-2), or stage IIIB (T4N0-2), ECOG 0-1, measurable disease, no previous treatment, and medical and psychological ability to comply with study requirements	within a week of beginning treatment with paclitaxel daily radiochemotherapy to breast and regional lymph nodes, to a total dose of 45 Gy (1.8 Gy/ fraction during 5 weeks), then modified radical mastectomy	-Modified radical mastectomy with TRAM reconstruction -Breast conserving therapy -Modified radical mastectomy TRAM= transverse rectus abdominis myocutaneous flap	paclitaxel 2x/week for 8 weeks, after completion of radiotherapy, patients completed final 2 weeks of paclitaxel regimen without radiotherapy	NR	-surgical complications in 41% of patients -n=2 paclitaxel 1x/week radiation at 200 cGy/fraction: vigorous skin and tumor response that degree of desquamation, necrosis, and subsequent scarring required flap reconstruction after mastectomy for cosmesis -n=2 paclitaxel and radiation at 200 cGy/fraction: MRM with transversus rectus abdominis myocutaneous flap reconstruction, n=1 failure of superior portion of flap on 3rd postoperative day requiring flap revision, n=1 wound separation and an infection around flap after second cycle of postoperative chemotherapy, delayed wound healing, requiring 2 months of local wound care n=2 partial mastectomy after treatment with paclitaxel and radiation: chronic noninfectious mastitis caused by radiation recall, the paclitaxel or the combination n=23 MRM: n=4 patchy flap necrosis with delayed wound healing (3 weeks to 3 months), n=1 (elderly diabetic patient) recurrent hematoma under skin flap, n=1 recurrent axillary seroma infected, n=1 wound cellulitis required admission for intravenous antibiotics, n=1 decreased range of motion of upper extremity despite vigorous rehabilitation n=0 lymphedema	NR

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Zinzindohoue et al. [89], 2016, Annals of Surgical Oncology	n=94 included n=83 were analyzed	invasive breast cancer, T1 (23.6%), T2 (55.6%, T3 (18.1%), WHO performance status of 0 or 1, neoadjuvant CT and RT	all patients received RT, neoadjuvant radiation: RT with 50 Gy irradiation of breast, additional irradiation of axillary, internal mammary or supraclavicular nodes, 3-6 weeks after CT	Skin-sparing mastectomy (SSM) with immediate breast reconstruction (IBR)	neoadjuvant chemo: all but one patient anthracyclines and taxanes	6-8 weeks after RT	NR	median follow-up 2 years: n=5 skin necrosis without surgical revision, necrosis healed within 6 postoperative months in all patients, n=1 infection associated with hematoma
Yaremko et al. [90], 2018, Int. J. Radiat. Oncol.	n=27, early-stage (<T3), estrogen-positive, clinically node-negative invasive carcinoma of the breast with tumors at least 2 cm away from skin and chest wall	Low-risk patients, postmenopausal women, with biopsy-proven ductal carcinoma, any grade, unifocal, ≤ 3 cm, ER-positive, without axillary involvement	Neoadjuvant single-fraction radiation therapy (SFRT) in 27 patients, prescription dose of 21 Gy was delivered in single fraction	lumpectomy and sentinel node dissection (SND) 1 week after surgery, SND in 23 pts	4 pts received chemotherapy	NR	6-months post-surgery toxicity was not different from baseline	NR
Gaui et al. [91], 2007, American Journal of Clinical Oncology	n=28, treatment rendered 23/ 28 patients (82%) operable, n=5 no surgery	inoperable locally advanced breast cancer (LABC) after primary anthracycline-based chemotherapy, TNM stage IIB or III, the latter comprising 3 categories: IIIA, IIIB, IIIC or inflammatory breast cancer , no pregnancy, ≥18 years, Karnofsky performance status ≥80%, absolute neutrophil count ≥1500/μL, platelet count ≥100.000/μL, hemoglobin level ≥10g/dL, normal	-irradiation to whole breast and lymph node -total radiation dose 50 Gy in 5 weeks (20cGy/d)	NR	concomitant capecitabine 850mg/m^2 twice daily for 14 days every 3 weeks	median time interval between completion of radiotherapy and date of surgery 1.6 months (1-4)	-treatment regimen well tolerated with no grade 3 or 4 events -acute allergic skin reaction in 46% (G1 in 35% and G2 in 11%) -no hand-foot syndrome -n=1 surgical complications and wound dehiscence in - 6 months after end of surgery 18 patient re-examined, lymphedema and functional restriction (G1 and G2) n=4 (22%) Treatment-Related Adverse Events (NCI Common Toxicity Criteria) Gastrointestinal (n=28) Nausea: Grade 0: n=24 (86%) Grade 1: n=3 (10%) Grade 2: n=1 (4%) Emesis: Grade 0: n=26 (94%) Grade 1: n=2 (6%) Grade 2: n=0 Diarrhea: Grade 0: n=23 (84%) Grade 1: n=4 (12%) Grade 2: n=1 (4%) Mucositis:	NR

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		tests of liver, renal and cardiac function, no previous malignancy					Grade 0: n=20 (72%) Grade 1: n=5 (18%) Grade 2: n=3 (10%)	
Woodward et al. [92], 2017, International Journal of Radiation Oncology biology physics	n=32, n=26 received protocol-specified treatment and therefore included	inoperable disease after chemotherapy, residual nodal disease after definitive surgical resection, unresectable chest wall and nodal recurrence after prior mastectomy, Eastern Cooperative Oncology performance status 0 to 1, ability to swallow and retain oral medication, age 18 or older, female, histologically confirmed invasive breast cancer, contraindication to radiation treatment to minimum dose of 50 Gc in 25 fractions or systemic disease in which RT is an absolute contraindication	-chest wall or breast and undissected draining lymphatics -internal mammary nodes treated with electrons -radiation dose 50-57 Gray -dose to potentially resectable disease limited to 54 Gy at 2 Gy per fraction or 57 Gy at 1.8 Gy per fraction to limit surgical complications -additional boost acceptable to total dose of 60- 72 Gy	n=32 (84%) mastectomy after RT	n=9 CAP twice daily continuously, because of toxicity, subsequent patients CAP only on radiation days	NR	-n=1 treated with 66 Gray preoperatively had chest wall abscess one week after surgery -no wound dehiscence, no surgical revision needed	median follow-up was 12.9 months (7.10-42.9 months) n=14 (53.9%) grade 3 non-dermatitis toxicity (7/ 9 treated with continuous dosing) -5-year postoperative complication rate 53%, and preoperative radiation doses ≥54 Gy significantly associated with complications requiring surgical revision Grade ≥ 3 treatment-related adverse events (National Cancer Institute Common Toxicity Criteria Fibrosis of deep connective tissue -Capecitabine continous dosing n=1 - Capecitabine weekday dosing n=0 Any grade ≥ 3 adverse event -Capecitabine continuous dosing n=7 -Capecitabine weekday dosing n=7
van der Leij et al. [93], 2015, Radiotherapy and Oncology	n=70	women ≥ 60 years, invasive, unifocal, low risk, cT1-2 (tumor size ≤ 3 cm), ECOG performance scale ≤ 2, Conformal 3D CRT, Intensity	Preoperative accelerated partial breast irradiation (PAPBI): 40 Gy in 10 fractions over 2 weeks	wide local excision, in case of positive resection margins re-excision performed (n=69 wide local excision with negative resection	4/70 (6%) adjuvant chemotherapy	6 weeks after last day of radiotherapy wide local excision	-n=39 (56%) no acute skin toxicity -n=30 grade 1 (43%) and n=1 (1%) grade 2 -n=11 postoperative complications (16%), -n=2 direct post-operative bleeding requiring re-surgery on same day -n=1 hematoma 2 months after surgery and re-surgery -n=8 postoperative wound infection (n=1 re-surgery for wound abscess, n=1 small fistula	follow-up of 23 months (3-44 months) postoperative infection rate : 11% at 1, 2 and 3 years of follow-up respectively 89%, 98% and 100% of patients had no or mild induration-fibrosis, fibrosis only in small volume of breast -breast pain, rib pain and presence of rib fracture evaluated according to EORTC/RTOG/late

