

First results from the clinically controlled randomized DBCG PBI trial

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Background

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



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

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

Closed trials Still recruiting

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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 (LBA 4, Elicium 15.45 today)



Randomization DBCG PBI

**Breast cancer, ≥ 60 yr,
breast conservation,
margin ≥ 2 mm,
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

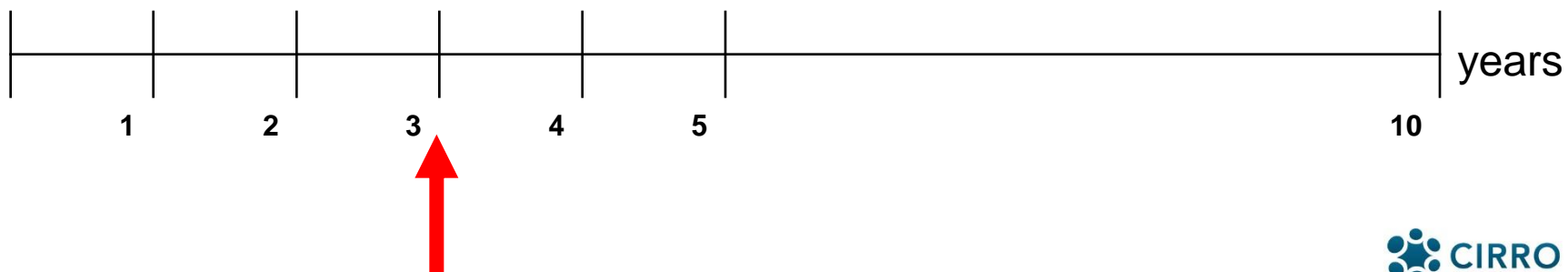
Partial breast RT 40 Gy / 15 fr



Endpoints

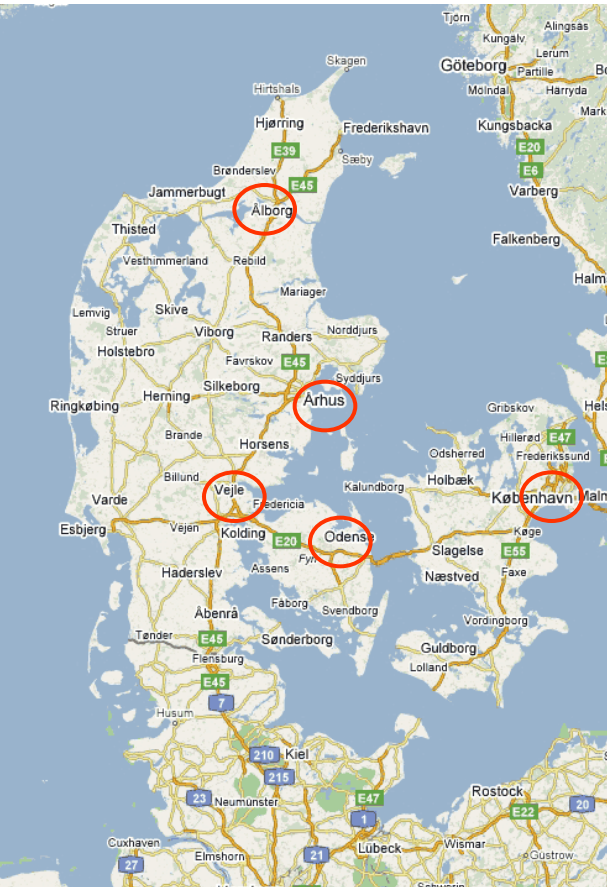
- Primary
 - grade ≥ 2 breast induration 3 years post RT

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



Workshop every year

Recruiting centres must participate, reproducibility is tested in selected patients with different types of late morbidity

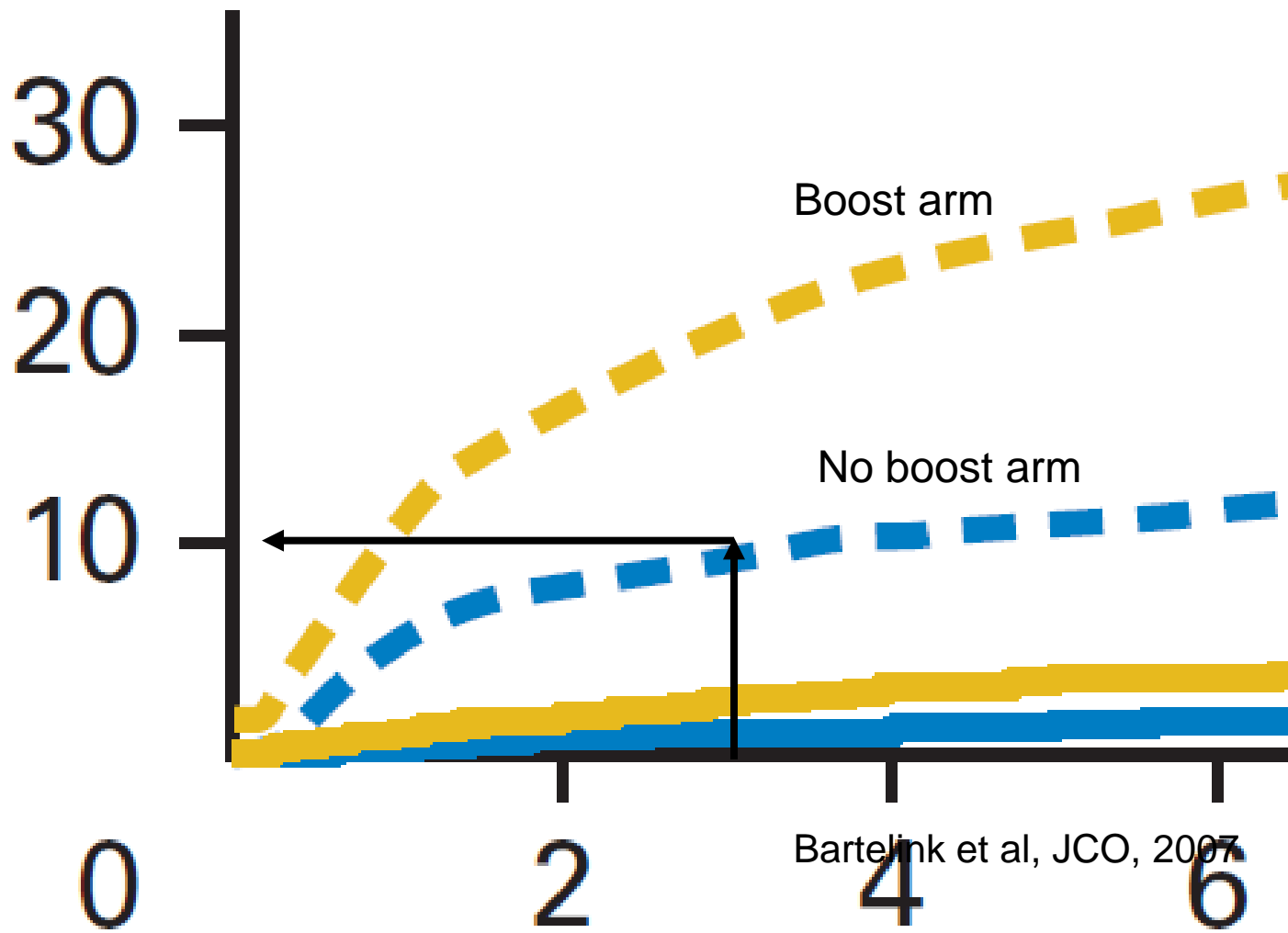


RT technique

- 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 a

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

Accept 10% absolute difference between
80% power, one-sided test, 5% sign lev

Number needed: 314 patients with 3 yr

ASTRO consensus patient/tumour crite

Strategy:

