Disposition

-DBCG HYPO
-DBCG PBI
-DBCG Skagen Trial 1
-Fremtiden

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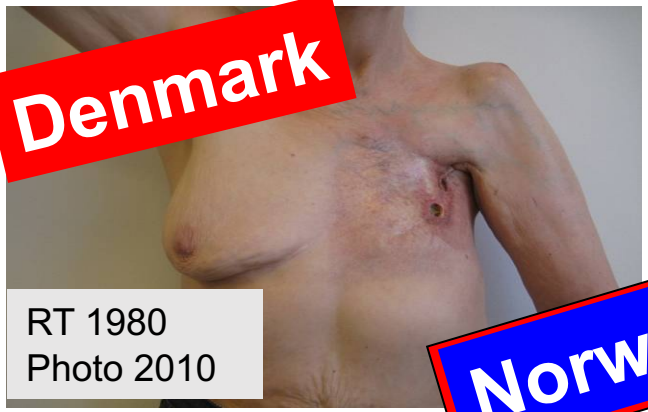
Hypo- versus normofractionated radiation therapy of early breast cancer in the randomized DBCG HYPO trial

BV Offersen, HM Nielsen, EH Jacobsen, MH Nielsen, M Krause, L Stenbygaard, I Mjaaland, A Schreiber, UM Kasti, J Alsner, M-B Jensen, J Overgaard

Background DBCG HYPO Trial

Moderate hypofractionation 36-42 Gy / 12 fr

DBCG standard before 1982



Denmark

RT 1980
Photo 2010

Norway

Komiteens tilråding

Komiteen viser for øvrig til proposisjonen og det som står foran, og rår Sto

vedtak:

I statsbudsjettet for 1998 gjøres følgende endring:

Kap. 739	Andre utgifter		
	73 (ny)	Erstatning for stråleskader, *kan overføres,*	
		bevilges med	kr 8500

~9.3 mio Euro

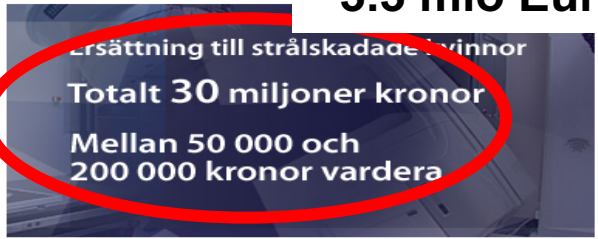
Besvär efter åtta år

En av de drabbade, Marianne Mosserud, berättade för Aktuellt om hur besvären i armen som började åtta år efter bröstoperationen nu gör henne allt mer handikappad.

-Jag kan ju inte lyfta ett papper ens. Jag kan inte knipa ihop med fingrarna. Jag kan inte.
Är det nånting som jag ska bära, så får jag ta det i munnen.
Och det är ju svårt med tunga sak
Ett papper kan man ju ta, nån fi

Marianne Mosserud

~3.3 mio Euro



Strålskadade får dela på 30 miljoner

SVT Nyheter | Publicerad 10 november 2005 - 17:55
Uppdaterad 20 juni 2006 - 11:26

De strålskadade kvinnor som Aktuellt har berättat om i flera reportage får nu ersättning från landstingen. De får dela på sammanlagt 30 miljoner kronor.

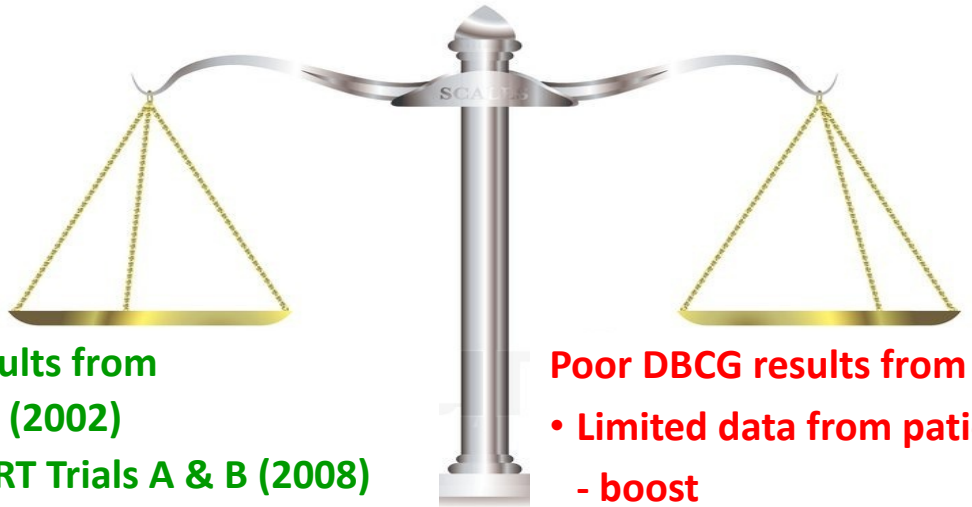
Det handlar om 200 kvinnor som mellan åren 1962 och 1980 drabbades av svåra skador vid strålbehandling i samband med bröstcanceroperationen.

Video

Få men höga doser

Sweden

Background DBCG HYPO



Positive results from

- **Canada (2002)**
- **UK START Trials A & B (2008)**
- **Modern techniques**
  - **CT based**
  - **delineation of target & OAR**
  - **dose homogeneity**
- **Waiting lists for RT**

Poor DBCG results from before 1982

- **Limited data from patients with**
  - **boost**
  - **large breasts**
  - **modern systemic therapy**
    - **Taxanes, Trastuzumab**
    - **Letrozole**

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DBCG HYPO

Aim

Reintroduce moderately hypofractionated adjuvant breast radiation therapy (RT) to early node-negative breast cancer patients in a controlled and systematic way in Denmark

Hypothesis

Using 40 Gy/15 fr, 2.67 Gy /fr, for breast RT does not result in more grade 2-3 breast induration at 3 years compared with 50 Gy/25 fr

Randomization DBCG HYPO

Invasive early breast cancer or DCIS, ≥41 yr,

breast conservation,

pTis-pT2, pN0-pN1(mic)

any histology / ER / HER2 / grade

Boost allowed

Any breast size

Any systemic therapy

R

Strata:
institution,
breast size ≤600 cc vs >600 cc,
chemotherapy yes/no,
boost yes/no

Whole breast RT 50 Gy/25f

Whole breast RT 40 Gy/15 f

Breast implants not allowed

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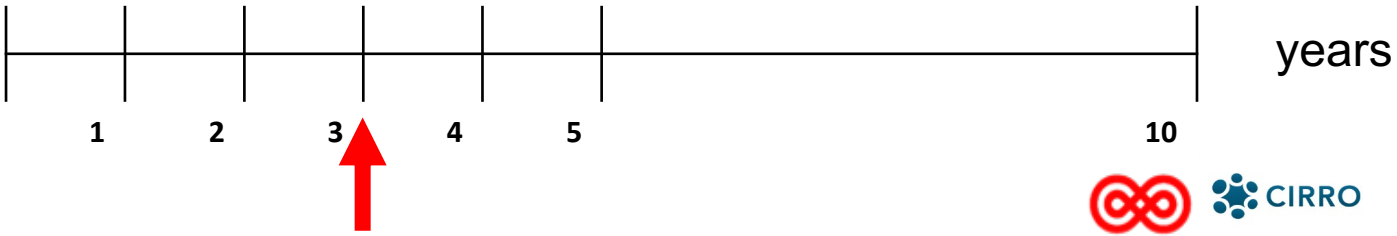
Endpoints

- Primary
  - grade ≥2 breast induration 3 years post RT
- Secondary
  - other RT-related morbidities
  - body image scale
  - patient satisfaction with therapy
  - pattern of recurrences
  - genetic risk profile for late RT-related morbidity