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		Modulated Radiotherapy (IMRT) or Volumetric Modulated Arc Therapy (VMAT) used as RT techniques		margins, n=1 positive resection margin)			closed within 10 months after treatment with antibiotics, n=6 successfully treated with oral antibiotics) -no other wound healing problems -n=7 (10%) persistent seroma	radiation morbidity scoring -4 patients transient edema in whole breast -in the first year increase of induration: from 52% (31/60 patients) to 69% (41/59) to 80% (40/50 patients) after 3, 6 and 9 months -at 12 months induration was scored for 57 patients: 11 (19%) had none, 40 (70%) mild and six (11%) moderate induration -at 24 months 19/ 41 (46%) mild fibrosis and n=1 (2%) patient moderate fibrosis -at 30 months 15/23 patients no fibrosis (65%) -after 36 months n= 11 patients, all none-mild fibrosis, area of fibrosis limited to volume of 1-2 cm -during total follow-up 27/ 70 (39%) grade 1 breast pain (transient in n=21, persistent in n=6 patients) and n=7 (10%) grade 2 breast pain -n=1 breast pain diminished from grade 2 to grade 1, n=5 pain was transient (grade 0), n=1 grade 3 breast pain, which diminished to grade 2 -n=11 (16%), n=9scored grade 1 (6 transient) and n=2 grade 2 (persistent) -no rib fractures
Rutqvist et al. [94], 1993, Radiotherapy and Oncology	n=960	-pre-and postmenopausal women with operable breast cancer aged below 71	radiation therapy individually planned, chest wall, internal mammary nodes, supraclavicular fossa, axilla, tumor dose 45 Gy given with 1.8 Gy per fraction, 5 days a week for about 5 weeks - n=316 preoperative radiation therapy -n=323 patients postoperative radiation therapy -n=321 patients surgery alone	modified radical mastectomy -axillary surgery included dissection of lymph nodes at level I and II below axillary vein	no adjuvant systemic therapy was used	NR	NR	NR
Pazos et al. [95], 2017, Strahlentherapie und Onkologie	n=22	locally advanced breast cancer (LABC) (cT1(m)-4a/cN0-2)	-n=22 neoadjuvant RT -RT dose 50.4 Gy (5x 1.8 Gy/week) -n=2 irradiation in IMRT technique	n=19 mastectomy and immediate breast reconstruction (IBR), n=3 autologous tissue-transfer reconstruction, n=2 DIEP (deep inferior epigastric perforator) , n=1 TRAM	n=18 neoadjuvant chemotherapy prior to RT, 4x EC (epirubicin, cyclophosphamide) followed by 12 x paclitaxel	median interval of 47 days (26-162 days) between RT and surgery, n=2 delayed surgery more than 150 days after end of radiotherapy	n=4 (25 %) wound-healing problems and implants had to be explanted -lymphedema of arm n 30% patients in upfront mastectomy group and 16% in second group	NR

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				(transverse rectus abdominis myocutaneous), n=16 implant based techniques		because of personal reasons		
Nichols et al. [96], 2017, International Journal of Radiation Oncology biology physics	n=28 enrolled, n=1 ineligible after enrollment, n=27 completed treatment	≥18 years old, T1-T2 (<3 cm), N0 tumors, histologically unifocal invasive carcinoma of breast <3 cm in maximum dimension	preoperative 3-dimensional conformal radiation therapy, preoperative partial breast irradiation, total dose 38.5 Gy in 10 fractions, treatment twice for 5 days, with at least 6 hours between fractions -n=27 patients preoperative RT	partial mastectomy and sentinel lymph node (SLN) biopsy	adjuvant chemotherapy administered according to standard of care, no systemic therapy given before surgery, n=6 adjuvant chemotherapy	>21 days after competition of RT or after all grade 3 toxicities resolved, whichever was later	NR	follow-up of 3.6 years (0.5-5 years): -no local or regional failures -no grade 4/5 events, no unexpected adverse event -no treatment delays in surgery due to acute side effects from RT or grade 3 or higher toxicities -after surgery n=,4 grade 3 events of seromas, h n=3 grade 2 seromas and n=1 grade 2 hematoma -n=3 wound infection (n=2 grade 2 and n=1 grade 3) -n=1 diabetes persistent fistula requiring 6 months to heal other side effects (all grade 0-1) fatigue, mild skin erythema, hyper- pigmentation, fibrosis, some intermittent breast discomfort, slight edema, dyspnea on exertion
Monrigal et al. [97], 2011, Eur J Surg Oncol	n=210	operable invasive breast cancer (OIBC) stage 0 to III disease	RT from Cobalt unit or 6-MeV linear accelator,starting 4-6 weeks after completion of CT, breast with 2 opposing tangential fields, total of 50 Gy on whole breast and chest wall, over 5 week period with daily target dose of 2 Gy -boost dose 10 Gy in 5 fractions	Radical non-skin-sparing mastectomy with level I and II axillary dissection and IBR (Immediate breast reconstruction) Reconstruction techniques: n=107 latissimus dorsi flap with implant (LDI), n=56 transverse rectus abdominis musculocutaneous (TRAM) flap, n=25 autologous latissimus dorsi flap (ALD), n=22 retropectoral implant (RI) reconstruction	Neoadjuvant chemotherapy (NACT) CT n=139 Taxanes	surgery after 6-8 weeks after completion of RT, median time interval between completion of RT and surgery 51.7 days	n=46 (21.9%) early events: n=20 necrosis, n=9 surgical site infections, n=6 haematomas, n=23 requiring further surgery more necrosis in TRAM flap reconstruction, more surgical revision than LD reconstruction Seromas 42% of early complication in LD reconstructions LDI n=107 TRAM n=56 ALD n=25 I n=22 Total n=210 early complications and surgical revisions depending on technique reconstruction: Necrosis: LDI n=2 TRAM n=14 ALD n=3 I n=1 Total n=20 Infection: LDI n=6 TRAM n=1 I n=2 Total n=9 delayed complications: after 1 months	n=55 late complications (26.2%) with implant complications (capsular contracture, infection, dislocation, deflation) (23.6%), n=14 reintervention -more delayed surgical revisions in RI reconstructions