"Always room for one more"

Moderate hypofractionation already routine in UK and NL

ASTRO criteria followed

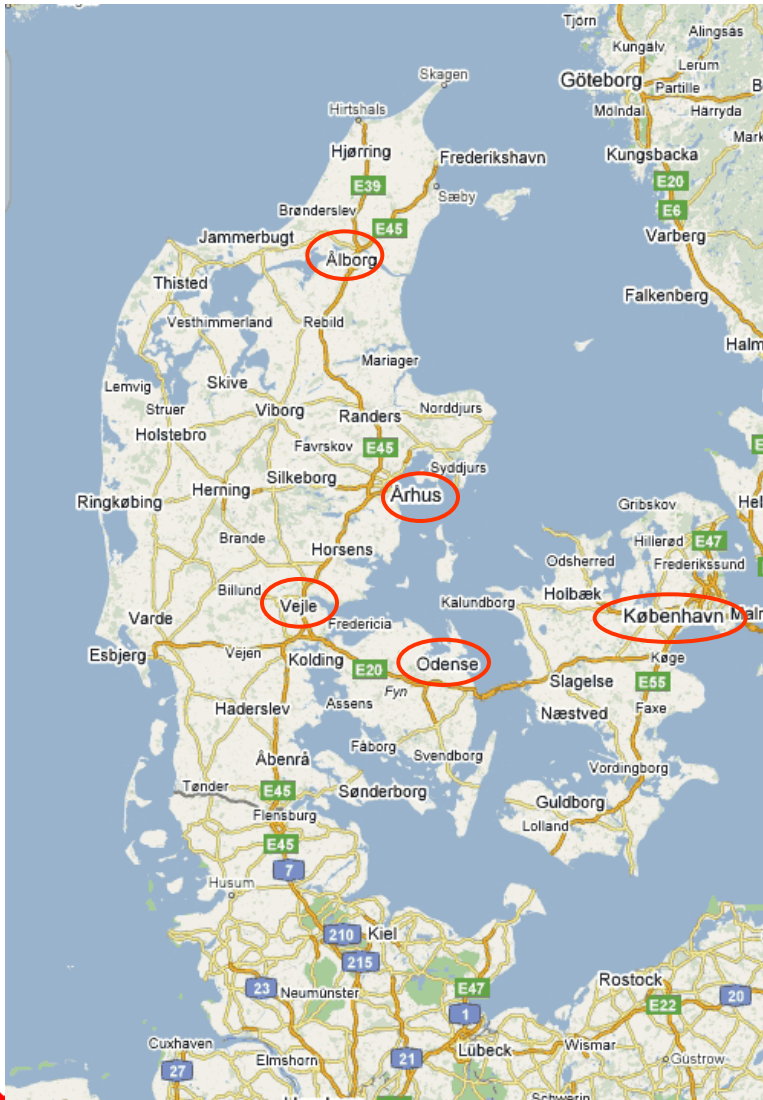
UK IMPORT Low

The DBCG PBI Trial closed Mar 8th, 2016.

As of March 1th, 2016, 882 patients were accrued



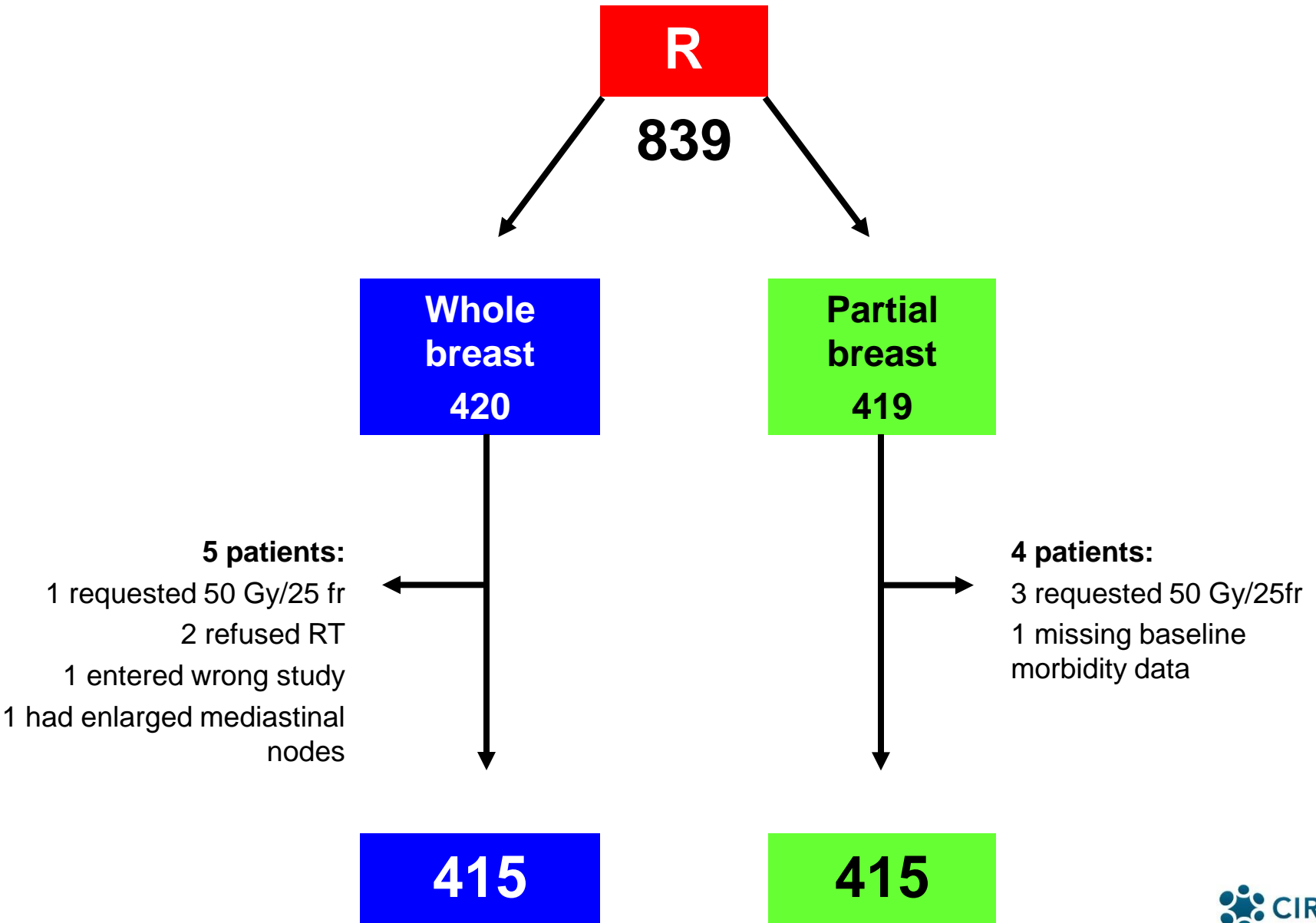
Baseline data



Center	Accrual
Aarhus	410
Vejle	157
Odense	111
Aalborg	87
RH Copenhagen	73
Dresden	1
Total	839

