ECCO2017
EUROPEAN CANCER CONGRESS

DBCG DANISH BREAST CANCER GROUP

27-30 January
Amsterdam,
The Netherlands

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

BV Offersen[1], HM Nielsen[1], EH Jacobsen[2], MH Nielsen[3], M Krause[4], L Stenbygaard[5], I Mjaaland[6], A Schreiber[7], UM Kasti[8], M Jensen[9],J Overgaard[10]

[1]Dept Oncol, Aarhus University Hospital, Aarhus, Denmark, [2]Dept Oncol, Lillebaelt Hospital, Vejle, Denmark, [3]Dept Oncol, Odense University Hospital, Odense, Denmark, [4]Clinic for Radiother and Oncol, University Clinic Carl Gustav Carus, Technical University Dresden, Dresden, Germany, [5]Dept Oncol, Aalborg University Hospital, Aalborg, Denmark, [6]Dept of Oncol, Stavanger University Hospital, Stavanger, Norway, [7]Dept Oncol, Academic Teaching Hospital Dresden-Friedrichstadt, Dresden, Germany, [8]Dept Oncol, Kristiansand, Norway, [9]Danish Breast Cancer Group, Copenhagen University Hospital, Rigshospitalet, Copenhagen, Denmark, [10]Dept of Expt Clin Oncol, Aarhus University Hospital, Aarhus, Denmark

FROM EVIDENCE TO PRACTICE IN MULTIDISCIPLINARY CANCER CARE
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No conflicts of interest

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Background DBCG HYPO Trial

Moderate hypofractionation 36-42 Gy / 12 fr DBCG standard before 1982

Denmark

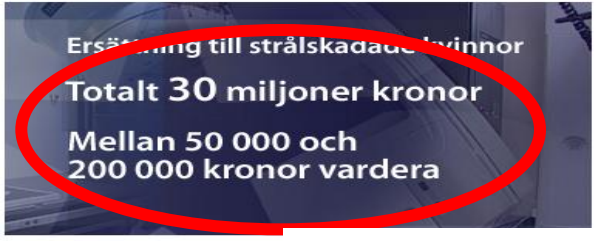
RT 1980
Photo 2010,
30 yr follow up

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.

Marianne Mosserud

-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 saker...
Ett papper kan man ju ta, nån filt eller så, berättade Marianne.



~3.3 mio Euro

Komiteens tilråding

Komiteen viser for øvrig til proposisjonen og det som står foran, og rår Stortinget til å gjøre følgende

vedtak:

I statsbudsjettet for 1998 gjøres følgende endring:

Kap. 739	Andre utgifter			
	73 (ny)	Erstatning for stråleskader, *kan overføres,*		
		bevilges med	kr	85000000

Norway

~9.3 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 bröstcanceroperationer.

Video

Tidigare inslag

Få men höga doser

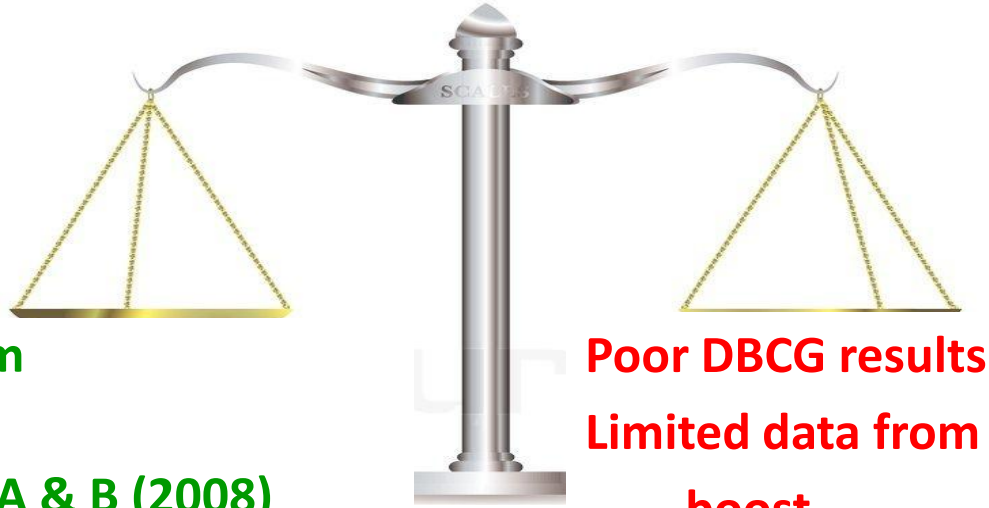
Den här unika ersättningen … till de kvinnor, som fi… strålbehandling … mycket stora s… *hypofraktionerin…*