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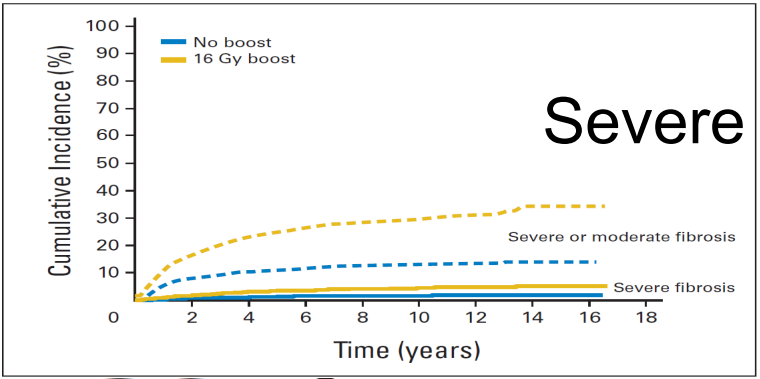
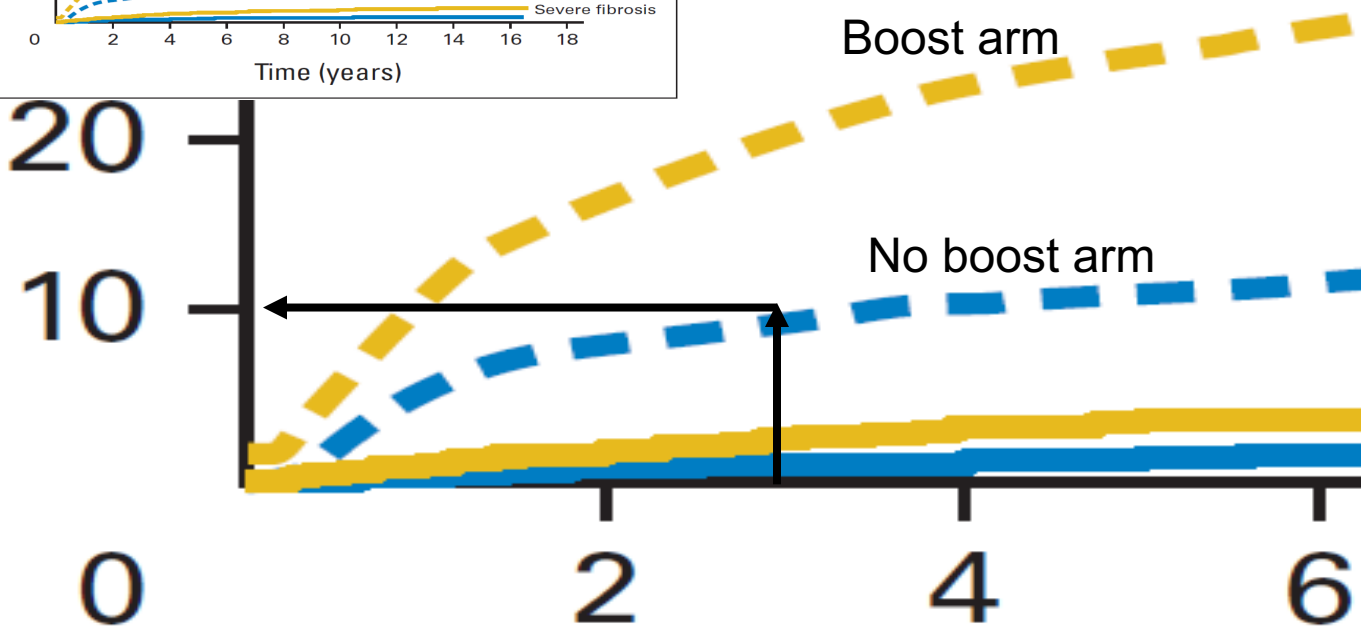


Severe or moderate fibrosis



Bartelink et al, JCO, 2007

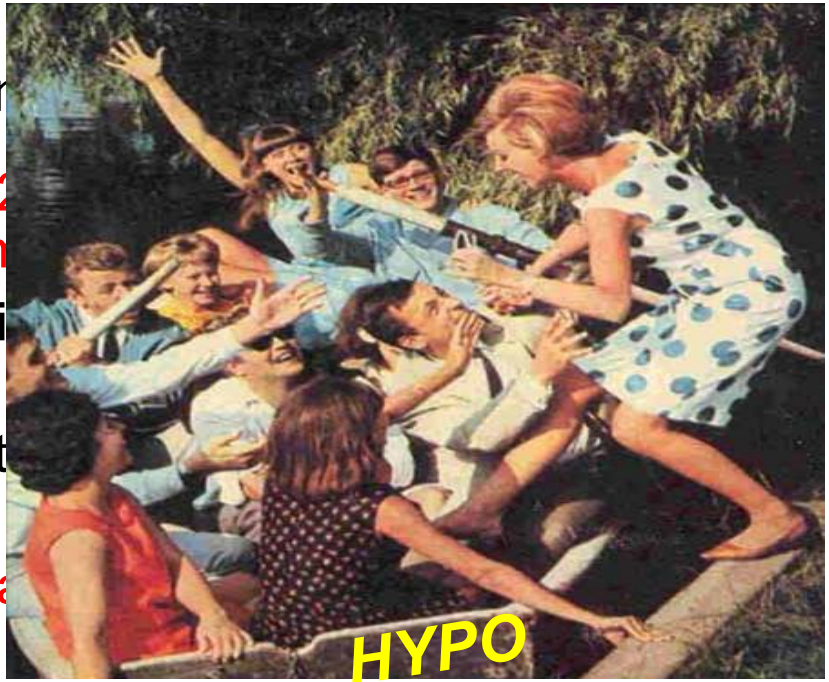
Statistical assumptio

Expected risk of grade 2
using 50 Gy/25 fr estim

Accept 10% absolute di
40 Gy/15 fr breast RT

80% power, one-sided t
drop out rate

Number needed: 338 pa



Strategy:

”Always room for one more”

Moderate hypofractionation already routine in UK, Canada and NL

1883

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Baseline data

8 Departments	Accrual
Aarhus	838
Vejle	291
Odense	254
Aalborg	167
Dresden, Gustav Carus	173
Dresden, Friedrichstadt	74
Stavanger	76
Kristiandsand	10
Total	**1883**

Accrual: May 2009 to Mar 2014

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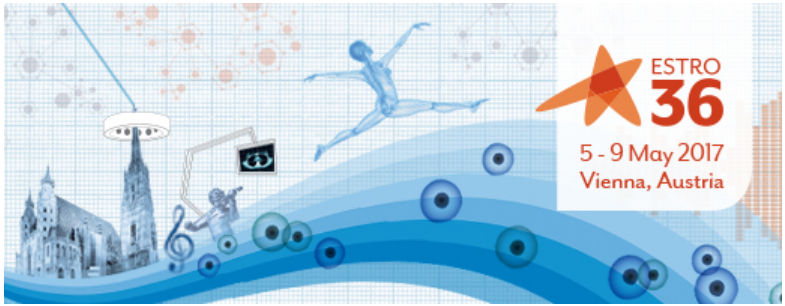
Conclusion

External beam forward planned IMRT whole breast irradiation based on 40 Gy/15 fr is feasible

- Large breast volume is an independent risk factor for developing breast induration 5 years post RT
- Use of boost, chemotherapy or hypofractionation have no impact on 5-year breast induration
- Few recurrences, and not related to fractionation

Moderately hypofractionated whole breast RT has become the new DBCG standard to all patients treated with breast only RT since 2014



DBCG DANISH BREAST CANCER GROUP

Accelerated partial breast radiotherapy after breast conservation for early breast cancer: early results from the clinically controlled randomized DBCG PBI trial

BV Offersen[1], HM Nielsen[1], MS Thomsen[1], EH Jacobsen[2], M Berg[2], MH Nielsen[3], E Lorenzen[3], L Stenbygaard[4], I Jensen[4], AN Petersen[5], M Josipovic[5], M-B Jensen[6], J Overgaard[7], on behalf of the DBCG RT Committee

[1]Dept Oncology Aarhus, [2]Dept Oncology Vejle, [3]Dept Oncology Odense, [4]Dept Oncology Aalborg, [5]Dept Oncology, Rigshospitalet, [6]DBCG, [7]Dept Expt Clin Oncology Aarhus, Denmark

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Background

- Risk of local recurrence low
- Most local recurrences appear in index quadrant (70-80%)
- Smaller treated volume

Aim of DBCG PBI trial

To investigate differences in morbidity following whole breast and partial breast irradiation in patients operated with breast conservation for breast cancer with low risk of recurrence

Hypothesis

Patients operated with breast conservation for breast cancer with low risk of recurrence can be treated with partial breast irradiation without experiencing more late radiation-induced morbidity compared with whole breast irradiation

Local recurrences?

