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Danish Breast Cancer Group

The DBCG RT Natural trial:
Partial breast *versus* no irradiation for women ≥ 60 years operated with breast conservation for early breast cancer, a clinically controlled randomized phase III trial

Sagsnr 1-10-72-205-18 Videnskabsetisk Komite
ClinicalTrials.gov NCT03646955

Edition 1.0 04/07/2018

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CONTENT

1.0 BACKGROUND

The purpose of this trial is to investigate differences in local recurrences between partial breast irradiation versus no irradiation for women operated with breast conservation for relatively low risk early breast cancer. Partial breast irradiation using external beam technique and 40 Gy in 15 fractions has been DBCG standard since April 2016. The primary endpoint in the trial is invasive local recurrence in the operated breast, and secondary endpoints are morbidities.

The hypothesis is that women operated with breast conservation for an early breast cancer with low risk of recurrence can omit partial breast irradiation without an unacceptable increase in the risk of local recurrence. It is estimated that the risk of invasive local recurrence will be around the same level as the risk of developing a new invasive contralateral breast cancer.

Partial breast irradiation can be provided with several techniques including interstitial or intracavitary brachytherapy (pre-, peri- or postoperative) as well as using external beam radiation therapy (RT) with different doses, dose per fraction and overall treatment time. In common is that technical issues and cosmetic results on short term are relatively well documented, whilst long-term documentation on recurrences and morbidities are still awaited. However, there are 5 year data on the GEC-ESTRO and IMPORT LOW trials documenting promising results using partial breast irradiation with either interstitial brachytherapy or external beam RT based on 40 Gy/15 fr. Results are still pending from other trials (figure 1, appendix) (1, 2). There are 6 randomized phase III trials investigating partial breast irradiation (NSABP/RTOG, OCOG/RAPID, GEC-ESTRO, IMPORT-LOW, an Italian trial and TARGIT) (figure 1, appendix). The rationale of these trials is that most local recurrences in the irradiated breast occur in or close to the tumor bed (3).

In Denmark, standard adjuvant RT after breast conservation for an early node-negative breast cancer is based on 40 Gy / 15 fractions, 2.67 Gy per fraction, to whole breast and in selected patients with low risk of local recurrence partial breast irradiation is recommended. When the dose per fraction is >2 Gy it is hypofractionation, and hypofractionation was reintroduced in Denmark for node-negative breast cancer through 2 randomized controlled trials starting in 2009 (DBCG HYPO and DBCG PBI), and for node-positive breast cancer since 2015 (The Skagen Trial 1). The DBCG HYPO trial stopped accrual in March 2014 with 1882 patients, who were randomized to 50 Gy/25 fr versus 40 Gy/15 fr for whole breast irradiation (WBI), and based on positive early results from the trial 40 Gy/15 fr became DBCG standard since March 27th, 2014. Partial breast irradiation (PBI) became national standard in Denmark since April 1th 2016 based on the initial results from the clinically controlled randomized DBCG PBI trial and 5 year results from the IMPORT LOW trial presented at the Early Breast Cancer Conference (EBCC 10) March 9th, 2016. The DBCG PBI trial was designed to use the same RT technique, dose and number of fractions as the IMPORT LOW trial, and accrual in the DBCG PBI trial should continue until results from the IMPORT LOW trial were available. Thus the DBCG PBI trial closed accrual March 8th, 2016, having randomized 882 patients, and the day after results from the IMPORT LOW trial became available.

The IMPORT LOW trial was an English multi-center trial with 3 arms, where *arm 1* was WBI 40 Gy/15 fr, *arm 2* was reduced breast irradiation with 40 Gy to partial breast and 36 Gy to residual breast and *arm 3* was PBI 40 Gy/15 fr. (figure 2, appendix). Inclusion criteria were woman ≥50 years operated with breast conservation ± adj systemic therapy, T≤3cm, pN0-N1, unifocal invasive adenocarcinoma, grade 1-3, margin ≥2mm. The primary endpoint was 5 year local recurrence, secondary endpoints were morbidities and pattern of recurrence. It was a non-inferiority trial based on

an expected 5 year local recurrence risk of 2.5%, and the trial would rule out that the local recurrence risk at 5 years did not exceed 5% in any of the treatment arms with reduced treated volume.A total of 2018 patients were included (arms 1, 2 and 3 had 674, 674 and 670 patients, respectively). At median follow up 71.2 months (interquartile range 60.6-74.1) there were 1.1% local recurrences in the WBI arm and non-significantly fewer recurrences in the 2 test arms with partial breast irradiation (figure 2). The risk of local recurrence was so low at 5 years that it was even less than the risk of a new contralateral invasive breast cancer, which was 2 % at 5 years. Depending on type of morbidity, all morbidities were either equal to or less frequent for PBI compared with the WBI arm (figure 2, appendix). PBI based on this technique and fractionation was thereafter accepted as UK standard if the patients fit the inclusion criteria (except grade 3 and lobular cancer).

The DBCG PBI trial used the same RT technique and fractionation as in the IMPORT LOW trial. In Denmark, a trial using local recurrence as primary endpoint was not feasible, thus focus was on morbidity. The inclusion criteria for the DBCG PBI trial were woman ≥60 years operated with breast conservation ± adj endocrine therapy, pT1, pN0, unifocal invasive non-lobular adenocarcinoma, grade 1-2, hormone receptor positive, HER2 negative, margin ≥2mm. The randomization was like the IMPORT LOW arms 1 versus 3, thus WBI versus PBI, and the trial used the same RT techniques, margins and doses, thus allowing for optimal comparison between the two trials (figure 3). The primary endpoint was grade 2-3 breast induration at 3 years, and secondary endpoints were other types of morbidities and pattern of recurrence. It was a non-inferiority trial based on 3 yr risk of grade 2-3 breast induration expected to be 8%, and the aim was to rule out a 10% increase to 18% risk of induration using PBI. It was estimated that the trial needed to include minimum 314 patients with information on morbidities at 3 years or 14 events, and thereafter the trial could stop accrual provided there were also 5 yr data from the IMPORT LOW trial on local recurrences available. The trial stopped accrual on March 8th, 2016, and March 9th the first results from the IMPORT LOW trial were published, and at that time there were 25 events and 353 patients with 3 years follow up, and a total of 882 patients accrued. The initial results revealed no difference between PBI and WBI regarding development of breast induration or any of the other morbidities, and in addition significantly less radiation dose to lungs and heart using PBI, and finally very few recurrences and new contralateral primary breast cancers with no differences between the arms (figure 3). Based on very few local recurrences using PBI in the IMPORT LOW trial (figure 2) and DBCG data showing low levels of morbidities, the DBCG RT Committee decided that PBI based on external beam technique and 40 Gy/15 fr was the new recommended standard for selected breast cancer patients fulfilling the inclusion criteria of the DBCG PBI trial as of April 1th, 2016.

