The DBCG RT Recon Trial:
Delayed-immediate versus delayed breast reconstruction
in early breast cancer patients
treated with mastectomy and adjuvant loco-regional radiation therapy.

A multicenter randomized and single arm clinical trial

Version 1 single arm trial

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BACKGROUND

Breast cancer is the most common cancer in Danish women affecting one out of 10 women. Breast cancer is treated in a multidisciplinary setting with a combination of surgery, chemotherapy, and radiation therapy according to the Danish Breast Cancer Group´s treatment protocol.[1] The treatment may leave the patient with highly visible scars, a lack of a breast, and deformity or asymmetry of the breasts. The prognosis has improved over the last decades, so more attention has been raised towards better cosmetic outcome and less alteration of the body image. Thus immediate as well as delayed breast reconstruction have become integrated in treatment of carcinoma in situ and invasive breast cancer.[2,3]

In Denmark, approximately 40% of the women undergoing mastectomy for breast cancer have a breast reconstructive procedure performed later.[4] Patients who have received a breast reconstruction attain a more positive body image and their thoughts about cancer and death are less intrusive.[5,6] Furthermore, high satisfaction among patients with breast reconstruction has been documented, with patients reporting greater freedom and a better quality of life (QoL) after the reconstruction.[7–9] In delayed reconstruction, autologous tissue based procedures turn out to be superior to implant-based reconstruction and yielding better QoL.[9–11]

Several studies have reported on the results after immediate as well as delayed breast reconstruction, and for the last fifteen years there have also been several studies published on the concept of delayed-immediate breast reconstruction.[12–16] The gain by delayed-immediate reconstruction is a preservation of the native skin envelope while radiation therapy is given, thus improving the results after final reconstruction when the radiation therapy is finished.

In the setting of post-mastectomy radiation therapy (PMRT), or any other adjuvant therapy for that matter, it is of utmost importance to choose the safest reconstructive technique in order not to delay adjuvant therapy[17,18]. This favors a surgical procedure with no donor-site and a simple reconstruction. Several studies on timing of radiation therapy and reconstructive procedures have been published including 3 reviews.[19–21] These papers systematically review the currently available evidence, describing in-coherent, retrospective, smaller or larger cohorts of patients from multiple centers, who had either implant-based or autologous reconstructions performed on very different time-points in the course of treatment.[19] The patients had, moreover, undergone various radiation protocols (different doses, with or without boost and bolus etc.). In addition, different outcomes are reported in the individual studies, and it is therefore not possible to draw any firm conclusion on which type of reconstructive procedure to prefer

Very recently published studies likewise do not give a clear indication on which type of reconstruction to prefer in patients undergoing radiation therapy as well,[22–24] although one of the studies reports acceptable results with autologous immediate breast reconstruction.[23] The long-term oncological outcome after reconstruction and radiation therapy is not well described, but recently the 10-year experience with delayed immediate reconstruction at MD Anderson Cancer Center was published.[25] Almost 400 patients were treated with skin-sparing mastectomy and immediate tissue expander placement and subsequent radiation thera-

py. Final reconstruction was performed around 12 months after the primary operation and 7 months after PMRT. Eighty-five percent had a final procedure performed. Thirteen percent had complications and had the expander removed. Five-years loco-regional control and overall survival was 99% and 92%, respectively. Data on target volume definition and radiation therapy technique used as well as cosmetic outcome in this patient cohort are still awaited.

The aim of the present study is to evaluate whether it is safe with regard to surgical complications to offer early breast cancer patients a possibility to preserve the native breast skin with a minimally invasive procedure at a very critical time in the patient pathway. Thus, more extensive reconstructive procedures may be postponed to a less critical point of time in the woman´s life.

The present study will add valuable prospectively collected data, to the DBCG population-based database on reconstructive procedures, morbidity, and final outcomes after reconstruction and PMRT.

The protocol for the current study has been changed as of june.2023 from a randomized controlled trial to a prospective study, due to unexpected low accrual (see below).