Similar to the UK IMPORT LOW Trial

The DBCG RT Committee agreed upon that decision on new standard partial breast radiotherapy in Denmark should await data on local recurrence from the IMPORT LOW Trial (presented at EBCC, March 9, 2016)

Randomization DBCG PBI

Breast cancer, ≥60 yr,
breast conservation,
margin ≥2mm,
non-lobular type,
pT1, pN0, ER pos,
HER2 neg, grade 1-2

(~ASTRO consensus)

R

Whole breast RT
40 Gy / 15 fr

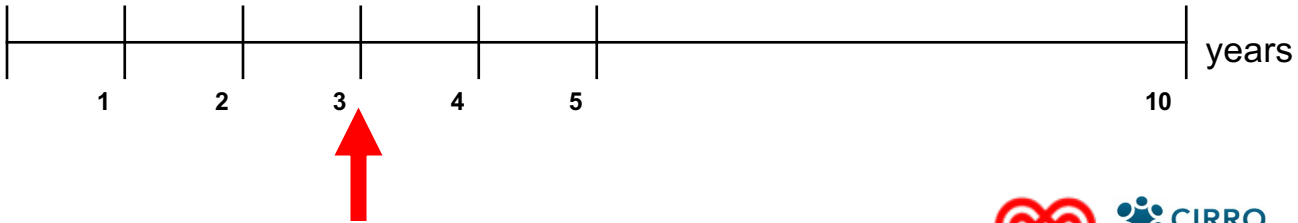
Stratum: institution, endocrine treatment

Partial breast RT
40 Gy / 15 fr

Endpoints

- Primary
  - grade ≥2 breast induration 3 years post RT

- Secondary
  - other RT-related morbidities
  - body image scale
  - patient satisfaction with therapy
  - pattern of recurrences
  - genetic risk profile for late RT-related morbidity



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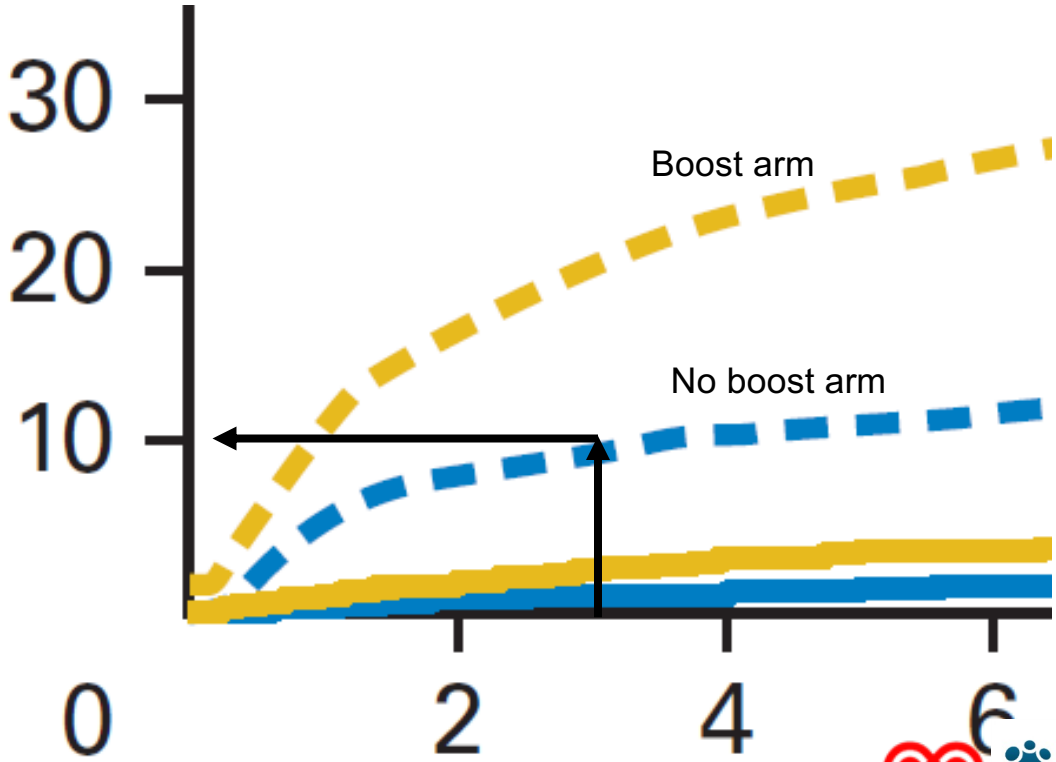
RT technique

- External beam, forward planned IMRT
- Planning CT prior to randomization
- CTV partial breast is tumour bed + 15 mm
- PTV is CTV + 5-8 mm depending on institution and fixation
- 40 Gy / 15 fr, 2.67 Gy per fr, 5 per week
- Dose distribution 95-105%
- V17Gy heart < 10%
- LADCA max point dose 17 Gy
- V17Gy ipsilat lung < 25%
- V40Gy whole breast max 50% if partial breast RT

Statistical assumptions



Bartelink et al, JCO, 2007

Statistical assumptions

Expected risk of grade 2+ breast induratio
Gy/15 fr is estimated 8%

Accept 10% absolute difference between

80% power, one-sided test, 5% sign level

Number needed: 314 patients with 3 yr f

ASTRO consensus patient/tumour criteria

Strategy:

”Always room for one more”
Moderate hypofractionation already routine in UK and NL
ASTRO criteria followed
UK IMPORT Low
The DBCG PBI Trial closed Mar 8th, 2016

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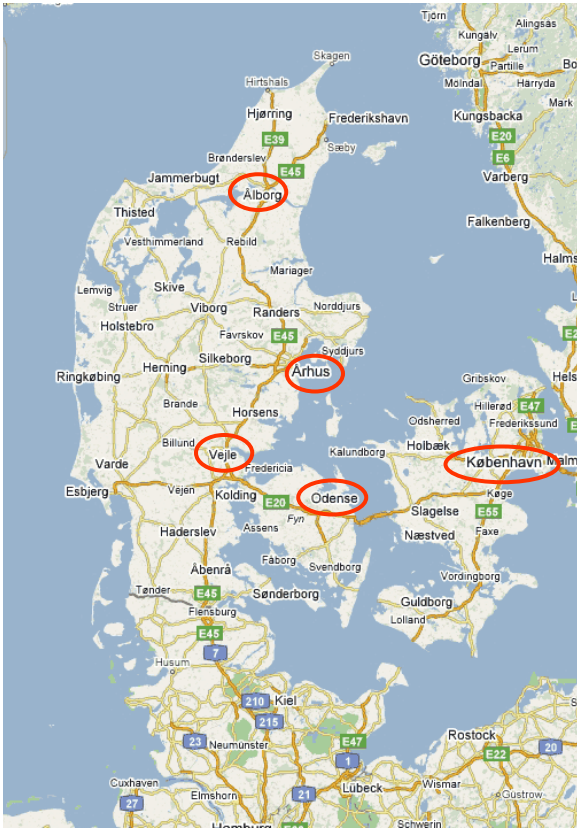
Baseline data



Center	Accrual
Aarhus	433
Vejle	161
Odense	116
Aalborg	91
RH Copenhagen	80
Dresden	1
Total	882

