Danish Breast Cancer Cooperative Group

The SKAGEN Trial 1

Moderately hypofractionated loco-regional adjuvant radiation therapy of early breast cancer combined with a simultaneous integrated boost in patients with an indication for boost: DBCG HYPO II, a randomised clinically controlled trial

Number 1-10-72-409-14 Ethical Committee

ClinicalTrials.gov Identifier:
NCT02384733

Protocol organisation

DBCG-sekretariatet
Strandboulevarden 49
2100 København Ø
Denmark
Tlf.: +45 35 38 65 30
Fax: +45 35 26 35 25
E-mail: dbcg@dbcg.dk

Principal Investigator:

Consultant, ass. prof., ph.d. Birgitte Vrou Offersen, Department of Oncology, Aarhus University Hospital, Noerrebrogade 44, DK-8000 Aarhus C, Denmark
E-mail: birgoffe@rm.dk

Participating departments

Dept. Oncology Aalborg Universitetshospital – Afsnit Syd Hobrovej 99 9100 Aalborg	Investigator Consultant Lars Stenbygaard laes@rn.dk
Dept . Oncology Aarhus University Hospital Noerrebrogade 44, 8000 Aarhus	Investigator Staff specialist Hanne Melgaard Nielsen hannie@rm.dk
Dept. Oncology Vejle Sygehus Kabbeltoft 25 7100 Vejle	Investigator Consultant Erik Hugger Jakobsen erik.hugger.jakobsen1@rsyd.dk
Dept. Oncology Odense University Hospital Sdr. Boulevard 29 5000 Odense C	Investigator Consultant Mette Holck Nielsen mette.h.nielsen@rsyd.dk
Technische Universität Dresden Klinik und Poliklinik für Strahlentherapie und Radioonkologie Universitätsklinikum Dresden Fetscherstrasse 74, 01307 Dresden Germany	Investigator Consultant Mechthild Krause Mechthild.Krause@uniklinikum-dresden.de
Praxis für Strahlentherapie Friedrichstrasse 41 01067 Dresden Germany	Investigator Consultant Andreas Schreiber Schreiber-An@khdf.de
Dept Oncology Stavanger Norway	Investigator Consultant Ingvil Mjaaland Ingvil.mjaaland@sus.no
Dept. Oncology Herlev Ringvej 75 2730 Herlev	Investigator Consultant Susanne Vallentin suva@heh.regionh.dk
Rigshospitalet Dept. Oncology Blegdamsvej 9 Copenhagen	Investigator Consultant Claus Kamby Claus.kamby@rh.regionh.dk
Dept. Oncology Naestved Sygehus Ringstedgade 61 4700 Næstved	Investigator Consultant Zahra Taheri-Kadkhoda ztk@regionsjaelland.dk
Service d´Oncologie Radiotherapie Institute Curie	Investigator Consultant Youlia Kirova Youlia.kirova@curie.fr

26, Rue d´Ulm 75005 Paris, France	
University Dept of Radiation Oncology University Hospital Tübingen Hoppe-Seyler-Strasse 3 72076 Tübingen Germany	Investigator Consultant Nicola Weidner N.Weidner@med.uni-tuebingen.de
SODC Radioterapia Oncologica Azienda Ospedaliero-Universitaria Careggi Firenze Italy	Investigator Consultant Icro Meattini / Lorenzo Livi Icro.meattini@unifi.it Lorenzo.livi@unifi.it
New South Wales Breast Cancer Institute Westmead Hospital New South Wales Sydney Australia	Investigator Consultant Verity Ahern Verity.Ahern@health.nsw.gov.au
Institute of Oncology Ljubljana Zaloska 2 1000 Ljubljana Slovenia	Investigator Consultant Tanja Marinko tmarinko@onko-i.si
Clinique Ste Elisabeth Namur Belgium	Investigator Consultant Vincent Remouchamps Vincent.REMOUCHAMPS@cmsenamur.be
Radiotherapy Department Université Catholique de Louvain, Cliniques Universitaires St-Luc, Brussels, Belgium	Investigator Consultant Carine Kirkove carine.kirkove@uclouvain.be
Department of Radiotherapy, Maria Sklodowska-Curie Memorial Cancer Centre and Institute of Oncology, Gliwice Poland	Investigator Consultant Dorota Gabrýs gabdorka@googlemail.com
Department of Oncology University Hospital of North Norway, Tromsø, Norway	Investigator Consultant Egil Støre Blix Egil.blix@uit.no

CONTENT

1.0 BACKGROUND

The purpose of this randomised trial is to investigate the morbidities following normofractionated *versus* moderately hypofractionated loco-regional radiation therapy of patients with early breast cancer with an indication for irradiation of regional lymph nodes levels (I), II, III, IV and the internal mammary nodes (IMN). The patients will be randomised to either 50 Gy / 25 fractions, 5 weeks, (standard therapy) *versus* 40 Gy / 15 fractions, 3 weeks, (experimental therapy). If the patient is also a candidate for boost radiation therapy this will be provided as a simultaneous integrated boost (SIB) without any randomisation of the boost, provided the boost is not to regional nodes. Boost therapy according to DBCG guidelines is provided sequentially either as 10 Gy / 5 fractions or 16 Gy / 8 fractions depending on individual risk factors. The simultaneous integrated boost therapy will be provided in a way that the overall treatment time is reduced by 5 treatment days compared to standard therapy, which is 30-33 treatment days (25 days + 5 or 8 sequential days for boost). A patient being a candidate for a 10 Gy boost and randomised to 50 Gy / 25 fractions will therefore be treated with a simultaneous boost based on 57 Gy / 50 Gy / 25 fractions (2.28 Gy per fraction to boost area). A patient being a candidate for a 16 Gy boost and randomised to 50 Gy / 25 fractions will be treated with 28 fractions in total with dose levels of 63 Gy / 51.52 Gy / 28 fractions. This corresponds to 2.25 Gy per fraction in the simultaneous boost volume, and 1.84 Gy per fraction to the non-boost areas. A patient being a candidate for a 10 Gy boost and randomised to 40 Gy / 15 fractions will be treated with a boost based on 45.75 Gy / 40 Gy / 15 fractions (3.05 Gy per fraction to boost area). A patient being a candidate for a 16 Gy boost and randomised to 40 Gy / 15 fractions will be treated with 18 fractions in total with dose levels of 52.2 Gy / 42.3 Gy / 18 fractions. This corresponds to 2.9 Gy per fraction in the boost volume, and 2.35 Gy per fraction to the non-boost areas. All treatments are based on 5 fractions per week. The proposed fractionation schemes are listed in Table 1.

Tabel 1.

Standard regime	α/β 2	α/β 3	α/β 4	α/β 5
50/25	100	83,33	75	70
40/15	93,4	75,6	66,7	61,36
60/30	120	100	90	84
66/33	132	110	99	92,4
76/38	152	126,67	114	106,4
40/15+10/5	93,4+20=113,4	75,6+16,67=92,27	66,7+15=81,7	61,36+14=75,36
40/15+16/8	93,4+32=125,4	75,6+26,67=102,27	66,7+24=90,7	61,36+22,4=83,76

All calculations are based on Biological Equivalent Dose, BED. All values are in Gray.
Formula: BED= D (1 + d/(α/β))

Randomization arm 50 Gy / 25 fractions combined with boost

Regime SIB	α/β 2	α/β 3	α/β 4	α/β 5
16 Gy boost				
66/33	132	110	99	92,4
58,8/28 (2,1)	120,54	99,96	89,67	83,50
61,6/28 (2,2)	129,36	106,77	95,48	88,70
63/28 (2,25)	133,88	110,25	98,44	91,35
50/25	100	83,33	75	70
50,96/28 (1,82)	97,33	81,88	74,15	69,51
51,24/28 (1,83)	98,12	82,50	74,68	69,99
51,52/28 (1,84)	98,92	83,12	75,22	70,48
10 Gy boost				
60/30	120	100	90	84
56,25/25 (2,25)	119,5	98,44	87,89	81,56
56,5/25 (2,26)	120,35	99,06	88,42	82,04
56,75/25 (2,27)	121,16	99,69	88,96	82,51
57/25 (2,28)	121,98	100,32	89,49	82,99

All calculations are based on Biological Equivalent Dose, BED. All values are in Gray. Formula: BED= D (1 + d/(α/β))
In green, the standard regime, in red, the regime with BED closest to the standard regime

Randomization arm 40 Gy / 15 fractions combined with boost

RegimeSIB	α/β 2	α/β 3	α/β 4	α/β 5
16Gyboost				
40/15+16/8	93,4+32=125,4	75,6+26,67=102,27	66,7+24=90,7	61,36+22,4=83,76
50,4/18(2,8)	120,96	97,44	85,68	78,62
51,3/18 (2,85)	124,4	100,04	87,85	80,54
52,2/18(2,9)	127,89	102,66	90,05	82,48
43,2/18(2,4)	95,04	77,76	69,12	63,94
41,4/18(2,3)	89,01	73,14	65,21	60,44
42,3/18 (2,35)	92,0	75,43	67,15	62,18
10Gyboost				
40/15+10/5	93,4+20=113,4	75,6+16,67=92,27	66,7+15=81,7	61,36+14=75,36
45/15 (3,0)	112,5	90	78,75	72
46,5/15(3,1)	118,58	94,55	82,54	75,33
45,75/15 (3,05)	115,52	92,26	80,63	73,66

All calculations are based on Biological Equivalent Dose, BED. All values are in Gray.
Formula: BED= D (1 + d/(α/β))
In green, the standard regime, in red, the regime with BED closest to the standard regime

The primary endpoint of the trial is radiation-induced late morbidity measured as lymph oedema of the arm on the treated side. A lymph oedema is present if the ipsilateral arm circumference is increased by ≥2 cm compared to the contralateral arm measured 15 cm proximal / 10 cm distal to the olecarnon or if the

patient uses an arm sleeve daily/almost daily. Secondary endpoints are breast induration, telangiectasia, dyspigmentation of the skin, global cosmetic score, range of arm movement, body image scale, QoL, and PROMS measured on a scheme previously used by the DBCG. Also recurrences and the location of recurrences will be investigated.

The hypothesis is that women operated for early breast cancer with an indication for regional nodes radiotherapy and in some cases also an indication for boost can be offered moderately hypofractionated loco-regional breast radiation therapy without an increased risk of radiation-induced late morbidity compared to women treated with standard radiation therapy to the same regions. In patients treated with a SIB we hypothesize that this will not cause an increased risk of radiation-induced late morbidity compared to therapy based on a sequential boost (standard therapy), because the fractionation regimens are based on identical biological effective doses. The risk of late morbidity after standard sequential boost therapy is currently being documented in the DBCG HYPO trial, where sequential boost therapy has been provided to patients treated both with 40 Gy / 15 fractions and 50 Gy / 25 fractions in different patient risk groups treated with varying systemic therapy.