At presentation at EBCC Mar 2016





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

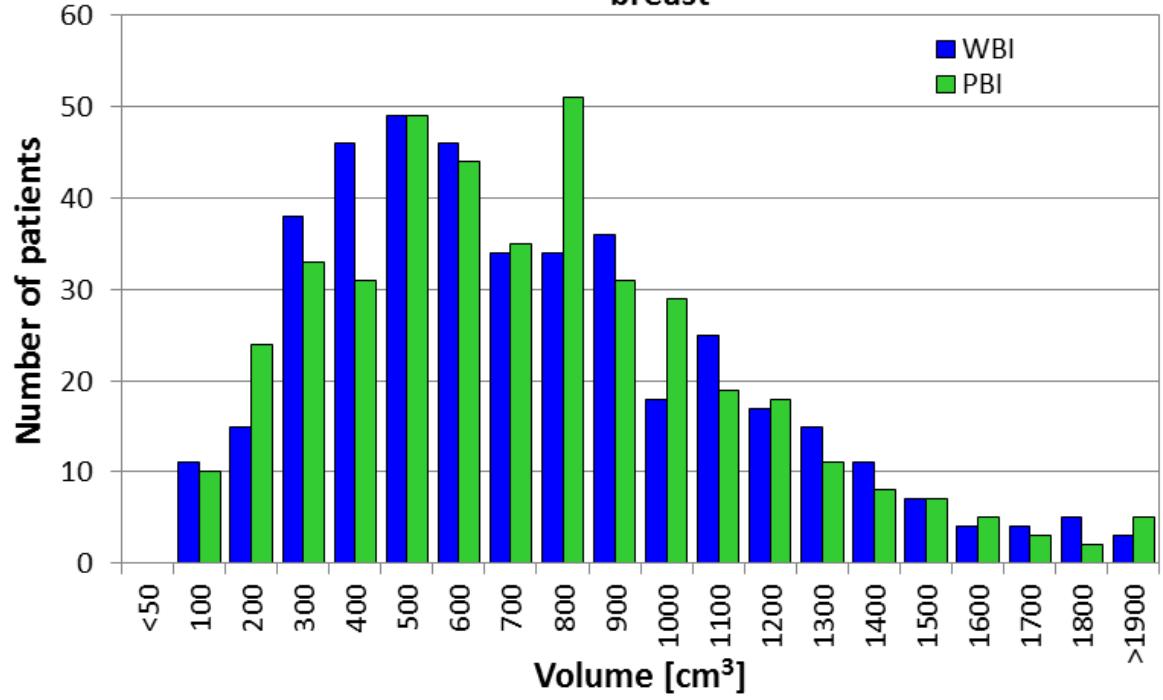
		Whole breast N=420	Partial breast N=419
Age	Median (years, range)	66 (60-86)	66 (60-83)
Tumour size	Median (mm, range)	14 (4-40)	14 (4-40)
Histology	Ductal	367 (87%)	367 (87%)
	Mucinous/Papillary/Tubular	53 (13%)	52 (12%)
Grade	1	144 (59%)	220 (60%)
	2	143 (40%)	139 (38%)
	Missing	4	5
Breast size	Median cc (range)	633 (64-4257)	704 (72-2345)
Endocrine therapy	No	186 (44%)	187 (45%)
	Yes	234 (56%)	232 (55%)
Smoking	At baseline	85 (20%)	102 (24%)
	At 3 years	30 (17%)	31 (18%)
Charlson comorbidity (N=738)	0	74%	80%
	1	21%	16%
	>1	5%	4%