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							LDI n=107 TRAM n=56 ALD n=25 I n=22 Total n=210 Implant complications: LDI n=7 I n=6 Total n=13 Capsular contracture LDI n=4 I n=3 Total n=7 Necrosis TRAM n=2 Total n=2 Seroma ALD n=1 Total n=1	
Ishitobi et al. [98], 2014, Breast Cancer	n=29 enrolled, n=24 began radiotherapy concurrently anastrozole, definitive surgery	postmenopausal with amenorrhea for at least 1-year, bilateral oophorectomy, or follicle-stimulating hormone and estradiol in postmenopausal range, breast cancer with hormone-receptor-positive tumors, (T (3 cm or larger), N0-2, M0), WHO performance status of 0 or 1	neoadjuvant anastrozole for 24 weeks, concurrent radiation from 12 weeks after start of anastrozole, total dose of 50 Gy in 25 fractions to breast, for clinical node-positive patients 50 Gy in 25 fractions to ipsilateral supraclavicular fossa in same period of irradiation to breast	definitive surgery	NR	primary anastrozole 24 weeks before definitive surgery, 12 weeks after start of anastrozole, RT, surgery 2 months after end of RT	after surgery grade 3 toxicities in 2/ 25 patients (8%) after surgery: grade 2 or higher toxicity: grade 2 seroma n=5 grade 2 n=2 and grade 3 n=1 wound infection, grade 3 hematoma n=1 grade 2 skin breakdown n=1) -no radiation pneumonitis	NR
Horton et al. [99], 2015, International Journal of Radiation Oncology biology physics	n=32	≥ 55 years, early-stage breast cancer, clinically node-negative, estrogen receptor-positive, and /or progesterone receptor-positive, HER2-, T1 invasive	Intensity modulated radiation therapy: 15 Gy (n=8), 18 Gy (n=8), or 21 Gy (=16) to tumor with 1.5-cm margin -PBI Partial breast irradiation	Lumpectomy within 10 days	NR	within 10 days	NR	median follow-up of 23 months (11-37 months, n=1 excluded) chronic toxicities grade 1 to 2 (fibrosis, hyperpigmentation) in patients with preoperative radiation only side-effects largely mild and consistent with expected sequelae of surgical and/or radiation therapy -fibrosis in 77% of patients, mostly grade 1, -dermatitis and breast pain were common

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		carcinomas, or low- to intermediate-grade in situ disease ≤ 2 cm						
Formenti et al. [100], 2003, Journal of Clinical Oncology	n=44	Stage IIB (limited to T3N0) to IIIA, and IIIB biopsyproven LABC (locally advanced breast cancer) patients, Eastern Cooperative performance score 0 to 1	preoperative RT initiated within 1 week from first paclitaxel dose at 1.8 to 2 Gy per fraction for total of 25 fractions (45 to 46 Gy) to breast, axilla, and supraclavicular nodes	n=41(93%) modified radical mastectomy. N=2 (5%) refused mastectomy and underwent lumpectomy	-primary chemoradiation paclitaxel, paclitaxel twice weekly for a total of 8 to 10 weeks -postoperative doxorubicin-based chemotherapy	mastectomy at least 2 weeks from last day of RT or 2 weeks after skin recovery of acute RT toxicity	n=6 postmastecomy complications (14%), included: n=4 infections with delayed wound healing, n=1 tram flap necrosis requiring revision, n=1 mastitis with grade 3 dermal injury	NR
Colleoni et al. [101], 1998, European Journal of Cancer	n=32	biopsy-proven T2-T4, N0-2 breast cancer, non-metastasic tumors, largest tumor diameter >2.5 cm, Eastern Cooperative Oncology Group (ECOG) performance status 0-1, white blood cell count > 4000 mm^3 and platelet count >100 000, serum creatinine < 1.2 mg/dl, bilirubin < 3 mg/dl, aspartate and alanine aminotransferase < 2.5 times the upper limit	50 Gy with 2 opposite tangential fields and with 10 Gy boost to tumor nodule	quadrantectomy and axillary node dissection, total mastectomy	doxorubicin and cyclophosphamide, every 21 days for three courses, radiotherapy 3-4 weeks after last course of chemotherapy	NR	no toxic death or no grade III-IV toxicities were observed, mild or moderate side-effects (related to chemotherapy) including mucositis, nausea/vomiting and leucopenia	NR
Coelho et al. [102], 2017, Breast	n=57	non-metastastic locally advanced breast cancer (LABC) treated with neoadjuvant chemotherapy and not eligible for surgical reconstruction,	whole breast by tangential fields and draining nodal chains (3 levels of axilla and supraclavicular fossa) and was deliviered with anteroposterior (AP)/posteroanterior (PA) fields	NR	chemotherapeutic regimens containing anthracyclines 98.2%, n=15 (26.3%) taxanes and anthracyclines,n=1 received docetaxel and cyclophosphamide	median time to surgery after radiotherapy was 20 weeks	surgical complications frequent but not severe, no patient died, most common events were chronic pain (12-21.1%), lymphoedema (10-17.5%), wound dehiscence (8-14%) and/or infection (6-10.5%)	NR

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		most frequent clinical stages IIIA and IIIB	Radiation dose of 50 Gy divided into 25 fractions					
Brackstone et al. [7], 2017, International Journal of Radiation Oncology biology physics	n=32, n=30 completed treatment	locally advanced breast cancer (LABC) (any T3 or T4 tumor stage or any N2 or N3), all female, ≥18 years of age, able to give informed consent, negative serum pregnancy test, no prior history of invasive cancer, adequate renal, hepatic, pulmonary, and cardiac function	neoadjuvant radiation delivered concurrently with docetaxel, Standard regional intensity modulated radiation therapy (IMRT) (45 Gy/25 fractions± 5.4 Gy/3 fractions or 9 Gy/5 fractions boost for gross residual disease), treatment delivered on megavoltage machines using 6-MV energy or greater	modified radical mastectomy (with level 1 and 2 axillary node dissection)	-neoadjuvant chemotherapy concurrent with radiation - 5-fluorouracil, epirubicin and cyclophosphamide for 3 cycles every 3 weeks, followed by weekly docetaxel for 9 cycles	5 weeks after chemotherapy, allowing 8 weeks of radiation recovery preoperatively	Dermatitis, grade 3 n=8 (25%) Pneumonitis: Grade 3 n=7 (22%) Grade 5 n=1 (3%) Postoperative seroma, grade 2 n=1 (3%) Wound infection n=0 (0%) Febrile neutropenia n=0 (0%) Toxicity included 25% of patients with grade 3 pneumonitis, 25% dermatitis, n=1 death	NR
Chakravarthy et al. [103], 2006, Clin Cancer Res	n=38, n=28 definitive surgery after completion of all phases of therapy	high-risk, operable breast cancer, Eastern Cooperative Oncology Group performance status (ECOG performance status) of 0 to 1, stages IIA to IIIB, women ≥ 18 years of age with biopsy-proven infiltrating breast cancer	neoadjuvant radiation with a dose of 4.680 cGy in 28 fractions to the breast and 4.500 cGy in 25 fractions to the regional nodes	definitive surgery (consisting of lumpectomy or mastectomy)	Neoadjuvant paclitaxel: 3 cycles of paclitaxel every 3 weeks, followed by twice-weekly paclitaxel and concurrent radiation Postoperative adjuvant therapy: 4 to 6 weeks following surgery adjuvant chemotherapy consisting of doxorubicin and cyclophosphamide given every 3 weeks for 4 cycles	3 to 4 weeks following completion of chemoradiation, after increased postoperative complications were noted in the first 12 patients, protocol was modified to delay surgery 5 to 7 weeks after last dose of radiation	Median follow-up time after surgery 23 months (1-46 months) Mastitis n=1 Wound infection n=3 Abscess n=2 Fat necrosis n=2 Neurologic n=1 Edema n=2 Seroma n=12 Hematoma n=2 Cellulitis n=6 Flap loss n=2 Herniation of expander n=1	NR
Bourgier et al. [104], 2012, Radiotherapy and Oncology	n=14	chemotherapy-refractory breast cancer, patients operable but non-conversable or locally advanced breast cancer, biopsy-proven invasive breast cancer	concurrent radiotherapy t at a total dose of 50 Gy in 2 Gy fractions over 5 weeks, irradiated volumes: breast, internal mammary chain, axillary-supraclavicular lymph nodes, additional dose to tumor bed (attaining 60-70 Gy) n=10	breast-conserving surgery or modified radical mastectomy	Chemotherapy in 4 cycles of a 3-weekly regimen combining vinorelbine and 5-FU-based chemotherapy (either continuous intravenous 5FU or oral capecitabine)	modified radical mastectomy 4-8 weeks after radiotherapy completition	no complications during surgery, grade 2 post-mastectomy complications and grade 3 post-mastectomy complications n=2 (n=1 hematoma and n=1 wound healing infection), when needed, hospitalization lasted less than 1 week (n=1)	NR