…dlingen gav nya

Samtidigt som d… …sätt att döda tumörceller dödas och skada… …an vävnad. Denna typ av strålbehandling le… …därmed i vissa fall till allvarliga brännskador, muskel- och skelettskador.

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

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Randomization DBCG HYPO

Invasive early breast cancer or DCIS, ≥41 yr,

breast conservation,

pTis-pT2, pN0-pN1(mic)

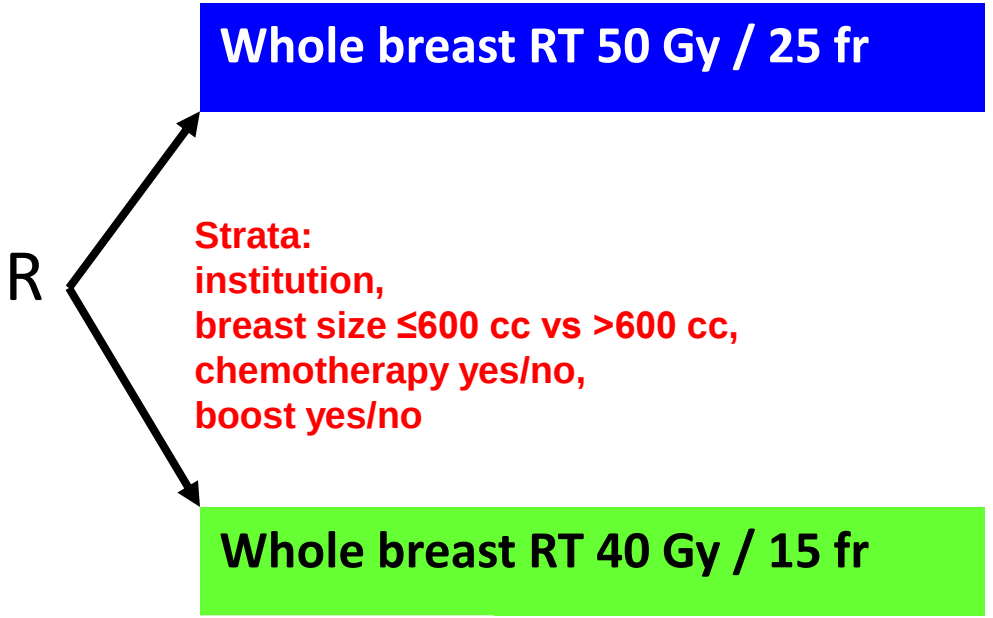
any histology / ER / HER2 / grade

Boost allowed

Any breast size

Any systemic therapy

Breast implants not allowed



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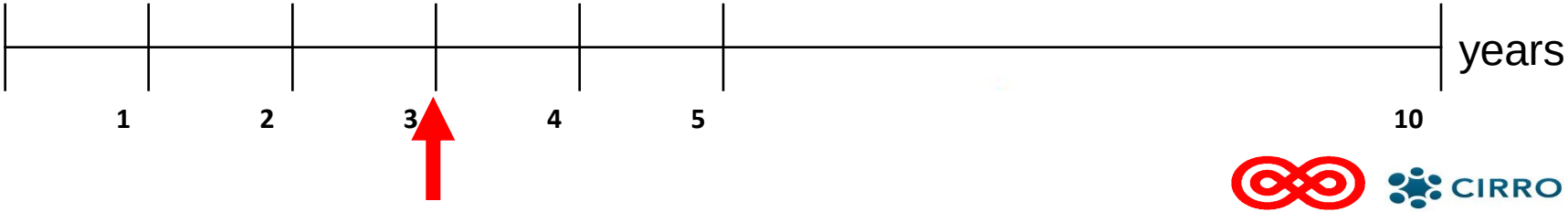
Endpoints