STANDARD LOCO-REGIONAL RADIATION THERAPY

According to DBCG guidelines loco-regional radiation therapy of early breast cancer is offered to patients operated with mastectomy or breast conserving therapy for a breast cancer with one to several macro-metastasis in the regional nodes (thus minimum pN1 disease) and in cases with pT3pN0 tumours. Standard loco-regional radiation therapy is based on 50 Gy / 25 fractions being the dose-fractionation scheme used in the DBCG 82b&c trials, which documented the beneficial effects of post-mastectomy radiation therapy given to patients with pT3 or minimum pN1 disease (1;2). The effects of radiation therapy both regarding recurrences and loco-regional morbidities have been extensively investigated in these patient cohorts, as also the risks of radiation-induced heart disease and second cancer (3-9). Patients treated with breast conservation and irradiated with 50 Gy / 25 fractions have also been investigated, thus the effects of this standard therapy is well documented in Danish breast cancer cohorts (10-12). Recently data from the DBCG IMN study has documented the beneficial effect on breast cancer mortality and overall mortality in >3.000 patients treated with loco-regional breast radiation therapy (13-15). The DBCG IMN study has been practice-changing in Denmark, thus since June 2014 it has been standard to include the IMN in the radiation therapy fields in all patients with an indication for regional nodes therapy.

As of March 27th, 2014, moderately hypofractionated breast radiation therapy based on 40 Gy / 15 fractions, 3 weeks, has been standard therapy in Denmark to patients with an indication for breast only radiation therapy, ie hypofractionation of regional lymph nodes is not allowed. This new DBCG guideline was based on initial results from a randomised clinically controlled trial, the DBCG HYPO trial. In this trial breast cancer patients being candidates for breast only radiation therapy were randomised to either 50 Gy / 25 fractions (standard therapy) *versus* 40 Gy / 15 fractions (experimental therapy). The primary endpoint was breast induration grade 2+. Other common radiation-induced late morbidities and pattern of recurrence were secondary endpoints. A total of 1883 patients are currently in follow up in that trial. The trial was prompted by promising results from the START Trial B, where 2015 patients were randomised to 50 Gy *versus* 40 Gy, and no significant differences were found regarding the pattern of recurrence, whilst the risk of some of

the radiation-induced morbidities were decreased by using the 40 Gy scheme (16). In most western countries loco-regional breast radiation therapy is still offered as 50 Gy / 25 fractions, however, in the UK virtually all breast cancer patients (irrespective of regional nodes radiation therapy) are now treated with 40 Gy / 15 fractions based on the results from the START Trial B (16) (John Yarnold, personal communication). This is the case even though only 7% of the 2015 patients in the START Trial B were treated with loco-regional radiation therapy, and the details of the morbidities have not been reported separately for this patient group. For example, it is not known what the absolute risk of arm lymphedema was in the START Trial B, except there was no difference in development of edema between the two dose schemes reported in a forest plot. In the Netherlands virtually all breast cancer patients (irrespective of regional nodes radiation therapy) are now treated with 42.5 Gy / 16 fractions based on results from the hypofractionated Canadian trial, even though no regional radiation therapy was prescribed in the Canadian trial (17). Furthermore the Dutch breast radiation therapy group is now discussing to change the dose from 42.5 Gy / 16 fractions to 40 Gy / 15 fractions to increase harmony with the British strategy (Philip Poortmans, personal communication).

Many experts in breast radiation therapy are reluctant to initiate moderately hypofractionated loco-regional breast radiation therapy outside trial. In the period 1977-1981 Danish breast cancer patients were irradiated with hypofractionated techniques after mastectomy, and an evaluation of radiation-induced morbidity documented severe problems using hypofractionation compared to standard fractionated therapy (18). However a reconstruction of the fields and doses provided in the DBCG 77 protocol on recent CT scanned patients has shown that the dose per fraction was up to 4.4 Gy, 12 fractions (Mette Skovhus Thomsen, personal communication). Based on the severe radiation induced morbidities observed hypofractionation was abandoned in Denmark until start of the DBCG HYPO trial in 2009. Many improvements have been made regarding therapy of breast cancer patients since the early 80-ies, however there is remarkably few data from subsets of randomized trials and small prospective / single-institutional studies regarding the feasibility of hypofractionated regional nodes radiation therapy, Table 2 (19).

Table 2

Hypofractionated RNI studies.

Study	Type	Year	Patients	Fractionation	Follow-Up (mo)	Outcomes
Marsden [12]	Randomized, prospective	1986–1998	1,410 (14% chemo, 20% RNI)	42.9/13 v. 39/13 v. 50/25 (All in 5 weeks)	115	No data regarding RNI subset of patients
START A [7]	Randomized, prospective	1998–2002	2,236 (36% chemo, 15% PMRT, 14% RNI)	41.6/13 v. 39/13 v. 50/25	61	No difference in chest wall appearance, chest pain/swelling, shoulder/arm function, and lymphedema compared with standard fractionation PMRT
START B [7]	Randomized, prospective	1999–2001	2,215 (22% chemo, 8% PMRT, 7% RNI)	40/15 v. 50/25	72	No difference in chest wall appearance, chest pain/swelling, shoulder/arm function, and lymphedema compared with standard fractionation PMRT
UZ Brussels [15]	Randomized, prospective	2007–2011	70 (33% RNI)	50/25 v. 42/15	28	Reduced skin changes and lung function with hypofractionation at 2 years; no difference in fibrosis, lymphedema, or cardiac function.
Greece [32]	Prospective	2003–2010	112 (all PMRT, 73 RNI)	35/10	44	97% local control; no cases of pneumonitis. Acute toxicity- 23% Grade 2 + dermatitis in boost, 13% beyond field, No Grade 2 + chest pain, pneumonitis, edema, or erythema. Late toxicity- Grade 2 + edema 4.4%, Grade 2 + fibrosis, 7.1%, Grade 2 + chest wall pain 1.8%, No Grade 2 + plexopathy 4% CT changes in lung
Thailand [33]	Retrospective	2004–2006	215 (all PMRT; 67 conventional, 148 Hypofractionated)	50/25 v. 42.4–47.7.2.65	39	No difference in loco-regional control; no difference in chest wall appearance, fibrosis, appearance, plexopathy, lymphedema, cardiac, pulmonary, or rib fractures

Most studies reporting poor outcome after hypofractionated radiation therapy have been based on older radiobiological models combined with poor radiation techniques. Today pre-operative imaging has been considerably improved, thus the surgeon has more optimal knowledge about the location and extent of the tumour before surgery. Oncoplastic surgical techniques are becoming more widely used, thus increasingly large tumours are being removed with breast conservation combined with breast tissue remodelling. The axilla in cN0 patients is investigated with sentinel node biopsy, and only patients with macro-metastasis are operated with an axillary clearance. In some countries up to two macrometastases are accepted in cN0 patients without leading to an axillary lymph node dissection, if the patient is treated with systemic and radiation therapy afterwards based on the ACOSOG Z0011

trial (20). The risk criteria for classifying the patient at high risk of recurrence have changed in a way so that the majority of patients today are offered systemic therapy, which has become increasingly intensive with taxan-based chemotherapy, trastuzumab and anti-hormonal therapy for 5-10 years (DBCG.dk). In this way the patient of today is different in many ways compared to previous patients, and data is needed on the combined morbidity after surgery, systemic therapy and radiation therapy of the modern treated patient. Since 1976 the LQ model has been the most widely used radiobiological model despite it being developed on skin reactions in irradiated mice (21). There are limitations to the model e.g. it is difficult to estimate the influence of radiation therapy in relation to overall treatment time and irradiated volume. Caution is therefore needed when different fractionation schemes are in play, and randomized clinically controlled trials with systematic follow up are therefore needed.

BOOST

Boost radiation therapy is offered to patients with an increased risk of local recurrence after breast conserving operation. After mastectomy there is very seldom an indication for boost; it only takes place if the tumour invaded through the fascia and was removed with <2mm margin in the major pectoral muscle. The effect of boost in patients operated with breast conservation is well documented, and the proportional risk reduction in local recurrence is the same in all age categories, however, the absolute risk reduction is largest in young patients (22). Based on unpublished data from the DBCG the Danish 5-year local recurrence risk after breast conservation therapy is below 3%, even though a boost according to DBCG guidelines is not offered to every breast cancer patient operated with breast conservation. The DBCG guideline recommends a boost of 10 Gy / 5 fractions to patients aged 41-49 years operated with breast conservation. A boost of 16 Gy / 8 fractions is offered to patients <41 years old operated with breast conservation, or (irrespective of mastectomy/breast conservation) if the resection margin is <2mm provided the margin was not to a fascia. A boost may also be provided after mastectomy and/or axillary lymph node dissection at the discretion of the radiation oncologist, if for example the mastectomy is not radical, or in cases with pathological lymph nodes in the axilla (any level) not removed during surgery. Special caution regarding boost in the area of regional nodes is however needed, and patients treated with a regional nodes boost are NOT candidates for this trial.

There is no data from randomised trials investigating SIB. The IMPORT HIGH Trial is accruing patients in the UK, and it is a 3-armed phase III randomised trial : arm 1 is 40 Gy / 15 fr and a sequential boost 16 Gy / 8 fractions, thus 23 fractions in total. Arm 2 is 53 Gy / 40 Gy / 36 Gy / 15 fractions, and arm 3 is 48 Gy / 40 Gy / 36 Gy / 15 fractions. The BED of the 53 Gy / 15 fractions compared to 40 Gy and sequential boost 16 Gy (arm 1) are 146.6 Gy versus 125.4 (α/β 2 Gy) and 90.45 Gy versus 83.76 Gy (α/β 5 Gy). The trial is expected to accrue 2568 patients by 2015, where it closes. Another prospective 2-armed, multi-center randomised phase III trial is running in Heidelberg and Mannheim, Germany (23). In arm 1 the regimen is 64.4 Gy / 50,4 Gy / 28 fr (2.3 Gy per fraction to boost area) and arm 2 is 50,4 Gy / 28 fr followed by sequential boost of 16 Gy / 8 fr. (BED values based on an α/β of 2 Gy and 5 Gy is 138.46 Gy and 94.02 Gy respectively in the test arm.) The primary endpoint is cosmetic result 6 weeks and 2 years after radiation therapy, and secondary endpoints are 2 and 5 year local recurrence rates. The planned accrual is 502 patients.

