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Hypofractionated Radiotherapy: For All Patients?

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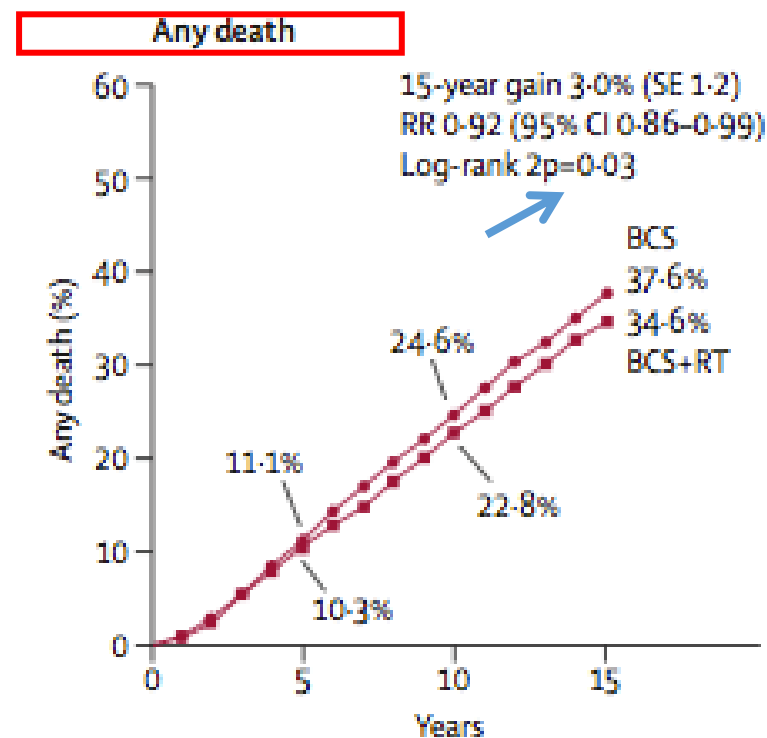
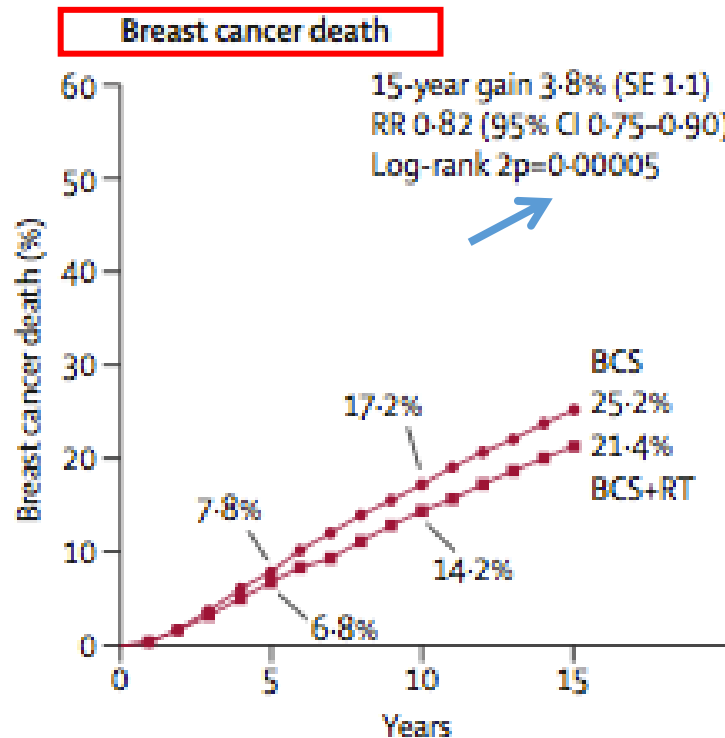
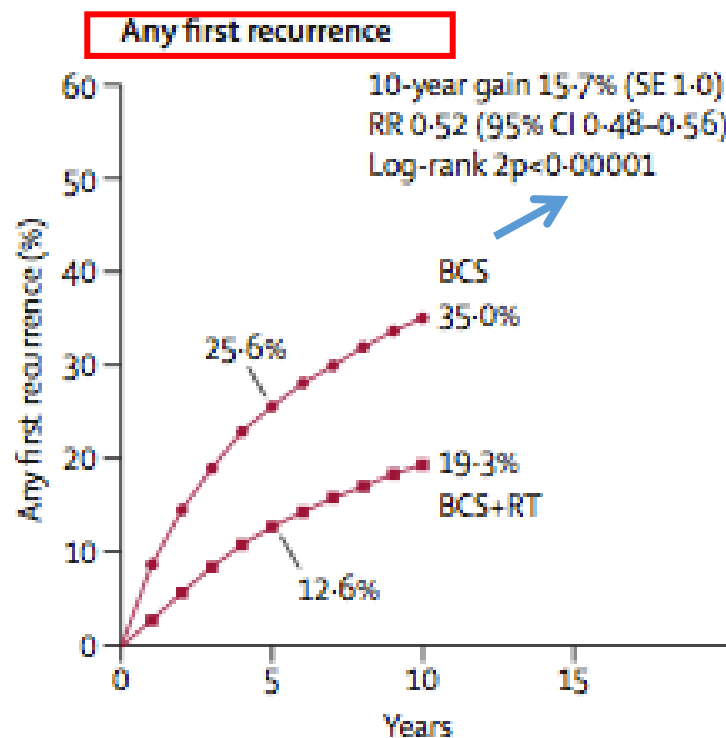
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Conflict of interest: None to declare



Effect of radiotherapy after breast-conserving surgery on 10-year recurrence and 15-year breast cancer death: meta-analysis of individual patient data for 10 801 women in 17 randomised trials