Accrual May 2009-Mar 2016

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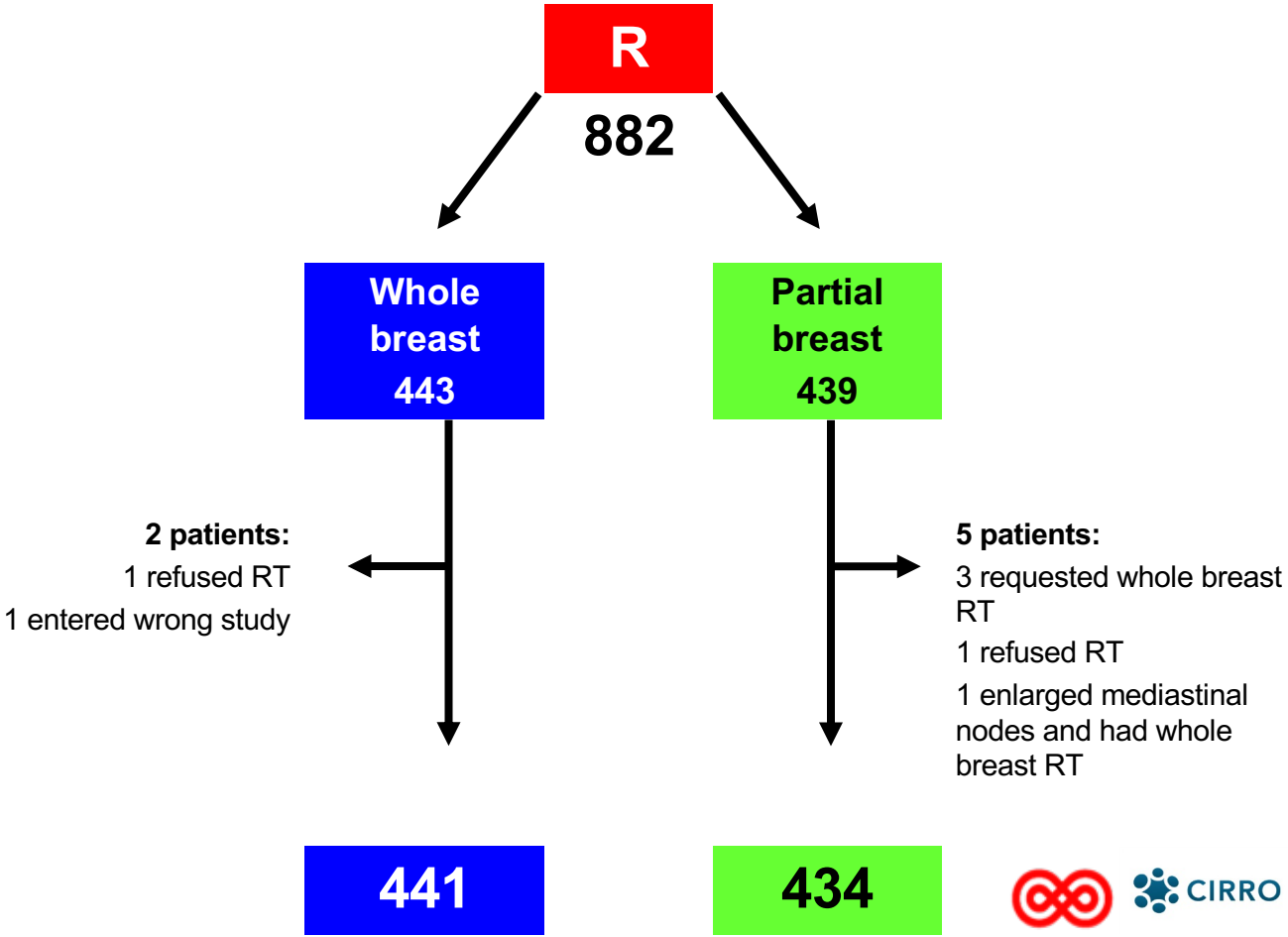
CONSORT diagram

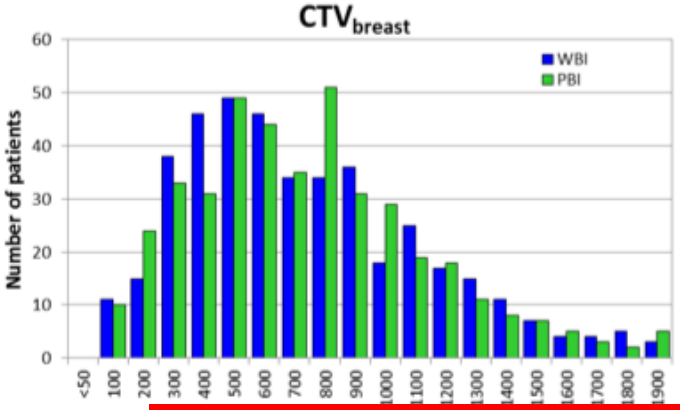


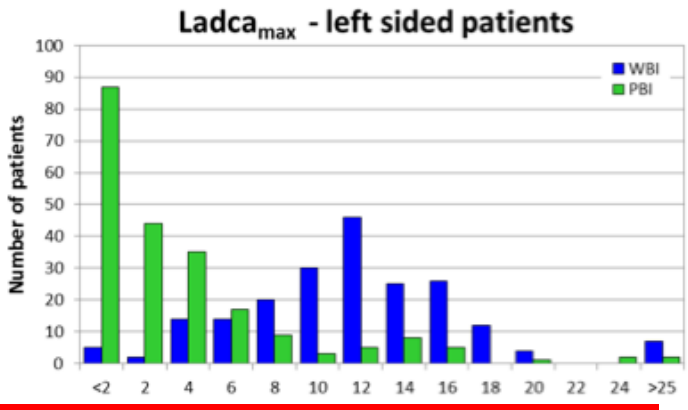
100% of patients/tumours were pN0, ER pos, HER2 neg and margin ≥2mm

		Whole breast N=441	Partial breast N=434
Age	Median (years, range)	66 (60-86)	66 (60-83)
Tumour size	Median (mm, range)	10 (1-20)	10 (1-20)
Histology	Ductal	382 (87%)	379 (87%)
	Mucinous/Papillary/Tubular/other	52 (12%)	52 (12%)
	Lobular	4	2
	DCIS	3	1
Grade	Ductal grade 1		59%)
	Ductal gr		0%)
Breast size			703 (72-2345)
Endocrine thera			186 (43%)
		245 (56%)	249 (57%)
Smoki	cline	88 (20%)	107 (25%)
	At 3 years	46 (16%)	54 (20%)
Charlson comorbid (N=781)	0	72%	80%
	1	23%	16%
	>1	5%	4%

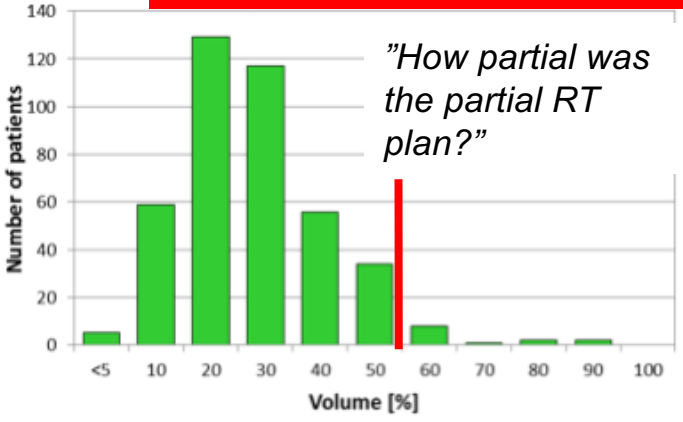
No difference

Results from dose plans

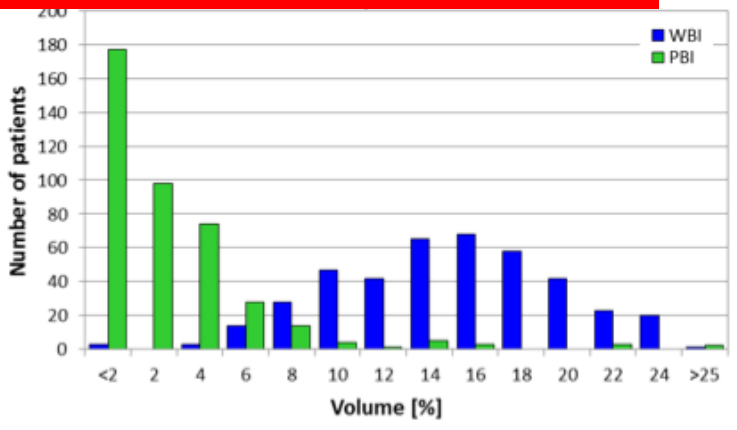




Overall results from evaluation of dose plans: Significantly less dose to heart and lung using PBI



”How partial was the partial RT plan?”