- 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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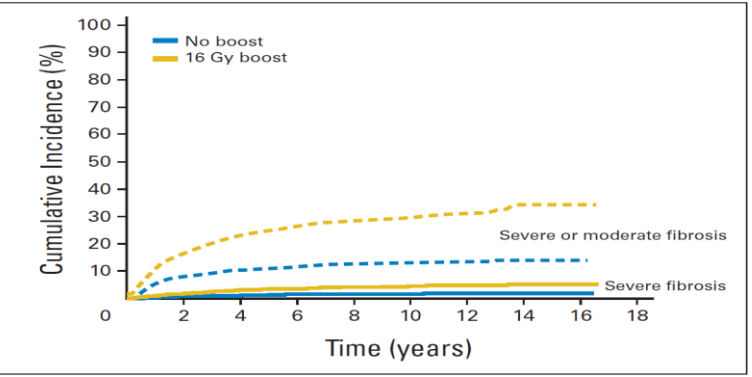
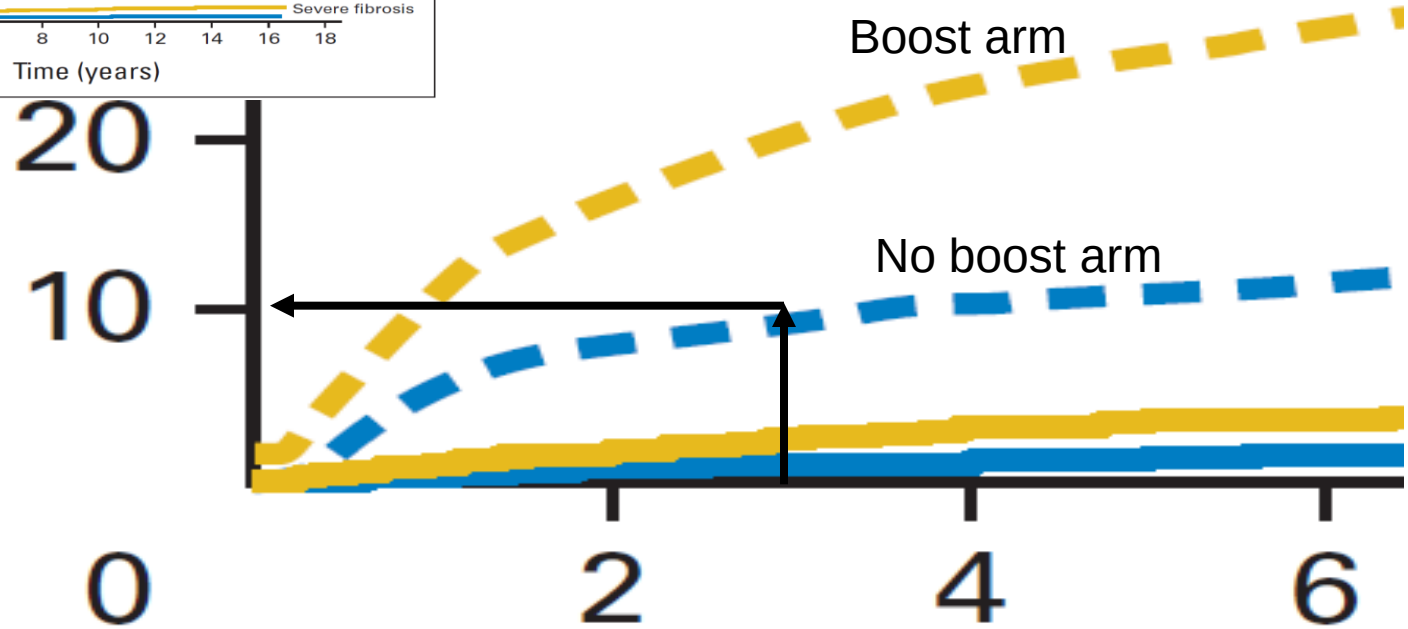
Statistical assumptions