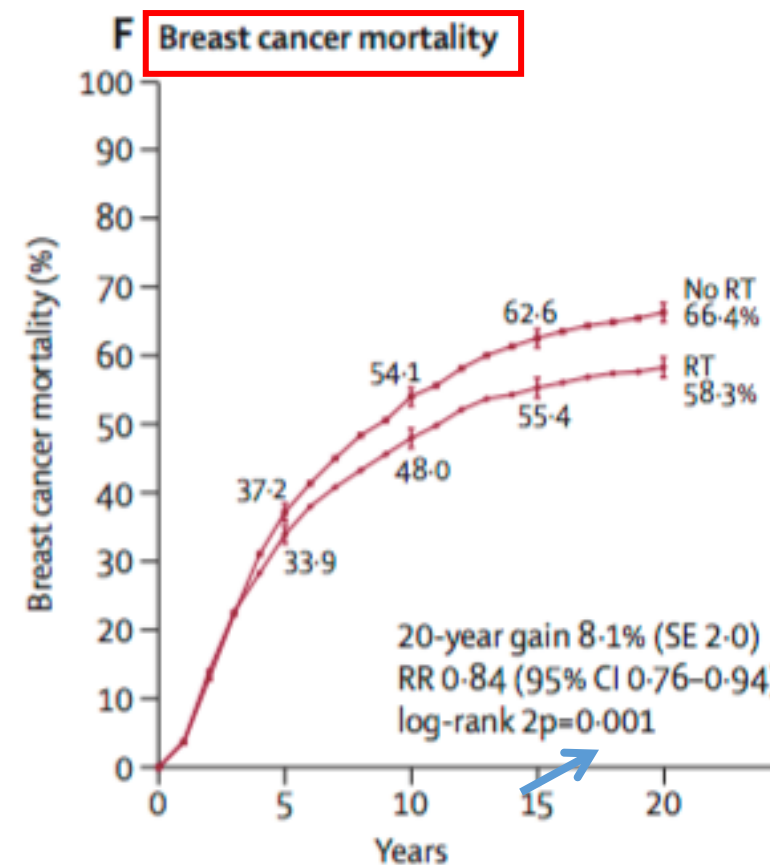
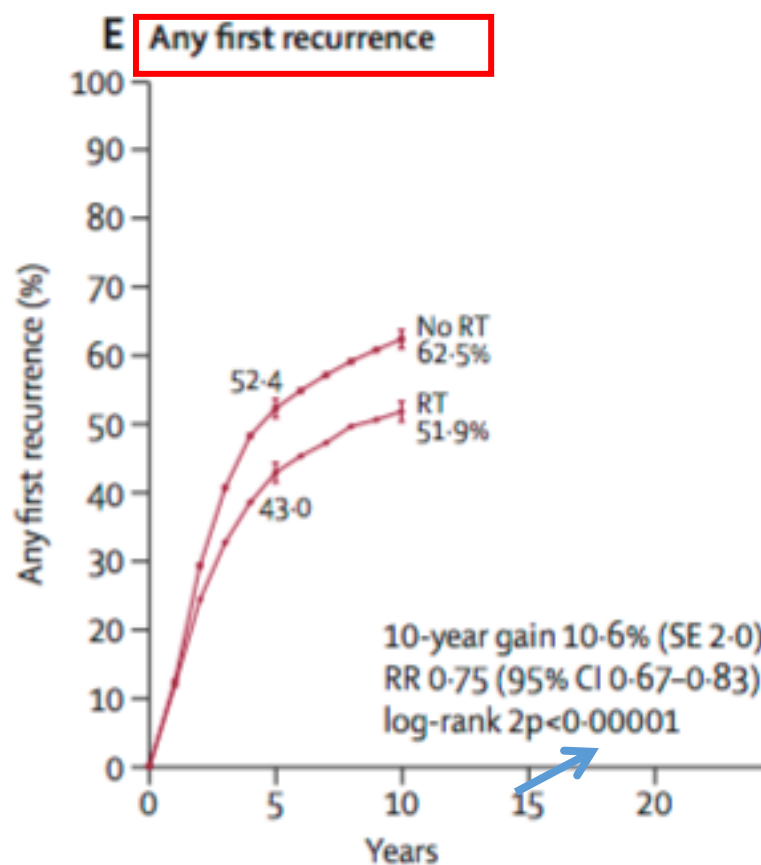
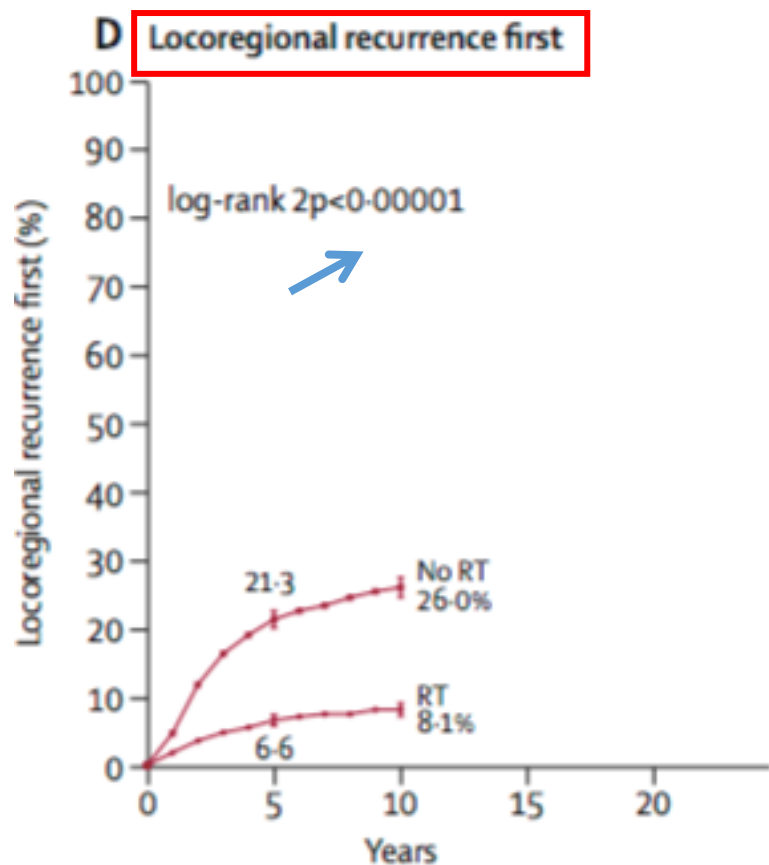
Early Breast Cancer Trialists' Collaborative Group (EBCTCG)*





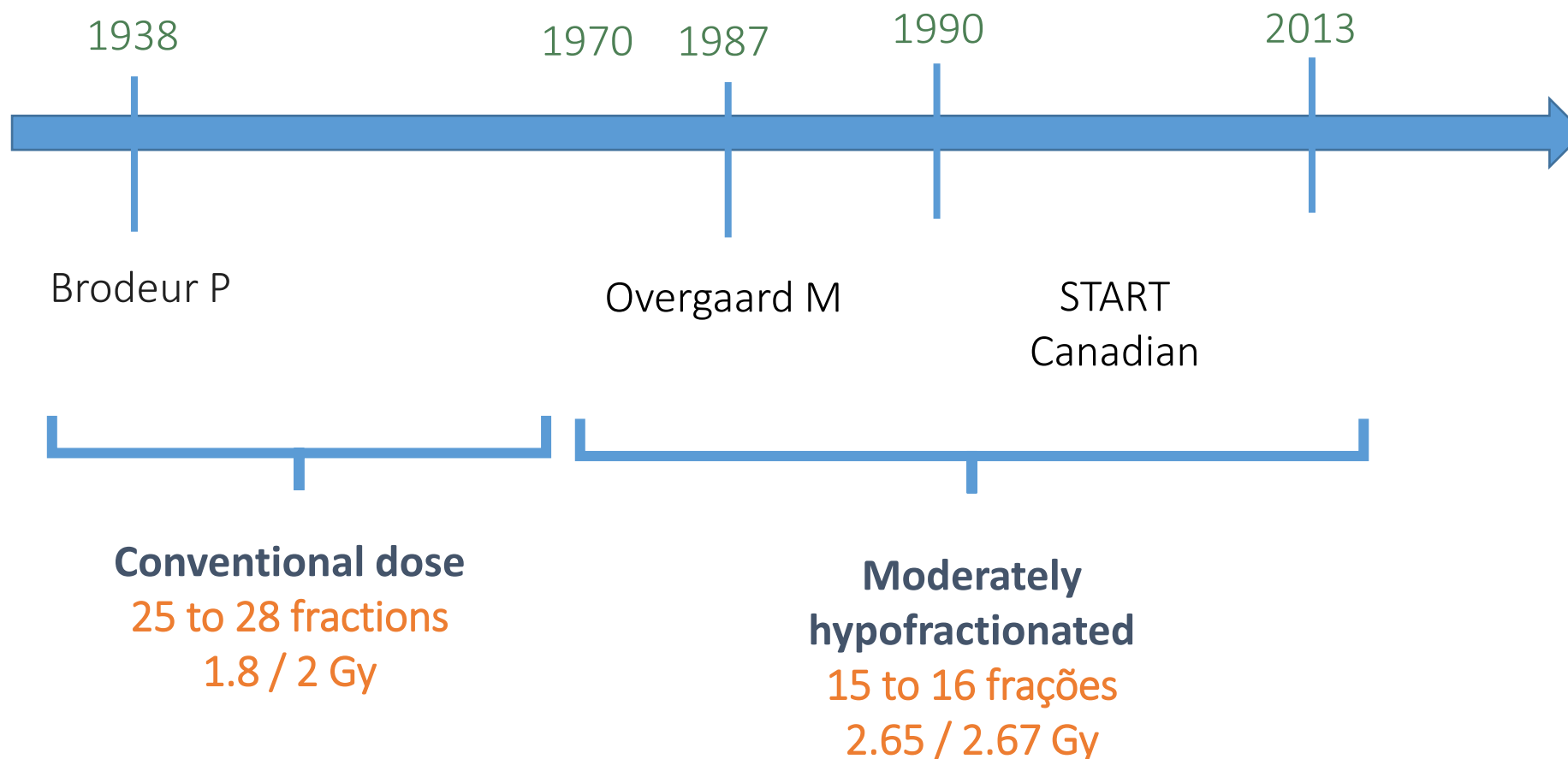
Effect of radiotherapy after mastectomy and axillary surgery on 10-year recurrence and 20-year breast cancer mortality: meta-analysis of individual patient data for 8135 women in 22 randomised trials