Breast induration

		Whole breast	%	Partial breast	%	P value
Baseli						1
Total						
Year 1						0
	Grade 1	193	45.7	181	43.4	
	Grade 2	65	**15.4**	48	**11.5**	
	Grade 3	10	**2.4**	6	**1.4**	
Total	839	422		417		
Year 2	Grade 0	167	48.0	189	53.8	**0.11**
	Grade 1	145	41.7	140	39.9	
	Grade 2	31	**8.9**	21	**6.0**	
	Grade 3	5	**1.4**	1	**0.3**	
Total	699	348		351		
Year 3	Grade 0	126	45.2	153	57.5	**0.02**
	Grade 1	125	44.8	99	37.2	
	Grade 2	26	**9.3**	13	**4.9**	
	Grade 3	2	**0.7**	1	**0.4**	
Total	545	279		266		

Scores
0:none
1:slightly palpable
2:palpable
3:clearly palpable, retraction of skin and fixation

DBCG

Breast induration

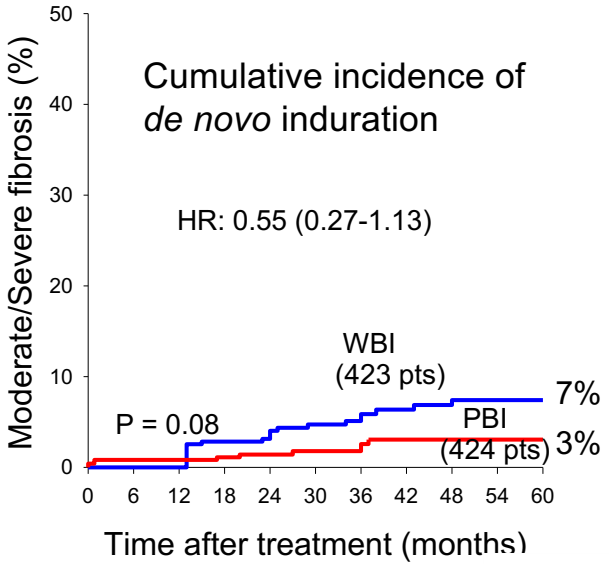
		Whole breast	%	Partial breast	%	P value
Baseline	Grade 0	129	29.7	108	24.8	**0.11**
	Grade 1	143	32.9	174	40.0	
	Grade 2	142	**37.4**	128	**35.1**	
	Grade 3	21		25		
Total	**870**	435		435		
Year 1	Grade 0	154	36.5	182	43.6	**0.10**
	Grade 1	193	45.7	181	43.4	
	Grade 2	65	**17.8**	48	**12.9**	
	Grade 3	10		6		
Total	**839**	422		417		
Year 2	Grade 0	167	48.0	189	53.8	**0.11**
	Grade 1	145	41.7	140	39.9	
	Grade 2	31	**10.3**	21	**6.3**	
	Grade 3	5		1		
Total	**699**	348		351		
Year 3	Grade 0	126	45.2	153	57.5	**0.02**
	Grade 1	125	44.8	99	37.2	
Year 3 induration 2-3		26	**10.0**	13	**5.3**	
		2		1		

Breast induration

Cumulative incidence of *de novo* breast induration grades 2-3

3 years: whole breast 6%
partial breast 2%

4 years: whole breast 7%
partial breast 3%



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Patient satisfaction with treated breast

		Whole breast	%	Partial breast	%	P value
Baseline	Grade 0 (poor)	4	1.2	1	0.3	**0.70**
	Grade 1 (fair)	21	6.1	22	6.5	
	Grade 2 (good)	188	**54.8**	189	**55.4**	
	Grade 3 (excellent)	130	**37.9**	129	**37.8**	
Total	684	343		341		
Year 3	Grade 0 (poor)	4	1.4	5	1.9	**0.45**
	Grade 1 (fair)	17	6.1	11	4.1	
	Grade 2 (good)	128	**45.9**	136	**51.1**	
	Grade 3 (excellent)	129	**46.2**	114	**42.9**	
	Grade 4 (unanswered)	1	0.4	0	0	
Total	545	279		266		

Patient satisfaction with treated breast

		Whole breast	%	Partial breast	%	P value
Baseline	Grade 0 (poor)	4	1.2	1	0.3	**0.70**
	Grade 1 (fair)	21	6.1	22	6.5	
	Grade 2 (good)	188	**92.7**	189	**93.2**	
	Grade 3 (excellent)	130		129		
Total	684	343		341		
Year 3	Grade 0 (poor)	4	1.4	5	1.9	**0.45**
	Grade 1 (fair)	17	6.1	11	4.1	
Excellent/good		128	**92.1**	136	**94.0**	
		129		114		
	Grade 4 (unanswered)	1	0.4	0	0	
Total	545	279		266		

Patient satisfaction with treated vs untreated breast

		Whole breast	%	Partial breast	%	P value
Baseline	Grade 0 (poor)	4	1.2	6	1.8	**0.94**
	Grade 1 (fair)	43	12.6	40	11.7	
	Grade 2 (good)	200	**58.5**	200	**58.7**	
	Grade 3 (excellent)	95	**27.8**	95	**27.9**	
Total	683	342		341		
Year 3	Grade 0 (poor)	7	2.5	6	2.2	**0.81**
	Grade 1 (fair)	37	13.3	28	10.5	
	Grade 2 (good)	140	**50.2**	143	**53.8**	
	Grade 3 (excellent)	94	**33.7**	89	**33.5**	
	unanswered	1	0.4	0	0	
Total	545	279		266		

Patient satisfaction with treated vs untreated breast

		Whole breast	%	Partial breast	%	P value
Baseline	Grade 0 (poor)	4	1.2	6	1.8	**0.94**
	Grade 1 (fair)	43	12.6	40	11.7	
	Grade 2 (good)	200	**86.3**	200	**86.6**	
	Grade 3 (excellent)	95		95		
Total	683	342		341		
Year 3	Grade 0 (poor)	7	2.5	6	2.2	**0.81**
	Grade 1 (fair)	37	13.3	28	10.5	
Excellent/good		140	**83.9**	143	**87.3**	
		94		89		
	unanswered	1	0.4	0	0	
Total	545	279		266		