It is expected that the delayed-immediate reconstructive procedure will become the new DBCG recommendation for patients operated with mastectomy and who will have PMRT. The decision will be made by the DBCG Surgical and Radiation Therapy Committees when the first results are available. Evaluation of morbidity in the accrued patients will continue for 10 years, and if the results at a later time point are not in harmony with the first results, the recommendation in the DBCG guidelines may be altered. The DBCG Surgical and Radiation Therapy Committees decide that.

Hypothesis

Delayed-immediate breast reconstruction does not increase the risk of complications compared with the conventional delayed reconstruction in patients who are to have post-mastectomy radiation therapy.

Aim

The aim of the present trial is to monitor the occurrence of complications after delayed-immediate breast reconstruction, and compare this with delayed reconstruction in breast cancer patients with post-mastectomy radiation therapy. In addition, patient-reported outcomes will be evaluated postoperatively and compared to preoperative measurements.

STUDY POPULATION

Inclusion criteria

- Woman >18 years who are offered a mastectomy for invasive breast can-

cer pT1-3, pN0-N3, M0 and wish reconstruction. The patient can be included no matter the status of estrogen receptor, progesterone receptor, malignancy grade, and HER2 status.

- The patient is a candidate for loco-regional radiation therapy according to national or institutional guidelines. In Denmark DBCG guidelines must be followed, thus axillary lymph node status (FNA or SN positive macrometastatic nodes) gives indication for regional nodes radiation therapy to levels (I), II, III, IV, interpectoral nodes and the internal mammary nodes (IMN).
- Highly selected patients with inflammatory breast cancer, namely those with complete or near complete response to neoadjuvant systemic therapy judged by imaging and clinical examination before surgery. Any skin edema and clinical signs of skin involvement must have disappeared during systemic therapy. It is highly recommended that the decision to offer an inflammatory breast cancer patient inclusion in the DBCG RT Recon trial is made during a multidisciplinary team conference.
- Adjuvant systemic therapy with chemotherapy, endocrine therapy, anti-HER2 treatment and other targeted therapies used in the adjuvant setting either as new standard or as part of a trial during the course of the trial is accepted.
- Neoadjuvant chemotherapy and primary systemic therapy of an operable breast cancer is accepted.
- Patient with previous non-breast malignancy is accepted if the patient has been without disease minimum 5 years, and the treating oncologist estimates a low risk of recurrence. Patients with the following diseases can be accepted despite less than 5 years disease free interval: carcinoma in situ cervicis, carcinoma in situ coli, melanoma in situ, basal cell carcino-ma of the skin, squamous cell carcinoma of the skin.
- Life expectancy minimum 10 years.

Exclusion criteria

- Pregnant or lactating.
- Previous breast cancer or DCIS.
- Bilateral breast cancer.
- Previous radiation therapy to the chest region.
- Previous non-breast malignancy (not including carcinoma in situ of the cervix or colon, melanoma in situ, basal cell carcinoma of the skin, and squamous cell carcinoma of the skin) within 5 years.
- Conditions indicating that the patient cannot go through breast reconstruction, the radiation therapy or follow up.
- Not being able to participate due to language or other personal issues.
- Life expectancy less than 10 years.

The patient can be included irrespective of the type and timing of systemic therapy. This trial accepts that randomized patients participate in other trial protocols testing new systemic therapies, e.g. inhibitors of CDK4 and CDK6 kinase activity like abemaciclib in the Monarch E trial. It is also accepted that the patient is included in trials testing loco-regional therapies, e.g. the SENOMAC trial and the

Skagen Trial 1.

TREATMENT PROTOCOL

The first version of tha trial was designed as a randomized trial. The inclusion started 1/1-2020. Due to slow accrual, the steering committee has decided to change the trial per 30/6-2023 to a prospective trial of arm A without randomization. It is expected that a prospective trial design will make is feasable for more departments to participate

Treatment arm A

Delayed-immediate reconstruction:

Primary Surgery: Skin sparing mastectomy (nipple sparing if appropriate) and axillary surgery according to guidelines or protocol. Reconstruction with silicone implant or expander covered by pectoral muscle and mesh or matrix.