Severe or moderate fibrosis



Bartelink et al, JCO, 2007

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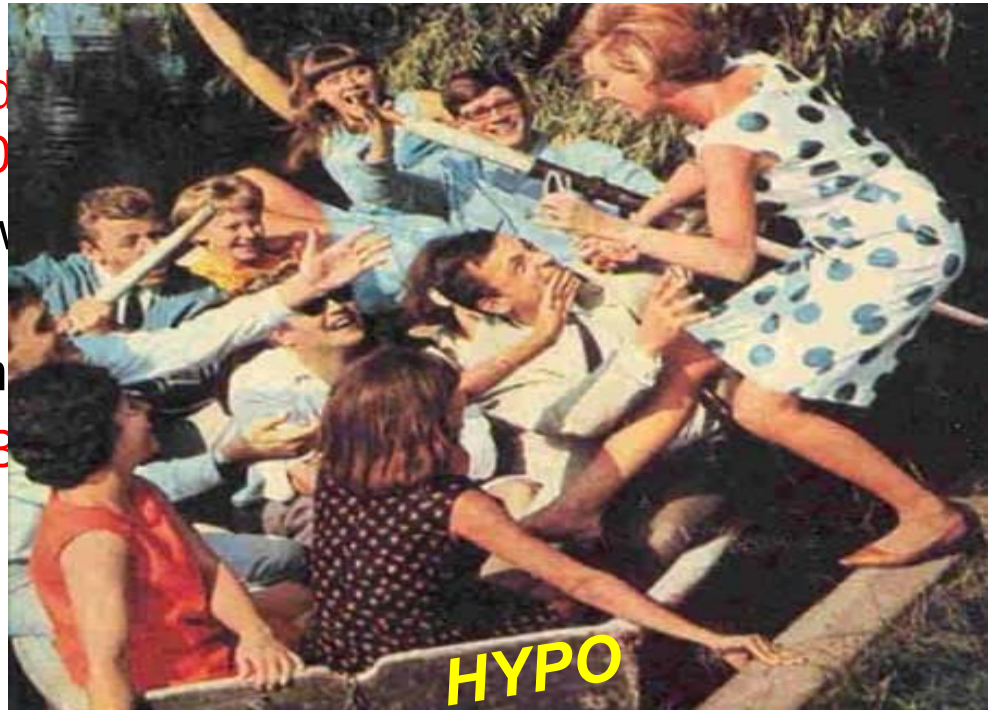
Statistical assumptions