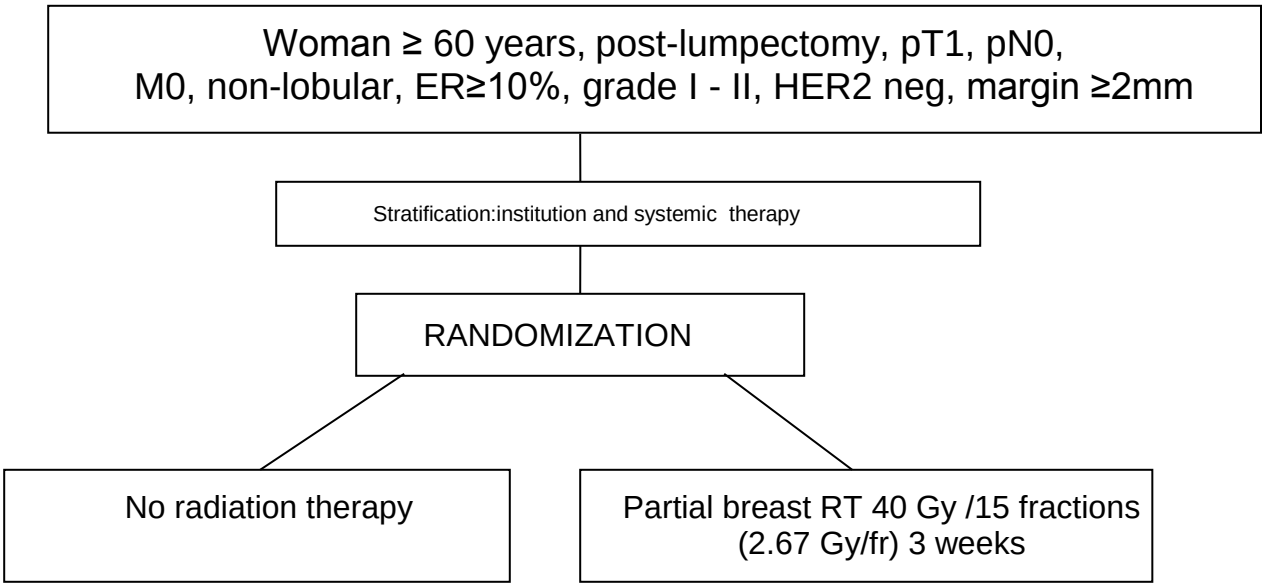
Given the very low local recurrence rates in the IMPORT LOW, GEC ESTRO and DBCG PBI trials, and in addition a 9 year actuarial risk of local recurrence of 1.8% in the Young Boost Trial, which includes young high-risk patients, there is increasing focus on studies/trials selecting patients operated with breast conservation for low risk breast cancer where RT may be omitted (figures 4 and 5, appendix) (4). These studies reflect that the local recurrence risk has become so low that the gain from RT may not outweigh the risk from RT. For example, in the development of the Dutch TOP-1 study, breast cancer patients >70 years old were invited to estimate an acceptable 5 year risk of local recurrence if RT was omitted, and these patients would accept up to 10% risk of local recurrence at 5 years if RT was not provided to patients >70 years.

Recently, a DBCG study investigated the influence from age on local recurrence, and demonstrated that with 17 years median follow up after breast conservation for a low risk breast cancer treated with RT but no systemic therapy, a 2:1 relation for local recurrence and distant failure was present if the patients

were<45 years old at initial breast cancer diagnosis, whilst patients >45 years old at initial diagnosis had no distant failures following a local recurrence (5). Thus, a local recurrence in elderly relatively low risk breast cancer patients does not threaten her life.

2.0 RANDOMIZATION

The randomization is between no breast irradiation (test arm) versus partial breast irradiation (control arm) based on external beam technique and 40 Gy / 15 fractions, 2.67 Gy per fraction.



All women who are to have adjuvant radiation therapy after breast conservation for breast cancer are routinely invited to have information on the therapy at the Dept Oncology, and they are invited to also bring an assessor. During the consultation the patient is first informed about the standard therapy, thus partial breast irradiation. Then she is informed about this trial proposal. Thus, before randomization the patient is informed about the standard and the test therapy orally and in writing, and thereafter she is given time to decide if she wants to participate in the trial. The patient is invited to come back to the hospital usually on another day to give her written consent, and she will be invited to ask questions. The consent is usually given to a doctor, however, the doctor may choose to delegate this task to other staff in the department, however, this staff must be trained in the protocol and be able to answer the questions the patient may ask. The randomization is online and the patient will be informed about the result of the randomization immediately. Baseline morbidity evaluation is carried out when randomization is performed. The planning CT scan for radiation therapy should be performed as soon as possible and the treatment should start without unnecessary delay.
If the patient is randomized to radiation therapy, and the tumor bed is not visible on the CT scan, the patient should receive whole breast irradiation, and she can remain in the trial. This will be a rare event,

since in the DBCG PBI trial it happened in <1% of the cases.

As part of participating in this trial the patient accepts that information is passed on from her patient file to the research database. The required information is related to tumor characteristics (tumor size, lymph node status, hormone receptor status, HER2, margin, histological type, laterality, position in the breast), and information on detection of the tumor (mammogram and if available MR mammogram, surgical date, type of surgery (e.g. lumpectomy with oncoplastic surgery) and surgical complications. Also requested is patient characteristics (height, weight, smoking, alcohol, comorbidity). All this information influence the risk of recurrence and treatment related morbidities. Information on systemic treatment is also required, and it is important to receive this information also during follow up to assure that the patient completed the recommended therapy. From the patient file, data regarding recurrences are collected: local, regional, distant recurrences, and other malignancies. The patient accepts that the protocol responsible doctor and/or other authorities can gain direct access to the patient file to collect information to validate the reported information.

Patients enrolled in this trial receive either standard therapy or no therapy, thus no excess radiation will be possible. As part of the follow up every patient will be offered yearly screen mammography (except the first one at 12 months after surgery, which will be a clinical mammography) for 10 years irrespective of the randomization arm, thus every patient will receive five more mammograms than standard over a decade. The usual Danish standard is a clinical mammography at 18 months after surgery and then screen mammography every 2 years. The total radiation dose from these five extra mammograms is so low that it is of no significance (please, see later in section on ethical considerations). There are no expected disadvantages; on the contrary, she may prefer to omit the radiation therapy. Regarding late morbidities there may be less events among patients not having radiation therapy.

Possibility to choose no irradiation

If the patient does not want to participate in the trial because she does not want any irradiation, she is invited to participate in the trial without randomization. By participating in the trial as a self-selecting patient, she can have yearly mammography for 10 years, which is otherwise not possible in the DBCG guidelines. In addition, she is invited to participate in the morbidity evaluations and respond on the questions regarding fear of recurrence. If she does not want trial participation nor wants to participate in the trial, she is followed according to the standard DBCG follow up program. If the patient does not participate in the randomization, she does not count in the power calculation. The option to choose no irradiation and still participate in the trial will be explained to the patient if she says no to randomization because she does not want irradiation. If she does not want irradiation, it is considered ethically correct to be able to offer her yearly mammography as part of the trial but without randomization. She is then followed regarding pattern of recurrences, and therefore her written consent is needed.

If the patient does not want to participate in the trial she will receive partial breast irradiation, and that is explained to her orally and in writing.

3.0 ENDPOINTS

Primary endpoint:
Invasive local recurrence 5 years after randomization.

Secondary endpoints:
Specialist and patient reported morbidities and fear of recurrence. Pattern of recurrence, death and cause of death. Identification of a genetic risk profile for local recurrence and gain from radiation therapy (please, see section on translational research).