Delayed reconstruction: Final reconstruction with any reconstructive procedure – being it autologous or implant-based (one- or two-stage, +/- acellular dermal matrix (ADM)) – is performed 6-12 months after completion of chemotherapy and RT. Any contralateral procedure is allowed when doing the delayed surgery, but not in relation to the initial cancer surgery.

Patients, who will not have the second delayed procedure performed will be included in the analysis of 'intention to treat'group and not excluded from the study.

Treatment arm B

Delayed reconstruction:

Primary surgery: Total mastectomy and axillary surgery according to guidelines or protocol.

Delayed reconstruction: 6-12 months after completion of PMRT: final reconstruction with any reconstructive procedure – being it autologous or implant-based (one-or two-stage, +/- ADM). Any contralateral procedure is allowed at any time point after PMRT has been delivered.

This arm recruited patients between 1/1-2020 and 30/6-2023

Concerning post mastectomy radiation therapy (PMRT)

This issue is described in the new ESTRO consensus guidelines for target volume delineation in implant based reconstruction [26].

In general, the tissue beneath the skin surface of the mammarian region is the clinical target volume in all cases.

Implant-based reconstruction and PMRT

In patients radically operated with mastectomy for an early breast cancer, which did not cross the dorsal breast fascia, the target for PMRT is ventral to the implant.

In patients operated for a locally advanced breast cancer (LABC) after complete or partial response to primary systemic therapy (PST), the target for PMRT should include the above described rim of tissue ventral to the implant with addition of relevant bolus to ensure dose in the skin and in addition the part of chest wall dorsal to the implant caudal to the pre-surgical insertion of the major pectoral muscle, in case the tumour was positioned in areas not ventral to the major pectoral muscle. To help identify this volume the surgeon may insert 2-3 clips in the chest wall where the major pectoral muscle inserted prior to placing the implant.

In patients operated for a large breast cancer (pT3) or a LABC with poor response to PST or a breast cancer invading into the major pectoral muscle/chest wall (in general not considered a good candidate for reconstruction though), the target must be individually modified accordingly and the clinician should consider to fully include the chest wall dorsal to the implant in the whole regio mammaria, the aim being to include the deep lymphatic plexus in the chest wall as well.

If the patient is not radically operated, re-operation is recommended. However, if it is decided not to re-operate but instead use a boost, then the patient can still be part of the DBCG RT Recon trial even if the boost is not provided.

RANDOMIZATION PROCEDURE

The randomization procedure was performed through the database of DBCG. It is an online system, which allows the treating staff to perform the randomization procedure within few minutes, and most of the patients was thus informed on the randomization while still at the hospital.
The randomization procedure has been in use between 1/1-2020 and 30/6-2023.
For the prospective part of the trial, a registration process similar to the randomization procedure (except the randomization part) will be used to register the patients.

RISK TO THE PATIENT

Breast cancer patients undergoing reconstruction irrespective of if done immediate or delayed have no increased risk of breast cancer mortality,[27] but more surgical complications are observed if reconstruction is performed. Thus, immediate reconstruction was shown to have a somewhat higher risk of surgical complications compared with patients having mastectomy alone in a large register based study from USA on more than 14.000 patients among whom almost 40% had immediate reconstruction.[22] Wound complications within the first 2 postoperative years was observed in 2.3%, 4.4%, and 9.5% after no reconstruction, reconstruction with implants, and after autologous reconstruction, respectively. Corresponding figures for infection was 12.7%, 20.5%, and 20.7%, respectively. The risk of infection was increased in patients receiving RT (odds ratio 1.29).

Radiotherapy almost doubled the risk of loss of implant (21.9% vs. 13.1%). Loss of reconstruction after autologous reconstruction was not reported.