Expected risk of grade 2+ breast ind
using 50 Gy/25 fr is estimated 10

Accept 10% absolute difference betv
breast RT

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

Number needed: 338 patients with 3



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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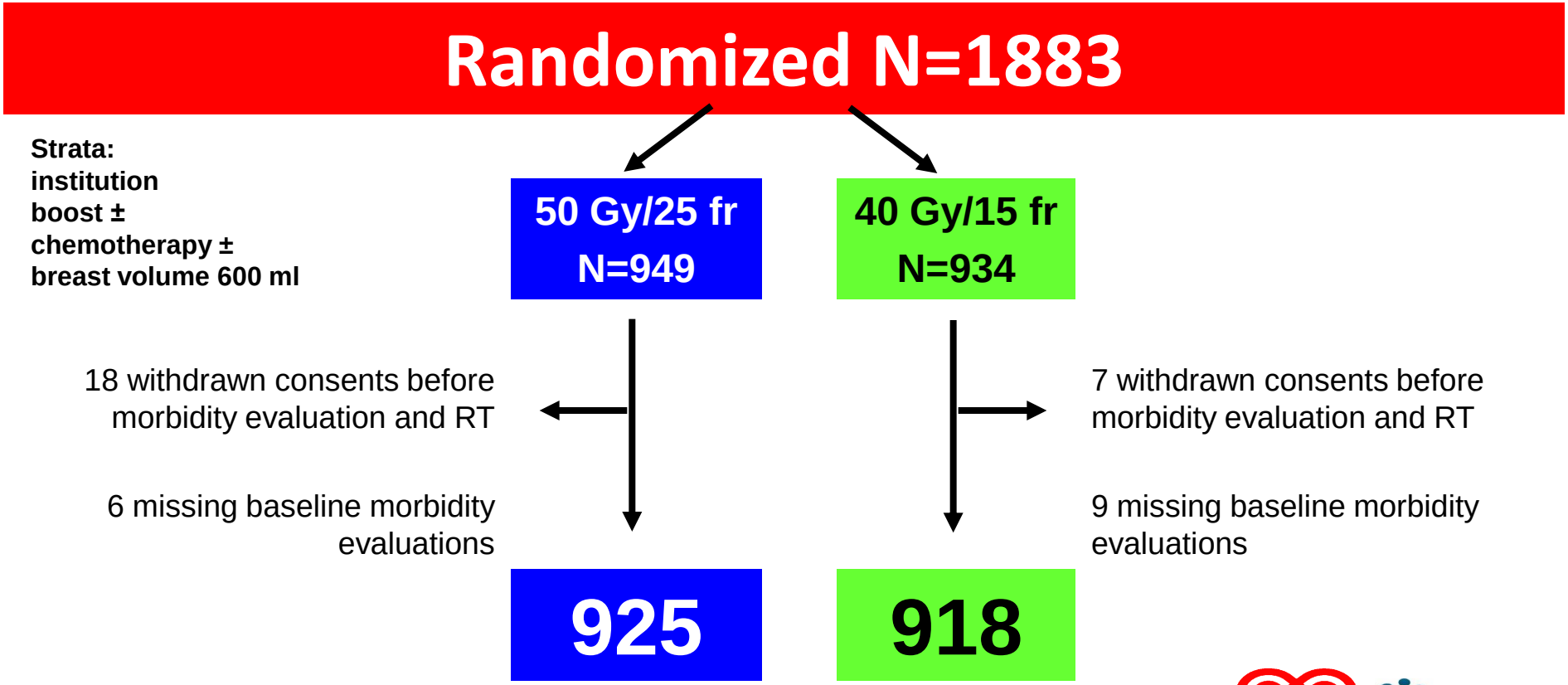
CONSORT diagram



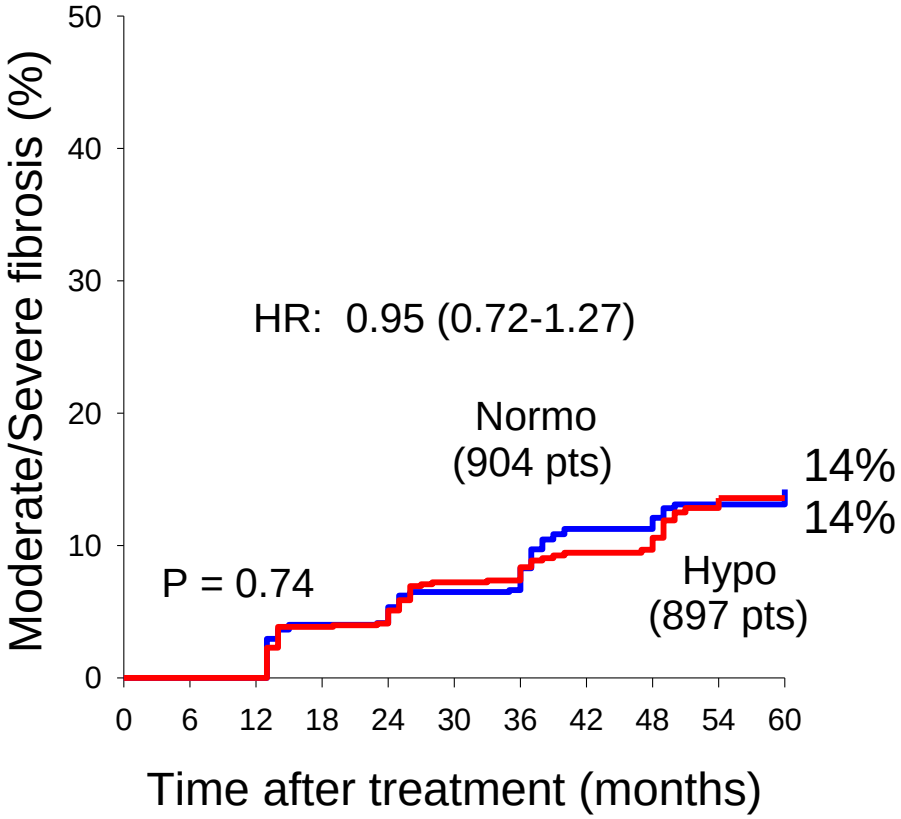
Thus 1843 randomized patients with baseline morbidity evaluation