A SIB has been used routinely in Groningen and Eindhoven in the NL since 2005 and 2007, respectively, and the dose has most often been 16 Gy (2 Gy per fraction). Based on retrospective data from these two centres, SIB is now routinely used in most Dutch radiation departments. Recently five year outcomes of hypofractionated SIB were reported regarding patterns of recurrence (24). In 752 consecutively treated patients from a single institution in Groningen a SIB was provided with doses of 67.2 Gy / 50.4 Gy / 28 fr if focally positive margins (2.4 Gy per fraction in the boost area), and 64.4 Gy / 50.4 Gy / 28 fr (2.3 Gy per fraction in the boost area) if other indications for boost. Using an α/β of 2 Gy, these boost doses correspond to 147.84 Gy and 138.46 Gy, respectively, whilst the highest BED used in Denmark now is 132 Gy (50 Gy / 25 fr followed by 16 Gy / 8 fr), Table 1. The actuarial 5-yr rate of local control is 98.9%, which is optimal. Morbidity has been reported in 940 patients treated 2005-10, and with 30 months median follow up (436 pts followed > 30 months) ≥grade 2 fibrosis in the boost area was observed in 8,5% of the patients (25). In almost half of the patients grade 1 fibrosis was detected in the non-boost areas of the breast, and chest wall pain was reported in nearly 7% of the patients. In 40% of the patients a fair/poor cosmetic outcome was seen, and this was associated with re-resection, large tumour and regional nodes radiation therapy, which 6% of the patients had been given. In Eindhoven 1274 patients were treated with a SIB in the period 2007-9, however, outcome data has not been reported yet. They have used a protocol, where a re-scan was performed if the first planning CT was made <30 days post-operatively and with >30 ml seroma (26). 9% of the patients fulfilled these criteria and were re-scanned and re-planned at treatment day 10. In 77% of the patients there was a significant reduction in the seroma volume from 60 ml to 27 ml on average, and this lead to significantly smaller boost volumes. A study from Atlanta, USA, has reported retrospective data from 354 patients with stadium I-III breast cancer and treated with a SIB (27). In 89% of the patients therapy was based on 59.95 Gy / 45 Gy / 25 fractions (2.14 Gy per fraction in the boost area) (based on an α/β 2 Gy the BED is 124.10 Gy). After median 33 months the 3 yr loco-regional recurrence rate was 2.8% for patients with invasive cancer and 1.4% in DCIS patients, and cosmetic evaluation was good/excellent in 96,5% and fair in 3,5% of the patients. In Lübeck a multicenter phase II trial was initiated in 2011, and plans to accrue 150 patients up to 2016. The trial investigates SIB based on 48 Gy / 40 Gy / 16 fractions. The study will stop if 20% of the patients have severe acute morbidity or if high quality dose plans cannot be made in >90% of the patients. The endpoints are morbidity.

COMBINED EFFECTS OF RADIATION AND SYSTEMIC THERAPIES

Data is missing on the combined effects of radiation therapy and different systemic therapies on morbidity, in particular if the radiation therapy was hypofractionated. Following normofractionated radiation therapy including a sequential boost, Bartelink et al reported a significantly increased risk of grade 2+ fibrosis if a boost was provided (26,9% after 10 years with boost versus 12,6% without boost), and the risk of morbidity was higher if chemotherapy was also given (22). This finding is supported by Lyngholm et al documenting a risk of grade 2+ fibrosis of 23% after median follow up 12 years, and this risk was significantly increased in patients treated with CEF whilst not with CMF (11). Currently two randomised phase II trials are investigating moderately hypofractionated breast radiation therapy in Denmark, the DBCG HYPO trial and the DBCG PBI trial. The hypofractionated therapy in these trials is based on 40 Gy / 15 fractions, 2.67 Gy per

fraction, 5 fractions per week. In both trials morbidity is the primary endpoint, and there is focus on reporting morbidity in relation to systemic therapy.

MORBIDITY OF THE SHOULDER/ARM

There is an increased risk of arm lymphedema and impaired range of motion of the shoulder (12), change in sensibility and pain following mastectomy (28), breast conserving surgery (29) and adjuvant radiation therapy for early breast cancer (3;10;30;31). Morbidity is more frequent following mastectomy compared to breast conservation (12) and axillary lymph node dissection more often causes problems compared to sentinel node biopsy (32). Morbidity increases with higher numbers of removed axillary lymph nodes (10;33;34). Regional nodes radiation therapy increases the risk of impaired shoulder motion (3).

Recently a systematic review and meta-analysis on the incidence of unilateral lymphedema after breast cancer was published (35). Based on 72 studies reporting on lymphedema, 38 (53%) of the studies reported edema based on arm circumference, which was by far the most frequent technique of measurement. A pooled estimate of lymphedema in the 72 studies showed an incidence of edema of 16.6%, however, this was based on studies with a wide range of study designs, different timing from surgery and different methods of assessment. In the review it was concluded that the incidence of lymphedema increased at least up to 2 years after diagnosis/surgery, and thereafter the incidence appeared to be more stable. It was also seen in studies reporting on patients treated with axillary lymph node dissection that the incidence of lymphedema was 14.8% (95% CI, 11.4-19.0) (Table 3). In 29 studies included in the systematic review risk factors for developing lymphedema were investigated, and there was a strong level of evidence (consistent finding in at least 75% of studies) that receipt of axillary lymph node dissection, having a mastectomy, a greater number of nodes dissected, and a high body-mass index increased the likelihood of developing a lymphedema. Moderate level of evidence for risk of developing lymphedema was found in patients with node-positive disease, receipt of chemotherapy or radiotherapy, and not participating in regular physical activity.

Since there is no consensus on how to measure lymphedema it was decided to use the circumference method and define lymphedema as a difference in arm circumference ≥10% on the upper and/or lower arm compared to the opposite arm. This method was also used in the AMAROS trial. It is inexpensive (little equipment needed, although it requires staff time), reliable when used by trained assessors, and might be the most appropriate method in the long term because it detects size change and inter-limb size differences irrespective of tissue composition of the lymphedema. However, it has little sensitivity to detect preclinical lymphedema, and since it is based on an absolute difference it also does not take into account the body composition of the patient. Self-report methods are also inexpensive and may have the potential to detect preclinical lymphedema, however, used on their own, self-report methods lack specificity, because many of the symptoms of lymphedema may also be common in many breast cancer patients without lymphedema.

Table 3

	Included studies (n)	Incidence (%; 95% CI)
Pooled estimate		
All studies	72	16·6 (13·6–20·2)
Prospective cohort studies	30	21·4 (14·9–29·8)
Randomised clinical trial	7	10·4 (7·9–13·5)
Retrospective cohort	10	8·4 (5·4–12·8)
Cross-sectional studies	25	17·7 (13·8–22·4)
Location of study		
Asia	4	18·0 (10·2–29·8)
Australasia	7	21·5 (15·0–29·8)
Europe	17	14·2 (10·9–18·4)
Middle East	1	17·5 (13·9–21·8)
North America	32	21·0 (15·1–28·5)
South America	3	13·7 (8·1–22·2)
UK	8	8·4 (5·1–13·6)
Axillary surgery		
SLNB	18	5·6 (6·1–7·9)
ALND	18	19·9 (13·5–28·2)
Measurement method*		
Lymphoscintigraphy	1	5·0 (1·6–14·4)
Bioelectrical impedance	3	15·9 (4·6–42·6)
Self-reported clinical diagnosis	5	12·5 (6·2–23·6)
Clinical diagnosis	7	12·6 (8·1–19·3)
Circumference	38	14·8 (11·4–19·0)
Perometry	17	16·4 (10·9–24·1)
Self-reported swelling	19	20·4 (13·8–29·0)
More than one measure	9	28·2 (11·8–53·5)
Time since breast cancer diagnosis or surgery*		
3 to <6 months	8	10·3 (6·2–16·7)
6 to <12 months	15	13·8 (7·3–24·5)
12 to <24 months	24	18·9 (14·2–24·7)
2 to <5 years	30	18·6 (13·6–24·8)
≥5 years	16	15·6 (10·0–23·5)
More than one time category	6	7·6 (2·7–19·5)

ALND=axillary-lymph-node dissection. SLNB=sentinel-lymph-node biopsy.
*Numbers (percentages) might not add to 72 (100%) because some studies measured lymphoedema with more than one method or at more than one timepoint.

In the START Trial B there was no difference in risk of morbidity from shoulder/arm between the arms of 50 Gy / 25 versus 40 Gy / 15 fractions, however, in that trial only few patients were treated with regional nodes radiation therapy (36).

There is no consensus on the definition of arm lymphedema, and it may be measured in many ways as shown in table 3. Shoulder-arm morbidity may be reported by the patient through questionnaires or by measuring range of motion and muscle strength comparing it to either pre-operative or contralateral measurements (3;10). One method is constant shoulder score: CSS (12;37). Strength may be measured as strength against resistance, or ADL (10) or by using a Isobex devise (12;37).

Related to this trial a meeting has been held with participants from other DBCG committees previously involved in investigating loco-regional morbidity (Marie Overgaard, Jens Overgaard, Peer Christiansen, Jørgen Johansen, Niels Kroman, Jens Jørgen Elberg, Hella Danø, Christina Lyngholm, Mette Holck Nielsen, Birgitte Offersen). A consensus was reached upon including the following in future DBCG trials reporting loco-regional morbidity:

Photos: Frontal and side-photos pre-operatively, at start of radiation therapy, and year 1, 2, 3, 4, 5 and 10. At any event new photos are taken.

Morbidity: a modification of the questionnaire designed, validated and used by Rune Gärtners et al (28), at baseline, year 1, 2, 3, 4, 5 and 10 after radiation therapy.
Objective lymphedema: defined by the clinician by measuring arm circumference 15 cm/ 10cm proximal/distal to the olecranon bilaterally. Any difference ≥2cm defines edema. The dominating arm is registered. (In this trial measurements are registered, and the definition of edema is ≥10%).
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˚.

EXTENT OF AXILLARY SURGERY

DBCG guidelines recommend axillary lymph node dissection (ALND) in patients diagnosed with macrometastasis in the axilla. However, since the publication of the Z0011 and the AMAROS trials some centres outside Denmark now omit ALND in selected patients with limited nodal disease. From the AMAROS trial data has shown the risk of arm lymphedema 3 and 5 years after therapy was 6% in patients treated with sentinel node biopsy and nodal radiation therapy.
Among participating centres in the Skagen Trial 1 the guidelines as per January 2015 for extent of axillary surgery after positive sentinel node biopsy vary :
Denmark, France, Poland and Italy: patients with macrometastasis in SN receive ALND.
Australia, Slovenia, Germany, Belgium and Norway: patients fulfilling minimum Z0011 criteria may be selected for no ALND after macrometastasis in SN. The frequency depends on institutional guidelines for the surgical departments.
In Holland and England, where routine hypofractionation of regional nodes is taking place, patients operated with sentinel node biopsy only (thus no ALND after macrometastasis in the sentinel node) are treated with hypofractionation (personal communication Philip Poortmans and Charlotte Coles).