The failure rate of implant-based breast reconstruction is high if combined with RT. In a systematic review where post-reconstruction radiotherapy was compared with reconstruction as a second procedure after simple mastectomy and radiotherapy, the failure rates were similar around 20%.[21]

In Denmark it has been found that the risk of surgical complications after secondary reconstruction seem to be comparable to the risk after immediate reconstruction. Thus, a recent survey from a Danish university department reported that in total 26% of patients had complications demanding further surgery.[11] In that study most patients had pure autologous or a combination of autologous and implant reconstruction.

Kronowitz et al. have published results from their experience with the delayed-immediate breast reconstruction procedure.[13] Fourteen percent had surgical complications after the initial procedure with mastectomy and expander implant (N=77). Among those who had RT after the primary procedure (N=24), 17% had complications while this was seen in only 7% of those not needing RT (N=44 - the definitive procedure was done within a few weeks in these cases).

Consequently, patients accepting participation in this study should be informed that reconstruction in combination with radiotherapy after mastectomy at least doubles the risk of surgical complications but does not increase the risk of dying of breast cancer. It is not expected that the new reconstruction method will increase the complication rate compared to standard reconstruction methods in combination with radiotherapy after mastectomy. The study is designed to show that the patients in the interventional study group will not have a risk exceeding 36% fore surgical complications needing further surgery.

INFORMATION OF THE PATIENT

Information is given in the plastic surgery clinic when patients are informed about the diagnosis and the treatment plan is discussed with her. The meeting takes place in a quiet and undisturbed room. The informing doctor first informs the patient about the standard therapy with total mastectomy, radiotherapy and delayed reconstruction, and it will be made clear to her that this is the standard therapy. Then the doctor informs about the posibility of participating in the trial with delayed-immediate reconstruction. The patient is informed about the pros and cons of proceding with delayed-immediate breast reconstruction and subsequent radiation therapy. This treatment is only offered as part of this study, and not outside the trial.. In the period with randomized trial design the patient was in addition informed about randomization be-tween standard therapy and experimental therapy. The patients will be informed according to the national guidelines regarding patient participation in trials. The patient is handed a written information about both standard therapy and the therapy on trial. The patient is invited to give her consent after she has had sufficient time to make her decision, and she is offered another session at the hospital to give her consent to participate in the trial after a 24 hour time of reflection. She is encouraged to

have an observer present, when giving her consent. After her written consent, baseline morbidity evaluation is performed,

At the first consultation and in the written information about the trial the patient is informed that we want information from her patient file passed on to the trial regarding tumour characteristics, and also about her recurrence and survival status for 15 years after randomization and on events related to the reconstruction. If she has a recurrence we need data passed on from her patient file regarding when and where the recurrence took place. The tumour characteristics are: tumour histological type, size, lymph node status (how many removed and how many with metastasis and what type of metastasis), malignancy grade/ER/PR/HER2/Ki67 status, Q score, resection margin, and surgical procedure, radiation therapy, and systemic treatment. Also information about serious events like a new cancer, heart disease, lung disease and stroke is passed on from her patient file, because these events may be related to the radiation therapy. If an increased risk of any of these events is associated with one of the radiation therapies on trial, it will influence the decision on what is to be future standard therapy.

The patient will be informed that the concent provides the investigators of the study direct access to obtain the necessary information from medical records to conduct the investigation and follow-up.