Recurrence, other malignancy and death

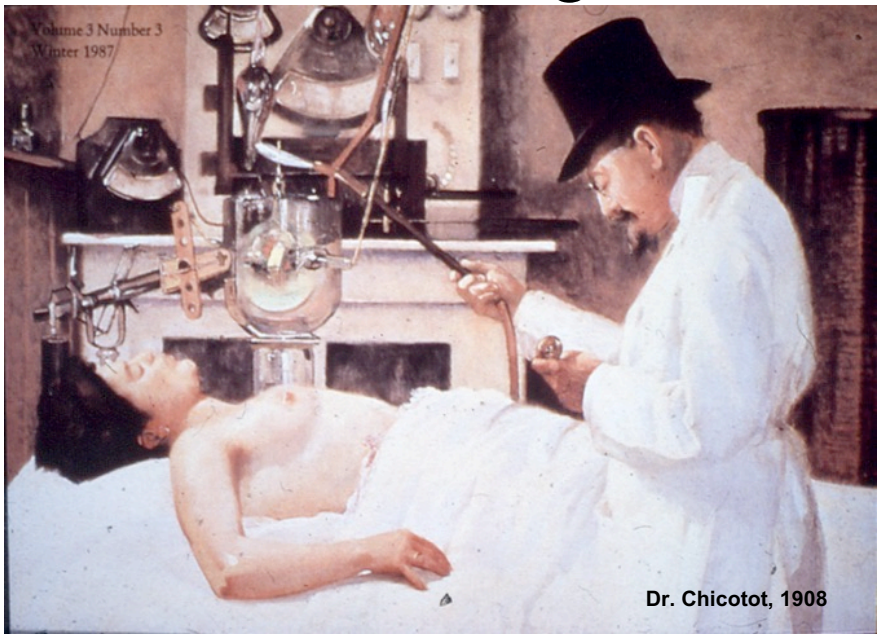
	N	Whole breast	Partial breast
Local recurrence	**6**	**2 LR[#] (1†)**	**4 LR[£]**
Regional recurrence	**2**	**0**	**2**
Distant recurrence	**4**	**1 (1†)**	**3 (3†)**
Contralateral new primary	**8**	**3**	**5**
Other malignancy	**34**	**14 (6†)**	**20 (5†)**
Dead with no cancer	**16**	**9**	**7**

1 LR with syncronous regional rec and 1 LR with syncronous liver metastasis
£ 1 new primary cancer (different histology and another quadrant)
Total 5 of the 6 local recurrences were true local recurrences (same histology, located in the scar/area of the first cancer)

Conclusion

- External beam forward planned IMRT partial breast irradiation based on 40 Gy/15 fr is feasible
- Lower radiation doses to the lung and heart
- Few side effects at 3 yr with no difference in breast induration, dyspigmentation, scar, edema, telangiectasia, global cosmetic outcome, pt satisfaction
- Few recurrences, and not related to PBI
- Since April 2016 DBCG standard to selected patients

Radiotherapy of early breast cancer, status on the Skagen Trial 1



AIM

- Assure a systematic and quality-controlled introduction of moderately hypofractionated loco-regional breast RT based on 40 Gy/15 fr in Denmark
- Introduce simultaneous integrated boost

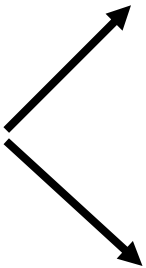
HYPOTHESIS

The risk of arm lymph edema does not increase 3 years after loco-regional RT using 40 Gy/15 fractions compared with 50 Gy/25 fractions

Randomization

stratification: institution, surgical type, systemic therapy

Woman ≥18 years
c. mammae
pT1-3, pN0-3,
ER/PgR +/-,
Grade I, II, III,
HER2 +/-,
Primary syst therapy,
breast implant, connective tissue disease accepted



50 Gy / 25 fractions

40 Gy / 15 fractions

If she is a boost candidate, the boost will be provided as a SIB shortening the overall treatment time with 5 days

Endpoints

- Primary: arm lymphedema
- Secondary: DBCG morbididy as previously used incl photos, PROM, ROM, use of sleeve, recurrence (where and when)

This will take place before RT, then yearly 1-5 and 10

Statistics

- Null hypothesis: hypofractionated RT does not increase the risk of lympedema 3 yr after RT compared to normofractionated RT
- Lymphedema is ≥10% increased arm circumference 15 cm above / 10 cm below olecranon
- Cross-sectional study in Aarhus, 2007-12, 277 pts (ALND, taxane, reg RT 50 Gy) showed 10% with lymphedema median 3 yr FU*
- We expect 10% risk of lymphedema, accept a 5% increase, 80% power, 1-sided test, 5% sign level, 5% yearly drop out rate, 3 yr accrual and 3 yr follow up
- Thus we need **131 events or 1012 patients with 3 yr follow up**
- Accrual continues until 131 events/1012 pts are followed for 3 yr
- Thus potential for >2000 pts included

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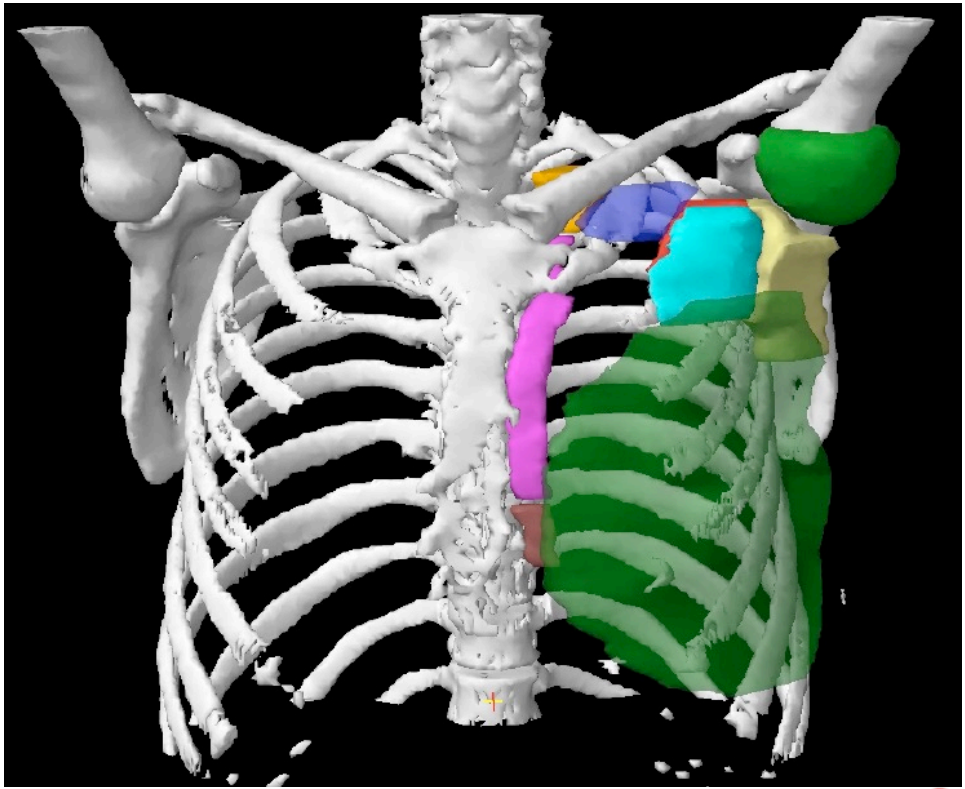
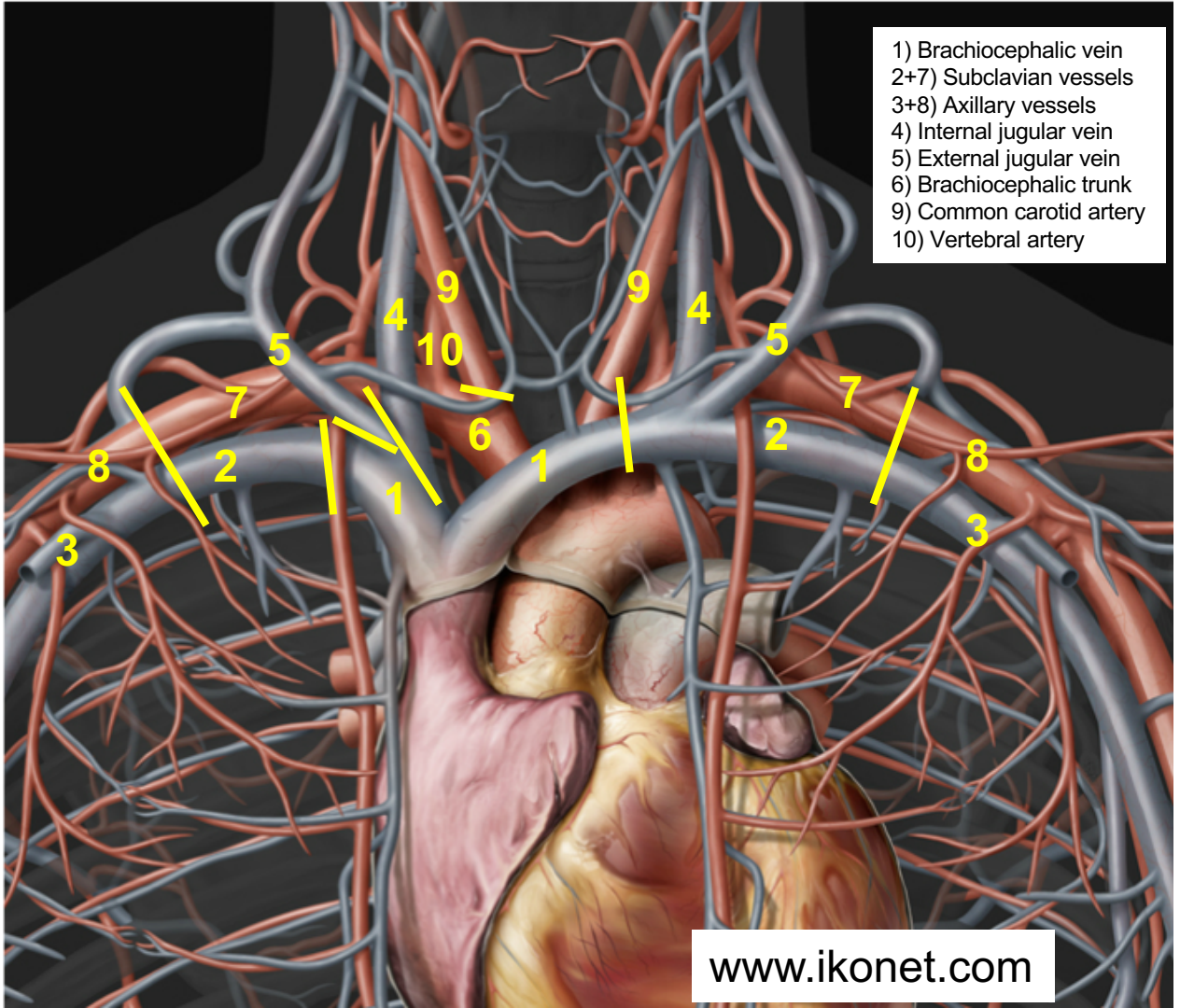
* Nielsen et al, Acta Oncol, 2017