CONCLUSION

Standard therapy in most European countries is 50 Gy / 25 fractions to whole breast and regional nodes, and a boost in selected patients of 10-16 Gy / 5-8 fractions. Table 1 shows calculated biological equivalent doses (BED) for different standard regimens, where the 76 Gy dose is used in the randomised phase III Young Boost Trial which ended in 2012 and data is still awaited. The calculated BED are based on a review by J. Fowler (21). Since March 2014 the DBCG guideline has recommended breast only radiation therapy to patients minimum 41 years old be 40 Gy / 15 fractions, and in selected patients a sequential boost guided by risk factors.

We now want to introduce moderately hypofractionated regional nodes radiation therapy to Danish breast cancer patients through a randomised clinically controlled trial. Patients with an indication for a boost will be offered a simultaneous integrated boost. This is based on the following arguments:

-40 Gy / 15 fractions is now standard for Danish patients ≥41 years old with indication for breast only radiation therapy based on results from the DBCG HYPO Trial

-All regional nodes radiation therapy in the UK and NL is now routinely offered as moderately hypofractionated therapy based on 40 Gy / 15 fractions or 42.5 Gy / 16 fractions. This is irrespective of boost and systemic therapy.

-A SIB is routinely used in the NL for patients with an indication for boost. This strategy is supported by retrospective studies.
-The DBCG HYPO II Trial will assure a nationwide, systematic and quality-controlled introduction of moderately hypofractionated radiation therapy to new categories of breast cancer patients.
-A SIB will be introduced in Denmark through the DBCG HYPO II Trial without a randomisation of the boost. This is because relatively few patients in Denmark are treated with a boost, and there is not enough patients to make a randomisation for this therapy relevant. The outcome after SIB will be compared to the outcome after sequential boost in relevant patients from the DBCG HYPO Trial.

Based on the pre-START trial the α/β for breast cancer was estimated to 4.0 Gy (95% CI 1.0-7.8 Gy), which is in the same range as for fibrosis with an α/β 2-3 Gy (8). But for the adjuvant setting it is estimated that around 70% of the patients are already cured by surgery alone, thus the dose-response curve for the adjuvant radiation therapy is not from 0-100%, it is in principle from 70-100%. In Table 1 BED are calculated for different α/β estimates, and the standard regimens (green colour) have been chosen as the "baseline", thus the new regimens (red colour) have been chosen to resemble to standard regimens as much as possible.

Through this trial moderately hypofractionated regional nodes radiation therapy and SIB will be introduced in Denmark in a controlled manner with special focus on late radiation-induced morbidity. The morbidities will be evaluated and reported in the context of the types of systemic therapy. Patients will be followed prospectively with morbidity evaluation for 10 years after radiation therapy, and any deviation from the expected course of development of morbidity will be monitored and reported. The trial is supported and has participation from departments in the DBCG RT committee, and consequences of the trial for Danish patients will be drawn in the DBCG RT committee.

We expect 10% of the included patients operated with ALND will have lymphedema of the arm on the treated side 3 years after radiation therapy. We can accept an increase up to 15% in patients treated with moderately hypofractionated radiation therapy. If the frequency of lymphedema in hypofractionated patients is max 15% 3 years after radiation therapy, moderately hypofractionated radiation therapy will become new standard therapy to patients fulfilling the criteria for this trial. For patients operated with sentinel node biopsy but not ALND the risk of arm lymphedema is expected to be 6% (based on data from the AMAROS trial), and we can accept an increase up to 11% in this patient group. It is unsure how many patients in the Skagen Trial 1 will be operated with sentinel node biopsy only.

2.0 RANDOMISATION

The randomisation is between 50 Gy / 25 fractions versus 40 Gy / 15 fractions as follows:
Woman, ≥18 years, operated for early breast cancer pT1-3, pN0-N3, M0 with an indication for regional nodes radiation therapy

Arm 1: 50 Gy / 25 fractions, 2.0 Gy per fraction, 5 fractions per week

Arm 2: 40 Gy / 15 fractions, 2.67 Gy per fraction, 5 fractions per week

If the patient is a candidate for a boost it will be provided as follows:

50 Gy + 10 Gy boost: 57 Gy / 50 Gy / 25 fractions

50 Gy + 16 Gy boost: 63 Gy / 51.52 Gy / 28 fractions

40 Gy + 10 Gy boost: 45.75 Gy / 40 Gy / 15 fractions

40 Gy + 16 Gy boost: 52.2 Gy / 42.3 Gy / 18 fractions

The strata for randomisation are:

- Surgical type: mastectomy versus lumpectomy
- Treating institution

INFORMATION OF THE PATIENT

All women being candidates for adjuvant breast radiation therapy are routinely invited to have information regarding this therapy in the Department of Oncology, and the invitation encourages her to bring along an assessor to the information. The meeting takes place in a quiet and undisturbed room. The informing doctor first informs the patient about the standard therapy, and it will be made clear to her what the standard therapy is. After this she will be informed according to the national guidelines regarding patient participation in trial about the trial and randomisation between standard therapy and experimental therapy. The patient is handed a written information about both standard therapy and the therapy on trial. The patient is invited to come to another session at the hospital to give her consent to participate in the trial, if that is what she wants. After her written consent, baseline morbidity evaluation is performed, and the patient is informed later on the same day (or 1 day later) what her randomisation showed. If she is a candidate for boost therapy, she will be informed that this will be delivered as a SIB no matter the result of the randomisation.
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 randomisation. 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, surgical procedure. 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.

RISK TO THE PATIENT

Patients included in this trial do not receive more radiation than they would otherwise,

nor during the planning CT scanning neither later on during therapy. The BED calculated for each therapy is based on the standard therapy, and the experimental therapy is chosen to be as close as possible to the standard therapy doses. For patients treated with 40 Gy / 15 fractions the BED is actually slightly lower compared to 50 Gy / 25 fractions as shown in Table 1, however, data from phase III trials have proven these doses sufficient to assure identical low recurrence rates compared to 50 Gy / 25 fractions (16;17). For patients operated without axillary lymph node dissection, regional nodes radiation therapy can be provided with 40 Gy/15 fractions which is believed no to increase the risk of recurrence. Such therapy already now takes place outside trial in Holland and England. For the SIB therapy the BED has been calculated and chosen to resemble as much as possible the sequential boost doses. It is expected that there will be no difference in the radiation induced late morbidities, and there is no data to indicate more morbidity with the 5 days shorter therapy. The discomfort for the patient during therapy is expected identical, except some patients will prefer the shorter overall treatment time with hypofractionation.

If the patient regrets her consent to the trial she can at any time withdraw her consent, and she will then be treated according to the standard DBCG guidelines. She will be informed about this during the first information about the trial and also in writing. If she withdraws her consent during radiation therapy, she will be treated with 2 Gy per fraction for the rest of her therapy, and the number of fractions then depends on how much dose she already has received (calculated based on the LQ model).

3.0 ENDPOINTS

Primary endpoint:
Ipsilateral arm lymphedema 3 years after radiation therapy. Arm lymphedema is present if there is ≥10% increase in arm circumference measured 15 cm proximal and/or 10 cm distal to the olecranon on the treated side compared to the contralateral arm.

Secondary endpoints:
Range of motion of the arms (flexion/abduction). Specialist and patient reported outcome measures regarding cosmesis and function. In the analysis of the primary/secondary endpoints the influence of extent of surgical procedures will be evaluated, both related to mastectomy/lumpectomy, and also related to +/- axillary lymph node dissection. Recurrences, localization of recurrences, death and cause of death. Please, see Appendix I-VI for details on the morbidity measurements.

4. 0 CRITERIA FOR INCLUSION AND EXCLUSION

Inclusion criteria:

- Woman ≥ 18 years who had radical operation for invasive breast cancer pT1-3, pN0-N3, M0 with either mastectomy or breast conservation. The patient can be included no matter the status of estrogen receptor, progesterone receptor, malignancy grade, HER2 status.

- Axillary lymph node dissection of the axilla where the findings give indication for regional nodes radiation therapy to levels (I), II, III, IV, interpectoral nodes and the IMN.
- Sentinel node biopsy documenting limited nodal disease without an indication for axillary lymph node dissection according to institutional, national or other trial guidelines.
- The patient may be a candidate for boost to the tumour bed.
- Adjuvant systemic therapy with chemotherapy, endocrine therapy and anti-HER2 treatment is accepted.
- Neoadjuvant chemotherapy to downstage a cT3-cT4 or cN2-cN3 breast cancer is accepted if there is *not* an indication for a boost in the area of regional nodes after surgery.
- Primary systemic therapy of an operable breast cancer is accepted.
- If the patient is not treated with chemotherapy she must be randomised within 42 days from last surgery. If she has received chemotherapy she must be randomised within 4 weeks after the last series of chemotherapy.
- Breast implants are accepted.
- Connective tissue disease is allowed if the treating clinical/radiation oncologist finds radiation therapy indicated
- Postoperative infection and/or seroma giving indication for drainage during RT 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 carcinoma of the skin, squamous cell carcinoma of the skin
- Life expectancy minimum 10 years

Exclusion criteria:

- Previous breast cancer or DCIS of the breast.
- Bilateral breast cancer
- The patient has an indication for boost to 1 or more regional nodes
- Previous radiation therapy to the chest region
- Pregnant or lactating
- Conditions indicating that the patient cannot go through the radiation therapy or follow up, or a condition where the treating oncologist thinks the patient should not participate in the trial for example due to language problems.

RANDOMISATION

The randomization procedure is 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 will thus be informed on the randomization while still at the hospital.
Randomisation will be stratified for institution and surgical type mastectomy versus lumpectomy. Since it is unsure how many patients will be operated without axillary lymph node dissection after macrometastatis in the sentinel node, no stratum for these patients is made in order not to loose power in the calculations.

5.0 RADIATION THERAPY

5.1 PLANNING CT SCAN AND TARGET VOLUMES

PLANNING CT SCAN

The patient is scanned in supine treatment position preferably with both arms abducted about 120˚. The head is positioned straight with the chin slightly upwards or a little tilted to the contralateral side, avoiding skin folds at the level of the lower neck. Fixation is done according to the guidelines of the treating department, and a daily reproducibility of approx. 5 mm must be achieved. The scanned volume is neck and breast region including both lungs. The slice thickness is max 3mm. Respiratory gated techniques should be used in all left-sided patients, and ideally also in right-sided patients in order to assure a sufficient dose coverage of the IMN and at the same time spare the ipsilateral lung as much as possible from dose.