No difference

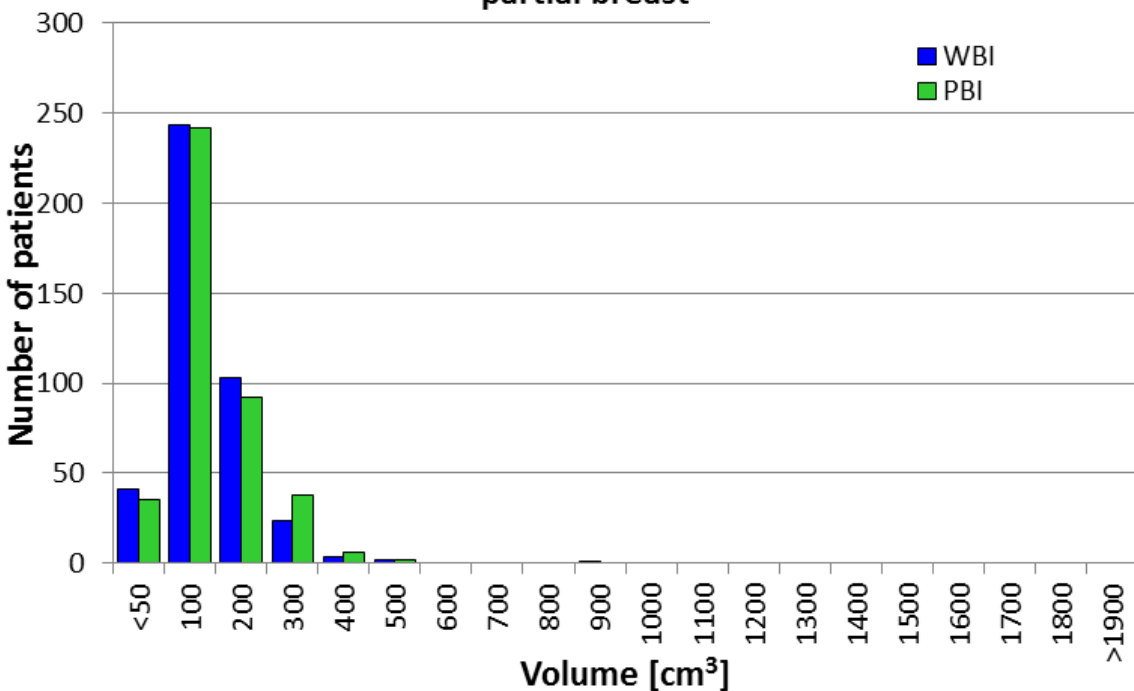


Results from dose plans

CTV_{breast}



CTV_{partial breast}

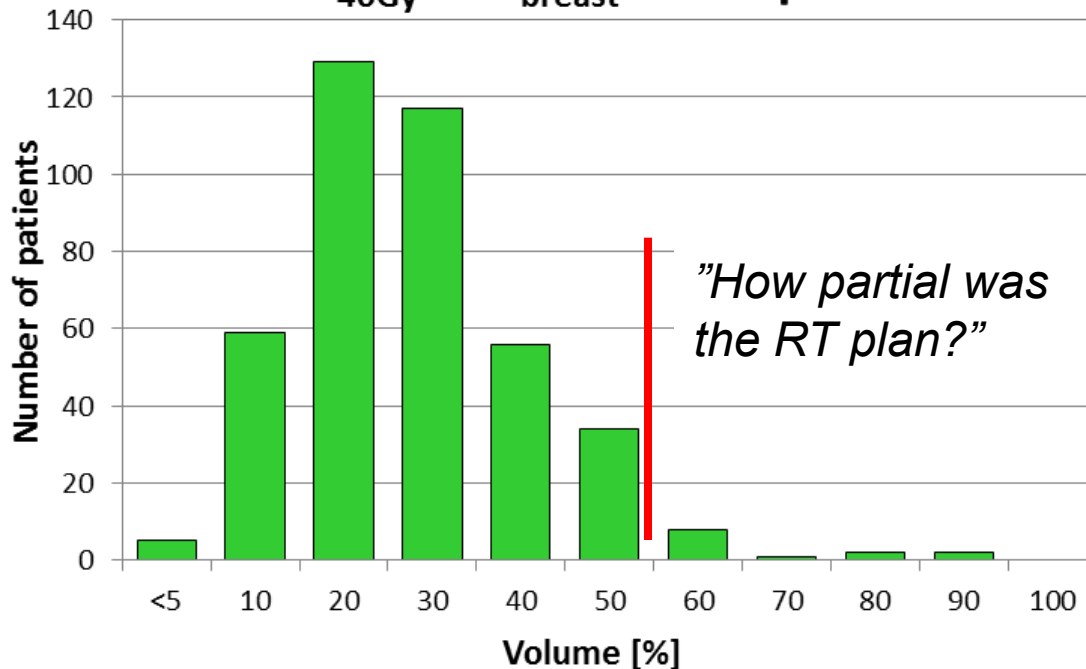


Legend for the bar charts:

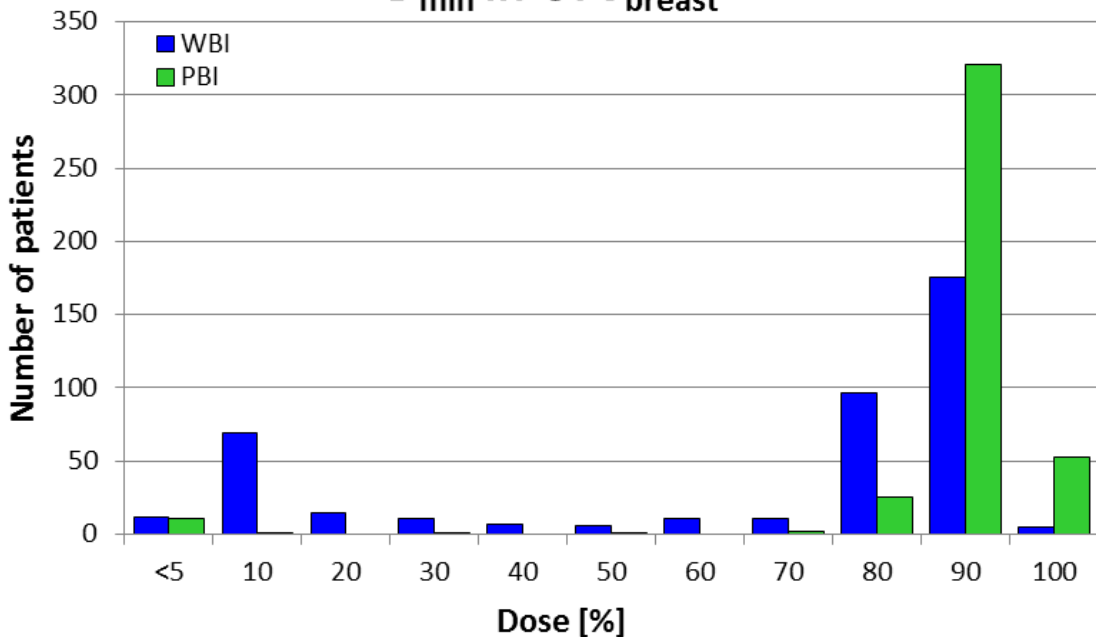
- WBI (Whole Breast Irradiation) - Blue square
- PBI (Partial Breast Irradiation) - Green square