OUTCOME

Primary endpoint

Any complication deeming *surgical intervention* necessary (excluding percutaneous drainage and antibiotic treatment for inflammation in cases without need for open drainage) within a period up to 1 year after the final reconstruction:

- Infection
- Hematoma
- Loss of implant/expander
- Necrosis
- Seroma

Secondary endpoints

- Necrosis not requiring surgical intervention
- Infection not requiring surgical intervention but antibiotic treatment
- Herniation at donor-site
- Patient´s satisfaction and QoL evaluated by BREAST-Q – appropriate modules.
- Psycho-oncological endpoints evaluated by validated questionnaires:
    - Depression (Becks Depression Inventory, BDI)
    - Fear of cancer recurrence (Concerns About Recurrence

Questionnaire-3, CARQ-3)

- Timely initiation of adjuvant therapy
- Morbidity including lymphedema, capsular contracture and range of motion (ROM) of the shoulder
- Breast photos
- Recurrence
    - Local recurrence
    - Regional recurrence
    - Distant metastasis
    - Disease-specific survival
    - Overall survival
- Death including cause of death

Concerning cancer related endpoints

Cancer related endpoints are secondary endpoints in this trial, and they are local recurrence, regional recurrence, distant metastasis, disease-specific survival and overall survival. Ipsilateral local recurrence is defined as any tumour in the breast or skin over the breast or chest wall. A detailed reporting on the localization of the local recurrence will be provided through evaluation among the oncologist, the pathologist, the radiologist and the surgeon. Deciding whether a recurrence is a true recurrence, or a new primary tumor depends on the tumour-biological tests made by the pathologist according to current guidelines at the treating hospital. Regional recurrence is defined as tumour in ipsilateral axilla level 1, 2, 3, 4, internal mammary nodes (IMN), or in the interpectoral nodes. Metastases other places in the body are distant metastases. Metastases will be identified by a combination of clinical, hematological, radiological and histopathological evaluations. There may be clinical situations where histopathological evaluation is not feasible or clinically meaningful, and the oncologist will then decide whether or not the patient has a recurrence.

REGISTRATION

The project will be reported to the Central Denmark Region's internal list of research projects. Data will be handled according to *The general data protection regulation.*

Primary endpoints, necroses and infection without surgical intervention, as well as initiation of adjuvant therapy, recurrence and survival data will be registered via online forms in the DBCG-database (Appendix IIa and IIb and general DBCG registration).

Patient´s satisfaction, QoL and psycho-oncological ednpoints:

The BREAST-Q-instruments, Becks Depression Inventory (BDI) and Concerns About Recurrence Questionnaire-3 (CARQ-3) (Appendix III-VIII).

For detailed sequence see pages 14 -15.

Data will be stored in REDCap. This part is only for Danish patients

Morbidity

Questionnaire

A modification of the questionnaire designed, validated and used by Rune Gärtner et al.[28] will be applied (Appendix IX). For detailed sequence see page 14 - 15.

Data will be stored in the DBCG database under RECON questionaire

Objective evaluation

Lymphedema

Defined by the clinician by measuring arm circumference 15 cm/10 cm proximal/distal to the olecranon bilaterally. Any difference ≥10% defines edema. The dominating arm is registered (Appendix X).

Range of motion of the shoulder

Is measured at abduction/flexion with the patient sitting in front of a poster with a circle with degrees 0-180˚ (Appendix X).

Capsular contracture

Capsular contracture is measured by Bakers Grading (Appendix X)

Objective evaluation will be done at follow-up before and 1 year after first surgery and at year ½,1,2,3,4,5, and 10 after second operation and stored in the DBCG database under RECON follow-up.

Photos

Frontal and side-photos pre-operatively with arms down and arms up, before first surgery, after first surgery but before start of radiation therapy, and at year 1, 2, 3, 4, 5, and 10. At any event new photos are taken.

The photos will be stored in a database established for that purpose at Aarhus University Hospital.

The guidelines for photos is in Appendix XI.