Patient characteristics, N=1883		50 Gy N=949	40 Gy N=934	P-value
Age (years)	Median (range)	59 (42-83)	59 (39-82)	NS
Histology	DCIS	123	125	NS
	Ductal	631	624	
	Other	195	184	
	Missing	0	1	
Tumour size	pT1a	48	66	NS
	pT1b	198	192	
	pT1c	420	411	
	pT2	160	140	
Grade (ductal)	1	217	196	NS
	2	261	255	
	3	144	167	
	NA	9	6	
Pathological nodes	pN0 (cN0)	825 (14)	835 (14)	NS
	pN1 (mic)	110	84	
	pN1	0	1	
ER status	Pos	724	691	NS
	Neg	108	122	
HER2 status	Pos	64	95	0.02
	Neg	767	710	

Max breast induration		50 Gy/25 fr	%	40 Gy/15 fr	%	P
Baseline	Grade 0	452	48.9	428	46.6	0.273
	Grade 1	289	31.2	311	33.9	
	Grade 2	158	**17.1**	163	**17.8**	
	Grade 3					
Total	**1843**					
Year 1	Grade 0					0.361
	Grade 1					
	Grade 2					
	Grade 3	10	**1.1**	11	**1.2**	
Total	**1779**	893		886		
Year 2	Grade 0	363	42.5	415	48.3	0.065
	Grade 1	379	44.4	360	41.9	
	Grade 2	100	**11.7**	74	**8.6**	
	Grade 3	12	**1.4**	11	**1.3**	
Total	**1714**	854		860		
Year 3	Grade 0	312	41.7	371	48.8	0.045
	Grade 1	336	44.9	302	39.7	
	Grade 2	89	**11.9**	75	**9.9**	
	Grade 3	11	**1.5**	12	**1.6**	
Total	**1508**	748		760		

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

Primary endpoint: Grade 2-3 breast induration at 3 years



Induration and boost

23% of the patients had a boost

		No Boost Stratum					Boost Stratum				
		50Gy/25fr	%	40Gy/15fr	%	P	50Gy/25fr	%	40Gy/15fr	%	P
Baseline	Grade 0	322	45.2	306	43.5	0.388	130	61.3	122	57.0	0.743
	Grade 1	227	31.8	242	34.4		62	29.2	69	32.2	
	Grade 2	141	**19.8**	142	**20.2**		17	**8.0**	21	**9.8**	
	Grade 3	23	**3.2**	14	**2.0**		3	**1.4**	2	**0.9**	
Total	**1843**	713		704			212		214		
Year 3	Grade 0	236	41.2	290	49.9	0.023	76	43.4	81	45.3	0.765
	Grade 1	261	45.5	222	38.2		75	42.9	80	44.7	
	Grade 2	68	**11.9**	59	**10.2**		21	**12.0**	16	**8.9**	
	Grade 3	8	**1.4**	10	**1.7**		3	**1.7**	2	**1.1**	
Total	**1508**	573		581			175		179		

Actuarial 3 year risk of grade 2-3 breast induration irrespective of fractionation using year 1 as baseline (boost no/yes)
HR 1.10 (95% CI 0.79-1.52), p=0.59