The Skagen Trial 1



Offersen BV, Boersma L, Kirkove C et al, Radiother & Oncol 2015 & 2016

CIRRO


1) Brachiocephalic vein
2+7) Subclavian vessels
3+8) Axillary vessels
4) Internal jugular vein
5) External jugular vein
6) Brachiocephalic trunk
9) Common carotid artery
10) Vertebral artery
9
9
4
4
10
5
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7
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6
8
2
2
8
1
1
3
3
www.ikonet.com

Simultant integreret boost, SIB

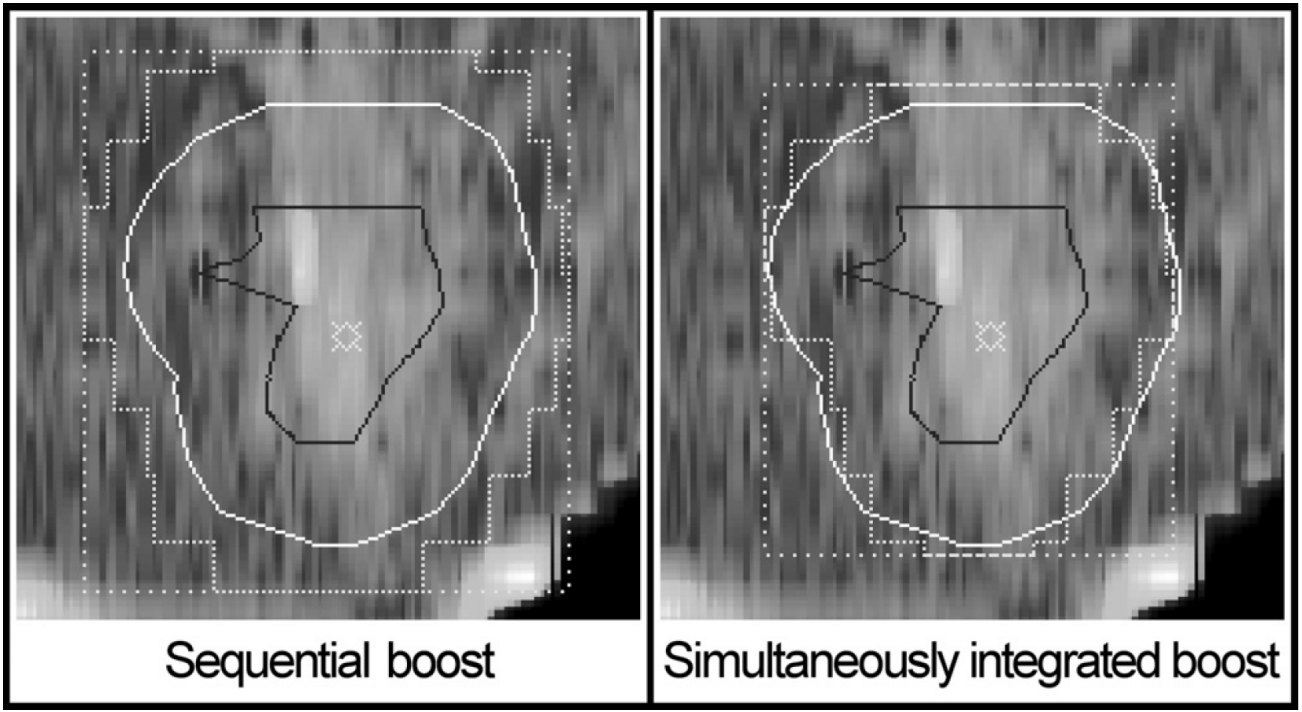
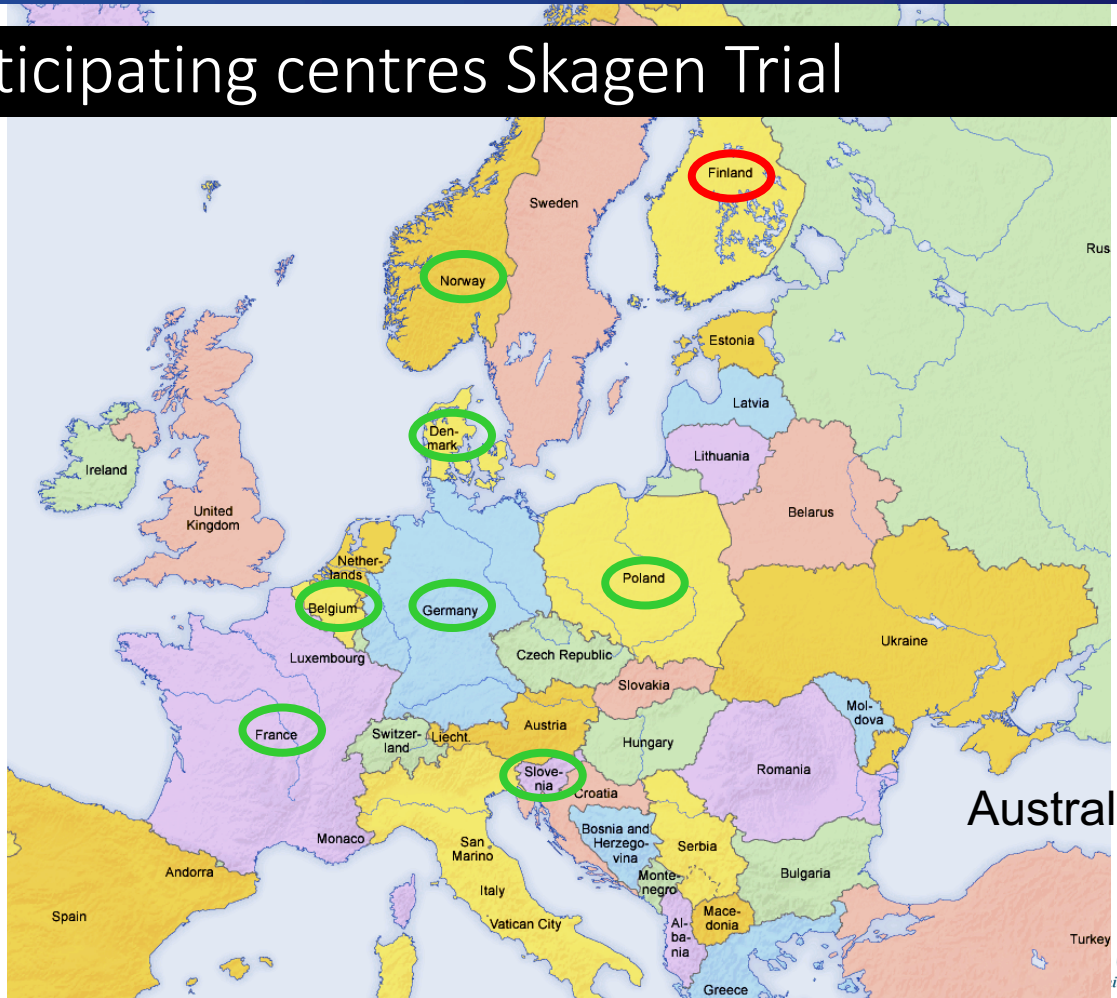