EBCTCG (Early Breast Cancer Trialists' Collaborative Group)*



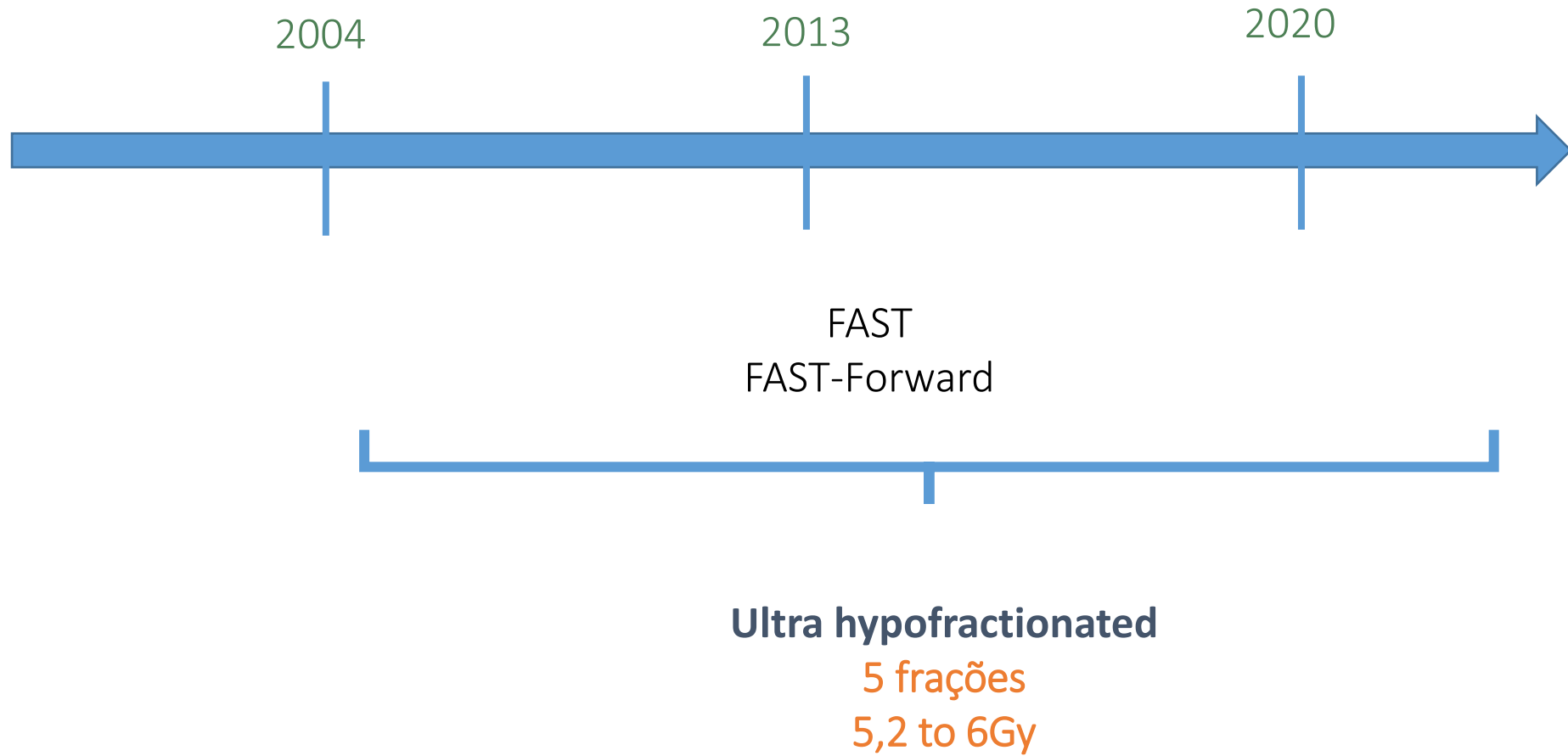


Schemes





Schemes





Moderately hypofractionated radiation therapy



Moderately hypofractionated radiation therapy

	Number of patients	Inclusion		Median follow-up - years (range)	Type of surgery N (%)		Chemotherapy N (%)	Boost N (%)	Regional nodal irradiation N (%)
		Years	Criteria		Breast-conserving surgery	Mastectomy			
Moderate Hypofractionation									
RMH/GOC611	1410	1986-1998	T1-3;N01;M0	9.7 (7.8-11.8)	1410 (100)	0	196 (14)	1051 (75)	290 (21)
START A712	2236	1998-2002	T1-3;N0-1;M0	9.3 (8.0-10.0)	1900 (85)	336 (15)	793 (35)	1152 (61)	318 (14)
START B812	2215	1999-2001	T1- 3;N0-1;M0	9.9 (7.5-10.1)	2038 (92)	177 (8)	491 (22)	875 (43)	161 (7)
OCOG514	1234	1993-1996	T1-2;N0;M0	12.0 (*)	1234 (100)	0	136 (11)	0	0
Beijing Trial	820	2008-2016	T3-T4;N2-3;M0	4.9 (3.7-6.8)	0	820 (100)	820 (100)	0	820 (100)
DBCg HYPO	1882	2009-2014	pTis-T2,N0-N1(mic);M0	7.3 (*)	1882 (100)	0	668 (35)	426 (23)	0
NCT01413269	734	2010-2015	T1-2;N0-2a;M0	6.1 (*)	734 (100)	0	477 (65)	732 (99.7)	28 (3.9)
BIG 3-07/TROG 07.01	1608	2007-2014	pTis;N0M0	6.6 (*)	1608 (100)	0	0	803 (50)	0