Induration and chemotherapy

36% of the patients had taxane-based chemotherapy

		No Chemotherapy Stratum					Chemotherapy Stratum				
		50Gy/25fr	%	40Gy/15fr	%	P	50Gy/25fr	%	40Gy/15fr	%	P
Baseline	Grade 0	231	39.3	210	35.8	0.135	221	65.6	218	65.9	0.875
	Grade 1	189	32.1	218	37.1		100	29.7	93	28.1	
	Grade 2	143	**24.3**	144	**24.5**		15	**4.5**	19	**5.7**	
	Grade 3	25	**4.3**	15	**2.6**		1	**0.3**	1	**0.3**	
Total	**1843**	588		587			337		331		
Year 3	Grade 0	209	43.2	235	49.4	0.266	103	39.0	136	47.9	0.07
	Grade 1	212	43.8	183	38.4		124	47.0	119	41.9	
	Grade 2	55	**11.4**	52	**10.9**		34	**12.9**	23	**8.1**	
	Grade 3	8	**2.6**	6	**1.3**		3	**1.01**	6	**2.1**	
Total	**1508**	484		476			264		284		

Actuarial 3 year risk of grade 2-3 breast induration irrespective of fractionation using year 1 as baseline (chemo no/yes)
HR 1.06 (95% CI 0.79-1.42), p=0.70

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Induration and breast volume

Median size of CTVp_breast 644 ml (50 Gy) and 635 ml (40 Gy)

		Small breasts Stratum (≤600 ml CTVp_breast)					Large breasts Stratum (>600 ml CTVp_breast)				
		50Gy/25fr	%	40Gy/15fr	%	P	50Gy/25fr	%	40Gy/15fr	%	P
Baseline	Grade 0	213	48.6	212	49.0	0.179	239	49.1	216	44.5	0.542
	Grade 1	134	30.6	146	33.7		155	31.8	165	34.0	
	Grade 2	74	**16.9**	68	**15.7**		84	**17.2**	95	**19.6**	
	Grade 3	17	**3.9**	7	**1.6**		9	**1.8**	9	**1.9**	
Total	**1843**	438		433			487		485		
Year 3	Grade 0	173	49.6	200	56.3	0.163	139	34.8	171	42.2	0.190
	Grade 1	135	38.7	124	34.9		201	50.4	178	44.0	
	Grade 2	38	**10.9**	26	**7.3**		51	**12.8**	49	**12.1**	
	Grade 3	3	**0.9**	5	**1.4**		8	**2.0**	7	**1.7**	
Total	**1508**	349		355			399		405		

Actuarial 3 year risk of grade 2-3 breast induration irrespective of fractionation using year 1 as baseline (small/large)
HR 1.56 (95% CI 1.16-2.09), p=0.003