BREAST-Q and QoL-questionnaires

TREATMENT ARM A/Pro-spective study **Delayed-immediate** **INSTRUMENT**	**PRE-OP**	**POSTOP** **2 WEEKS**	**POST-OP** **9-15 MO** **(pre-final recon)** **###**	**POST-FINAL** **RECON** **½+1+2+3+4+5+10 YEARS**
DBCG RT Recon Questionnaire*	X	X	X	X
BREAST Q **Part I_B**	X		X	
BREAST Q Recon ** **Part II_B		X	X	X
BDI **Becks Depression Inventory****	X	X	X	X
CARQ-3 **Concerns About Recur-rence Questionnaire -3****	X	X	X	X

* Mandatory Questionnaires

**Optional Questionnaires for Danish patients only. Data can be stored in RedCap

If the patient does not undergo a final reconstruction, they will have the same POST-FINAL RECONS-questionnaires as the ones who do and at the same time-points, but will not have the PRE-FINAL RECON-questionnaire.

TREATMENT ARM B Delayed reconstruction INSTRUMENT	PRE-OP	POSTOP 2 WEEKS	POST-OP 9-15 MO (pre-final recon)	POST-FINAL RECON ½+1+2+3+4+5+10 YEARS
DBCG RT Recon Questionnaire*	X	X	X	X
BREAST Q** Part I_A	X			
BREAST Q** Part II_A		X		
BREAST-Q** Part I_B			X	
BREAST-Q** Part II_B				X
BDI Becks Depression Inventory**	X	X	X	X
CARQ-3 Concerns About Recurrence Questionnaire -3**	X	X	X	X

* Mandatory Questionnaires

**Optional Questionnaires for Danish patients only. Data can be stored in RedCap

STATISTICAL CONSIDERATIONS

According to a study from our group,[11] the risk of having complications that lead to surgical interventions was 26% in patients undergoing delayed reconstruction. Thus, the success rate according to the primary endpoint is 74%. We expect a somewhat worse outcome in this study, but we will not accept a deterioration of more than 10% point, corresponding to a success rate of at least 64. In order to show that, the randomized study should include 295 patients in each group (power 80%, type 1 error 5 % [one-sided test], drop-out rate at 3 years 10%). There will be continuous inclusion of patients until patient No. 590 has been followed for 12 months. The estimation of the inclusion period is thus estimated to 5 years.

After an inclusion period of three years 55 patients from one center have been randomized, whereas the expected number is 354 patients. Due to the slow accrual rate and only one center randomizing patients the trial was changed for a prospective trial without randomization and only one treatment arm. The steering committee will consider then inclusion after another two years to decide whether to close the trial or continue.

12 month after end of inclusion in the prospective part, the complication rate for the randomized part will be calculated in the two groups, though acknowliging that there will not be sufficient power for a statistical comparision. In addition, the complication rate for all patients included in arm A with delayed-immediate reconstruktion, included after randomizasion or in the prospective arm, will be calculated. It is anticipated that the complication rate will not exceed 26%, as for delayed reconstruktion.

With a the sample size of 178, a one sided exact test will have 80% power to reject the null hypothesis of inferiority, in favor of the alternative hypothesis that the test proportion is non-inferior to the pre-specified standard, assuming that the expected actual proportion is 0,74, the non-inferiority proportion is 0,64 and that the test is made at the 2,5% significance level. With additional centres participating it is expected that a smaple size of 178 patients will be reached after additional two years of inclusion

During the active RCT is was found that some of the included patients did not wish for the delayed (autologous) reconstruction, but rather kept their primary implant. It therefore seems that the rate of capsular contracture is lower than originally expected, perhaps due to a more gentle radiation therapy in the protocol.

For the prospective study, all participants will be included in the analyses, but stratification for type of final reconstruction will be performed.

ETHICAL CONSIDERATIONS

This trial is being conducted according to the 5th version of the Helsinki Declaration. The trial can only start after the approval of the regional ethical committee for Region Midt.

The risk of complications and failure is increased in breast reconstruction after mastectomy in patients who have RT. This is well known but still more and more patients request and receive such procedures.

Patients participating in the present study will be informed that reconstrution combined with RT doubles the risk of complications no matter which treatment arm they belong to. Presumably, delayed-immediate reconstruction will lead to better results and a higher satisfaction to the patients than will delayed, secundary reconstruction if patients have a uncomplicated trajectory. Therefore, if delayed-immediate reconstuction can be performed without increasing other risks, it could turn out to be preferable, and that is what the present study aims to prove.