Fig. 1. Reconstructed radiograph from boost beam's-eye-view with sequentially planned and simultaneously integrated boost. With simultaneously integrated boost technique, multileaf collimator shielding (short dotted lines) can be applied without use of margins around boost planning target volume (white solid line), resulting in substantial reduction of excess volumes irradiated.

van der Laan et al, IJROBP 68: 1018-1023, 2007

DBCG

Participating centres Skagen Trial

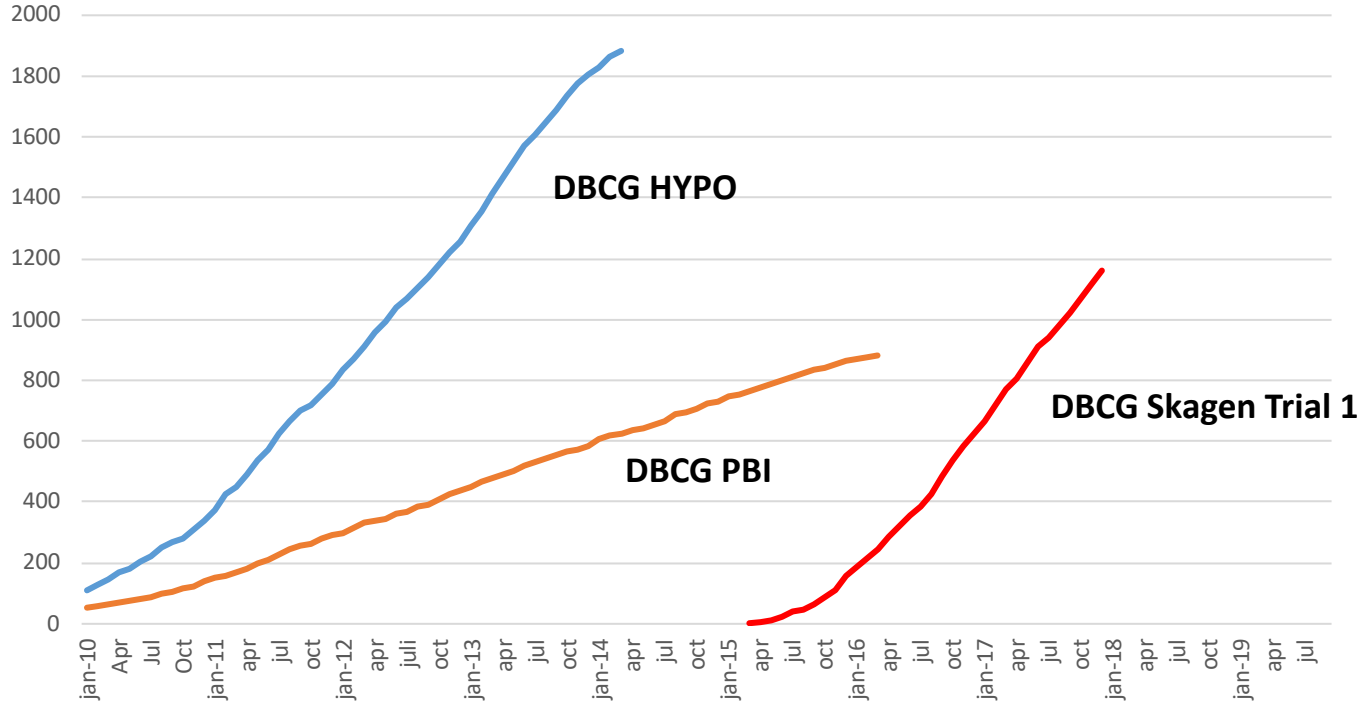


Australien

iversity Hospital

	Jan 1, 2016	Jan 1, 2018
Aarhus	88	334
Vejle	2	113
Rigshospitalet	24	103
Odense	7	103
Næstved	0	59
Aalborg	0	55
Stavanger	19	109
St.Luc, Bruxelles	10	102
Tromsø	2	55
Dresden 2	1	48
Kristiansand	0	37
Dresden 1	2	33
Kielce, Poland	0	7
Ljubljana	0	3
Total	155	1161

Rekruttering i DBCG HYPO, DBCG PBI & DBCG Skagen Trial 1



CIRRO

DBCG office involvement

- Online system for Danish research data (~easy, $)
- Online system for foreign departments (~NOT easy)
  - Randomisation procedure
  - Pt and tumour characteristics
  - All endpoints (morbidity, relapse)
  - Ask for missing data
- Constantly provide help at mistakes

Non-DBCG involvement:

National Dose Plan Bank

Online system for storage of photos

Conclusion

- The Skagen Trial 1 is active in 6 DK / 8 foreign depts
- France active with a copy trial since Sept 2016
- Australia/Finland expected to join us 2018
- The DBCG system for data storage is running
- QA of RT technique has been published including all depts: high QA

- In 3 years we will have the answer on the safety of 40/15

Fremtiden

- DBCG RT Natural trial, randomiseret studie
- DBCG RT Recon trial, randomiseret studie
- DCCC COR, internatmøde Sandbjerg Gods 18.-20. juni, 2018, mhp at skrive nationale studie-protokoller vedr det onkologiske hjerte (registrer dig på www.dccccor.dk)
- DBCG RT Nation study, 12.000 stråleplaner fra højrisiko-brystkræft
- DBCG RT DCIS study
- Knæk Cancer DCCC Stråleonkologi, 25 mio kr, DBCG RT Udvalg
- Knæk Cancer DCCC Senfølgecenter, 10 mio kr, DBCG RT Udvalg
- Genetisk risikoprofil for gavn af strålebehandling
- DBCG RT IMN-2 study
- DBCG Proton trials, starter med fase II mhp at lede til fase III trial
- Opretholde fokus på komplet indberetning til DBCG databasen
- Deltage i randomiseret studie med behandling af stråleinduceret fibrose
- Introducere shared decision making gennem evidensgenererende studie
- QA på RT i DBCG RT Recon trial
- -og meget mere

CIRRO

DBCG

PATIENTS, investigators, physicists, radiographers, nurses and research support staff

Sponsored by the Danish Cancer Society, CIRRO (Centre for Interventional Research in Radiation Oncology) and Breast Friends