Moderately hypofractionated radiation therapy

	RMH/GOC	START A	START B	OCOG	Beijing Trial
Hypofractionated schedule	42.9 Gy / 13 fractions	39 Gy / 13 fractions	40 Gy / 15 fractions	42.6 Gy / 16 fractions	43.5 / 15 fractions
	39 Gy / 13 fractions	41.6 Gy / 13 fractions			
10-year local recurrence (%)					
CF-WBI arm (50 Gy / 25 fractions)	12.1	6.7	5.2	7.5	8.1*
HF-WBI (42.9 Gy / 13 fractions)	9.6	-	-	-	-
HF-WBI (39 Gy / 13 fractions)	14.8	8.1	-	-	-
HF-WBI (41.6 Gy / 13 fractions)	-	5.6	-	-	-
HF-WBI (42.6 Gy / 16 fractions)	-	-	-	7.4	-
HF-WBI (40 Gy / 15 fractions)	-	-	3.8	-	-
HF-WBI (43.5 / 15 fractions)	-	-	-	-	8.3*



Moderately hypofractionated post-operative radiation therapy for breast cancer: Systematic review and meta-analysis of randomized clinical trials

Gustavo Nader Marta^{a,b,*}, Rachel Riera^c, Rafael Leite Pacheco^d,
Ana Luiza Cabrera Martimbianco^{e,f}, Icro Meattini^g, Orit Kaidar-Person^{h,i,j}, Philip Poortmans^k

12,139 breast cancer patients

Local recurrence

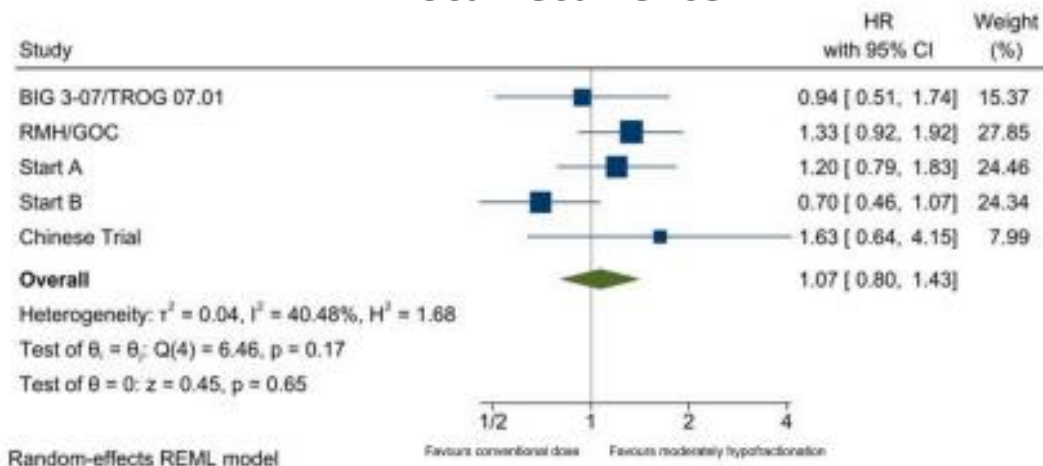


Fig. 1. Local recurrence.

Overall Survival

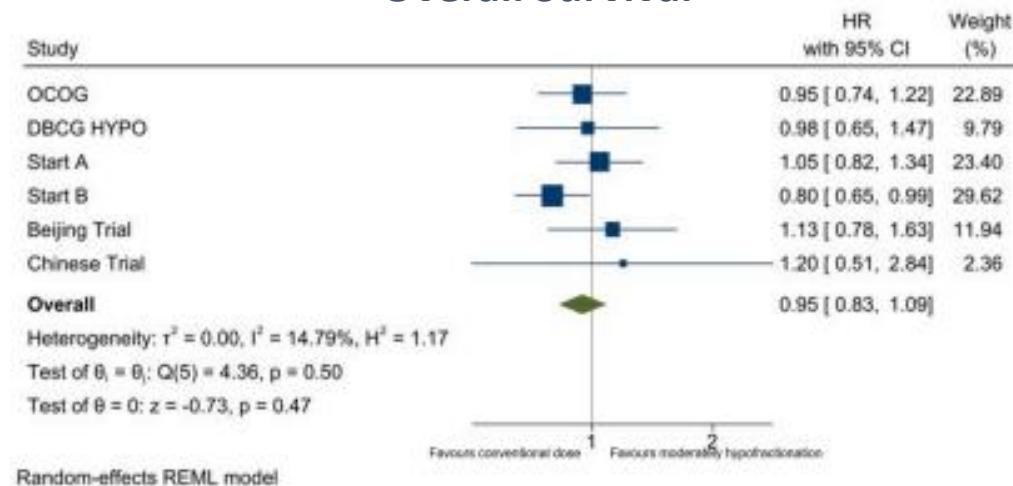
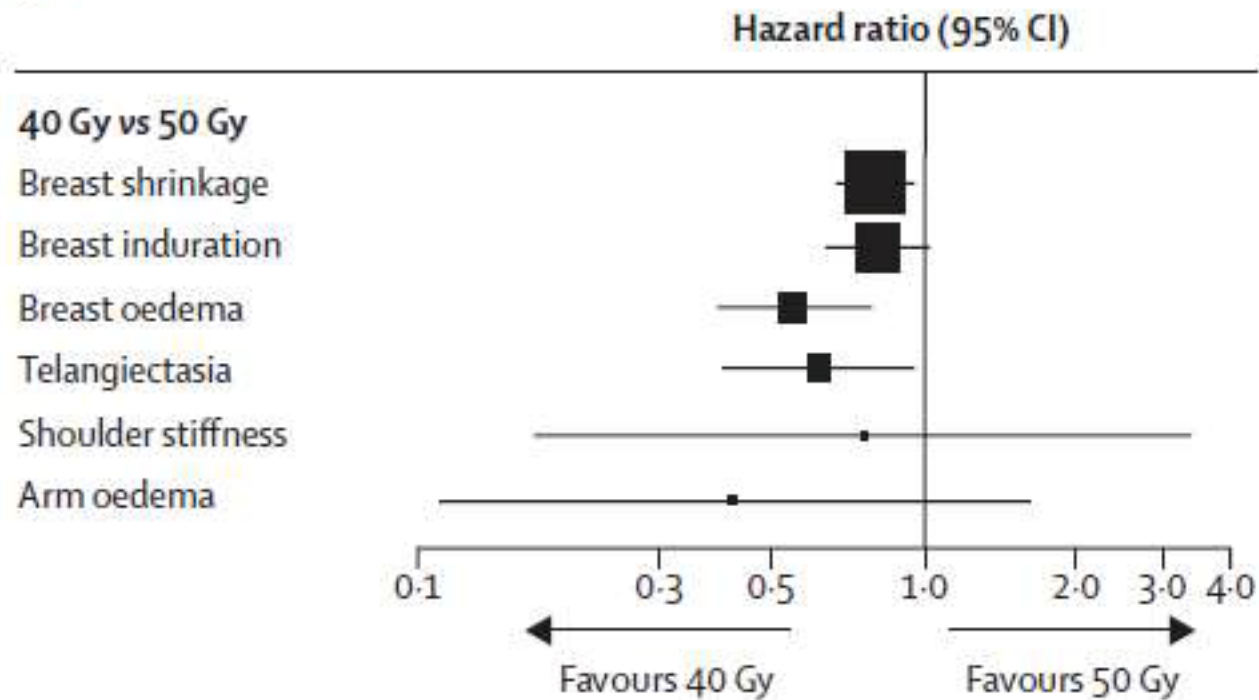
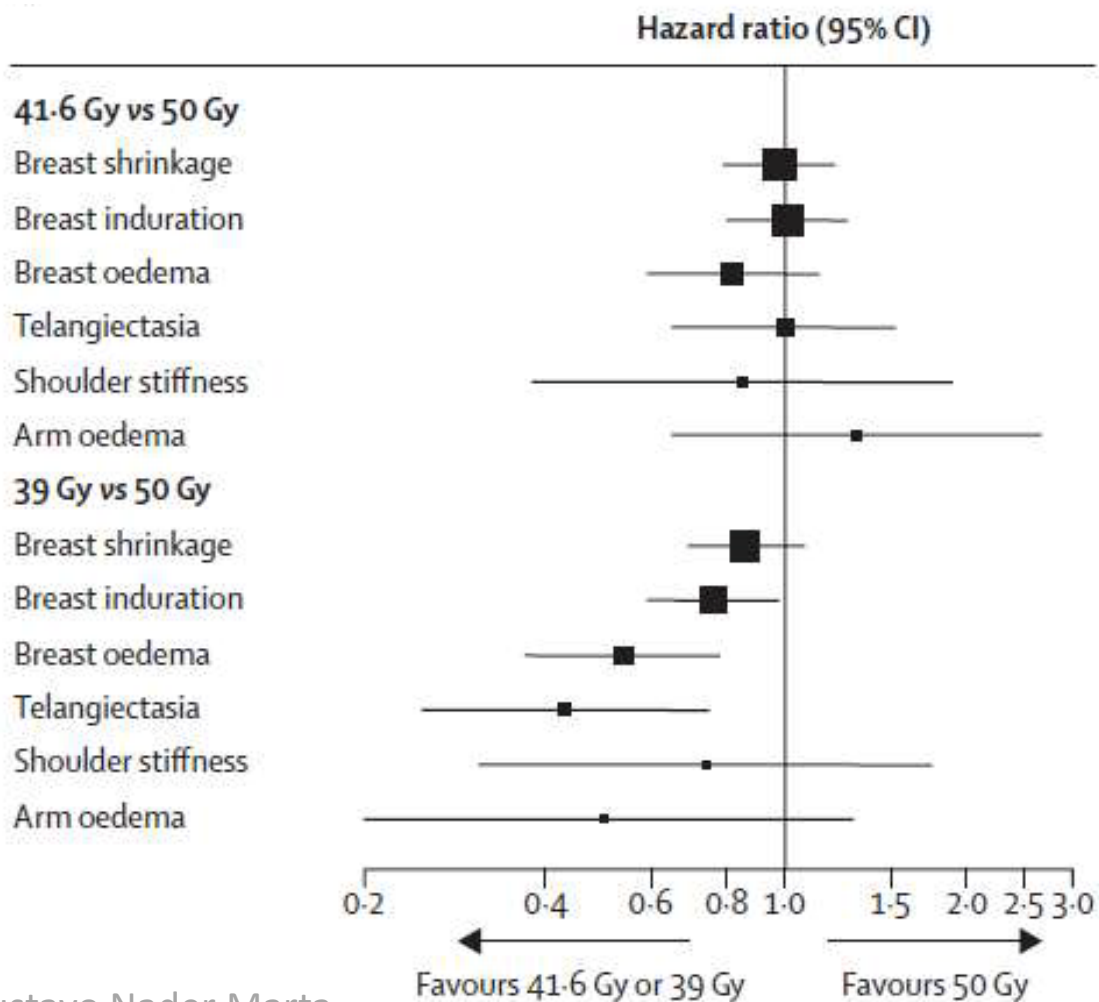