4.0 INCLUSION AND EXCLUSION CRITERIA

CRITERIA FOR INCLUSION

The following criteria for patient and tumor characteristics must be present:

1. Woman minimum 60 years old at day of lumpectomy.
2. Breast conserving surgery with minimum resection margin from invasive carcinoma and/or DCIS ≥2mm. No demands on distance to skin/dorsal fascia, if the tumor was removed with inclusion of the subcutaneous or dorsal fascia. Invasion of the fascia/skin is not allowed.
3. Tumor must be non-lobular adenocarcinoma ≤20 mm (pT1), unilateral and unifocal.
4. Tumor must be malignancy grade I or II (if ductal), ≥10% estrogen receptor positive, and HER2 negative status.
5. If DCIS is present in the tumor, the DCIS component must be minimal and account for <20% of the tumor size[#]. DCIS at a distance from the invasive tumor is not allowed.
6. The patient must be examined in the axilla either with sentinel node biopsy or by removal of nodes in axillary levels 1&2. The patient must be classified pN0M0. Single cell metastasis is allowed, however, micrometastasis is not accepted.
7. The patient should be randomized within 42 days from last surgery for breast cancer (lumpectomy, re-excision or axillary surgery).
8. Patients previously diagnosed with non-breast malignancy can be included if they have been without disease minimum 5 years and their doctor estimates a low risk of recurrence from the previous cancer. Patients with the following types of tumor can be included despite a follow up of less than 5 years: carcinoma in situ cervicis, carcinoma in situ coli, melanoma in situ, basal cell carcinoma and squamous cell carcinoma of the skin.
9. Follow up is feasible for 10 years, thus the estimated survival is minimum 10 years.

[#]The estimate of 20% DCIS is a guide for the radiation oncologist and not a figure the pathologist is expected to report.

PATIENT EXCLUSION CRITERIA

Men cannot participate in this trial. Women with one or more conditions mentioned below cannot participate in the trial:

1. Lobular carcinoma, DCIS or non-epithelial tumor.

2. Histologically positive nodes classified as micrometastasis or macrometastasis. Notice, pathological nodes in the breast are classified as positive axillary nodes.
3. Previous invasive breast cancer or DCIS
4. Hereditary breast cancer, e.g. BRCA mutated or otherwise with genetic high risk of new primary breast cancer
5. The patient must not be treated with other systemic therapies than those accepted in the national guidelines, thus endocrine therapy and zoledronic acid are accepted.
6. Previous radiation therapy of the breast or chest wall irrespective of the cause.
7. Psychiatric or any problems of abuse or other conditions, which prohibit the patient from fulfilling the demands of the trial, this includes language problems.

Notice that the patient can enter the trial irrespective of breast implants.

5.0 RADIATION THERAPY

TREATMENT PLANNING

Only patients randomized to radiation therapy have a planning CT scan. The patient is scanned in treatment position according to DBCG or institutional guidelines. Standard position is supine position, however, prone position is accepted. Fixation according to current guidelines in the institution is used, and a daily reproducibility of max 5mm is to be preferred. Treatment CT scan using a 3mm slice thickness is optimal. The scanned area of the patient includes the breasts, lungs and heart.

SURGICAL CLIPS

Surgical clips are used to identify the tumor bed. The clips are part of standard therapy in Denmark, and they are positioned such that clips 1-4 identify the medial, lateral, cranial and caudal resection cavity wall, and if clips 5-6 are placed these should mark the dorsal and ventral walls of the tumor bed.

The following is based upon a planning CT scan with 3mm slice thickness as recommended in the DBCG guidelines.

WHOLE BREAST ”CLINICAL TARGET VOLUME” (CTV)

This CTV includes the palpable / radiological breast tissue including the tumor bed and surgical clips. The dorsal border is the deep fascia of the breast positioned on the ventral side of the major pectoral muscle. If the anatomy is not clear in the patient, the dorsal border should be 5mm ventral to the pleura. Ventrally the border is 5mm cropped from the skin surface. Medially the glandular tissue is limited by the vessels running into the breast from the internal mammary vessels, but if these vessels cannot be identified the medial border is the lateral border of the sternal bone. The lateral border is up to the lateral vessel of the glandular tissue and caudally the CTV includes the visible breast tissue. Cranially, the CTV breast includes visible glandular tissue, and in general, it should not be delineated at the

caudal level of the sterno-clavicular joint. A wire can be placed before scanning to guide delineation. To include partial volume effect, a slice may be added cranial/caudal.

PARTIAL BREAST "CLINICAL TARGET VOLUME" (CTV)

The partial breast CTV is not a clearly demarcated anatomical structure, but it is often corresponding to a quadrant of the breast. First, the tumor bed is defined as the volume encompassed by the clips, seroma, and scarred tissue in the breast. Pre-operative imaging and the surgical report are often very helpful. To include the partial volume effect, an extra slice may be added to the tumor bed. Then the tumor bed is expanded with 15 mm and cropped inside the CTVp_breast to result in CTVp_PBI.
All patients randomized to PBI must have a CTVp_whole breast and a CTVp_partial breast.

"PLANNING TARGET VOLUME" (PTV)

To account for set-up variation, swelling of the breast and respiratory movements during RT, a margin is added to the CTVp_partial breast to create a PTV. Typically, a margin from CTV to PTV is 5-8 mm (depending on type of fixation), and the PTV is cropped 5 mm from the skin surface. If the distance from CTV to PTV cannot be divided by the thickness of the slices, an extra section is delineated to account for the partial volume effect cranial/caudal.

TREATMENT PLANNING

Treatment planning is according to the ICRU 50 and 62 guidelines (5). In principle, two tangential fields with parallel dorsal borders are used. There is one isocenter. PTV is covered by 95%-105% of the prescribed dose. Small hot spots of dose 105-110%, preferably deeply positioned in the breast tissue, are accepted, however, such hot spots should be avoided and they should maximum in total constitute $<2cm^3$ and preferably scattered over several small volumes. Disregarding build-up zones, all CTVp_PBI should be covered with minimum 95% dose. Wedges and electronic compensation may be used, and inverse IMRET and VMAT are also allowed. The photon energy is chosen at the discretion of the therapist, however, 95% dose should be achieved 5mm below the skin surface. No bolus on the scar is used. To minimize dose to organs at risk multi-leave collimators are used. The prescribed dose is 40 Gy/15 fractions, 5 fractions per week, and it is prescribed to the CTVp_PBI according to ICRU guidelines.
In order to be a partial breast irradiation treatment plan, the following should be achieved: max 50% of the CTVp_breast should receive 100% of the dose, thus V_{40} of CTV whole breast is max 50%. In patients with relatively small breasts, this may be difficult to achieve, however, it is not an absolute constraint, and more than 50% of the breast may receive full dose, thus the patient should not leave the trial based on this issue.

ORGANS AT RISK

Organs at risk are the heart, lung, chest wall and contralateral breast. Dose-volume histograms are made for the heart and ipsilateral lung. DBCG guidelines for 40 Gy/15 fractions recommend that max 1% of the heart may receive 35 Gy, and max 5% of the heart may receive 17 Gy ($\alpha/\beta=3$). If the left

anterior descending coronary artery is delineated, the dose there should be as low as possible. For the ipsilateral lung the DBCG guidelines recommend max average dose to the lung is 16 Gy, and max 25% of the ipsilateral lung may receive 17 Gy. Contralateral breast should receive as low dose as possible. Notice, these dose limits are not safety limits, and efforts to keep the doses to organs at risk as low as possible should be done.

	% of organ at risk	**Max. dose**
Heart	1%	35 Gy
	5%	17 Gy
Lung	Average physical dose	16 Gy
	25%	17 Gy

Priority: heart>lung>CTV>PTV>contralateral breast.
If a compromise is necessary on the ICRU guidelines, the risk of double trouble also in organs at risk should be considered.

VERIFICATION OF THE RADIATION THERAPY

Every participating center should use their routine system for verification including control photos, use of orthogonal pictures/conebeam CT or equivalent methods.