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Bondiau et al. [105], 2013, International Journal of Radiation Oncology biology physics	n=26 enrolled, n=1 withdrawn, n=25 assessable patients treated concomitanly with NACT	unifocal breast cancer not suitable for breast-conservation therapy, age ≥ 18 years, Eastern Cooperative Oncology Group performance status (ECOG) ≤ 2 and human epidermal growth factor receptor-negative disease	neoadjuvant stereotactic body radiation therapy (SBRT) on 3 consecutive days during second cycle but not on same days as chemotherapy, escalation level (19.5 Gy, 22.5 Gy, 25.5 Gy, 28.5 Gy or 31.5 Gy) to the 70% isodose line encompassing 95% of GTV -then conventional radiation therapy performed 4 to 6 weeks after surgery	-breast-conserving surgery (including lumpectomies, quadrantectomies, partial mastectomies), total mastectomy	Neoadjuvant Chemotherapy (NACT): n=6 cycles: docetaxel and 3 perfusions of FEC (fluorouracil), epirubicine and cyclophosphamide -chemotherapy given once every 3 weeks	surgery 4 to 8 weeks after last chemotherapy cycle	no surgical complications, surgery not associated with any increase in morbidity or technical difficulty according to surgeons, no secondary cutaneous healing problems	NR
Bollet et al. [26], 2012, Radiotherapy and Oncology	n= 59	NR	PRT (cobalt-60 or 4-6 MV) -RT 50 Gy to whole breast internal mammary chain (combination of photons and electrons) and supra/infra-clavicular areas irradiated to 46 Gy in 23 daily fractions and 4.6 weeks	tumorectomy or modified radical mastectomy, axillary lymph node dissection of the first 2 levels	yes	minimal 6 weeks after PRT	Acute toxicities n=5: wound infections after tumorectomy, n=2: surgical drainage n=2 voluminous hematoma after tumorectomy, n=1 surgical drainage	Late toxicities with median follow-up of 7 years n= 4 (8%) at least one grade III toxicity (n=1 telangectasia and n=3 fibrosis)
Alvarado-Miranda et al. [106], 2009, Radiation Oncology	n=112	Locally advanced breast cancer (LABC) stage IIB-IIIB	CCRTh: 60 Gy to whole breast and nodal areas divided into 50 Gy in 5 weeks plus boost to palpable residual disease with a 10 Gy electron beam in 1 week	modified radical mastectomy and axillary lymph-node dissection performed post-CCRTh	Neoadjuvant chemotherapy (NCT) (5-fluorouracil, doxorubicin and cyclophosphamide or doxorubicin and cyclophosphamide in four 21-day courses) followed by concurrent chemo-radiotherapy (CCRTh) based on mitomycin C, 5-fluorouracil,dexamethasone or cisplatin, gemcitabine and dexamethasone	6-8 weeks	-toxicity profile was acceptable grade 1-2 neutropenia in 32.2% grade 1-2 anemia in 5.2% grade 3 radioepithelitis in 22.4 %	NR
Adams et al. [107], 2010, Breast Cancer Res Treat	n=105	LABC (stages IIB-IIIC), Eastern Cooperative Oncology Group performance status (ECOG) 0	preoperative RT: daily radiotherapy to breast, axillary and supraclavicular lymph nodes during weeks 2 to 7 of	level I/II axillary lymph node dissection was required for all patients, type of surgery (breast-	paclitaxel twice a week for 10-12 weeks	4 weeks after completion of preoperative therapy or upon recovery of chemoradiation-	NR	NR

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		to 1, adequate bone marrow and organ function	paclitaxel treatment, at 1.8 Gy per fraction to a total dose of 45 Gy with a tumor boost of 14 Gy at 2 Gy/fraction	conserving vs. mastectomy) was decided by surgeon		induced dermatitis		
Skinner et al. [108], 1997, Ann J Surg	n=30	locally adanced breast cancer unresectable with primary wound closure, stage IIB, III, or IV (supraclavicular adenopathy only) breast cancer, Karnofsky performance score greater or equal 80%	neoadjuvant: 50 Gy (25 fractions at 200 cGy/fraction, Monday through Friday)	Modified radical mastectomy (MRM)	5-FU for 8 weeks	surgery within 4-6 weeks of treatment	Surgical morbidity not increased, no significant operative complications, n=1 delayed wound healing, no intervention required, no early lymphedema, despite undergoing axillary irradiation followed by axillary lymphadenectomy	NR
Roth et al. [13], 2010, Strahlentherapie und Onkologie	n=315 LABC receiving preoperative RCT and n=329 adjuvant RCT	LABC without distant metastases, untreated, histologically confirmed, invasive adenocarcinoma of the breast not amenable to breast-conserving surgery (tumor size relative to breast volume, unfavorable location of the tumor bed, or multifocal T1, and extended intraductal component [EIC]), stages IIA-IIIC according to the International Union Against Cancer (ICRU), institutionally approved written consent	Preoperative RT: one course of external-beam RT of 50 Gy (ICRU) to the breast and the supra-/ infraclavicular lymph nodes, using 5x2.0 Gy/week via tangential fields Adjuvant RT after primary surgery consisted of 50Gy plus a 10Gy electron boost in case of breast conservation; irradiation of supraclavicular field 188/329 n=101 interstitial boost of 10Gy	Mark up and photo documentation of original tumor location, irrespective of the primary tumor response as assessed by palpation, ultrasound or MRI, extent of resection depended on relative volume of the tumor prior to RCT and of breast-tumor-relationship	Neoadjuvant RCT group: chemotherapy consisting of 4x epirubicin and cyclophosphamide (EC) in 53%, mitoxantrone in 35.6%, 4x Adriamycin and cyclophosphamide in 6.7%, no chemotherapy in 3.2%, 3x cyclophosphamide, methotrexate and 5-fluorouracile (CMF) in 0.3% and 6x EC in 0.3%, chemotherapy was applied before RT n=192, simultaneously n=113, n=10 no chemotherapy adjuvant RCT group: 37% no chemotherapy, 27% 4x EC, 16% mitoxatrone, 9% 3c CMF, 5% 6xCMF; Neoadjuvant group: n=241 additional hormonal treatment with tamoxifen or a LHRH agonist, n=74 no antihormonal treatment Adjuvant group: n=213 additional hormonal treatment with tamoxifen or an LHRH agonist, n=116 no antihormonal treatment	NR	NR	NR