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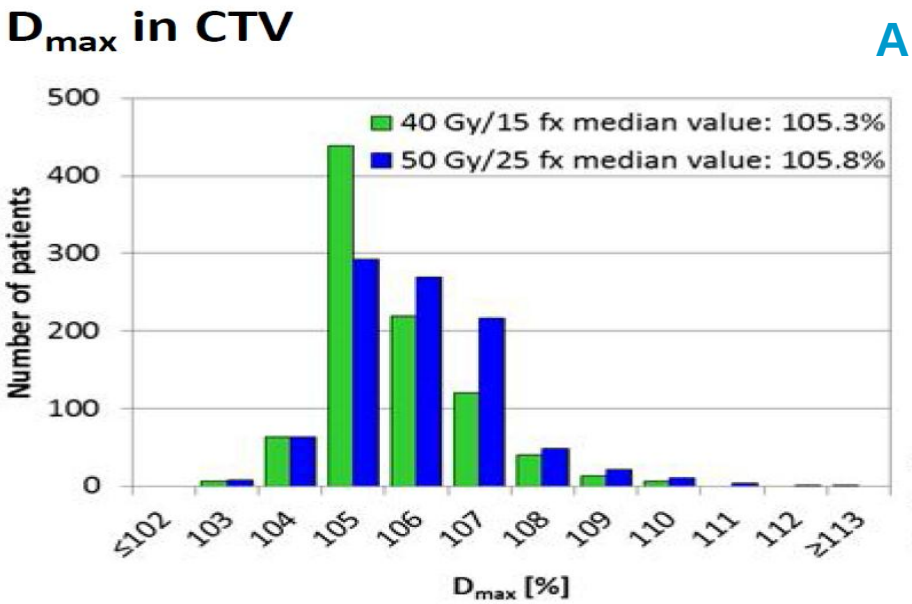
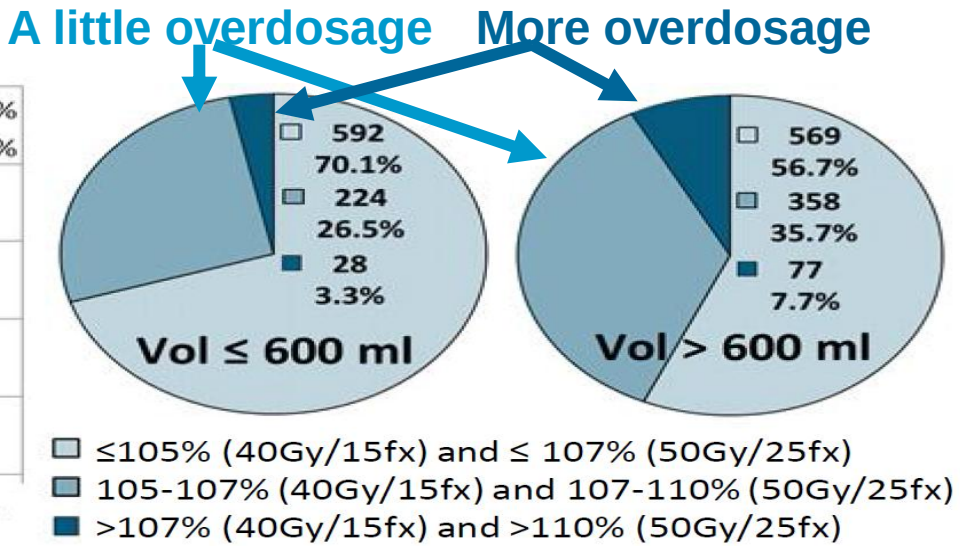
Breast volume and dose distribution





Significantly more inhomogeneous dose distribution in large breasts, P<0.0001

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Thomsen MS et al, E-poster ESTRO 2016, EP-1936

Cox proportional hazards analysis using breast induration grades 2-3 as endpoint

VARIABLE	P value	RR	95% CI
UNIVARIATE			
Hypo (40 Gy vs 50 Gy)	0.74	0.95	(0.72-1.27)
Breast size (S vs L)	*0.003*	*1.56*	*(1.16-2.09)*
Chemotherapy (no vs yes)	0.70	1.06	(0.79-1.42)
Boost (no vs yes)	0.59	1.10	(0.79-1.52)
MULTIVARIATE			
Hypo (40 Gy vs 50 Gy)	0.74	0.95	(0.72-1.27)
Breast size (S vs L)	*0.003*	*1.56*	*(1.16-2.09)*
Chemotherapy (yes vs no)	NS		
Boost (yes vs no)	NS		

Recurrences and new events

	50 Gy / 25 fr	40 Gy / 15 fr
Local recurrence	**7**	**7**
Loco-reg recurrence	**10**	**7**
Contralateral DCIS/BC	**2/12**	**3/7**
Distant recurrence	**14**	**16**
Other malignant disease	**18**	**19**

		P	HR	95% CI
Local recurrence	40 vs 50	0.88	0.92	0.33-2.55
Loco-reg recurrence	40 vs 50	0.57	1.31	0.51-3.32
Distant recurrence	40 vs 50	0.65	0.81	0.32-1.97
All failures	40 vs 50	0.94	1.03	0.53-1.97

Conclusion

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

- Few side effects at 3 yr with no difference in breast induration comparing 40 Gy/15 fr with 50 Gy/25 fr
- Large breast volume is an independent risk factor for developing breast induration 3 years post RT
- Use of boost, chemotherapy or hypofractionation have no impact on 3-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

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Acknowledgements

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