BREAST CTV AND LYMPH NODE TARGETS

The CTV lymph node targets are delineated according to the ESTRO consensus guideline, and the structure names must follow the nomenclature of the ESTRO consensus, Table 4. It is not acceptable to delineate all the CTVn´s as one large volume. Regarding dose coverage of the CTVn_IMN, it is recommended to include intercostal levels 1, 2, 3 in all patients. In patients with a tumour localization in the lower-inner quadrant of the breast the IMN intercostal level 4 is also recommended included in the target. This may cause high doses to the heart for left-sided patients, and respiratory gated techniques should be used to lower the dose to this organ. It has been estimated that the number needed to treat to save one breast cancer death is significantly lower than the “number needed to harm” with ischaemic heart death when evaluating dose coverage of the IMN and the heart (14).

Table 4
List of nomenclature to be used in this trial according to the ESTRO and DBCG guidelines. Surface is the body outline without fixation and couch.
Contralat breast* is recommended delineated in cases where dose planning is based on intensity modulated technique.

Name of target
CTVn_L1
CTVn_L2
CTVn_L3
CTVn_L4
CTVn_IMN
CTVn_interpect
CTVp_breast
CTVp_chestwall
CTVp_tumourbed
Heart
LADCA
Ipsilat lung
Humeral head
PRV_Humeral head

Contralat breast*
Surface

BOOST CTV

Tumour bed should be delineated based on all available information from pre-operative imaging, surgical report, pathology report and the localization of the surgical clips. The clips must be positioned according to a protocol, and the radiation oncologist must be aware of this protocol. If oncoplastic surgery has been carried out, a close collaboration between the surgeon and the oncologist is particularly important if the patient is a candidate for a boost. The CTV boost is generated by adding a 5mm margin to the tumour bed inside the CTV breast.

LUNG AND HEART

Delineation of lung, heart and LADCA is according to DBCG guidelines (38).

PLANNING TARGET VOLUME (PTV)

PTV is generated by adding a margin around the CTV to account for set up errors during therapy. When the lymph nodes are target, a PTVn including all the CTVn´s is defined. Correspondingly a PTVp_breast/chest wall is generated from CTVp_breast / chest wall. In general PTV should be cropped to 5 mm beneath the skin. A typical CTV to PTV margin is 5mm in all directions. However the actual setup error depends on immobilisation of the patient and on the image guidance strategy, and therefore varies among departments. Each department should perform measurements to determine their CTV to PTV margin. The PTV_boost is typically defined as the CTV_boost + 5mm margin in all directions (39).

5.2 DOSIMETRY AND ORGANS AT RISK

DOSE PLANNING

Dose planning is based on the ICRU 50, 62 and 83 recommendations (40). Dose is prescribed and dosed in CTV. For 3D-CRT planning it is recommended to use a technique based on a single isocenter with tangential fields with parallel posterior field edges to cover PTVp_breast / PTVp_chest wall. A 25mm skinflash is applied (when applicable) to account for potential swelling of the breast/chest wall. In case of SIB, fields are added to cover the PTV_boost. For regional nodes radiation therapy an anterior periclavicular field is used, and an opposing posterior field may be added to ensure homogeneous dose in the target. Wedges and electronic compensation may be used to obtain dose homogeneity. It is accepted to use intensity-modulated RT techniques including VMAT and Tomotherapy. A bolus on the lumpectomy scar is not accepted as routine, but may be indicated in special cases, whilst a bolus on the mastectomy scar in general is accepted.
CTVp_breast / chest wall is to be covered with doses of 95-107% if therapy is normofractionated, and 95-105% if therapy is hypofractionated. The volume of CTVp_breast / chest wall receiving 107%<dose≤110% (normofractionated) or 105%<dose≤108% (hypofractionated) must be <2%. The overdosage should preferably be distributed over several areas.

CTVn's are to be covered with doses 90-107% with $D_{2\%} \leq$ 108% (normofractionated therapy) and 90-105% with $D_{2\%} \leq$ 106% (hypofractionated therapy). No volume except in the build-up zones must in principle receive dose <95%. The maximum dose to the treated volume should be kept below 108% (hypofractionated therapy) / 110% (normofractionated therapy). Photon energy is chosen to fulfil 95% dose 5 mm under the skin surface. Multi-leaf collimation is used to minimise the risk of dose to organs at risk.
Dose calculation must be based on modern dose algorithms (Monte Carlo, AAA, Collapsed Cone or similar) with inhomogeneity correction.

DOSE PLANNING OF SIB

In most patients optimal plans can be obtained with 3D-CRT encompassing the PTV boost. However, some patients may have a challenging anatomy in relation to the position of the PTV boost, and in those situations it may be optimal to use more advanced techniques for example VMAT as part of the dose plan. However, it is important that the final dose plan delivers dose in the breast when sparing the OAR as much as possible. Therefore in general the advanced techniques should preferably make up only part of the treatment plan (unless IMRT techniques for the whole treatment are used).
No international consensus exists, but in the RTOG 1005 Trial using hypofractionated breast radiation therapy and SIB guidelines are proposed for dose planning of SIB. The Skagen Trial 1 will follow the same guidelines, and the following is therefore recommended:
No more than 30% of the breast PTV will exceed 100% of the boost prescribed dose. In difficult cases it may be accepted that no more than 35% of the breast PTV will exceed 100% of the boost prescribed dose.
Please, notice that it is not the intention that patients where these constraints cannot be met are withdrawn from the trial. If the treating oncologist finds that the patient is going to be treated with a boost, the approved dose plan is considered the best solution in that case. It will be part of the quality control to investigate in how many patients the constraints are met.
In few patients the CTV boost is positioned at the border between the breast and the regional nodes. In these rare occasions it must be avoided that the field edges overlap in the area of the CTV boost due to the risk of triple trouble in the hypofractionated are in particular

DOSES

Patients randomised to 50 Gy / 25 fractions are treated with 2.00 Gy per fraction, 5 days weekly, to breast or chest wall and regional nodes. Patients randomised to 40 Gy / 15 fractions are treated with 2.67 Gy per fraction, 5 days weekly, to breast or chest wall and regional nodes. If the patient is a candidate for boost either to tumour bed after lumpectomy or due to a non-radical surgical procedure on the chest wall, the boost will be provided as a simultaneous integrated boost with the doses listed in Table 5.

Table 5
Doses for simultaneous integrated boost and non-boost areas in patients randomised to either 50 Gy /

25 fr or 40 Gy / 15 fr and with an indication for boost. The boost levels in the first column (Boost) indicate the different options in play according to DBCG guidelines.

Boost	SIB	Boost dose / fraction	Breast/chestwall	Non-boost dose/fraction	Fract
50Gy+10Gy	57 Gy	2.28 Gy	50 Gy	2.00 Gy	25
50Gy+16Gy	63 Gy	2.25 Gy	51.52 Gy	1.84 Gy	28
40Gy+10Gy	45.75 Gy	3.05 Gy	40 Gy	2.67 Gy	15
40Gy+16 Gy	52.2 Gy	2.90 Gy	42.3 Gy	2.35 Gy	18

ORGANS AT RISK

Organs at risk are the heart, LADCA, lung, chest wall and contralateral breast, and in the nodal areas it is the spinal cord, brachial plexus, the shoulder joint and the vessels. DBCG guidelines for therapy are listed in Table 6

The LADCA should be delineated and may max receive 17 Gy (as point dose). Contralateral breast should receive as little dose as possible.

The risk of radiation induced brachial plexopathy is closely related to dose per fraction and total dose (41). In the 1950s the use of 60 Gy total dose to regional nodes and 5Gy / fraction caused plexopathy in 66% of patients, in the 1960s therapy was 45-50 Gy using 4Gy / fraction and patient removal between each radiation field (because the gantry was fixed) resulting in overlapping doses caused plexopathy in 50% of patients, in the 1970s-1980s therapy was based on 45-50 Gy using 3Gy / fraction resulting in 10-15% patients with plexopathy. The incidence of brachial plexopathy is today <1-2% in patients receiving plexus total doses <55 Gy in 2 Gy/fraction. The DBCG guideline recommends a max dose in the brachial plexus of 54 Gy (2 Gy/fraction). Using an α/β 2 Gy, this corresponds to a BED of 108 Gy, so if therapy was based on 2.67 Gy/fraction a max dose of 46.25 Gy has the same BED (=108 Gy). Thus a dose of 40 Gy/15 fractions is expected to be acceptable.

The shoulder joint and the connective tissues around it should receive as low a dose as possible, and preferably less than 50% dose.

The constraints for organs at risk in this trial will follow the DBCG guidelines, and if changes are made in the DBCG guidelines during the course of this trial, these changes will also be implemented and followed by this trial.

Table 6
Overview of maximal accepted doses according to randomization arm.

OAR	V17 (hypo)	V20 (normo)	V35 (hypo)	V40 (normo)	Max dose (Gy)
Heart	10%	10%	5%	5%	
Ipsilat lung	35%	35%	-	-	Mean 18 (normo) Mean 16 (hypo)
Brachial plexus					54 (normo) 46.25 (hypo)
Spinal cord					45 (normo) 38.54 (hypo)

Priority:

The highest priority is given to the tumour bed irrespective of breast conservation or mastectomy. Thereafter priority should be given to the internal mammary nodes based on recent data from the DBCG IMN study. A respiratory gated planning CT scan is recommended in all patients to assure inclusion of intercostal spaces I-III of the

internal mammary nodes and at the same time achieve a sufficient low dose to the heart and lung, which are the next in the priority line. Fields should be arranged in a way to lower the dose to heart and lung, and therefore compromises may be accepted on CTVp_breast or CTVp_chest wall. Lower priority is given to PTV provided that the compromise is distant from the tumor bed, and finally contralateral breast has priority.

The balance between dose coverage of the CTVn_IMN versus the LADCA/heart should be evaluated based on the individual patient characteristics and technical aspects.
The above mentioned accepted doses for organs at risk are not to be considered safety doses. At any time it is important to strive to achieve as low doses in the organs at risk whilst assuring sufficient doses to the targets. If it is chosen to violate the ICRU recommendations when approving the dose plan focus should be on avoiding *double trouble*.

VERIFICATION OF THE RADIATION THERAPY

Every participating centre will use its own routine system for verification of the radiation therapy. The verification must be independent of the randomisation arms of the trial, and independent of the tumour localisation.

QUALITY ASSUARANCE OF THE RADIATION THERAPY

Before inclusion of the first patient a workshop for all participating Danish departments has been held to assure as little variation in dose planning among radiation centres as possible. Principal investigator was responsible for that.
For participating centres outside Denmark detailed information about the protocol and dose planning is assured by the principal investigator either visiting the centre abroad or by people from the centre abroad visiting the RT department in Aarhus.
Within the first 3 months after initiation of the protocol in a Danish department, 2 planning approved plans must be evaluated by another Danish RT department for quality assurance. This will be done through the national dose plan bank, and the principal investigator will notify the relevant departments in due time. For patients treated outside Denmark, the 2 planning approved plans from every department will be evaluated by the principal investigator. All dose plans will be submitted to the Danish national dose plan bank and detailed quality assurance based on a protocol for QA will be performed based on these plans. The dose calculation algorithm will be registered per centre. For other details, please read the paragraph “5.3 National dose plan bank”.
A protocol for quality control of target delineation and dose planning / delivery will be used in the trial. Quality assurance will among other things include an estimation of energy emparted in the patient outside the target areas in order to assure that the radiation fields are sized according to the delineated targets. Also boost dose in the PTV breast outside the PTV boost will be reported.