Author, Year of publication, Journal	Number of patients	Inclusion criteria	RT Technique/ dose/ fractions	Surgical procedure	Chemotherapy	Time interval between end of neoadjuvant therapy and surgery	Acute toxicity (up to three months after surgery) + Subacute toxicity (three months until one year after surgery)	Late toxicity (from one year after surgery)
Brooks et al. [16], 2011, The breast journal	n= 560 RT: n=97 (13%) PRT: n=27 (partial ME+RT defined as PRT	NR	NR	PRT: NR n= 385: unilateral, n=174 bilateral tissue expander/ implant reconstructions	NR	NR The PRT-group is defined by former irradiation after partial mastectomy. The surgical procedure is performed after recurrence	Patients with RT: total complication rate: 58.8% and major complication rate 45.4% Patients with no PRT: 27.6% complications, 21.2% major complication rate PRT: not analyzed	
Nahabedian et al. [17], 2003, Plastic and Reconstructive Surgery	n=130 RT: n=23 (13,7%), PRT: before implant reconstruction: n=13 (57%) Adjuvant RT: after implant reconstruction: n=10 (43%)	NR	NR	n=168 breast reconstructions in n=130 PRT: NR	NR	NR	Infectious complications: n=10/130 (7.7%) PRT: n=1 (7,7%) infected of total implants (n=13)	
Colwell et al. [18], 2011, Plastic and Reconstructive Surgery	n=211 RT: n=51 PRT: n=33 Adjuvant RT: n=18	NR	NR	n=331 direct-to-implant reconstructions 120 bilateral, 91 unilateral procedures	NR	NR	All patients: n=10 infections (3.0%), n=5 seromas (1.5%), n=4 hematomas (1.2%) 9.1%, skin necrosis leading to n=5 implant losses (1.5%) Early complication rate in PRT: Single-Stage: 24,2%, Two-Stage: 41,1%. Postoperative RT: Single-Stage: 16,7%, Two-Stage: 23% Conclusion: highest complication rate in PRT and Two-Stage reconstruction	PRT: NR
Sbitany [19], 2014, Plastic and Reconstructive Surgery	n=580: 903 breast reconstructions following total skin-sparing mastectomy Cohort 1: total SSM and reconstruction with no RT n=727 breasts Cohort 2: prior history of radiation before SSM and reconstruction n=63 breasts Cohort 3: Adjuvant RT	NR	PRT: NR Adjuvant RT to fully inflated tissue expander, before expander-implant exchange	Immediate breast reconstruction with tissue expander placement	Cohort 1: Neoadjuvant CTX: n=226 (31.1%), adjuvant CTX: n=113 (15.5%) Cohort 2: neoadjuvant n=13 (20.6%), adjuvant n=9 (14.3%) Cohort 3: n=83 neoadjuvant CTX (73.5%), n=28 adjuvant CTX (24.8%)	NR	Cohort 1: n=20 Hematoma (2.8%), n=36 seroma (5.0%), n=95 infections requiring PO antibiotics (13.1%), n=53 infections requiring IV antibiotics (7.3%), n=24 infections requiring procedure (3.3%), n=3 partial nipple necrosis (0.4%), n=6 complete nipple necrosis (0.8%), n=12 partial-thickness skin necrosis (1.7%), n=27 full-thickness necrosis (3.7%), n=23 incisional breakdowns (7.2%), n=33 expander/ implant exposure (4.5%), n=37 expander/ implant removal (5.1%) Cohort 2: n=0 hematoma (0%), n=7 seroma (11.1%), n=17 infections requiring PO antibiotics (27.0%), n=13 infections requiring IV antibiotics (20.6%), n=6 infections requiring procedure (9.5%), n=1 partial nipple necrosis (1.6%), n=1 complete nipple necrosis (1.6%), n=2 partial-thickness skin necrosis (3.2%), n=5 full-thickness necrosis (7.9%), n=6 incisional breakdowns (24.0%), n=7 expander/ implant exposure (11.1%), n=13 expander/ implant removal (20.6%) Cohort 3: n=3 hematoma (2.7%), n=7 seroma (6.2%), n=30 infections requiring PO antibiotics (26.5%), n=25 infections requiring IV antibiotics (22.1%), n=7 infections requiring procedure (6.2%), n=0 partial nipple necrosis (0%), n=0 complete nipple necrosis (0%), n=4 partial-thickness skin necrosis (3.5%), n=13 full-thickness necrosis (11.5%), n=2 incisional breakdowns (6.1%), n=12 expander/ implant exposure (10.6%), n=20 expander/ implant removal (17.7%) Conclusion: Cohort 2 (PRT) had a higher complication rate	

Author, Year of publication, Journal	Number of patients	Inclusion criteria	RT Technique/ dose/ fractions	Surgical procedure	Chemotherapy	Time interval between end of neoadjuvant therapy and surgery	Acute toxicity (up to three months after surgery) + Subacute toxicity (three months until one year after surgery)	Late toxicity (from one year after surgery)
	n=113 breasts							
Matuschek et al. [12], 2019, Strahlentherapie und Onkologie	n=315 LABC receiving PRT (study group partially [1]). After a median follow-up of 17.7 years (14-21 years) n=203 were alive. n=107 were investigated in the follow up (n=64 after BCS and 43 after ME)	NR	Preoperative RT: external-beam RT of 50 Gy/2 Gy SD to the breast and the supra-/ infraclavicular lymph nodes, n=101 patients: interstitial boost of 10 Gy	ME (+/- reconstruction) and in 50.8% BCS with a tumor-specific immediate reconstruction. n=1 refused surgery after complete response.	simultaneously in 113 patients	2-11 months (median 4.5 months)	No grade III and IV late side effects were detected. Grade II: BCS: pigmentation change °II: 2%, teleangiectasia° II: 7% Grad: II: ME: Pigmentation change°II: 6,3%, teleangiectasia°II: 6.3%	

15. REFERENCES

1. Early Breast Cancer Trialists' Collaborative, G., *Long-term outcomes for neoadjuvant versus adjuvant chemotherapy in early breast cancer: meta-analysis of individual patient data from ten randomized trials.* Lancet Oncol, 2018. **19**(1): p. 27-39.
2. Wallgren, A., et al., *Preoperative radiotherapy in operable breast cancer: results in the Stockholm Breast Cancer Trial.* Cancer, 1978. **42**(3): p. 1120-5.
3. Wallgren, A., et al., *Radiation therapy in operable breast cancer: results from the Stockholm trial on adjuvant radiotherapy.* Int J Radiat Oncol Biol Phys, 1986. **12**(4): p. 533-7.
4. *Favourable and unfavourable effects on long-term survival of radiotherapy for early breast cancer: an overview of the randomized trials. Early Breast Cancer Trialists' Collaborative Group.* Lancet, 2000. **355**(9217): p. 1757-70.
5. Poortmans, P.M., et al., *Internal Mammary and Medial Supraclavicular Irradiation in Breast Cancer.* N Engl J Med, 2015. **373**(4): p. 317-27.
6. Poleszczuk, J., et al., *Neoadjuvant radiotherapy of early-stage breast cancer and long-term disease-free survival.* Breast Cancer Res, 2017. **19**(1): p. 75.
7. Brackstone, M., et al., *Concurrent Neoadjuvant Chemotherapy and Radiation Therapy in Locally Advanced Breast Cancer.* Int J Radiat Oncol Biol Phys, 2017. **99**(4): p. 769-776.
8. Matuschek, C., et al., *Long-term outcome after neoadjuvant radiochemotherapy in locally advanced noninflammatory breast cancer and predictive factors for a pathologic complete remission : results of a multivariate analysis.* Strahlenther Onkol, 2012. **188**(9): p. 777-81.
9. Huober, J., et al., *Neoadjuvant chemotherapy with paclitaxel and everolimus in breast cancer patients with non-responsive tumors to epirubicin/cyclophosphamide (EC)+/-bevacizumab - Results of the randomized GeparQuinto study (GBG 44).* Eur J Cancer, 2013. **49**(10): p. 2284-93.
10. von Minckwitz, G., et al., *Intensified neoadjuvant chemotherapy in early-responding breast cancer: phase III randomized GeparTrio study.* J Natl Cancer Inst, 2008. **100**(8): p. 552-62.
11. Houssami, N., et al., *Meta-analysis of the association of breast cancer subtype and pathologic complete response to neoadjuvant chemotherapy.* Eur J Cancer, 2012. **48**(18): p. 3342-54.
12. Matuschek, C., et al., *Long-term cosmetic outcome after preoperative radio-/chemotherapy in locally advanced breast cancer patients.* Strahlenther Onkol, 2019. **195**(7): p. 615-628.
13. Roth, S.L., et al., *Retrospective study of neoadjuvant versus adjuvant radiochemotherapy in locally advanced noninflammatory breast cancer : survival advantage in cT2 category by neoadjuvant radiochemotherapy.* Strahlenther Onkol, 2010. **186**(6): p. 299-306.
14. Gerlach, B., et al., *Remission rates in breast cancer treated with preoperative chemotherapy and radiotherapy.* Strahlenther Onkol, 2003. **179**(5): p. 306-11.
15. Baltodano, P.A., et al., *Preoperative Radiotherapy Is Not Associated with Increased Post-mastectomy Short-term Morbidity: Analysis of 77,902 Patients.* Plast Reconstr Surg Glob Open, 2017. **5**(3): p. e1108.
16. Brooks, S., et al., *Risk factors for complications of radiation therapy on tissue expander breast reconstructions.* Breast J, 2012. **18**(1): p. 28-34.