Results from dose plans

V_{40Gy} CTV_{breast} in PBI plan

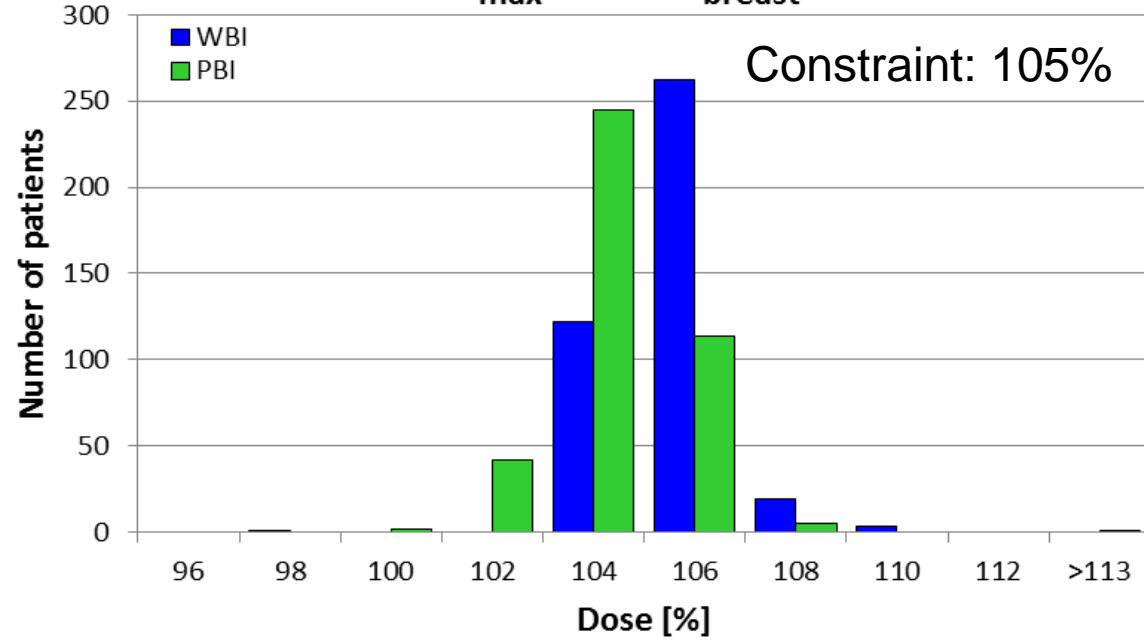


D_{min} in CTV_{breast}

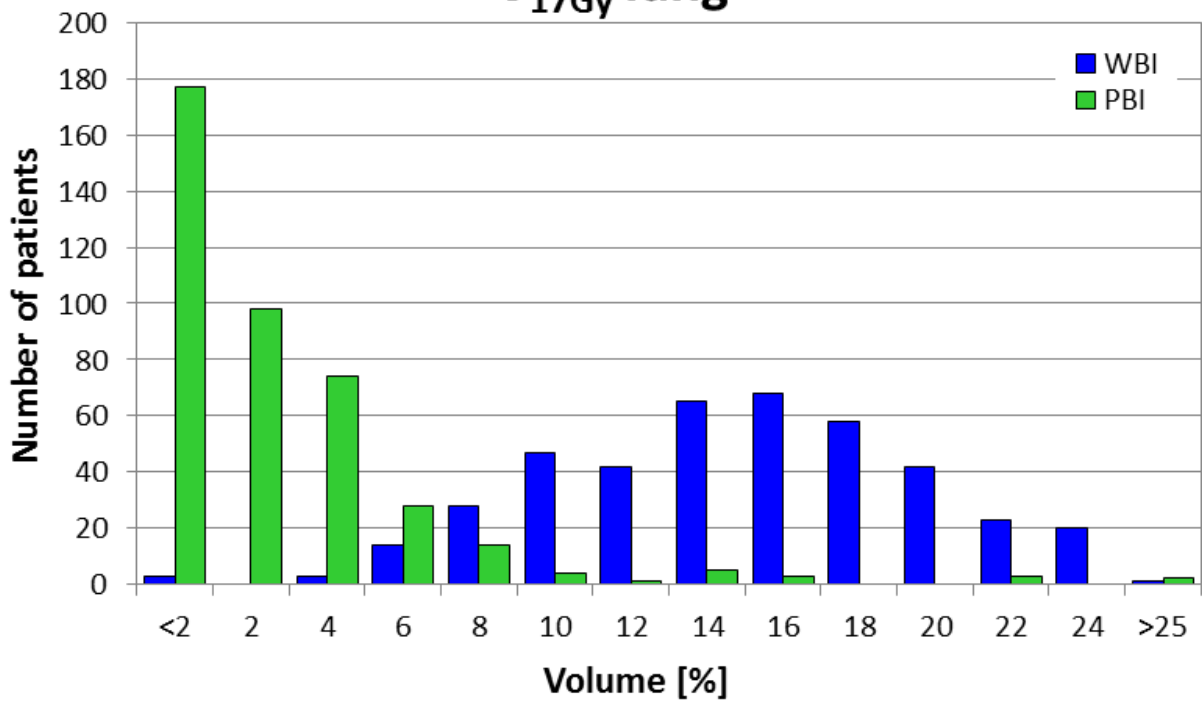


Results from dose plans

D_{max} in CTV_{breast}

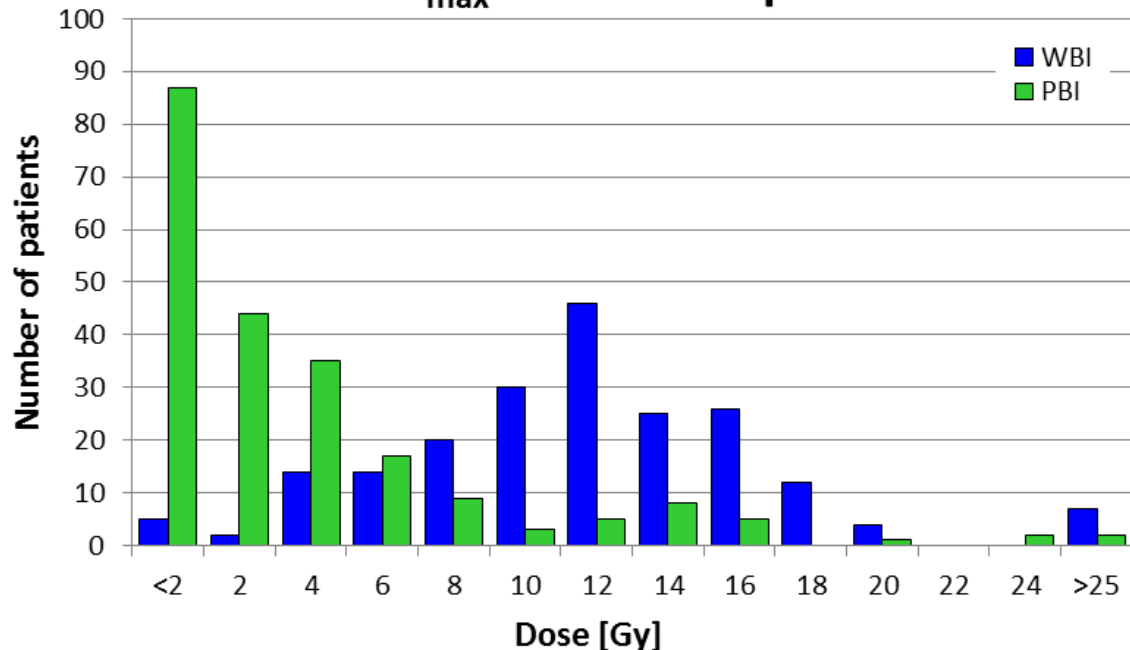


V_{17Gy} lung

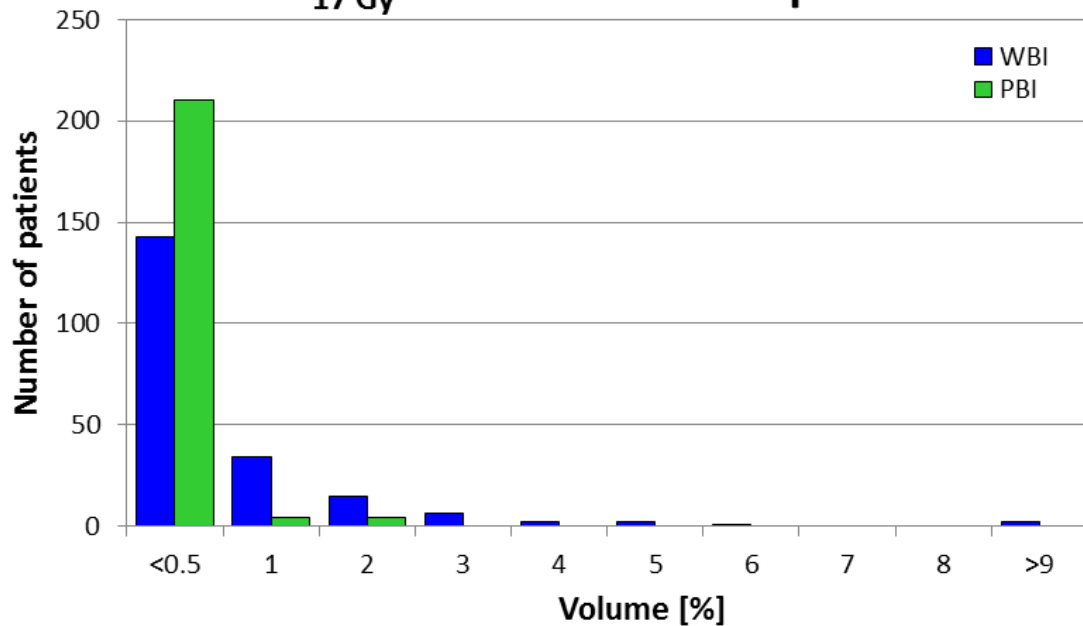


Results from dose plans

Ladca_{max} - left sided patients



V_{17Gy} heart - left sided patients



		Whole breast	%	Partial breast	%	P value
Baseline	Grade 0	Scores 0:none 1:slightly palpable 2:palpable 3:clearly palpable, retraction of skin and fixation			25.8	0.28
	Grade 1				40.0	
	Grade 2				28.7	
	Grade 3				5.5	
	Not graded					
Total	830					
Year 1	Grade 0	128	37.9	152	44.1	0.12
	Grade 1	157	46.4	146	42.3	
	Grade 2	47	13.9	38	11.0	
	Grade 3	6	1.8	5	1.1	
	Not graded	0		4		
Total	683	338		345		
Year 2	Grade 0	128	48.9	144	56.9	0.24
	Grade 1	107	40.8	90	35.6	
	Grade 2	22	8.4	18	7.1	
	Grade 3	4	1.5	1	0.4	
	Not graded	1		0		
Total	515	262		253		
Year 3	Grade 0	81	44.8	96	55.8	0.07
	Grade 1	86	47.5	63	36.6	
	Grade 2	14	7.7	11	6.4	
	Grade 3	0	0	0	0	
	Not graded	0		2		
Total	353	181		172		