QUALITY ASSURANCE OF THE RADIATION THERAPY

Partial breast irradiation is already national guideline in Denmark, and all departments use the same radiation technique. For all Danish patients randomized to radiation therapy the treatment plan must be submitted to the National Dose Plan Bank to be included in a quality assurance program lead by the DBCG RT Committee. Patients randomized to no radiation do not have a treatment CT scan. Five treatment plans from patients enrolled in the trial from non-Danish departments are also referred to the National Dose Plan Bank. All delineated target volumes and organs at risk must follow the guidelines described in the DBCG PBI trial, and these guidelines apply to the DBCG RT Natural trial. Collected data includes planning CT scans, delineated volumes, radiation parameters and dose-volume histograms. Every center must report the algorithm of the treatment planning system they use.
For non-Danish patients included in the trial, radiation parameters will be reported to the DBCG database, and up to 5 treatment plans must be submitted to the Danish National Dose Plan Bank for further quality assurance.

POSTPONEMENT OF THE RADIATION THERAPY

Any postponement of the therapy should be according to the guidelines of the participating center.

6.0. EVALUATION OF PATIENTS BEFORE AND AFTER RADIATION THERAPY

TUMOUR RELATED ENDPOINTS

All patients included in this trial are offered yearly mammography. The first mammography should be a clinical mammography according to DBCG guidelines, and then screen mammograms are performed yearly for 10 years.

MORBIDITY RELATED ENDPOINTS

This scheme highlights the evaluations performed in the trial. In addition to these yearly evaluations, an evaluation (including all the items) must be registered if a radiation induced morbidity is detected. Charlson comorbidity index is also reported at baseline. In Denmark, breast surgeons fill in that scheme.

Evaluations	**Before RT**	**Year after radiation therapy (RT)**					
		1	**2**	**3**	**4**	**5**	**10**
Clinical examination	X	X	X	X	X	X	X
Photo[1]	X	X	X	X	X	X	X
Functional and cosmetic result[2]	X	X	X	X	X	X	X
Patient question-naires[3,4,5]	X	X	X	X	X	X	X

[1] Appendix 2. Photos are also taken if a ≥ grade 2 morbidity is detected. Analysis of photos is according to BCCT.core (6).
[2] DBCG functional and cosmetic result (Appendix 1)
[3] Section on "Patient reported outcome" on DBCG scheme functional and cosmetic result (Appendix 1)
[4] Body Image Scale (BIS, Appendix 3) (7).
[5] Fear of recurrence, Appendix

Reporting of morbidity is online to DBCG preferably during the patient consultation or minimum once per month. The protocol responsible doctor at each center is responsible for this. Data is collected into a clinical database approved by the Danish authorities, and the collection of data follows Danish legislation. Any additional information on morbidities may be obtained through patient questionnaires or through the internet in relation to the follow up of the patient. The staff involved in morbidity evaluations is invited to participate in workshops arranged by the principal investigator on morbidities after radiation therapy. Patients with relevant radiation induced morbidities will take part in these workshops also.

TUMOR RELATED ENDPOINTS

The primary endpoint in the DBCG RT Natural trial is ipsilateral invasive local recurrence, whilst other tumor related events are secondary endpoints (regional and distant metastasis, disease specific survival and overall survival). Ipsilateral invasive local recurrence is any invasive carcinoma in the residual breast or the skin of the breast. A detailed reporting of local recurrences will take place through a collaboration among the treating doctor, radiologist, pathologist and breast surgeon. The decision upon the new tumor is a recurrence or a new primary depends on the histopathology performed by the pathologist according to current guidelines at that time. Regional metastasis is defined as metastasis in ipsilateral axilla, fossa supraclavicularis or in the internal mammary nodes. All other metastases are distant metastases. Metastatic disease is detected with a suitable combination of clinical, hematological, imaging and histopathological evaluations; however, there may be situations where it is not meaningful or technically feasible to verify metastasis based on histopathology.

7.0 TRANSLATIONAL RESEARCH

In this trial one of the secondary endpoints is to validate a hypothesis on the predictive potential of a genetic profile on gain from adjuvant radiation therapy. The predictive gene profile was developed and validated in the DBCG 82b&c cohort (8). Based on local recurrences from the DBCG RT Natural trial, the DBCG HYPO and the DBCG PBI trials the DBCG 7-gene risk profile on gain from radiation therapy will be investigated. This will include tumor material from Danish patients, and tissue will be collected from the primary tumor and the local recurrence. For every local recurrence, 2 controls will be selected so that the primary tumor tissue is evaluated regarding the 7 gene profile. The primary goal of this translational research is to validate the DBCG 7-gene profile, but other promising international gene profiles and combinations of immunohistochemical analysis will also be included in the evaluations.
This translational research will be part of a separate study, and the Ethical Committee is asked for consent later.

8.0 STATISTICAL CONSIDERATIONS

In this non-inferiority trial patients at low risk of local recurrence are randomized to no irradiation, and the frequency of local recurrences will be followed closely. The trial uses randomization to minimize bias, such that the conclusions are valid. Since women have two breasts, there is an opportunity to use the other breast as an internal control, thus the risk of a new contralateral breast cancer is an extra control. The DBCG RT Committee has decided that the risk of local recurrence without radiation therapy is acceptable if it is within 2% difference from the risk of a new primary invasive breast cancer on the other side at 5 years.

From the IMPORT LOW trial results, the 5- year risk of local recurrence after partial breast irradiation was 0.5% and contralateral new primary cancer risk was 2%. Meta-analyses have shown that adjuvant radiation therapy of early breast cancer reduces the risk of local recurrence to 1/3 (9). The DBCG RT Committee has decided that it is acceptable to omit radiation therapy if the risk of ipsilateral invasive local recurrence is max 4% at 5 years. The internal control is the contralateral new invasive breast cancer risk, which is expected to be 2%, thus without radiation therapy the patient may experience a 2% higher risk of invasive local recurrence than the risk of new contralateral cancer at 5 years.

The statistical considerations below are in harmony with the Australian EXPERT trial (Examining PErsonalised Radiation Therapy for low-risk early breast cancer).
A 5-year local recurrence risk of max 4% is considered acceptable when considering the balance between risk and gain from adjuvant radiation therapy. Assuming a non-inferior boundary of 3%, 926 patients (463 patients in each arm) will have 80% power with one-sided 97.5% confidence interval to show that omission of radiation therapy is non-inferior to radiation therapy provided 4 years inclusion period and 3 years follow up (resulting in 5 years follow up). This number of patients includes 7% drop-out of the trial after randomization. The number of patients needed may be re-assessed if the pooled event rate differs substantially from expected, if the accrual rate is higher than expected and/or if the drop-out rate is substantially lower than 7%.
There are around 320 eligible patients yearly in Denmark. The Norwegian Breast Cancer Group has accepted to participate in the trial as of June 2018.

The first analysis will be performed when 463 patients have median 5 years follow up. If there is no statistical difference in local recurrence between the test arms at that time point, and there are no unexpected findings in the trial, omission of partial breast irradiation will become standard in Denmark. However, for this to occur, comparable and/or similar international trials should have reached the same conclusions, namely that omission of radiation therapy in selected patients is safe. The final decision is made by the DBCG RT Committee. All patients are followed for 10 years, and as more events accumulate, the initial conclusion may be altered. The DBCG RT Committee follows this situation and decides how to manage new results.