17. Nahabedian, M.Y., et al., *Infectious complications following breast reconstruction with expanders and implants.* Plast Reconstr Surg, 2003. **112**(2): p. 467-76.
18. Colwell, A.S., et al., *Retrospective review of 331 consecutive immediate single-stage implant reconstructions with acellular dermal matrix: indications, complications, trends, and costs.* Plast Reconstr Surg, 2011. **128**(6): p. 1170-8.
19. Sbitany, H., et al., *Immediate implant-based breast reconstruction following total skin-sparing mastectomy in women with a history of augmentation mammaplasty: assessing the safety profile.* Plast Reconstr Surg, 2014. **134**(1): p. 1-9.
20. Selber, J.C., et al., *Risk factors and complications in free TRAM flap breast reconstruction.* Ann Plast Surg, 2006. **56**(5): p. 492-7.
21. Reish, R.G., et al., *Breast reconstruction outcomes after nipple-sparing mastectomy and radiation therapy.* Plast Reconstr Surg, 2015. **135**(4): p. 959-66.
22. Sauer, R., et al., *Preoperative versus postoperative chemoradiotherapy for rectal cancer.* N Engl J Med, 2004. **351**(17): p. 1731-40.
23. O'Sullivan, B., et al., *Preoperative versus postoperative radiotherapy in soft-tissue sarcoma of the limbs: a randomized trial.* Lancet, 2002. **359**(9325): p. 2235-41.
24. Thomas, M., et al., *Effect of preoperative chemoradiation in addition to preoperative chemotherapy: a randomized trial in stage III non-small-cell lung cancer.* Lancet Oncol, 2008. **9**(7): p. 636-48.
25. Calitchi, E., et al., *Long-term results of neoadjuvant radiation therapy for breast cancer.* Int J Cancer, 2001. **96**(4): p. 253-9.
26. Bollet, M.A., et al., *Preoperative radio-chemotherapy in early breast cancer patients: long-term results of a phase II trial.* Radiother Oncol, 2012. **102**(1): p. 82-8.
27. Ricci, J.A., et al., *A meta-analysis of implant-based breast reconstruction and timing of adjuvant radiation therapy.* J Surg Res, 2017. **218**: p. 108-116.
28. Berbers, J., et al., *'Reconstruction: before or after postmastectomy radiotherapy?' A systematic review of the literature.* Eur J Cancer, 2014. **50**(16): p. 2752-62.
29. Kuehlmann, B., et al., *Capsular fibrosis in aesthetic and reconstructive-cancer patients: A retrospective analysis of 319 cases.* Clin Hemorheol Microcirc, 2018. **70**(2): p. 191-200.
30. Haviland, J.S., et al., *Late normal tissue effects in the arm and shoulder following lymphatic radiotherapy: Results from the UK START (Standardisation of Breast Radiotherapy) trials.* Radiother Oncol, 2018. **126**(1): p. 155-162.
31. Lipa, J.E., et al., *Pathogenesis of radiation-induced capsular contracture in tissue expander and implant breast reconstruction.* Plast Reconstr Surg, 2010. **125**(2): p. 437-45.
32. Bentzen, S.M., et al., *The UK Standardisation of Breast Radiotherapy (START) Trial B of radiotherapy hypofractionation for treatment of early breast cancer: a randomized trial.* Lancet, 2008. **371**(9618): p. 1098-107.
33. Budach, W., et al., *Adjuvant radiation therapy of regional lymph nodes in breast cancer - a meta-analysis of randomized trials- an update.* Radiat Oncol, 2015. **10**: p. 258.
34. Bartelink, H., 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 randomized phase 3 trial.* Lancet Oncol, 2015. **16**(1): p. 47-56.
35. Budach, W., E. Bolke, and C. Matuschek, *Hypofractionated Radiotherapy as Adjuvant Treatment in Early Breast Cancer. A Review and Meta-Analysis of Randomized Controlled Trials.* Breast Care (Basel), 2015. **10**(4): p. 240-5.
36. Poortmans P., S.H., Kirkove C., Budach V., Maingon P., Valli M.C., Collette S., Fourquet A., Bartelink H., Van den Bogaert W., *Irradiation of the internal mammary*