Breast induration

		Whole breast	%	Partial breast	%	P value
Baseline	Grade 0	122	29.4	107	25.8	0.28
	Grade 1	140	33.7	166	40.0	
	Grade 2	132	36.6	119	34.2	
	Grade 3	20		23		
	Not graded	1		0		
Total	830	415		415		
Year 1	Grade 0	128	37.9	152	44.1	0.12
	Grade 1	157	46.4	146	42.3	
	Grade 2	47	15.7	38	12.1	
	Grade 3	6		5		
	Not graded	0		4		
Total	683	338		345		
Year 2	Grade 0	128	48.9	144	56.9	0.24
	Grade 1	107	40.8	90	35.6	
	Grade 2	22	9.9	18	7.5	
	Grade 3	4		1		
	Not graded	1		0		
Total	515	262		253		
Year 3	Grade 0	81	44.8	96	55.8	0.07
	Grade 1	86	47.5	63	36.6	
Induration 2-3		14	7.7	11	6.4	
		0		0		
	Not graded	0		2		
Total	353	181		172		



DBCG Breast induration *de novo*

		Whole breast	%	Partial breast	%	P value
Baseline	Grade 0	122	29.4	107	25.8	
	Grade 1	140	33.7	166	40.0	
	Grade 2		0		0	
	Grade 3					
	Not graded					
Total						
Year 1	Grade 0					
	Grade 1					
	Grade 2					
	Grade 3					
	Not graded					
Total						
Year 2	Grade 0					
	Grade 1					
	Grade 2					
	Grade 3					
	Not graded					
Total						
Year 3	Grade 0	54	45.4	57	55.9	
	Grade 1	59	50.0	38	37.3	
Induration 2-3		6	5.0	7	6.7	
		0		0		
	Not graded	0		0		
Total		119		102		



		Whole breast	%	Partial breast	%	P value
Baseline	Grade 0					
	Grade 1					
	Grade 2	132	36.6	119	34.2	
	Grade 3	20		23		
	Not graded	1		0		
Total						
Year 1	Grade 0					
	Grade 1					
	Grade 2					
	Grade 3					
	Not graded					
Total						
Year 2	Grade 0					
	Grade 1					
	Grade 2					
	Grade 3					
	Not graded					
Total						
Year 3	Grade 0	27	43.5	39	55.7	
	Grade 1	27	43.5	25	35.7	
Induration 2-3		8	12.9	4	5.7	
		0		0		
	Not graded	0		2		
Total		62		70		

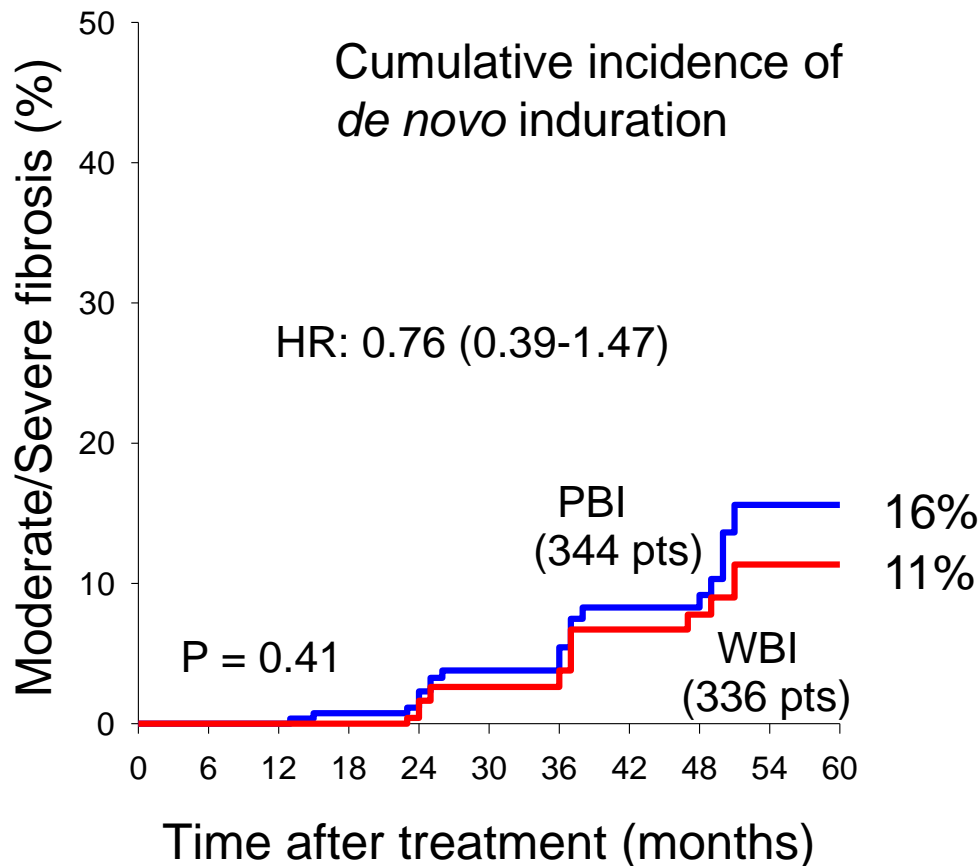


Breast induration

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

3 years: whole breast 6.4%
partial breast 4.8%

4 years: whole breast 8.3%
partial breast 7.7%



		Whole breast	%	Partial breast	%	P value
Baseline	Gr					81
	Gr					
	Gr					
	Gr					
	Not					
Total	83					
Year 1	Grade 0	132	39.0	154	44.6	0.0001
	Grade 1	127	37.6	147	42.6	
	Grade 2	76	22.5	40	11.6	
	Grade 3	3	0.9	0	0	
	Not graded	0		4		
Total	683	338		345		
Year 2	Grade 0	97	37.0	127	50.2	0.005
	Grade 1	124	47.3	106	41.9	
	Grade 2	40	15.3	20	7.9	
	Grade 3	0	0	0	0	
	Not graded	1		0		
Total	515	262		253		
Year 3	Grade 0	79	43.6	75	43.6	0.40
	Grade 1	82	45.3	81	47.1	
	Grade 2	20	11.0	14	8.1	
	Grade 3	0	0	0	0	
	Not graded	0		2		
Total	353	181		172		

Scores
0:none
1:papilla or skin lighter/darker than on non-irradiated side
2:Both papilla and skin lighter/darker than on non-irradiated side
3:Dramatic difference btw sides, either papilla and/or skin



		Whole breast	%	Partial breast	%	P value
Baseline	Grade 0	323	77.8	328	79.0	0.81
	Grade 1	85	20.6	81	19.5	
	Grade 2	4	1.5	5	1.4	
	Grade 3	2		1		
	Not graded	1		0		
Total	830	415		415		
Year 1	Grade 0	132	39.0	154	44.6	0.0001
	Grade 1	127	37.6	147	42.6	
	Grade 2	76	23.4	40	11.6	
	Grade 3	3		0		
	Not graded	0		4		
Total	683	338		345		
Year 2	Grade 0	97	37.0	127	50.2	0.005
	Grade 1	124	47.3	106	41.9	
	Grade 2	40	15.3	20	7.9	
	Grade 3	0		0		
	Not graded	1		0		
Total	515	262		253		
Year 3	Grade 0	79	43.6	75	43.6	0.40
	Grade 1	82	45.3	81	47.1	
Dyspigmentation 2-3		20	11.0	14	8.1	
		0		0		
	Not graded	0		2		
Total		181		172		