8.1 INTERIM ANALYSIS

An interim analysis is planned when 200 patients are included and followed for 2 years. At that time the pooled event rate in the study will be compared with the expected event rate. This calculation depends on the actual accrual rate. The interim analysis will be made in collaboration with the DBCG

chief statistician, and the DBCG Radiation Therapy Committee will decide if the results are acceptable. Since the DBCG RT Natural Trial has large similarity to the EXPERT Trial, it is also relevant to include information from their interim analysis (if available) and from other relevant trials internationally when evaluating the safety of omission of radiation therapy.

8.2 STOPPING RULES

Accrual stops and full data analysis takes place when one of the following issues happens:

1. When 926 patients have been included.

2. If the interim analysis shows statistical significant difference in invasive local recurrences between the randomization arms.

8.3 ANALYSES

Usual statistical methods like competing risk analysis for the primary endpoint and cumulative incidences with respect to competing risks are planned. For regression analyses with competing risks cause specific Cox regression analysis or Fine-Gray sub-distribution hazard regression will be applied. Follow-up starts at the day of randomization.

Follow up regarding the primary endpoint stops at A) local recurrence, B) regional recurrence, C) distant failure, and D) death.

9.0 PUBLICATION

The results from this trial will be published irrespective them being positive or negative or inconclusive. After approval by the Ethical Committee, the trial was registered on www.clinicaltrials.gov according to current guidelines.
Co-authorship is assigned the principal investigator and one representative from each center with >5% of the accrued patients. Two co-authors from a center are accepted, if the center contributes with 30% of eligible patients in the trial. Co-authors are also people who have contributed to collecting, validation and analysis of data, and other people who have contributed significantly to the accrual and/or evaluation of the trial. If several departments contribute with <5% of the patients, they can join each other into a group of <5% and then alternating be co-authors.
The principal investigator is responsible for drafting a manuscript, where thereafter is discussed with co-authors. It is accepted to publish results on the primary and secondary endpoints from one´s department, if the manuscript has been shown to the other participating departments before submission. However, this cannot be accepted until the primary and secondary endpoints from the whole study have been published. Other information from the trial (e.g. local quality assurance on radiation therapy or of

the morbidity evaluations) can be published from that/those participating center(s), where the work was done, however, the principal investigator must be informed about this before submission.
Co-authorship follows the Vancouver rules, however, these rules can be deviated, if it turns out that a person expected to be active is not active after all, and/or if an active person joins the trial at a later point of time. This is to the benefit of all involved participants. Projects defined at a later point of time using results/data from this trial, can be published solely with those persons who are involved in that project as co-authors, and this must be in agreement with the other participating centers and the DBCG RT Committee.
All publications from this trial must be on behalf of the DBCG RT Committee, and either ”DBCG” must be in the title or stated ”on behalf of the DBCG Radiotherapy Committee”. Relevant funding e.g. from CIRRO (The Danish Cancer Society Center for International Research in Radiation Oncology) and the Danish Cancer Society must be mentioned and thanked when results are published (contact the principal investigator or the DBCG office for more details).
This is a DBCG initiated and conducted trial. DBCG collaborates with CIRRO to provide data and handling of data. The trial follows DBCG guidelines.

10.0 ETHICAL CONSIDERATIONS

The trial will follow the 5. edition of the Helsinki Declaration. The trial can only start when approved by the Ethical Committee of Region Midt, Denmark.

The trial includes a randomized arm with experimental therapy, i.e. omission of radiation therapy. At every participating center, there is a trial responsible person, who assures that every patient is informed, orally and in writing, about the trial with respect to the content of the trial and the detailed follow up before the patient can enter the trial. This includes benefits and risks from participating in the trial. All patients receive a trial specific patient information booklet, which follows the Danish guidelines for patient information. The advantage to the patient in participating in the trial is not to have radiation therapy, thus she does not have 15 visits at the hospital and there will be no acute and late effects from radiation therapy. However, the risk of a local recurrence in the breast is slightly higher with no radiation therapy, but this increased risk is very small, because there are strict inclusion criteria to enter the trial. The risk of a local recurrence at 5 years after omission of radiation therapy is estimated at the same level or within 1% of the risk of developing a new primary breast cancer in the other breast. The patient can withdraw from the trial at any time, and she does not have to give a reason for withdrawal. If she chooses to have standard therapy, this will be external beam partial breast irradiation 40 Gy/15 fr following the DBCG guidelines. The patient signs the consent before randomization. The patient will be offered one or more days to consider participation in the trial, before she comes back to the department and signs the acceptance. If the patient requests immediate randomization, she must be advised to read all the information before randomization is accepted. It is recommended to book the time schedule for visits in the department so that there is at least one day between information and accept.

All patients in the trial have yearly mammography for 10 years. The standard is a clinical mammography 1½ years after surgery and then a screen mammography every 2 years. In the trial, the first mammography at 1 year will be a clinical mammography, and then yearly for 9 years a screen

mammogram. The purpose of all these mammograms is to detect a local recurrence at an early phase. However, there is exposure for radiation from a mammogram. The Danish National Health Board has published a guide on radiation exposure in 2013: a Danish citizen on average receives 0.4 mSv yearly from food, 0.3 mSv from cosmic radiation, 0.3 mSv from the earth and 2 mSv from Radon. For comparison, a mammogram with 4 images results in 0.5 mSv. It is therefore acceptable to expose a patient at this small dose to be able to detect a recurrence at an early phase.

11.0 WITHDRAWAL OF CONSENT

Patients, who for some reason do not receive the allocated therapy, are to be treated at the doctor´s discretion. The analysis of data will be according to the intention-to-treat principle. Unless the patient does not accept it, she is followed as all other patients in the trial regarding the primary and secondary endpoints. For patients not receiving the allocated therapy or withdrawing from the trial at a later point of time, the date of exit from the trial is registered as also the reason if possible. The patient is informed about the burden of follow up before randomization to minimize withdrawal from the trial. The patient can withdraw from the trial without telling a reason at any time.

12.0 ECONOMICAL ISSUES

This trial protocol is initiated and developed by the DBCG RT Committee, and the trial will be nationwide in Denmark. Radiation therapy is already standard to all patients included in this trial, so the costs for the radiation therapy are already available in the departments. The individual radiation therapy department participating in the trial will cover the costs related to follow up. The principal investigator and the trial responsible staff have no economic interests in the trial. The principal investigator will apply for funding for establishing a DBCG RT Natural trial database and for statistical support from the DBCG office. As per April 2018, 300.000 kr for salary for academical help has been obtained.

13.0 REFERENCES

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REPORTING OF THE RADIATION THERAPY

The data are applicable for those patients randomized to partial breast irradiation

2018 Natural

DBCG ~~2009~~ RT ~~PBI~~ protokol Planlægning og behandling

Delbryst vs helbryst

Navn – CPR.nr.	Sygehus, afd.

Øverste del (planlægning) af skemaet udfyldes inden behandling i protokollen.
Nederste del (strålebehandling) udfyldes i stedet for konventionelt DBCG strålebehandlingsskema.
Såfremt der er afvigelse fra planlagte behandling markeres dette, og afvigelser anføres i de respektive felter.