POSTPONEMENT OF THERAPY AND TREATMENT BREAKS

Postponement of radiation therapy must be balanced between randomisation arms, and should take place according to the guidelines of every participating centre. Treatment breaks must be kept as short as possible. Since the radiation therapy in this trial is adjuvant it is in general not indicated to compensate for lost fractions, thus when the patient is ready to resume therapy after a break, she will continue her

radiation plan until all fractions planned are given.

5.3 NATIONAL DOSE PLAN BANK

All dose plans for patients treated in this protocol must be submitted to the Danish national dose plan bank for quality assurance. It is of utmost importance that the delineated structures are named according to the nomenclature used in the ESTRO target consensus, and the local trial investigator is responsible for this. For patients treated outside Denmark it may however be acceptable to submit only a sample of treatment plans (minimum 10%) from every centre to the Danish national dose plan bank.
The submission must take place prospectively with max 6 months intervals. This is to assure access to plans for quality assurance.

6.0. EVALUATION OF PATIENT MORBIDITY DURING AND AFTER RADIATION THERAPY

6.1 MORBIDITY RELATED ENDPOINTS

In this trial detailed evaluation of late radiation-induced morbidity is a key factor. Evaluation of acute morbidity will only take place in a minority of the patients, because the clinical significance of the acute morbidities is considered acceptable due to the reversibility of these effects (please, see below). However, all randomised patients are to be evaluated for late morbidity. Table 7 illustrates when and what evaluation of late radiation-induced morbidity is to take place. It is emphasized that at any time a late radiation-related morbidity is detected a full morbidity evaluation must be performed. Charlson´s comorbidity index is registered at the Danish surgical departments. For participating departments outside Denmark, Charlson´s comorbidity index must be filled in also.

EVALUATION OF LATE RADIATION-INDUCED MORBIDITY IN RESIDUAL BREAST, CHEST WALL AND REGIONAL NODES

The primary endpoint of this trial is arm lymphedema on the treated side 3 years after adjuvant radiation therapy. The definition of arm lymphedema is ≥10% increased arm circumference measured 15cm proximal and /or 10cm distal of the olecranon on the treated side compared to the contralateral side. If the patient uses an arm sleeve she is asked to not wear this sleeve 24 hours before measurement. This information is included in the patient information folder. There is no published data on how long time it takes for an arm edema to reach steady state after use of an sleeve, so 24 hours is an estimate. Also range of motion of the shoulders will be measured by investigating flexion / abduction of the upper arms. The late radiation induced morbidity will be evaluated and estimated in harmony with previous DBCG trials where the same endpoints have been reported, thus ensuring optimal conditions for comparison (3;10;11). Fibrosis estimates as tissue induration, telangiectasia, oedema of the breast/chest wall and dyspigmentation will be evaluated according the LENT-SOMA scoring scale, and evaluation of the lumpectomy/mastectomy scar will be made according to a scale presented by Aaronson et al (42). The global cosmetic result after breast conservation will be based on Harris´ 4-point scale (43). A modification of the questionnaire designed, validated and used by Rune Gärtner et al

will also be used in order to report on pain, swellings, discomfort and daily function (28). The patient evaluates her satisfaction on The Body Image Score (BIS) (44), where to we have added an extra question regarding clothing habits and furthermore based on the study by Lyngholm et al also 2 more questions regarding her satisfaction with the appearance of the treated breast after breast conservation with and without comparison to the opposite breast (11). In addition we ask if the patient treated with breast conservation has had lipo-injection in her breast during follow up. This BIS is used in the DBCG HYPO and DBCG PBI trials.
Brachial plexopathy is a potential but seldom risk in patients treated with axillary lymph node dissection, taxan-based chemotherapy and loco-regional radiation therapy. It is however very difficult to distinguish between brachial plexopathy and the classical side effects from chemotherapy and surgical traumas (e.g. paresthesia). In this trial brachial plexopathy is therefore present if diagnosed by a neurologist. Thus if the patient has ipsilateral symptoms indicating plexopathy, she is recommended referred to a neurologist.

Tabel 7

Evaluations	Before RT	Years after radiation therapy					
		1	2	3	4	5	10
Arm lymph edema and ROM	X	X	X	X	X	X	X
Photos	X	X	X	X	X	X	X
Functional and cosmetic scores	X	X	X	X	X	X	X
Patient questionnaire (BIS and DBCG scheme)	X	X	X	X	X	X	X

Reporting of morbidity is online via www.dbcg.dk, and should take place after every morbidity evaluation. The paper version of every morbidity evaluation should be kept in the archives until the patient comes for her next evaluation to assure that correct reporting has taken place. The local investigator is responsible for this. Data is collected in DBCG which is a public register supervised by the Datatilsyn. The study has been sent for approval by Datatilsynet by DBCG. Data is managed according to the law about how to handle confidential information. Additional information regarding morbidity may be collected through questionnaires or the internet between to planned visits in the department. Staff involved in performing morbidity evaluation will be invited to participate in yearly workshops with focus on morbidity evaluation. The principal investigator is responsible for that. At these workshops patients with radiation related morbidity are invited for demonstration. Test of reproducibility of the morbidity evaluation should take place during the course of the trial, and the local investigator is responsible for assuring that the staff can reproduce the evaluations among them.

EVALUATION OF ACUTE RADIATION-INDUCED MORBIDITY IN RESIDUAL BREAST, CHEST WALL AND REGIONAL NODES

Many women develop acute morbidity during a radiation therapy course. The acute morbidity is radiation dermatitis, itching, pain, fatigue, dyspnea, cough, pneumonitis, dysphagia, increased sensation of tightness of the shoulder and lymphedema. There are 2 internationally recognised systems for scoring acute radiation-induced morbidity,

and they are the Common Toxicity Criteria (CTC), version 4.0 (45), and the Toxicity criteria of the RTOG and EORTC (46). Both systems overlap in scoring radiation dermatitis grades 0-4, whilst in the CTC system itching, pain, fatigue and dyspnoea, cough, pneumonitis, and dysphagia are also addressed.
Acute radiation-induced morbidity has not been systematically evaluated in Denmark since 1987, where evaluations were made in patients operated with mastectomy (18). In that report 30% of women treated with normofractionated radiation therapy to a total of 42 Gy developed relatively severe erythema combined with dry desquamation (~grade 2), and 10% of the women developed moist desquamation (~grade 3). A study based on moderately hypofractionated breast radiation therapy reported radiation dermatitis grades 0, 1, 2, 3, and 4 in 10%, 69%, 18%, 4% and <1% of 339 women when they finished 42.5 Gy / 16 fractions (47).
All evaluations are made according to the scheme listed below, and breast photos are also taken at every evaluation. The scoring system is shown in Appendix VI.
For patients treated with 50 Gy / 25 fractions, the biologically effective dose per week is 10 Gy. For patients treated with 40 Gy / 15 fractions, based on an $\alpha/\beta = 10$, the dose per week is 14.14 Gy. It is a fact that acute radiation-induced morbidity is delayed in time about 2 weeks.
Irrespective of randomisation arm evaluations listed in Table 8 are made 3 and 5 weeks after initiation of radiation therapy. After this time evaluations including breast photos are made every 2 weeks as long as there are visible changes in the skin. When the visible skin changes have ceased, other acute morbidities (for example pruritus) may be evaluated by phone calls to the patient in 2 week intervals until the morbidity has reached the pre-radiation therapy level.
Each participating radiation centre will perform evaluation of acute morbidity in the first accrued 40 patients, and minimum 50% of these patients must be patients treated with a simultaneous boost, because these patients receive the highest doses. To assure this, up to 20 non-boost patients are accrued, and thereafter only consecutive boost patients are scored for acute morbidity.
All acute morbidities will be reported online to the DBCG database.

Table 8

	Before RT	**3 weeks after RT start**	**5 weeks after RT start**	**7 weeks after RT start**	**9 weeks after RT start**
Date					
Radiation dermatitis					
Pruritus					
Pain					
Fatigue					
Dyspnea					
Cough					
Pneumonitis					
Dysphagia					
Arm lymphedema					
Range of motion of shoulders					

Photo					

6.2. 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 localisation 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 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, IMN or in the interpectoral nodes. Metastases other places in the body are distant metastases. Metastases will be identified by a combination of clinical, haematological, 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.

7.0 TRANSLATIONAL RESEARCH

In this protocol different types of radiation induced morbidity are evaluated in a prospective way. A translational research protocol may be developed to investigate relevant issues in relation to this randomised trial, however, such a translational research protocol is not ready at the time.

8.0 STATISTICS

8.1 CALCULATION OF SIZE OF COHORT

This trial is a non-inferiority trial. The null hypothesis is that the risk of lymphedema evaluated 3 years after radiation therapy is not increased after hypofractionated compared to normofractionated radiation therapy of regional nodes. To our knowledge no data on modern treated breast cancer patients is available, therefore a single-institution cross-sectional study was conducted at Aarhus University Hospital (manuscript in preparation). 277 patients all operated with breast conservation and axillary lymph node dissection in the period 2007-2012, treated with docetaxel as part of their chemotherapy and whole breast irradiation 50 Gy/25 fr (pN0/1(mic)) (N=92 patients) and locoregional radiation therapy 50 Gy/25 fr (pN+(macromet) (N=185 patients).

This trial will be active in different countries, and there may be different strategies in these countries for prescribing an arm sleeve, thus our primary endpoint cannot include the use of a sleeve. The primary endpoint will be lymphedema of the upper and/or lower arm defined as ≥10% difference in arm circumference measured 15 cm proximal and/or 10 cm distal to the olecranon compared to the opposite arm. 8% had this event. However, in the Aarhus study 25 patients used an arm sleeve weekly, and among them 4 patients had lymphedema by measurement. We therefore estimate that among patients treated with axillary lymph node dissection, 50 Gy regional nodes

radiation therapy and taxan-based systemic therapy 10% will have an arm lymphedema 3 years after radiation therapy.
From the latest systematic review and meta-analysis the incidence of lymphedema after axillary lymph node dissection was 19.9% (95%, 13.5-28.2) (35). No median follow up was given to this estimate, but the review stated that the incidence was increasing up to minimum 2 years after surgery. The median follow up in the Aarhus study was 3-4 years. In our basic assumptions we therefore estimate the incidence of arm lymphedema to 10% 3 years after breast operation, axillary lymph node dissection, taxan-containing chemotherapy and regional nodes radiation therapy with 50 Gy/25 fractions. It is expected that a subgroup of patients included in this trial will be operated with sentinel node biopsy without an axillary lymph node dissection if limited nodal disease was detected. Based on the AMAROS trial the risk of arm lymphedema in that situation 3 and 5 years after therapy was 6%.