Fig. 4. Overall survival.



Start A / B (10-year follow-up)

Side effects





Issues

Moderately hypofractionated radiation therapy

Mastectomy?

Regional lymph nodes?

Reconstruction?

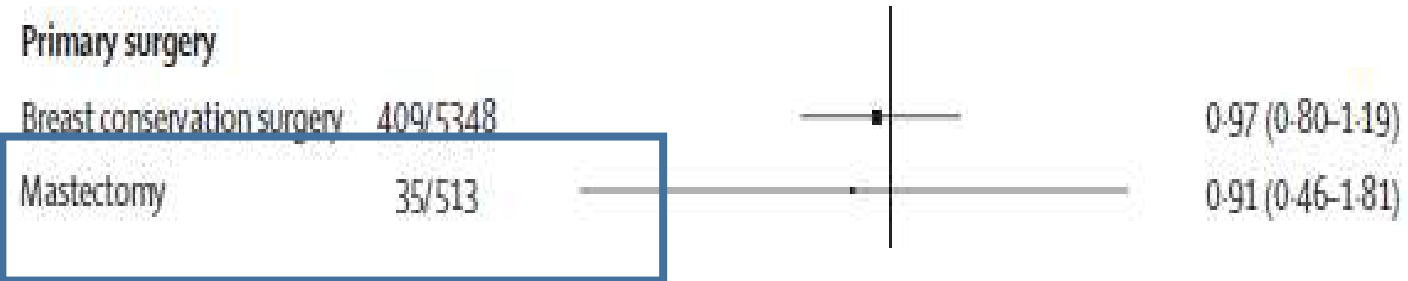


Start A / B

Mastectomy versus Breast conservation surgery

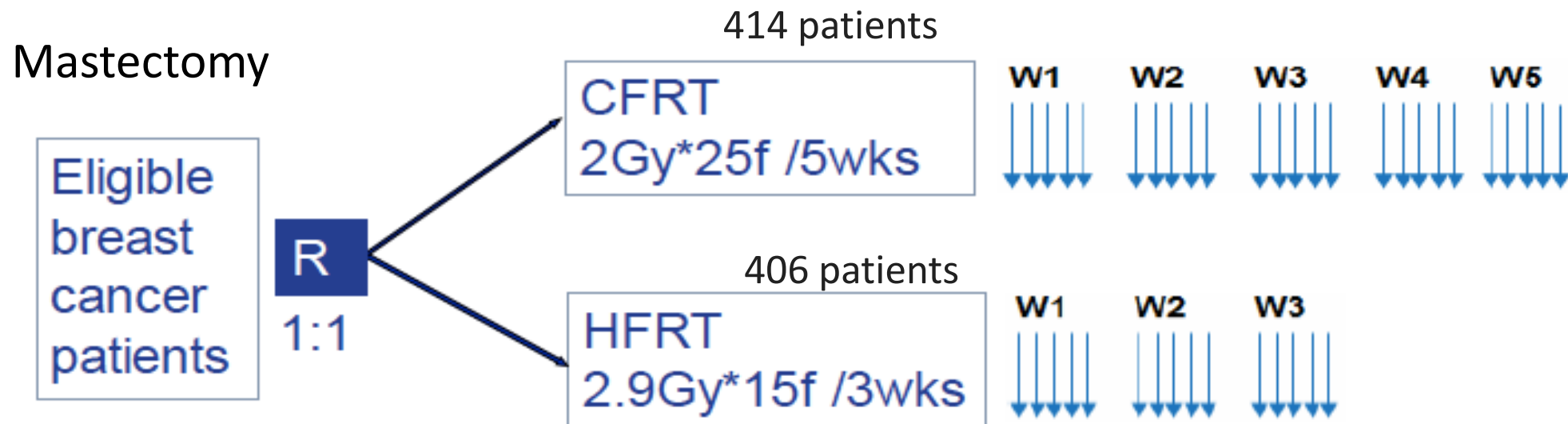
No difference

- Local control
- Side effects



	Type of primary surgery	
	Breast-conserving surgery (n=911)	Mastectomy (n=126)
Change in skin appearance since radiotherapy		
50 Gy	1	1
40 Gy	0.80 (0.63-1.03)	0.48 (0.20-1.16)
Skin problems on or in area of affected breast†		
50 Gy	1	1
40 Gy	0.86 (0.65-1.15)	2.26 (0.43-11.80)
Pain in area of affected breast†		
50 Gy	1	1
40 Gy	0.97 (0.74-1.26)	0.63 (0.22-1.79)
Oversensitivity in area of affected breast†		
50 Gy	1	1
40 Gy	1.18 (0.91-1.53)	0.55 (0.19-1.54)
Swelling in area of affected breast†		
50 Gy	1	1
40 Gy	0.89 (0.62-1.29)	4.18 (0.61-28.37)
Arm or shoulder pain†		
50 Gy	1	1
40 Gy	1.03 (0.83-1.29)	0.92 (0.47-1.80)
Shoulder stiffness†		
50 Gy	1	1
40 Gy	0.94 (0.70-1.25)	1.10 (0.47-2.58)
Difficulty in raising or moving arm sideways†		
50 Gy	1	1
40 Gy	0.99 (0.73-1.35)	0.79 (0.35-1.77)
Arm or hand swelling†		
50 Gy	1	1
40 Gy	1.12 (0.78-1.60)	0.65 (0.20-2.17)