Strålebehandling, planlægning af delbryst RT

~~☐ Helbryst~~ ☐ Højre
~~☐ Delbryst~~ ☐ Venstre

	Planlagt	Afvigelse
Total dosis (Gy)		
Fraktioner		
Gating ja=1, nej=0, uoplyst = 9		

CTV-mamma	Planlagt	Afvigelse
Dækning, min (%) ICRU: 95%		
Dækket <95% (% af CTV)		
Dækning, max (%) ICRU:105%		
>105% men ≤110% (ml) Skal <2 ml		

Hjerte, V17 (Max 1% af hjertet må få ≥35 Gy, max ~~10%~~ 5% må få ≥17 Gy)		
Hjerte, V35		
LADCA max dosis (Gy)		
Ipsilateral lunge, V17 (Max 25% af ipsilat lunge må få ≥17 Gy)		
CTV mamma delbryst (ml) ~~Begge udfyldes uanset randomiseringsarm~~		
CTV mamma helbryst (ml)		
CTV mamma partiel V40 (%) (hvis partiel plan) Bør være max 50%		

Biobank

Hudbiopsi	ja=1, nej=0	
Blodprøve	ja=1, nej=0	

Skemaet vedr. planlægning udfyldt af:

Navn:_____
(BLOKBOGSTAVER)

Sign.:_____

Dato |_|_|_|_|_|_| ddmmyy

Strålebehandling

Type ~~☐ Helbryst~~ ☐ Delbryst

Afvigelser fra den planlagte behandling ja=1, nej=0

Dato første strålebehandling |_|_|_|_|_|_| ddmmyy

Dato sidste strålebehandling |_|_|_|_|_|_| ddmmyy

Skemaet vedr. givne behandling udfyldt af:

Navn:_____
(BLOKBOGSTAVER)

Sign.:_____

Dato |_|_|_|_|_|_| ddmmyy

Maj 2009 (rev.13.12.2010, 29.08.2012)

TILLÆG

Tillæg I. DBCG kosmese og funktionelt scoringsskema.
Samme skema bruges i DBCG RT HYPO, PBI og Skagen Trial 1.

OBS: Der vil blive spurgt mere delaljeret til tobaksanamnese:
Aldrig ryger, tidligere ryger, aktuel ryger, ryge start, ryge stop, gennemsnitsligt tobaksforbrug i pakkeår

DBCG 2009 RT protokol Kosmetik og funktion 0.-10.år

Navn – CPR. nr.		**Sygehus, afdeling**						
Startår	År efter RT (0 er før RT)	0	1	2	3	4	5	10
	Dag, md.							
Onkoplastisk kirurgi før stråleterapi	0 = nej 1 = ja							
Vægt (kg)								
Højde (cm)								
Rygning: pakkeår								
Rygning: aktuel ryger	0 = nej 1 = ja							
Specialist rapporteret morbiditet								
Dyspigmentering, mamma	1)							
~~Dyspigmentering, boost~~	~~1) 4 = boost ikke givet~~							
Telangiektasier, mamma	0 = ingen, 1 = <1/cm2, 2 = 1-4/cm2 3 = >4/cm2							
~~Telangiektasier, boost~~	~~0 = ingen, 1 = <1/cm2, 2 = 1-4/cm2, 3 = >4/cm2, 4 = boost ikke givet~~							
Fibrose, mamma	0 = ingen, 1 = letfølelig, 2 = tydelig fasthed 3 = meget udtalt fasthed, indtrækning og fixering							
~~Fibrose, boost~~	~~0 = ingen, 1 = letfølelig, 2 = tydelig fasthed, 3 = meget udtalt fasthed, indtrækning og fixering, 4 = boost ikke givet~~							
Arrets udseende	2)							
Ødem, mamma	0=ingen, 1=asymptomatisk 2=symptomatisk, 3=sekundær dysfunktion							
Samlet kosmetisk vurdering (subjektivt)	3)							
Ønsker at ophøre i RT protokol	0 = nej 1 = ja							
Andet:								
Patientrapporteret morbiditet								
Smerter, mamma	0=ingen, 1=af og til 2=hyppigt, 3=konstant							
Analgetika	0=ingen, 1=af og til milde 2=hyppigt milde, 3=opiod-krævende							
Ændret sensibilitet, mamma	0=ingen, 1=let 2=moderat, 3=svær							
Kropsbevidsthed	4)							
Klæder sig anderledes	0=nej 1=ja							

1) 0=ingen farveforskel på brysterne, såvel hud som brystvorte
1=brystvorte eller hud på behandlet bryst lysere/mørkere end på ubehandlet side
2=både brystvorte og hud på behandlet bryst lysere/mørkere end på ubehandlet side
3=dramatisk forskel i farve mellem behandlet og ubehandlet bryst, enten sv.t. brystvorte eller huden eller begge dele

2) 0=stort set usynligt, 1=synligt, men på-virker ikke det kosmetiske resultat
2=synligt og påvirker det kosmetiske resultat i nogen grad, 3=synligt og trækker det kosmetiske resultat betydeligt ned, 4=not applicable

3) 0=særdeles tilfredsstillende. Symmetri, og normal kontur uden synlig deformiteter eller hudforandringer og ingen væsentlig konsistensforøgelse
1=tilfredsstillende. Let asymmetri og/eller let deformitet og/eller let øget pigmentering/telangiektasier og/eller let ødem i mamma og/eller nogen konsistensforøgelse
2=acceptabelt. Tydelig asymmetri og/eller tydelig deformitet og/eller tydelig øget pigmentering/telangiektasier og/eller ødem i mamma og/eller udbredt fibrose
3=uacceptabelt. Udtalt asymmetri og/eller svær deformitet og/eller svær dyspigmentering/telangiektasier og/eller ødem i mamma og/eller svær fibrose eller nekrose

4) 0=føler stor selvtillid, 1=føler mindre selvtillid, mindre feminin
2=mangler selvtillid, undgår at spejle sig, 3=skammer sig over sin krop

Feb. 2010 (rev.01.10.2013)

Tillæg II. Guide i forbindelse med fotografi

Digitale fotografier tages ved indgang i studiet (postoperativt) før start på strålebehandling og derpå år 1, 2, 3, 4, 5 og 10 efter strålebehandling. Derudover skal der tages fotografier på det tidspunkt, hvor der ved en konsultation kommer kendskab til en ≥ grad 2 senfølge efter strålebehandlingen. Billederne skal tages efter ens retningslinier. De personer, som er ansvarlige for at tage fotos, skal deltage i en workshop, før de kan tage fotos til studiet.

1. Placer patienten i stående position mod en hvid baggrund.

2. Der påsættes en hvid seddel (ca 10 x 10 cm) på patientens mave på den ikke-behandlede side med protokolnavn, patientens protokolnummer samt en dato for foto. Dette mhp dels fotoidentifikation men også for bedre at kunne behandle billedet i fotoshop.

3. Marker med tusch i midtlinien den nedre afgrænsning af jugulum samt et punkt 25 cm caudalt herfra mhp at kunne beregne målestoksforhold.

4. Tag to frontale billeder af brystområdet, et med hænderne ned langs siden, og et med armene løftet så højt som muligt over hovedet. Billedets overkant skal inkludere halsen og underkanten skal være i niveau med umbilicus. Patientens ansigt skal ikke med på billedet.

5. Tag 1 sidebillede fra hhv den behandlede side (cirka vinkelret på brystet) med armene løftet op så højt som muligt og 1 billede tilsvarende fra den modsatte side. Med armene løftet tegnes der en målestok lodret under aksillen på 5 cm før fotografering.

6. Gem billederne elektronisk. Filformatet skal være jpeg. Billederne gemmes online efter samme retningslinier som bruges i DBCG RT Skagen trial 1.

Billederne vil blive evalueret baseret på retningslinier beskrevet af Cardoso et al (6).

Tillæg III BODY IMAGE SCALE

(also used in the DBCG RT HYPO trial, DBCG PBI trial and the Skagen Trial 1)

I dette spørgeskema bliver du spurgt om, hvad du synes om din fremtræden, og om de ændringer, du har oplevet i din krop efter konstateringen af sygdommen og behandlingen af den. Vær venlig at læse spørgsmålet grundigt og derpå sætte et tydeligt kryds svarende til det svar, som kommer nærmest den følelse, som du har oplevet i løbet af den sidste uge.