Further basic assumptions are acceptance of up to a 5% increase in arm lymphedema (thus accept of 15% of the patients having arm lymphedema ≥10% of the upper and/or lower arm with hypofractionated radiation therapy) in the group of patients operated with ALND, 80% power, 5% significance level, 1-sided test, 5% yearly drop-out rate of evaluable patients. Accrual is expected to take 3 years. The far majority of patients are expected to be treated with chemotherapy. We have no data on the risk of lymphedema in patients treated with endocrine therapy, but it may be the same risk as for patients treated with chemotherapy.
A small group of accrued patients are expected to be operated with sentinel node biopsy only (thus no ALND), and for that group of patients the 3 year risk of arm lymphedema is estimated to be 6% and accepted to increase to 11%.

Based on that all accrued patients are operated with axillary lymph node dissection and the above mentioned assumptions this requires 131 events, assuming 1012 patients, 506 patients in each randomisation arm, are included over 3 years and with 3 years additional follow up. The non-inferiority limit on the hazard ratio is 1.543.

Based on that 15% of the accrued patients are not operated with axillary lymph node dissection and the above mentioned assumptions this requires 120 events, assuming 980 patients, 490 patients in each randomisation arm, are included over 3 years and with 3 years additional follow up. The non-inferiority limit on the hazard ratio is 1.575.
It is, however, very unsure how many patients will be operated without axillary lymph node dissection, therefore the dimensions of the study are based on all patients being operated with axillary lymph node dissection.

Since moderately hypofractionated regional nodes radiation therapy is now offered routinely to breast cancer patients in the UK and the Netherlands, and also to patients operated with sentinel node biopsy only , we expect that the results of this trial will be positive. Therefore we find it acceptable to continue accrual of patients into trial until 1012 patients have been followed up for 3 years. When 1012 patients have been followed for 3 years after radiation therapy we expect that minimum 2000 patients have been accrued assuming a steady inclusion over the years. This number of patients will allow for more detailed morbidity evaluation of patients for example in relation to the type of systemic therapy, type of surgery and boost.

Patients will be included until 1012 patients have been randomised and evaluated for morbidity for 3 years or 131 patients are diagnosed with lymphedema on the upper and/or lower arm on the treated side. At the time where one of these goals is met, analysis of data will be performed. If the data shows that after minimum 3 years follow up after radiation therapy there is no statistical difference in lymphedema between the 2 arms of the trial, the moderately hypofractionated radiation therapy with 40 Gy/15 fr will become new national standard therapy in Denmark to patients eligible for the trial. Patients already included in the trial will continue morbidity evaluation for 10 years, and if a difference in morbidity is detected later on showing problems with hypofractionation the first conclusion will be changed, and normofractionation will be reintroduced as standard in Denmark. The DBCG Radiotherapy Committee will make this decision.

8.2 INTERIM ANALYSIS

An interim analysis is planned when 50% of the planned cohort has been included and followed for 3 years. This is independent of the subgroups of systemic therapy (endocrine only versus chemotherapy).
Thus the interim analysis will be performed when 506 patients has been included and followed for 3 years.

8.3 STOP RULES

Further accrual of patients into the trial will stop and full data analysis will be performed when one of the following conditions happens:

1. When there are 131 events in the trial

2. When minimum 1012 patients have been randomised and followed for 3 years after radiation therapy

3. If the interim analysis shows significant difference between the arms of the trial

ANALYSES

Standard statistical methods as Kaplan-Meier analyses and Cox proportional hazards regression methods for comparison of frequencies of late morbidity, local, regional and distant failures between the randomisation arms will be applied.
Follow-up starts from the first day of radiation therapy.

The patient is censured at A) local recurrence, at B) regional recurrence, at C) distant recurrence, at D) second malignancy and at E) death.

If a patient has a reconstructive surgical procedure performed after radiation therapy, for example a reconstruction of a breast after mastectomy, she can remain in the trial for morbidity evaluations, because the primary endpoint is arm lymphedema. However, a reporting of the surgical procedure must take place. It is also expected that the patient receives relevant therapy for an arm lymphedema and is given an arm

sleeve, if she has symptoms indicating an arm lymphedema. She is not censored because of therapy by a physiotherapist.

9.0 PUBLICATIONS

The results from this study will be published irrespective them being positive or negative. 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 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 analysing 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 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. Information, other than the primary and secondary endpoints, gathered from the study (for example through locally conducted studies regarding quality assurance of the radiotherapy or of the evaluation of morbidity) can be published from the institution(s) where this activity has been done, however, the principal investigator must be informed about this.
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 accept from the protocol responsible investigators from the participating departments.
All publications from this trial should mention and thank relevant support including the support from CIRRO (The Lundbeck Foundation Centre for International Research in Radiation Oncology) (contact the trial principal investigator or DBCG for specific information).

10.0 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 protocol contains an arm with experimental therapy. At each radiotherapy center a protocol responsible person will take care that every patient is informed both verbally and in writing about the purpose and the course of the study. The patient will be informed about effects and side effects by participating in the study, and the patient will receive a written folder of information specifically regarding the study. This folder will meet the criteria for patient information in Denmark. The advantage for the patient by participating in the study is to spare 10 treatment days compared to standard therapy. Based on already published data where the new fractionation (40 Gy / 15 fr) has been evaluated there is no expected increased radiation morbidity. If the

patient is a candidate for a boost to the tumour bed, her overall treatment time will be shortened by 5 days irrespective of the randomisation arm. The dose per fraction in the boost area has been calculated to provide the same biologically effective dose. A simultaneous integrated boost is already a standard treatment in Holland based on positive results in retrospective studies.
Both verbally and in writing the patient will be informed about the opportunity to withdraw consent at any time without given a reason. If the patient chooses standard therapy this will consist of whole breast irradiation combined with regional nodes radiation therapy with 50 Gy / 25 fractions, and boost if indicated. Before randomization can take place the informed consent must be signed.

11.0 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 minimise withdrawal the patient should be carefully informed before randomisation 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.

12.0 ECONOMICAL ISSUES

The initiative for this trial was taken by the principal investigator, who has also written the majority of the protocol. The protocol has support from the DBCG Radiotherapy Committee and the trial will be nationwide. All patients being candidates for this protocol are candidates for radiation therapy, thus the financial means are already available in the radiotherapy departments for the radiation therapy. The cost for morbidity evaluation will be paid by the different radiotherapy departments and is considered an operating cost.
The trial principal investigator has received funding for 3 years from the Danish Cancer Society to pay half time salary for a consultant (1.800.000 kroner, of which 300.000 kroner is for cost running the trial). The money will be paid by the Danish Cancer Society directly to the Dept. Oncology, Aarhus University Hospital. The trial has support from CIRRO, 250.000 kroner for running cost, for example salary to a statistician). The principal investigator has no personal relations to the Danish Cancer Society. The protocol responsible doctor and the staff in each centre have no financial interests in the trial.

13.0 REFERENCES

(1) Overgaard M, Hansen PS, Overgaard J, Rose C, Andersson M, Bach F, Kjaer M, Gadeberg CC, Mouridsen HT, Jensen MB, Zedeler K. Postoperative radiotherapy in high-risk premenopausal women with breast cancer who receive adjuvant chemotherapy. Danish Breast Cancer Cooperative Group 82b Trial. N Engl J Med 1997 October 2;337(14):949-55.

(2) Overgaard M, Jensen MB, Overgaard J, Hansen PS, Rose C, Andersson M, Kamby C, Kjaer M, Gadeberg CC, Rasmussen BB, Blichert-Toft M, Mouridsen HT. Postoperative radiotherapy in

high-risk postmenopausal breast-cancer patients given adjuvant tamoxifen: Danish Breast Cancer Cooperative Group DBCG 82c randomised trial. Lancet 1999 May 15;353(9165):1641-8.

(3) Hojris I, Andersen J, Overgaard M, Overgaard J. Late treatment-related morbidity in breast cancer patients randomized to postmastectomy radiotherapy and systemic treatment versus systemic treatment alone. Acta Oncol 2000;39(3):355-72.

(4) Hojris I, Overgaard M, Christensen JJ, Overgaard J. Morbidity and mortality of ischaemic heart disease in high-risk breast-cancer patients after adjuvant postmastectomy systemic treatment with or without radiotherapy: analysis of DBCG 82b and 82c randomised trials. Radiotherapy Committee of the Danish Breast Cancer Cooperative Group. Lancet 1999 October 23;354(9188):1425-30.

(5) Grantzau T, Mellemkjaer L, Overgaard J. Second primary cancers after adjuvant radiotherapy in early breast cancer patients: a national population based study under the Danish Breast Cancer Cooperative Group (DBCG). Radiother Oncol 2013 January;106(1):42-9.

(6) McGale P, Darby SC, Hall P, Adolfsson J, Bengtsson NO, Bennet AM, Fornander T, Gigante B, Jensen MB, Peto R, Rahimi K, Taylor CW, Ewertz M. Incidence of heart disease in 35,000 women treated with radiotherapy for breast cancer in Denmark and Sweden. Radiother Oncol 2011 August;100(2):167-75.

(7) Nielsen HM, Overgaard M, Grau C, Jensen AR, Overgaard J. Loco-regional recurrence after mastectomy in high-risk breast cancer--risk and prognosis. An analysis of patients from the DBCG 82 b&c randomization trials. Radiother Oncol 2006 May;79(2):147-55.

(8) Nielsen HM, Overgaard M, Grau C, Jensen AR, Overgaard J. Study of failure pattern among high-risk breast cancer patients with or without postmastectomy radiotherapy in addition to adjuvant systemic therapy: long-term results from the Danish Breast Cancer Cooperative Group DBCG 82 b and c randomized studies. J Clin Oncol 2006 May 20;24(15):2268-75.

(9) Kyndi M, Sorensen FB, Knudsen H, Overgaard M, Nielsen HM, Overgaard J. Estrogen receptor, progesterone receptor, HER-2, and response to postmastectomy radiotherapy in high-risk breast cancer: the Danish Breast Cancer Cooperative Group. J Clin Oncol 2008 March 20;26(9):1419-26.

(10) Johansen J, Overgaard J, Blichert-Toft M, Overgaard M. Treatment of morbidity associated with the management of the axilla in breast-conserving therapy. Acta Oncol 2000;39(3):349-54.