At present there is no firm evidence and no consensus on which procedure to preferre, but there is an international trend towards primary reconstruction also in this group of patients, and there is a risk that this approach will be routinely adopted before sufficient evidence is available, for which reason it is crucial to first explore this option through a study.

PUBLICATIONS

The results from this study will be published irrespective them being positive, negative, or inconclusive. After approval of the study from the local scientific committee, the study will be registered on www.clinicaltrials.gov according to current recommendations.

Co-authorship will be given to the principal investigator, the Steering Committee, and a representative from each participating department contributing with more than 5% of evaluable patients (2 representatives if contributing with more than 30%), and to the statistician who has contributed to collecting/validating and analyzing data, and other persons who have contributed substantially to the implementation and/or evaluation of the trial. If some departments contribute with less than 5% of evaluable patients, they can combine their contribution and share co-authorship alternating. The principal investigator is first or last author on manuscripts reporting the primary and secondary endpoints of the trial. Manuscripts reporting quality assurance on for example radiation therapy or plastic surgical techniques used in the trial may have one of the experts in the Steering Committee as last author. The principal investigator is responsible for carrying out a draft manuscript for discussion among the co-authors. It is allowed to publish data regarding the primary and secondary endpoints from one´s own institution if the manuscript has been shown to the investigators of the other participating departments before submission, however, this must not take place before the results regarding the primary and secondary endpoints of the whole study cohort have been published. Co-authorship is given according to the Vancouver rules, however, these rules can be deviated from, for example should it happen that a person expected to be active turns out not to be active and/or an active person joins the study at a later time. This is to consider all involved parties. Projects defined at a later time and which uses some results/data from this trial can be published with the involved active persons only as co-authors together with the trial principal investigator only after accepting from the protocol responsible investigators from the participating departments and the Steering Committee.

WITHDRAWAL OF CONSENT TO PARTICIPATE

Patients who for some reason do not receive the allocated treatment should be treated according to best standard of care. Analysis of data will be according to the ”intention to treat” principle. Unless the patient does not want to, she must be followed up just like everybody else in the trial with respect to the primary and secondary endpoints in the trial. For patients who do not receive the allocated treatment, or who withdraw from the trial after treatment, the date of withdrawal must be recorded in the DBCG database so that an updated status of participating patients can be made at every time desired. To minimize withdrawal the patient should be carefully informed before randomization about the yearly detailed morbidity evaluation including photos. The patient may withdraw from the trial at any time and she does not need to explain the reason.

ECONOMICAL ISSUES

Funding applications will be sent to relevant funds to obtain funding expanding the DBCG database and if possible also help pay running costs of the trial. No salary per accrued patient will be paid to active centers, since this is an investigator-initiated trial. Since breast reconstruction should be offered to all eligible patients, participating surgical departments will not be compensated for any additional costs they may feel they have in relation to this trial. The delayed-immediate surgical technique is expected to become future DBCG standard therapy, and it is introduced in an evidence-based way through this trial. The centers support this strategy by participating.

Danish patients participating in the study are covered by the general national insurance rules by Patient Compensation Association.

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APPENDIX

IIa	DBCG RT RECON Primary endpoints after first surgery
IIb	DBCG RT RECON Primary endpoints after second surgery
III	BDI Becks Depression Inventory
IV	CARQ-3 Concerns About Recurrence Questionnaire-3
V	Breast-Q Part I_A Questionaire before mastectomy
VI	Breast-Q Part I_B Questionaire before reconstruction
VII	Breast-Q Part II_A Questionaire after mastectomy
VIII	Breast-Q Part II-B Questionaire after reconstruction
IX	DBCG RT RECON Questionaire (morbidity)
X	DBCG RT RECON Registration form (morbidity and cosmesis)
XI	DBCG RT RECON Manual for clinical photos