DBCG 2009 RT protokol Patientspørgeskema

Navn – CPR. nr.	**Sygehus, afdeling**			
I dette spørgeskema bliver du spurgt om, hvad du synes om din fremtræden, og om de ændringer, du har oplevet i din krop efter konstateringen af sygdommen og behandlingen af den. Vær venlig at læse spørgsmålet grundigt og derpå sætte et tydeligt kryds svarende til det svar, som kommer nærmest den følelse, som du har oplevet i løbet af den sidste uge.				
Dato |_|_|_|_|_|_| ddmmyy				
	Slet ikke	Lidt	Meget	Rigtig meget
Har du følt dig selvsikker omkring dit ydre?				
Har du følt dig mindre fysisk tiltrækkende som en følge af din sygdom og behandling?				
Har du være utilfreds med dit udseende, når du har været påklædt?				
Har du følt dig mindre feminin/maskulin som følge af din sygdom eller behandling?				
Har du svært ved at se på dig selv nøgen?				
Har du følt dig mindre seksuelt attraktiv som en følge af din sygdom eller behandling?				
Har du undgået folk pga. den måde du oplever dit udseende?				
Føler du, at behandlingen har efterladt din krop mindre hel?				
Er du utilfreds med din krop?				
Er du utilfreds med udseendet af dit ar?				
	Dårligt	Rimeligt	Godt	Fremragende
Hvor tilfreds er du med det overordnede resultat af det opererede bryst?				
Hvor tilfreds er du med det overordnede resultat af det opererede bryst sammenlignet med det ikke-opererede bryst?				
det opererede bryst	Ja		Nej	
Er der sprøjtet fedt/fedtceller i ~~højre bryst~~ siden sidst? Dette besvares ikke ved baseline				
Er der sprøjtet fedt/fedtceller i ~~venstre~~ bryst siden sidst? Dette besvares ikke ved baseline modificeje				
Tager du cholesterolsænkende medicin?				
Hvis ja, hvilket præparat og hvornår startede du med det? _____ |_|_|_|_|_|_| mmyyyy				
Tog du medicinen under strålebehandlingen?				

Maj 2009 (rev. 14.06.11, 01.10.12 og 01.08.13)

Frygt for tilbagefald af kræftsygdommen (FCRI-SF)

De fleste som har fået diagnosen kræft er, i varierende grad, bekymrede for tilbagefald af kræften. Med *tilbagefald* mener vi muligheden for at kræften kan vende tilbage, forværres eller opstå et nyt sted i kroppen. Dette spørgeskema skal hjælpe til en bedre forståelse af dine bekymringer for at kræften vender tilbage. Læs venligst hvert udsagn og angiv, i hvilken grad det passede på dig i den seneste måned ved at *tegne en cirkel om det tal, som passer bedst på din oplevelse.*

	0 Slet ikke	1 Lidt	2 Noget	3 En hel del	4 Virkelig meget
1	Jeg er bekymret eller ængstelig for at kræften vender tilbage	**0**	**1**	**2**	**3**	**4**
2	Jeg er bange for at kræften vender tilbage	**0**	**1**	**2**	**3**	**4**
3	Jeg tror, det er normalt at være bekymret eller ængstelig for at kræften vender tilbage	**0**	**1**	**2**	**3**	**4**
4	Hvis jeg tænker på, at kræften kan vende tilbage, udløser det andre ubehagelige tanker eller billeder (som fx død, lidelse, konsekvenserne for min familie)	**0**	**1**	**2**	**3**	**4**
5	Jeg tror, jeg er helbredt, og at kræften ikke vender tilbage	**0**	**1**	**2**	**3**	**4**
6	Risikerer du efter din egen mening at kræften vender tilbage?	**0**	**1**	**2**	**3**	**4**

7	Hvor ofte tænker du på, at kræften kan vende tilbage?				
	0	**1**	**2**	**3**	**4**
	Aldrig	**Et par gange om måneden**	**Et par gange om ugen**	**Et par gange om dagen**	**Flere gange daglig**

8	Hvor meget tid bruger du dagligt på at tænke på, at kræften kan vende tilbage?				
	0	**1**	**2**	**3**	**4**
	Jeg tænker ikke over det	**Et par sekunder**	**Et par minutter**	**Et par timer**	**Adskillige timer**

9	Hvor længe har du tænkt på, at kræften kan vende tilbage?				
	0	**1**	**2**	**3**	**4**
	Jeg tænker ikke over det	**Et par uger**	**Et par måneder**	**Et par år**	**Adskillige år**

APPENDIX

DBCG

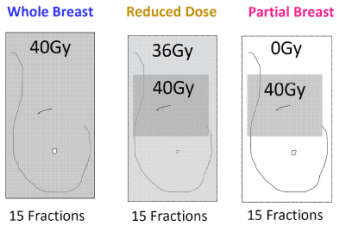
Large randomized APBI studies using external beam RT according to ClinicalTrials.gov 2016

Name	Endpoint	N	Start - end	Standard arm, WBI	APBI arm	Principal Investigator
NSABP B39/RTOG 0413, USA	IBTR	4216	2005-2013	Normofractionated 5-6 weeks	RT bid using 3D CRT, MammoSite; IBT	Norman Wolmark
RAPID Canada	IBTR	2135	2006-2011	50 Gy / 25 fr or 42.5 Gy / 16 fr	38.5 Gy / 10 fr / 5 days	Ivo Olivotto, Tim Whelan
IMPORT LOW England	IBTR	1935	2006-2010	40 Gy / 15 fr	Arm 1:40Gy/ 36Gy / 15 fr Arm 2:40 Gy / 15 fr	John Yarnold Charlotte Coles
Livi, Italy	IBTR	520	2005-2014	50 Gy / 25 fr	30 Gy / 5 fr / 5 days	Lorenzo Livi
IRMA Europe	IBTR	3302	2007	50 Gy / 25 fr	38.5 Gy / 10 fr / 5 days	Giovanni Frezza
SHARE France	IBTR	2796 (964)	2010-2016	50 + 16 Gy boost or 40 Gy / 15 fr or 42.5 Gy / 16 fr	38.5 Gy / 10 fr / 5 days or 40 Gy / 10 fr / 5 days	Y.Belkacemi E. Lartigau C. Bougier
DBCG PBI Denmark	Grade 2/3 induration	882	2009-2016	40 Gy / 15 fr	40 Gy / 15 fr	Birgitte Offersen
APBI Colorado	Breast pain	660	2009	No standard arm	38.5 Gy / 10 fr / 5 days in both arms. R is IMRT vs 3D CRT	Charles Leonard

Closed trials Still recruiting

Figure 1

Intensity Modulated Partial Organ RT



Baseline characteristics

		Whole N=674	Reduced N=674	Partial N=670
		%	%	%
Age (years)	Median (range)	63 (50-90)	64 (50-91)	63 (50-91)
Tumour size (cm)	Median (range)	1.2 (0.1-3.0)	1.1 (0.1-3.0)	1.2 (0.1-3.0)
Grade	1	45	41	43
	2	46	49	48
	3	9	11	10
Pathological node status	Positive	3	3	2
	Negative	97	97	98
Lymphovascular invasion	Present	7	10	7
	Absent	93	90	93
ER status	Positive	95	95	95
	Poor	5	5	5
HER2	Positive	4	5	6
	Poor	96	95	94