(11) Lyngholm CD, Christiansen PM, Damsgaard TE, Overgaard J. Long-term follow-up of late morbidity, cosmetic outcome and body image after breast conserving therapy. A study from the Danish Breast Cancer Cooperative Group (DBCG). Acta Oncol 2013 February;52(2):259-69.

(12) Lauridsen MC, Overgaard M, Overgaard J, Hessov IB, Cristiansen P. Shoulder disability and late symptoms following surgery for early breast cancer. Acta Oncol 2008;47(4):569-75.

(13) Thorsen LB, Thomsen MS, Overgaard M, Overgaard J, Offersen BV. Quality assurance of conventional non-CT-based internal mammary lymph node irradiation in a prospective Danish Breast Cancer Cooperative Group trial: the DBCG-IMN study. Acta Oncol 2013 October;52(7):1526-34.

(14) Thorsen LB, Thomsen MS, Berg M, Jensen I, Josipovic M, Overgaard M, Overgaard J, Skogholt P, Offersen BV. CT-planned internal mammary node radiotherapy in the DBCG-IMN study: Benefit versus potentially harmful effects. Acta Oncol 2014 August;53(8):1027-34.

(15) Thorsen LB, Berg M., Brodersen H.J., Danø H., Jensen I., Overgaard J, Overgaard M, Pedersen AN, Zimmermann S, Offersen BV. Improved survival with internal mammary node irradiation, the DBCG-IMN study. Radiother.Oncol . 2014.
Ref Type: Abstract

(16) Bentzen SM, Agrawal RK, Aird EG, Barrett JM, Barrett-Lee PJ, Bentzen SM, Bliss JM, Brown J, Dewar JA, Dobbs HJ, Haviland JS, Hoskin PJ, Hopwood P, Lawton PA, Magee BJ, Mills J, Morgan DA, Owen JR, Simmons S, Sumo G, Sydenham MA, Venables K, Yarnold JR. The UK Standardisation of Breast Radiotherapy (START) Trial B of radiotherapy hypofractionation for treatment of early breast cancer: a randomised trial. Lancet 2008 March 29;371(9618):1098-107.

(17) Whelan TJ, Pignol JP, Levine MN, Julian JA, MacKenzie R, Parpia S, Shelley W, Grimard L, Bowen J, Lukka H, Perera F, Fyles A, Schneider K, Gulavita S, Freeman C. Long-term results of hypofractionated radiation therapy for breast cancer. N Engl J Med 2010 February 11;362(6):513-20.

(18) Overgaard M, Bentzen SM, Christensen JJ, Madsen EH. The value of the NSD formula in equation of acute and late radiation complications in normal tissue following 2 and 5 fractions per week in breast cancer patients treated with postmastectomy irradiation. Radiother Oncol 1987 May;9(1):1-11.

(19) Badiyan SN, Shah C, Arthur D, Khan AJ, Freedman G, Poppe MM, Vicini FA. Hypofractionated regional nodal irradiation for breast cancer: examining the data and potential for future studies. Radiother Oncol 2014 January;110(1):39-44.

(20) Giuliano AE, Hunt KK, Ballman KV, Beitsch PD, Whitworth PW, Blumencranz PW, Leitch AM, Saha S, McCall LM, Morrow M. Axillary dissection vs no axillary dissection in women with invasive breast cancer and sentinel node metastasis: a randomized clinical trial. JAMA 2011 February 9;305(6):569-75.

(21) Fowler JF. 21 years of biologically effective dose. Br J Radiol 2010 July;83(991):554-68.

(22) Bartelink H, Horiot JC, Poortmans PM, Struikmans H, Van Den Bogaert W, Fourquet A, Jager JJ, Hoogenraad WJ, Oei SB, Warlam-Rodenhuis CC, Pierart M, Collette L. Impact of a higher radiation dose on local control and survival in breast-conserving therapy of early breast cancer: 10-Year results of the randomized boost versus no boost EORTC 22881-10882 trial. Journal of Clinical Oncology 2007;25(22):3259-65.

(23) Askoxylakis V, Jensen AD, Hafner MF, Fetzner L, Sterzing F, Heil J, Sohn C, Husing J, Tiefenbacher U, Wenz F, Debus J, Hof H. Simultaneous integrated boost for adjuvant treatment of breast cancer--intensity modulated vs. conventional radiotherapy: the IMRT-MC2 trial. BMC Cancer 2011;11:249.

(24) Bantema-Joppe EJ, Vredeveld EJ, De Bock GH, Busz DM, Woltman-van IM, Dolsma WV, van der Laan HP, Langendijk JA, Maduro JH. Five year outcomes of hypofractionated simultaneous integrated boost irradiation in breast conserving therapy; patterns of recurrence. Radiother Oncol 2013 August;108(2):269-72.

(25) Bantema-Joppe EJ, Schilstra C, De Bock GH, Dolsma WV, Busz DM, Langendijk JA, Maduro JH. Simultaneous integrated boost irradiation after breast-conserving surgery: physician-rated toxicity and cosmetic outcome at 30 months' follow-up. Int J Radiat Oncol Biol Phys 2012 July 15;83(4):e471-e477.

(26) Hurkmans CW, Dijckmans I, Reijnen M, van der LJ, van Vliet-Vroegindeweij C, van der SM. Adaptive radiation therapy for breast IMRT-simultaneously integrated boost: three-year clinical experience. Radiother Oncol 2012 May;103(2):183-7.

(27) McDonald MW, Godette KD, Whitaker DJ, Davis LW, Johnstone PA. Three-year outcomes of breast intensity-modulated radiation therapy with simultaneous integrated boost. Int J Radiat Oncol Biol Phys 2010 June 1;77(2):523-30.

(28) Gartner R, Jensen MB, Kronborg L, Ewertz M, Kehlet H, Kroman N. Self-reported arm-lymphedema and functional impairment after breast cancer treatment--a nationwide study of prevalence and associated factors. Breast 2010 December;19(6):506-15.

(29) Tengrup I, Tennvall-Nittby L, Christiansson I, Laurin M. Arm morbidity after breast-conserving therapy for breast cancer. Acta Oncol 2000;39(3):393-7.

(30) Lee TS, Kilbreath SL, Refshauge KM, Herbert RD, Beith JM. Prognosis of the upper limb following surgery and radiation for breast cancer. Breast Cancer Res Treat 2008 July;110(1):19-37.

(31) Lundstedt D, Gustafsson M, Malmstrom P, Johansson KA, Alsadius D, Sundberg A, Wilderang U, Holmberg E, Anderson H, Steineck G, Karlsson P. Symptoms 10-17 years after breast cancer radiotherapy data from the randomised SWEBCG91-RT trial. Radiother Oncol 2010 November;97(2):281-7.

(32) Burak WE, Hollenbeck ST, Zervos EE, Hock KL, Kemp LC, Young DC. Sentinel lymph node biopsy results in less postoperative morbidity compared with axillary lymph node dissection for breast cancer. Am J Surg 2002 January;183(1):23-7.

(33) Liljegren G, Holmberg L. Arm morbidity after sector resection and axillary dissection with or without postoperative radiotherapy in breast cancer stage I. Results from a randomised trial. Uppsala-Orebro Breast Cancer Study Group. Eur J Cancer 1997 February;33(2):193-9.

(34) Hayes S, Battistutta D, Newman B. Objective and subjective upper body function six months following diagnosis of breast cancer. Breast Cancer Res Treat 2005 November;94(1):1-10.

(35) DiSipio T, Rye S, Newman B, Hayes S. Incidence of unilateral arm lymphoedema after breast cancer: a systematic review and meta-analysis. Lancet Oncol 2013 May;14(6):500-15.

(36) Hopwood P, Haviland JS, Sumo G, Mills J, Bliss JM, Yarnold JR. Comparison of patient-reported breast, arm, and shoulder symptoms and body image after radiotherapy for early breast cancer: 5-year follow-up in the randomised Standardisation of Breast Radiotherapy (START) trials. Lancet Oncol 2010 March;11(3):231-40.

(37) Constant CR, Gerber C, Emery RJ, Sojbjerg JO, Gohlke F, Boileau P. A review of the Constant score: modifications and guidelines for its use. J Shoulder Elbow Surg 2008 March;17(2):355-61.

(38) Nielsen MH, Berg M, Pedersen AN, Andersen K, Glavicic V, Jakobsen EH, Jensen I, Josipovic M, Lorenzen EL, Nielsen HM, Stenbygaard L, Thomsen MS, Vallentin S, Zimmermann S, Offersen BV. Delineation of target volumes and organs at risk in adjuvant radiotherapy of early breast cancer: National guidelines and contouring atlas by the Danish Breast Cancer Cooperative Group. Acta Oncol 2013 February 19.

(39) Bantema-Joppe EJ, van der Laan HP, De Bock GH, Wijsman R, Dolsma WV, Busz DM, Langendijk JA, Maduro JH. Three-dimensional conformal hypofractionated simultaneous integrated boost in breast conserving therapy: results on local control and survival. Radiother Oncol 2011 August;100(2):215-20.

(40) Gregoire V, Mackie TR, De Neve W, Gospodarowicz M, Purdy JA, van Herh M, Niemierko A. ICRU Report 83. Prescribing, recording and reporting photon-beam intensity-modulated radiation therapy (IMRT). Journal of the ICRU 10[1]. 2010.
Ref Type: Journal (Full)

(41) Delanian S, Lefaix JL, Pradat PF. Radiation-induced neuropathy in cancer survivors. Radiother Oncol 2012 December;105(3):273-82.

(42) Aaronson NK, Bartelink H, van Dongen JA, van Dam FS. Evaluation of breast conserving therapy: clinical, methodological and psychosocial perspectives. Eur.J.Surg.Oncol. 14[2], 133-140. 1988.
Ref Type: Journal (Full)

(43) Harris JR, Levine M, Svensson G, Hellman S. Analysis of the cosmetic results following primary radiation therapy for stages I and II carcinoma of the breast. International Journal of Radiation Oncology Biology Physics 1979;5:257-61.

(44) Hopwood P, Fletcher I, Lee A, Al GS. A body image scale for use with cancer patients. Eur J Cancer 37[2], 189-197. 2001.
Ref Type: Journal (Full)

(45) Common terminology criteria for adverse events (CTCAE) version 4.0. 2009.
Ref Type: Internet Communication

(46) Cox JD, Stetz J, Pajak TF. Toxicity criteria of the Radiation Therapy Oncology Group (RTOG) and the European Organization for Research and Treatment of Cancer (EORTC). International Journal of Radiation Oncology Biology Physics 1995;31(5):1341-6.

(47) Plataniotis GA, Theofanopoulou MA, Sotiriadou K, Kyrgias G. Hypofractionated radiotherapy for breast cancer patients treated by breast-conserving surgery: short-term morbidity and preliminary results. Breast Cancer 2010;17(1):42-7.