DBCG Global cosmetic outcome

		Whole breast	%	Partial breast	%	P value
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Scores

0:Excellent. No asymmetry, no deformities or skin changes, only slight increase in breast induration

1:Good, slight asymmetry and/or slight deformity and/or slight dyspigmentation / telangiectasia / edema and/or some increase in breast induration

2:Fair, distinct asymmetry / deformity / dyspigmentation / telangiectasia / edema and/or scattered breast induration

3:Poor, considerably asymmetry, and /or severe deformity / dyspigmentation / telangiectasia / edema / induration

Total	683	338		345		
Year 2	Grade 0 (excel)	66	25.2	76	30.0	0.02
	Grade 1 (good)	147	56.1	154	60.9	
	Grade 2 (fair)	42	16.0	18	7.1	
	Grade 3 (poor)	6	2.3	5	2.0	
	Not graded	1		0		
Total	515	262		253		
Year 3	Grade 0 (excel)	39	21.5	44	25.6	0.86
	Grade 1 (good)	113	62.4	101	58.7	
	Grade 2 (fair)	25	13.8	21	12.2	
	Grade 3 (poor)	4	2.2	4	2.3	
	Not graded	0		2		
Total	353	181		172		



DBCG Global cosmetic outcome

		Whole breast	%	Partial breast	%	P value
Baseline	Grade 0 (excel)	101	82.6	102	83.9	0.88
	Grade 1 (good)	242		246		
	Grade 2 (fair)	63	15.2	60	14.5	
	Grade 3 (poor)	8	1.9	7	1.7	
	Not graded	1		0		
Total	830	415		415		
Year 1	Grade 0 (excel)	93	81.1	100	86.7	0.046
	Grade 1 (good)	181		199		
	Grade 2 (fair)	56	16.6	36	10.4	
	Grade 3 (poor)	8	2.4	6	1.7	
	Not graded	0		4		
Total	683	338		345		
Year 2	Grade 0 (excel)	66	81.3	76	90.9	0.02
	Grade 1 (good)	147		154		
	Grade 2 (fair)	42	16.0	18	7.1	
	Grade 3 (poor)	6	2.3	5	2.0	
	Not graded	1		0		
Total	515	262		253		
Year 3		39	83.9	44	84.3	0.86
	Excellent/good	113		101		
	Grade 2 (fair)	25	13.8	21	12.2	
	Grade 3 (poor)	4	2.2	4	2.3	
	Not graded	0		2		
Total	353	181		172		



Patient satisfaction with treated breast

		Whole breast	%	Partial breast	%	P value
Baseline	Grade 0 (poor)	4	1.1	1	0.3	0.72
	Grade 1 (fair)	18	5.1	20	5.6	
	Grade 2 (good)	178	50.7	179	50.1	
	Grade 3 (excellent)	113	32.2	114	31.9	
	Grade 4 (unanswered)	38	10.8	43	12.0	
Total	708	351		357		
Year 3	Grade 0 (poor)	1	0.6	4	2.3	0.12
	Grade 1 (fair)	10	5.5	7	4.1	
	Grade 2 (good)	78	43.1	88	51.2	
	Grade 3 (excellent)	87	48.1	71	41.3	
	Grade 4 (unanswered)	5	2.8	2	1.2	
Total	353	181		172		

Patient satisfaction with treated breast

		Whole breast	%	Partial breast	%	P value
Baseline	Grade 0 (poor)	4	1.1	1	0.3	0.72
	Grade 1 (fair)	18	5.1	20	5.6	
	Grade 2 (good)	178	82.9	179	82.0	
	Grade 3 (excellent)	113		114		
	Grade 4 (unanswered)	38	10.8	43	12.0	
Total	708	351		357		
Year 3	Grade 0 (poor)	1	0.6	4	2.3	0.12
	Grade 1 (fair)	10	5.5	7	4.1	
Excellent/good		78	91.2	88	92.5	
		87		71		
	Grade 4 (unanswered)	5	2.8	2	1.2	
Total		181		172		

Patient satisfaction with treated vs untreated breast

		Whole breast	%	Partial breast	%	P value
Baseline	Grade 0 (poor)	4	1.1	6	1.7	0.94
	Grade 1 (fair)	40	11.4	36	10.1	
	Grade 2 (good)	189	53.8	188	52.7	
	Grade 3 (excellent)	80	22.8	84	23.5	
	Grade 4 (unanswered)	38	10.8	43	12.0	
Total	708	351		357		
Year 3	Grade 0 (poor)	3	1.7	5	2.9	0.48
	Grade 1 (fair)	24	13.3	21	12.2	
	Grade 2 (good)	87	48.1	92	53.5	
	Grade 3 (excellent)	61	33.7	51	29.7	
	Grade 4 (unanswered)	6	3.3	3	1.7	
Total	353	181		172		

Patient satisfaction with treated vs untreated breast

		Whole breast	%	Partial breast	%	P value
Baseline	Grade 0 (poor)	4	1.1	6	1.7	0.94
	Grade 1 (fair)	40	11.4	36	10.1	
	Grade 2 (good)	189	76.6	188	76.2	
	Grade 3 (excellent)	80		84		
	Grade 4 (unanswered)	38	10.8	43	12.0	
Total	708	351		357		
Year 3	Grade 0 (poor)	3	1.7	5	2.9	0.48
	Grade 1 (fair)	24	13.3	21	12.2	
Excellent/good		87	81.8	92	83.2	
		61		51		
	Grade 4 (unanswered)	6	3.3	3	1.7	
Total	353	181		172		

Recurrence, other malignancy and death

	N	Whole breast	Partial breast
Local recurrence	3	1 (true LR)	2 (true LR)
Regional recurrence	0	0	0
Distant recurrence	3	1 (†)	2
Contralateral DCIS/BC	4	2	2
Other malignancy	24	8 (3†)	16 (4†)
Dead with no recurrence	7	5	2 (1♥ with 1Gy to LADCA)



EBCC
European
Breast Cancer
Conference **10**



Multidisciplinary Innovation in Breast Cancer Care

9 - 11 MARCH
2016

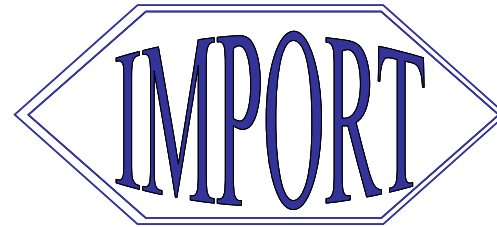
AMSTERDAM
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Organised by



ICR The Institute of
Cancer Research

Cambridge University Hospitals **NHS**
NHS Foundation Trust



Intensity modulated partial breast radiotherapy (IMPORT) for women with early breast cancer: First analysis of local relapse (CRUK/06/003)