and medial supraclavicular lymph nodes in stage I to III breast cancer: 10 years results of the EORTC Radiation Oncology and Breast Cancer Groups phase III trial 22922/10925. EJC, 2011. **47 Suppl 2**.
37. Group, S.T., et al., *The UK Standardisation of Breast Radiotherapy (START) Trial B of radiotherapy hypofractionation for treatment of early breast cancer: a randomized trial.* Lancet, 2008. **371**(9618): p. 1098-107.
38. Whelan T.J., O.I., Ackerman I., Chapman J.W., Chua B., Nabid A., Vallis K.A., White J.R., Rousseau P., Fortin A., Pierce L.J., Manchul L., Craighead P., Nolan M.C., Bowen J., McCready D.R., Pritchard K.I., Leine M.N., Parulekar w., *NCIC-CTG MA.20: An intergroup trial of regional nodal irradiation in early breast cancer.* Journal of Clinical Oncology ASCO Annual Meeting Proceedings (Post-Meeting Edition), 2011. **29**(18_suppl (June 20 Supplement)).
39. Haviland, J.S., et al., *The UK Standardisation of Breast Radiotherapy (START) trials of radiotherapy hypofractionation for treatment of early breast cancer: 10-year follow-up results of two randomized controlled trials.* Lancet Oncol, 2013. **14**(11): p. 1086-94.
40. Shahid, A., et al., *Post mastectomy adjuvant radiotherapy in breast cancer: a comparision of three hypofractionated protocols.* J Pak Med Assoc, 2009. **59**(5): p. 282-7.
41. Owen, J.R., et al., *Effect of radiotherapy fraction size on tumor control in patients with early-stage breast cancer after local tumor excision: long-term results of a randomized trial.* Lancet Oncol, 2006. **7**(6): p. 467-71.
42. Badiyan, S.N., et al., *Hypofractionated regional nodal irradiation for breast cancer: examining the data and potential for future studies.* Radiother Oncol, 2014. **110**(1): p. 39-44.
43. Haffty, B.G. and T.A. Buchholz, *Hypofractionated breast radiation: preferred standard of care?* Lancet Oncol, 2013. **14**(11): p. 1032-1034.
44. Guenzi, M., et al., *Hypofractionated irradiation of infra-supraclavicular lymph nodes after axillary dissection in patients with breast cancer post-conservative surgery: impact on late toxicity.* Radiat Oncol, 2015. **10**: p. 177.
45. Bellefqih, S., et al., *Hypofractionated Regional Nodal Irradiation for Women With Node-Positive Breast Cancer.* Int J Radiat Oncol Biol Phys, 2017. **97**(3): p. 563-570.
46. Richter, H., et al., *Is Breast Surgery Necessary for Breast Carcinoma in Complete Remission Following Neoadjuvant Chemotherapy?* Geburtshilfe Frauenheilkd, 2018. **78**(1): p. 48-53.
47. Matuschek, C., et al., *Post-Neoadjuvant Treatment Strategies in Breast Cancer.* Cancers (Basel), 2022. **14**(5).
48. Haussmann, J., et al., *Predictive Factors of Long-Term Survival after Neoadjuvant Radiotherapy and Chemotherapy in High-Risk Breast Cancer.* Cancers (Basel), 2022. **14**(16).
49. Offersen, B.V., et al., *ESTRO consensus guideline on target volume delineation for elective radiation therapy of early stage breast cancer, version 1.1.* Radiother Oncol, 2016. **118**(1): p. 205-8.
50. EMA, *Points to consider switching between superiority and non-inferiority.* CPMP/EWP, 2000.
51. Delanian, S., J.L. Lefaix, and P.F. Pradat, *Radiation-induced neuropathy in cancer survivors.* Radiother Oncol, 2012. **105**(3): p. 273-82.
52. Olsen, N.K., et al., *Radiation-induced brachial plexus neuropathy in breast cancer patients.* Acta Oncol, 1990. **29**(7): p. 885-90.

53. Olsen, N.K., et al., *Radiation-induced brachial plexopathy: neurological follow-up in 161 recurrence-free breast cancer patients.* Int J Radiat Oncol Biol Phys, 1993. **26**(1): p. 43-9.
54. Mondrup, K., et al., *Clinical and electrodiagnostic findings in breast cancer patients with radiation-induced brachial plexus neuropathy.* Acta Neurol Scand, 1990. **81**(2): p. 153-8.
55. Cavanagh, J.B., *Effects of previous x-irradiation on the cellular response of nervous tissue to injury.* Nature, 1968. **219**(5154): p. 626-7.
56. Cavanagh, J.B., *Effects of x-irradiation on the proliferation of cells in peripheral nerve during Wallerian degeneration in the rat.* Br J Radiol, 1968. **41**(484): p. 275-81.
57. Denham, J.W. and M. Hauer-Jensen, *The radiotherapeutic injury--a complex 'wound'.* Radiother Oncol, 2002. **63**(2): p. 129-45.
58. Stoll, B.A. and J.T. Andrews, *Radiation-induced Peripheral Neuropathy.* Br Med J, 1966. **1**(5491): p. 834-7.
59. Johansson, S., H. Svensson, and J. Denekamp, *Dose response and latency for radiation-induced fibrosis, edema, and neuropathy in breast cancer patients.* Int J Radiat Oncol Biol Phys, 2002. **52**(5): p. 1207-19.
60. Galecki, J., et al., *Radiation-induced brachial plexopathy and hypofractionated regimens in adjuvant irradiation of patients with breast cancer--a review.* Acta Oncol, 2006. **45**(3): p. 280-4.
61. Kwan, W., et al., *Chronic arm morbidity after curative breast cancer treatment: prevalence and impact on quality of life.* J Clin Oncol, 2002. **20**(20): p. 4242-8.
62. Nesvold, I.L., et al., *Arm/shoulder problems in breast cancer survivors are associated with reduced health and poorer physical quality of life.* Acta Oncol, 2010. **49**(3): p. 347-53.
63. Brix, N., et al., *Abscopal, immunological effects of radiotherapy: Narrowing the gap between clinical and preclinical experiences.* Immunol Rev, 2017. **280**(1): p. 249-279.
64. Hader, M., et al., *Immune biological rationales for the design of combined radio- and immunotherapies.* Cancer Immunol Immunother, 2020. **69**(2): p. 293-306.
65. Ngwa, W., et al., *Using immunotherapy to boost the abscopal effect.* Nat Rev Cancer, 2018. **18**(5): p. 313-322.
66. Orth, M., et al., *Current concepts in clinical radiation oncology.* Radiat Environ Biophys, 2014. **53**(1): p. 1-29.
67. Bristow, R.G., et al., *Combining precision radiotherapy with molecular targeting and immunomodulatory agents: a guideline by the American Society for Radiation Oncology.* Lancet Oncol, 2018. **19**(5): p. e240-e251.
68. Reinhardt, F., et al., *Navigation through inter- and intratumoral heterogeneity of endocrine resistance mechanisms in breast cancer: A potential role for Liquid Biopsies?* Tumor Biol, 2017. **39**(11): p. 1010428317731511.
69. Fehm, T. and M. Banys, *Circulating free DNA: a new surrogate marker for minimal residual disease?* Breast Cancer Res Treat, 2011. **130**(1): p. 119-22.
70. Franken, A., et al., *Detection of ESR1 Mutations in Single Circulating Tumor Cells on Estrogen Deprivation Therapy but Not in Primary Tumors from Metastatic Luminal Breast Cancer Patients.* J Mol Diagn, 2020. **22**(1): p. 111-121.
71. Chang, D.W., M.T. Friel, and A.A. Youssef, *Reconstructive strategies in soft tissue reconstruction after resection of spinal neoplasms.* Spine, 2007. **32**(10): p. 1101-6.
72. Grinsell, D., et al., *Immediate autologous breast reconstruction after neoadjuvant chemoradiotherapy for breast cancer: initial results of the first 29 patients.* ANZ J Surg, 2018. **88**(3): p. E137-E141.