Phase 3 non-inferiority study



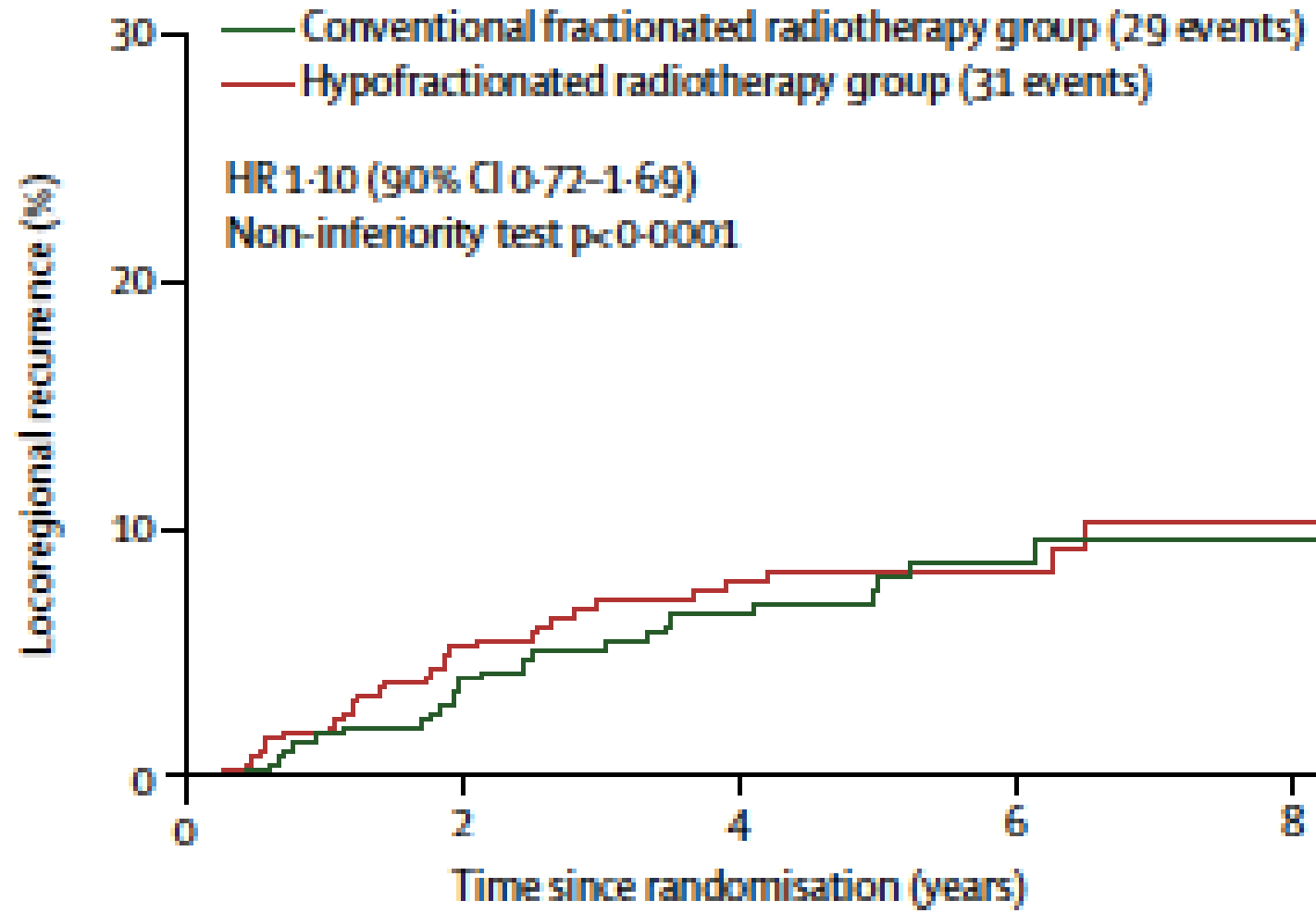
- T3-T4 e/ ou ≥ 4 LN +

- chest wall + regional lymph nodes

Primary outcome: locoregional recurrence at 5 years

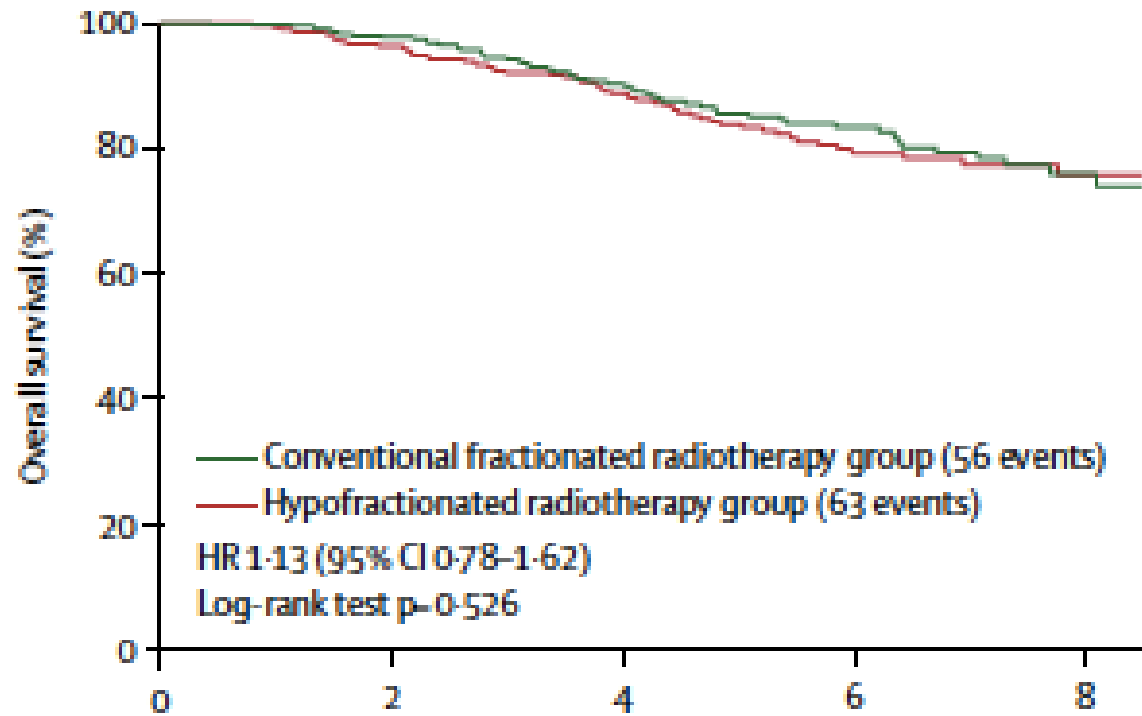


Locoregional recurrence

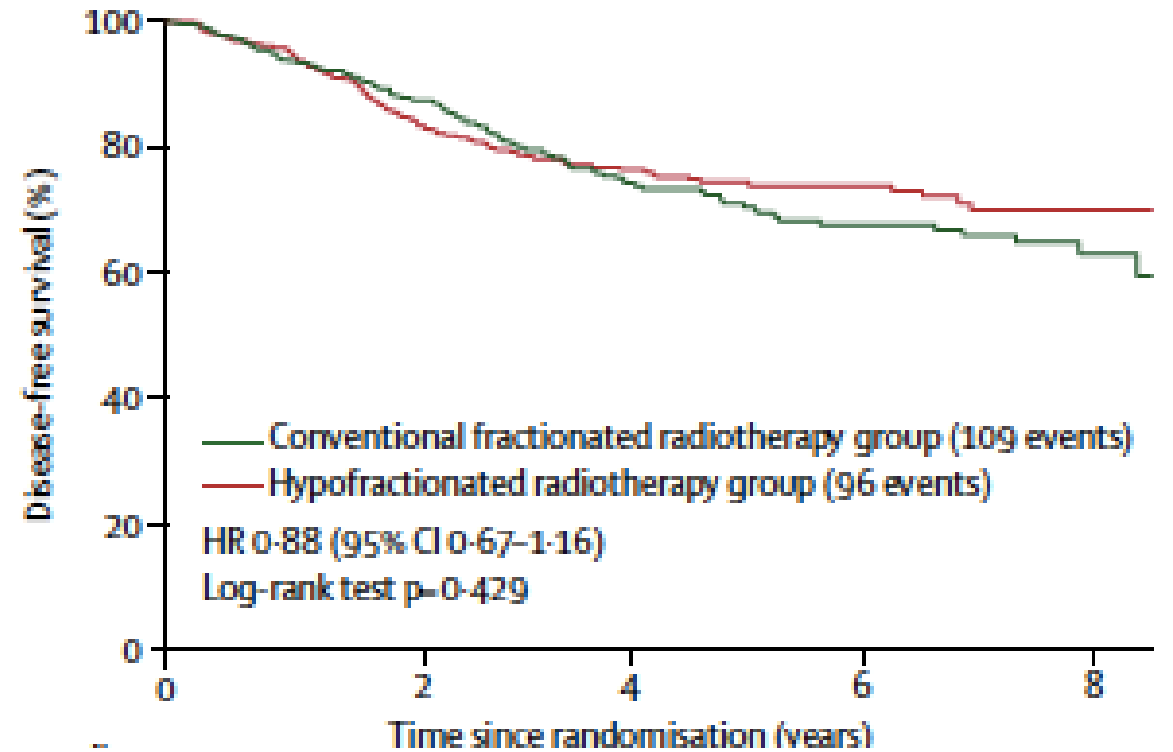




Overall Survival



Disease-Free Survival





Side effects

	Conventional fractionated radiotherapy group (n=409)	Hypofractionated radiotherapy group (n=401)	p value
Acute toxicity			
Skin toxicity	--	--	<0.0001
Grade 1-2	357 (87%)	351 (89%)	--
Grade 3	32 (8%)	14 (3%)	--
Pneumonitis	--	--	0.278
Grade 1	62 (15%)	61 (15%)	--
Grade 2	7 (2%)	14 (3%)	--
Grade 3	--	--	--
Late toxicity			
Skin toxicity	--	--	0.669
Grade 1-2	90 (22%)	86 (21%)	--
Grade 3	0	1 (<1%)	--
Lymphoedema	--	--	0.961
Grade 1-2	81 (20%)	78 (19%)	--
Grade 3	3 (1%)	3 (1%)	--
Shoulder dysfunction	--	--	0.734
Grade 1-2	13 (3%)	7 (2%)	--
Grade 3	1 (<1%)	1 (<1%)	--
Lung fibrosis	--	--	0.081
Grade 1-2	42 (10%)	62 (15%)	--
Grade 3	0	0	--
Ischaemic heart disease	--	--	0.569
Grade 1-2	1 (<1%)	3 (1%)	--
Grade 3	3 (1%)	4 (1%)	--

Data are n (%). The χ^2 test was used to calculate p values. No grade 4 events or deaths due to adverse effects were reported.

Table 2: Adverse events



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Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com



Original article

Late normal tissue effects in the arm and shoulder following lymphatic radiotherapy: Results from the UK START (Standardisation of Breast Radiotherapy) trials

Joanne S Haviland^{a,*}, Mariella Mannino^b, Clare Griffin^a, Nuria Porta^a, Mark Sydenham^a, Judith M. Bliss^{a,1}, John R. Yarnold^{c,1}, on behalf of the START Trialists' Group

Haviland JS, et al. Radiother Oncol. 2018;126(1):155-162.