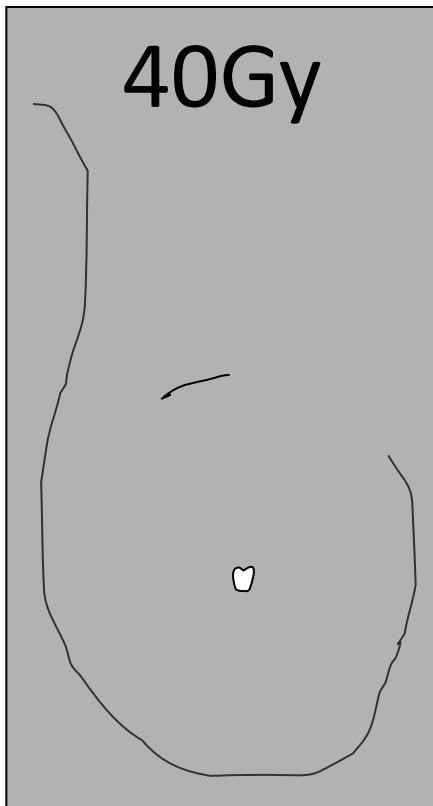
Dr Charlotte Coles

(R.Agrawal, M.L.Ah-See, H.Algurafi, A.Alhasso, A.M.Brunt, C.Chan, C.Griffin, A.Harnett, P.Hopwood, A.Kirby, E.Sawyer, I.Syndikus, J.Titley, Y.Tsang, D.Wheatley,

M.Wilcox, J.Yarnold, J.M.Bliss on behalf of the IMPORT Trial Management Group)

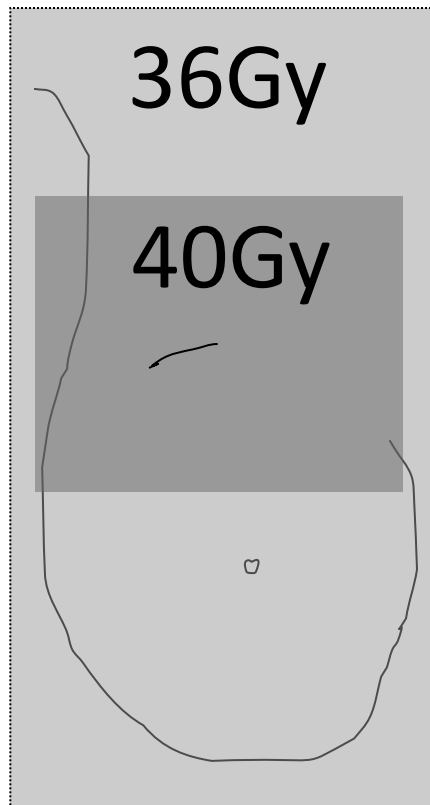
Intensity Modulated Partial Organ RT

Whole Breast



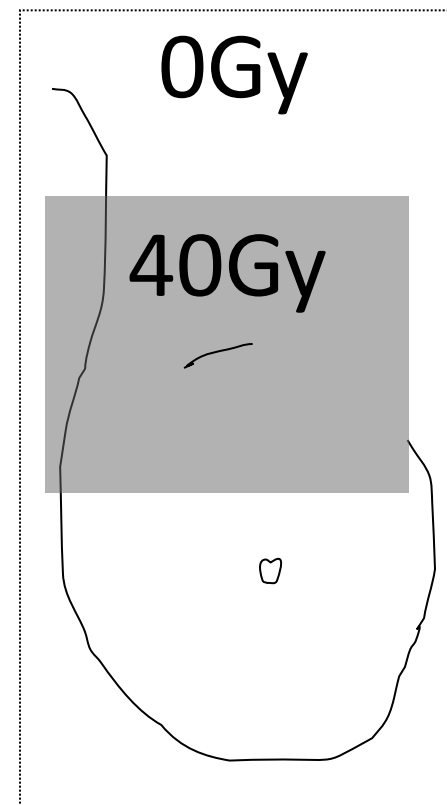
15 Fractions

Reduced Dose



15 Fractions

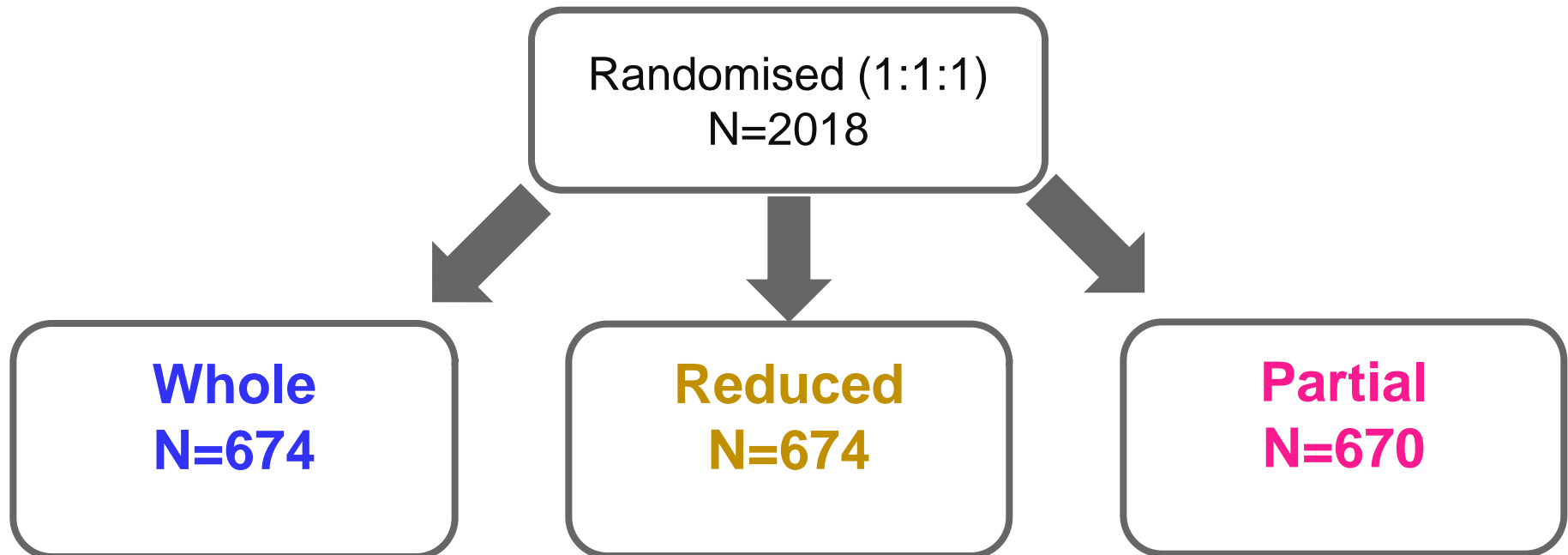
Partial Breast



15 Fractions

Trial design: Inclusion Criteria

- Breast conservation surgery ± adjuvant systemic therapy
- Age ≥ 50 , female
- Pathological tumour size ≤ 3 cm
- Invasive unifocal adenocarcinoma
- Grade I, II or III
- pN0 or pN1
- Minimum microscopic margin ≥ 2 mm



Endpoints

Primary Endpoint: LR in ipsilateral breast

Secondary Endpoints

Normal tissue effects assessed by:

- Physicians (at 1, 2, 5 & 10 years)
- Patients (EORTC QLQ-C30, BR23, HADS, EQ5D at baseline, 6 months, 1, 2 & 5 years)
- Photographs (at baseline, 2 & 5 years)

Contralateral breast tumour

Regional & distant metastases

Baseline characteristics

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

Primary endpoint: Local relapse

Median follow up: 71 months

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

Event status

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

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
- The UK IMPORT LOW trial reports no increase of local recurrences in patients treated with PBI
- Has become new DBCG standard to selected patients



THANKS

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