73. Hartmann, K.A., et al., *[Preoperative irradiation and interstitial radiotherapy-hyperthermia boost in breast tumors > or = 3 cm. The Dusseldorf experience]*. Strahlenther Onkol, 1997. **173**(10): p. 519-23.
74. Hultman, C.S. and S. Daiza, *Skin-sparing mastectomy flap complications after breast reconstruction: review of incidence, management, and outcome.* Ann Plast Surg, 2003. **50**(3): p. 249-55; discussion 255.
75. Krueger, E.A., et al., *Complications and patient satisfaction following expander/implant breast reconstruction with and without radiotherapy.* Int J Radiat Oncol Biol Phys, 2001. **49**(3): p. 713-21.
76. Lerouge, D., et al., *Combined chemotherapy and preoperative irradiation for locally advanced noninflammatory breast cancer: updated results in a series of 120 patients.* Int J Radiat Oncol Biol Phys, 2004. **59**(4): p. 1062-73.
77. Mukai, H., et al., *Final results of a safety and efficacy trial of preoperative sequential chemoradiation therapy for the nonsurgical treatment of early breast cancer: Japan Clinical Oncology Group Study JCOG0306.* Oncology, 2013. **85**(6): p. 336-41.
78. Ogunleye, A.A., et al., *An analysis of delayed breast reconstruction outcomes as recorded in the American College of Surgeons National Surgical Quality Improvement Program.* J Plast Reconstr Aesthet Surg, 2012. **65**(3): p. 289-94.
79. Paillocher, N., et al., *Evaluation of mastectomy with immediate autologous latissimus dorsi breast reconstruction following neoadjuvant chemotherapy and radiation therapy: A single institution study of 111 cases of invasive breast carcinoma.* Eur J Surg Oncol, 2016. **42**(7): p. 949-55.
80. Riet, F.G., et al., *Preoperative radiotherapy in breast cancer patients: 32 years of follow-up.* Eur J Cancer, 2017. **76**: p. 45-51.
81. Semiglazov, V.F., et al., *Primary (neoadjuvant) chemotherapy and radiotherapy compared with primary radiotherapy alone in stage IIb-IIIa breast cancer.* Ann Oncol, 1994. **5**(7): p. 591-5.
82. Unukovych, D., et al., *Predictors of Reoperations in Deep Inferior Epigastric Perforator Flap Breast Reconstruction.* Plast Reconstr Surg Glob Open, 2016. **4**(8): p. e1016.
83. Shanta, V., et al., *Retrospective analysis of locally advanced noninflammatory breast cancer from Chennai, South India, 1990-1999.* Int J Radiat Oncol Biol Phys, 2008. **70**(1): p. 51-8.
84. Touboul, E., et al., *Possibility of conservative local treatment after combined chemotherapy and preoperative irradiation for locally advanced noninflammatory breast cancer.* Int J Radiat Oncol Biol Phys, 1996. **34**(5): p. 1019-28.
85. Aryus, B., et al., *Remission rates following preoperative chemotherapy and radiation therapy in patients with breast cancer.* Strahlenther Onkol, 2000. **176**(9): p. 411-5.
86. Ascherman, J.A., et al., *Implant reconstruction in breast cancer patients treated with radiation therapy.* Plast Reconstr Surg, 2006. **117**(2): p. 359-65.
87. Weintraub, J.L. and D.M. Kahn, *The timing of implant exchange in the development of capsular contracture after breast reconstruction.* Eplasty, 2008. **8**: p. e31.
88. Skinner, K.A., et al., *Preoperative paclitaxel and radiotherapy for locally advanced breast cancer: surgical aspects.* Ann Surg Oncol, 2000. **7**(2): p. 145-9.
89. Zinzindohoue, C., et al., *A Prospective Study on Skin-Sparing Mastectomy for Immediate Breast Reconstruction with Latissimus Dorsi Flap After Neoadjuvant Chemotherapy and Radiotherapy in Invasive Breast Carcinoma.* Ann Surg Oncol, 2016. **23**(7): p. 2350-6.
90. Yaremko, B., et al., *Results of a Prospective Cohort Trial: Stereotactic Image-Guided Neoadjuvant Ablative Radiation Then Lumpectomy (SIGNAL) for Early-Stage Breast*

Cancer. International Journal of Radiation Oncology • Biology • Physics, 2018. **102**(3): p. S69.
91. Gaui, M.F., et al., *A phase II study of second-line neoadjuvant chemotherapy with capecitabine and radiation therapy for anthracycline-resistant locally advanced breast cancer.* Am J Clin Oncol, 2007. **30**(1): p. 78-81.
92. *Erratum to: Woodward WA, Fang P, Arriaga L, et al. A phase 2 study of preoperative capecitabine and concomitant radiation in women with advanced breast cancer. Int J Radiat Oncol Biol Phys 2017;99:777-783.* Int J Radiat Oncol Biol Phys, 2018. **101**(2): p. 497.
93. van der Leij, F., et al., *First results of the preoperative accelerated partial breast irradiation (PAPBI) trial.* Radiother Oncol, 2015. **114**(3): p. 322-7.
94. Rutqvist, L.E., D. Pettersson, and H. Johansson, *Adjuvant radiation therapy versus surgery alone in operable breast cancer: long-term follow-up of a randomized clinical trial.* Radiother Oncol, 1993. **26**(2): p. 104-10.
95. Pazos, M., et al., *Neoadjuvant radiotherapy followed by mastectomy and immediate breast reconstruction : An alternative treatment option for locally advanced breast cancer.* Strahlenther Onkol, 2017. **193**(4): p. 324-331.
96. Nichols, E., et al., *Preoperative Accelerated Partial Breast Irradiation for Early-Stage Breast Cancer: Preliminary Results of a Prospective, Phase 2 Trial.* Int J Radiat Oncol Biol Phys, 2017. **97**(4): p. 747-753.
97. Monrigal, E., et al., *Mastectomy with immediate breast reconstruction after neoadjuvant chemotherapy and radiation therapy. A new option for patients with operable invasive breast cancer. Results of a 20 years single institution study.* Eur J Surg Oncol, 2011. **37**(10): p. 864-70.
98. Ishitobi, M., et al., *Phase II study of neoadjuvant anastrozole and concurrent radiotherapy for postmenopausal breast cancer patients.* Breast Cancer, 2014. **21**(5): p. 550-6.
99. Horton, J.K., et al., *Preoperative Single-Fraction Partial Breast Radiation Therapy: A Novel Phase 1, Dose-Escalation Protocol With Radiation Response Biomarkers.* Int J Radiat Oncol Biol Phys, 2015. **92**(4): p. 846-55.
100. Formenti, S.C., et al., *Preoperative twice-weekly paclitaxel with concurrent radiation therapy followed by surgery and postoperative doxorubicin-based chemotherapy in locally advanced breast cancer: a phase I/II trial.* J Clin Oncol, 2003. **21**(5): p. 864-70.
101. Colleoni, M., et al., *Pre-operative chemotherapy and radiotherapy in breast cancer.* Eur J Cancer, 1998. **34**(5): p. 641-5.
102. Coelho, R.C., et al., *Is there a role for salvage radiotherapy in locally advanced breast cancer refractory to neoadjuvant chemotherapy?* Breast, 2017. **31**: p. 192-196.
103. Chakravarthy, A.B., et al., *Neoadjuvant concurrent paclitaxel and radiation in stage II/III breast cancer.* Clin Cancer Res, 2006. **12**(5): p. 1570-6.
104. Bourgier, C., et al., *Exclusive alternating chemotherapy and radiotherapy in nonmetastatic inflammatory breast cancer: 20 years of follow-up.* Int J Radiat Oncol Biol Phys, 2012. **82**(2): p. 690-5.
105. Bondiau, P.Y., et al., *Phase 1 clinical trial of stereotactic body radiation therapy concomitant with neoadjuvant chemotherapy for breast cancer.* Int J Radiat Oncol Biol Phys, 2013. **85**(5): p. 1193-9.
106. Alvarado-Miranda, A., et al., *Concurrent chemo-radiotherapy following neoadjuvant chemotherapy in locally advanced breast cancer.* Radiat Oncol, 2009. **4**: p. 24.

107. Adams, S., et al., *Preoperative concurrent paclitaxel-radiation in locally advanced breast cancer: pathologic response correlates with five-year overall survival.* Breast Cancer Res Treat, 2010. **124**(3): p. 723-32.
108. Skinner, K.A., et al., *Preoperative 5-fluorouracil and radiation therapy for locally advanced breast cancer.* Am J Surg, 1997. **174**(6): p. 705-7; discussion 707-8.

16. APPENDIX

Appendix 1 Participating institutions

Appendix 2 Patient information and patient informed consent form for the study

Appendix 3 Subject insurance

Appendix 4 CTCAE Version 5.0

Appendix 5 EORTC QLQ-C30, EORTC QLQ-B23