Primary endpoint: Local relapse

Local relapse (LR)	Whole N=674	Reduced N=674	Partial N=670
Number of LR events	9	3	4
KM 5 year cumulative LR incidence estimate (95% CI)	**1.1% (0.5-2.3)**	**0.2% (0.02-1.2)**	**0.5% (0.2-1.4)**
Hazard ratio (95% CI)		0.32 (0.09, 1.20)	0.44 (0.14, 1.42)
Pr(HR>2.03), test for NI		p=0.003	p=0.005
Log rank p-value		p=0.08	p=0.16
Absolute difference in LR rate at 5 years (95% CI)		**0.74% (0.99, -0.21)**	**0.61% (0.94, -0.46)**

Event status

	Whole N=674 n	Reduced N=674 n	Partial N=670 n
Local relapse	**9**	**3**	**4**
Regional relapse	**1**	**1**	**1**
Distant metastases	**11**	**11**	**12**
Contralateral BC (invasive)	**10**	**11**	**11**
Deaths	**39**	**36**	**35**
Breast cancer	*8*	*4*	*8*
Other cause	*31*	*32*	*27*
Other cancer	*14*	*16*	*10*
Cardiac	*5*	*3*	*4*
Other	*12*	*12*	*13*
Unknown	*0*	*1*	*0*

NTEs: Time to first moderate/marked clinician assessed NTE

	Whole N=674	Reduced N=674	Partial N=670
Number of patients with moderate/marked events (%)	134 (20)	108 (16)	92 (14)
KM 5 year event-free (95% CI)	**72.1% (66.0 - 77.3)**	**78.9% (74.2 - 82.8)**	**80.9% (75.8 - 85.0)**
Hazard ratio (95% CI)		0.77 (0.60, 0.99)	0.68 (0.52, 0.89)
Log rank p-value		p=0.042	p=0.004

Courtesy Charlotte Coles, slides from Late Breaking Abstract no 4, EBCC 10, March 9, 2016

Figure 2, data and results from the IMPORT LOW Trial. NTE, normal tissue effect

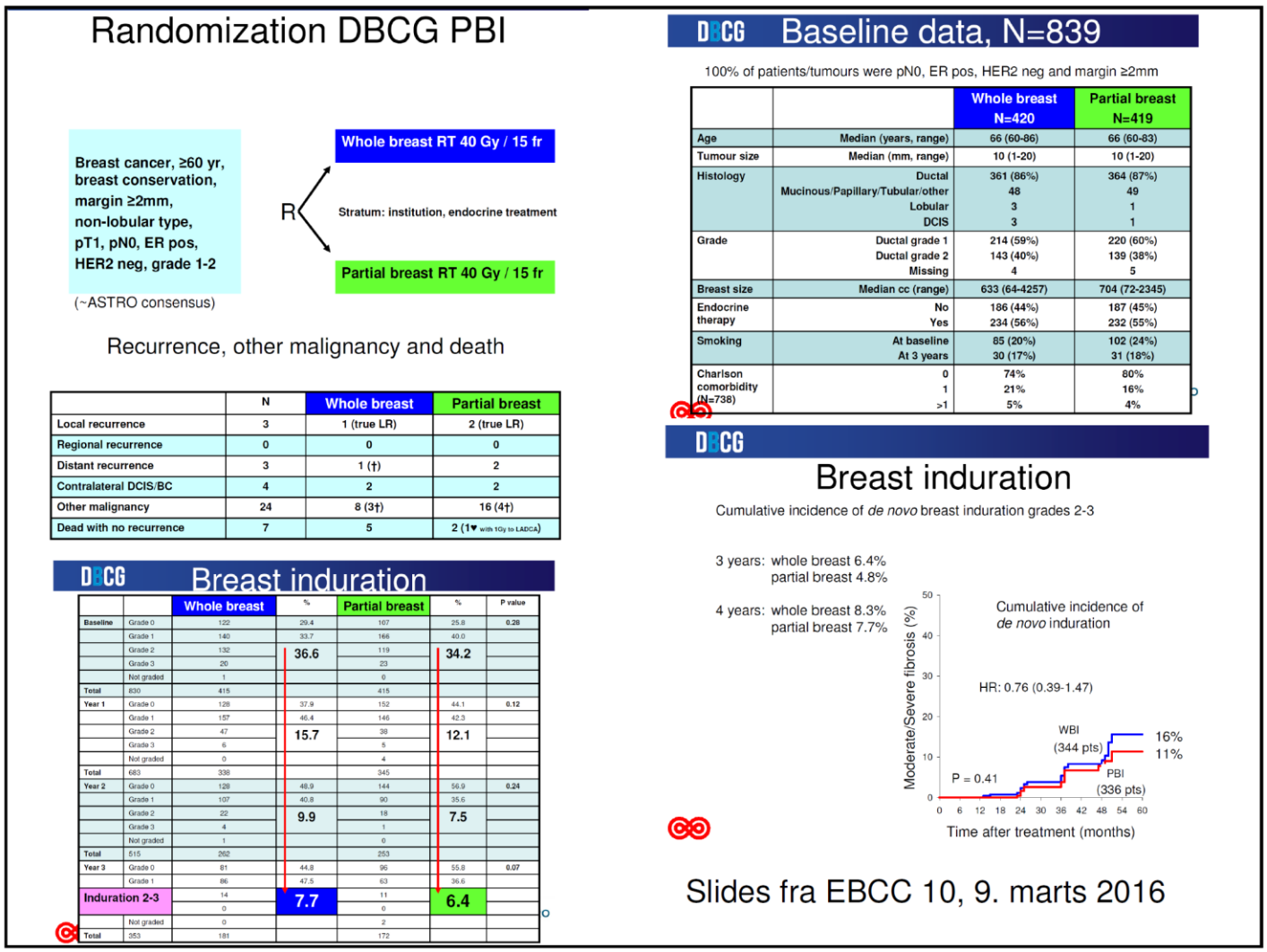


Figure 3, data and results from the DBCG PBI Trial. As of April 2018, median 4 yr follow up, the DBCG PBI trial has 7 local recurrences.

Figure 4, randomized trials testing omission of APBI.
The *DBCG low risk* trial is the DBCG RT Natural trial.

xx is 928 patients

No RT non-randomized studies

Name	TOP-1	Precision	Primetime	IDEA	LUMINA
Study type	Single prospective	Single prospective	Single prospective	Single prospective	Single prospective
Age (yr)	≥70	50-75	≥60	50-69	≥55
Tumour	pT1N0	pT1N0 Grade 1-2	pT1N0	pT1N0	pT1N0 Non-lobular
Characteristics	T<1cm grade 1+2 T1-2 cm grade 1	PAM-50 Luminal A	IHC4+ (ER/PR/ HER2,Ki67)	Oncotype-DX RS≤18	Luminal A (IHC)
Receptors	ER>50% pos HER2 neg	ER/PR+ HER2 neg	ER/PR+ HER2 neg	ER/PR+ HER2 neg	ER≥1% PR>20% HER2 neg
Margins	neg	neg	≥1mm	≥2mm	≥1mm
Therapy	No ET	ET only	"very low risk" ET only	ET only	ET only
Endpoint	5-yr LRR <10% accepted	5-yr LRR 1% expected <5% accepted	5-yr LR <5% expected	5-yr LRR	5-yr LR <5% expected
Number pts	800	345	1500	200	500
Country Principal invest	NL Liefers	USA Harris	UK Coles	USA Jagsi	Canada OCOG

Status Oct 2016 ClinicalTrials.gov and personal communications

Figure 5, studies testing omission of radiation therapy without randomization.