UK trials

- Royal Marsden Hospital study = 385
- START-A = 318
- START-B = 161

Total: 864 patients



- Patient-assessed moderate/marked normal tissue effects

Schedule	Total moderate/ marked events (n/total, %)	Estimated cumulative incidence by 5 years, % (95%CI)	Hazard ratio (95% CI) ¹	P-value ²	Prevalence of moderate/ marked events at 5 years, n/total (%)	P-value ³
Arm/shoulder pain						
START-A						
50 Gy	30/95 (31.6)	32.3 (23.3-43.7)	1		12/65 (18.5)	
41.6 Gy	24/78 (30.8)	31.4 (22.1-43.6)	1.03 (0.60-1.77)	0.92	5/58 (8.6)	0.13
39 Gy	23/77 (29.9)	30.8 (21.4-43.0)	0.96 (0.56-1.66)	0.89	7/58 (12.1)	0.45
START-B						
50 Gy	13/46 (28.3)	29.7 (18.0-46.6)	1		2/28 (7.1)	
40 Gy	15/52 (28.9)	23.6 (14.1-37.9)	0.94 (0.44-2.00)	0.87	4/35 (11.4)	0.68
Swelling in arm or hand						
START-A						
50 Gy	15/95 (15.8)	14.2 (8.3-23.8)	1		6/65 (9.2)	
41.6 Gy	13/78 (16.7)	18.2 (11.0-29.3)	1.01 (0.46-2.18)	0.99	1/58 (1.7)	0.12
39 Gy	13/77 (16.9)	16.1 (9.2-27.3)	1.15 (0.54-2.47)	0.72	6/58 (10.3)	>0.99
START-B						
50 Gy	5/46 (10.9)	9.5 (3.7-23.3)	1		1/28 (3.6)	
40 Gy	3/51 (5.9)	6.0 (2.0-17.4)	0.55 (0.13-2.36)	0.42	0/36 (0)	0.44
Difficulty in raising arm						
START-A						
50 Gy	17/95 (17.9)	18.8 (11.9-29.0)	1		3/65 (4.6)	
41.6 Gy	9/78 (11.5)	9.5 (4.7-19.0)	0.63 (0.28-1.43)	0.27	2/58 (3.4)	>0.99
39 Gy	11/77 (14.3)	15.4 (8.8-26.1)	0.83 (0.39-1.80)	0.64	2/58 (3.4)	>0.99
START-B						
50 Gy	8/46 (17.4)	18.6 (9.2-35.4)	1		3/28 (10.7)	
40 Gy	7/51 (13.7)	10.1 (4.3-22.6)	0.64 (0.23-1.78)	0.40	3/36 (8.3)	>0.99
Shoulder stiffness						
START-A						
50 Gy	25/96 (26.0)	27.5 (19.0-38.7)	1		8/65 (12.3)	
41.6 Gy	15/78 (19.2)	17.7 (10.6-28.5)	0.75 (0.39-1.43)	0.39	4/58 (6.9)	0.37
39 Gy	10/77 (13.0)	14.0 (7.8-24.4)	0.52 (0.25-1.11)	0.09	2/58 (3.4)	0.10
START-B						
50 Gy	5/46 (10.9)	12.0 (5.2-26.5)	1		1/28 (3.6)	>0.99
40 Gy	7/52 (13.5)	14.2 (7.0-27.6)	0.88 (0.26-2.97)	0.83	2/36 (5.6)	>0.99



- Physician-assessed moderate/ marked normal tissue effects in the arm or shoulder

Schedule	Total moderate/ marked events (n/total, %)	Estimated cumulative incidence by 5 years, % (95%CI)	Estimated cumulative incidence by 10 years, % (95%CI)	Hazard ratio (95% CI)	P-value ¹	Prevalence of moderate/ marked events at 5 years, n/total (%)	P-value ²	Prevalence of moderate/ marked events at 10 years, n/total (%)	P-value ²
Arm oedema									
START-pilot									
50 Gy	8/102 (7.8)	6.6 (3.0-14.1)	8.2 (4.0-16.7)	1		0/57 (0)		1/36 (2.8)	
42.9 Gy	14/99 (14.1)	13.9 (8.1-23.3)	17.0 (10.4-27.3)	1.95 (0.82-4.66)	0.13	2/56 (3.6)	0.24	2/27 (7.4)	0.57
39 Gy	5/97 (5.2)	3.6 (1.2-10.9)	3.6 (1.2-10.9)	0.63 (0.21-1.93)	0.42	2/63 (3.2)	>0.99	1/33 (3.0)	0.19
START-A									
50 Gy	15/117 (12.8)	12.8 (7.6-12.2)	16.3 (9.9-26.2)	1		2/80 (2.5)		1/27 (3.7)	
41.6 Gy	16/95 (16.8)	11.9 (6.6-21.0)	22.5 (14.1-34.7)	1.31 (0.65-2.66)	0.45	3/63 (4.8)	0.65	2/32 (6.3)	>0.99
39 Gy	6/92 (6.5)	6.4 (14.1-34.7)	8.2 (3.7-17.6)	0.50 (0.20-1.30)	0.16	2/61 (3.3)	>0.99	2/29 (6.9)	>0.99
START-B									
50 Gy	7/73 (9.6)	6.0 (2.3-15.3)	13.5 (6.4-27.0)	1		0/51 (0)		0/27 (0)	
40 Gy	3/81 (3.7)	2.8 (0.7-10.7)	4.7 (1.5-14.0)	0.42 (0.11-1.63)	0.21	2/57 (3.5)	0.50	0/20 (0)	-
Shoulder stiffness									
START-pilot									
50 Gy	13/102 (12.8)	12.3 (7.2-20.7)	13.7 (8.2-22.6)	1		1/57 (1.8)		0/35 (0)	
42.9 Gy	34/99 (34.3)	33.4 (24.7-44.1)	36.6 (27.3-47.7)	3.07 (1.62-5.83)	0.001	1/56 (1.8)	0.50	2/27 (7.4)	>0.99
39 Gy	14/97 (14.4)	11.9 (6.8-20.6)	14.9 (8.9-24.5)	1.09 (0.51-2.31)	0.83	5/63 (7.9)	0.21	1/33 (3.0)	0.48
START-A									
50 Gy	14/117 (12.0)	8.8 (4.7-16.4)	17.5 (10.2-29.1)	1		1/80 (1.3)		1/27 (3.7)	
41.6 Gy	10/95 (10.5)	7.1 (3.3-15.2)	14.8 (8.0-26.6)	0.85 (0.38-1.91)	0.69	0/63 (0)	>0.99	0/32 (0)	0.46
39 Gy	8/92 (8.7)	7.5 (3.4-16.0)	11.0 (5.6-21.0)	0.74 (0.31-1.76)	0.49	0/61 (0)	>0.99	0/29 (0)	0.48
START-B									
50 Gy	4/73 (5.5)	2.9 (0.7-11.0)	8.2 (2.9-21.8)	1		1/51 (2.0)	>0.99	1/27 (3.7)	>0.99
40 Gy	3/81 (3.7)	3.1 (0.8-11.9)	3.1 (0.8-11.9)	0.76 (0.17-3.39)	0.72	1/57 (1.8)	>0.99	1/20 (5.0)	>0.99



Hypofractionated Adjuvant Radiation Therapy Is Effective for Patients With **Lymph Node–Positive** Breast Cancer: A Population-Based Analysis

Canada: *prospective database*

5487 patients (4006 HF / 1481 CF)

High risk patients

Table 2 Multivariable HRs for selected outcomes of hypofractionated vs conventional fractionated regional nodal radiation therapy for the entire cohort and by high-risk features

Feature	Survival outcome	HR (HF:CF)	95% CI	P value
Entire cohort (n = 5487)	LRRFS	0.87	0.59-1.27	.5
	DRFS	0.90	0.76-1.06	.2
	BCSS	0.92	0.76-1.10	.4
Grade 3 (n = 2639)	LRRFS	0.76	0.48-1.2	.3
	DRFS	0.91	0.74-1.12	.4
	BCSS	0.93	0.74-1.17	.5
≥4 positive LN (n = 1617)	LRRFS	0.86	0.46-1.60	.6
	DRFS	1.01	0.79-1.29	.9
	BCSS	1.02	0.77-1.34	.9
HER2+ (n = 773)	LRRFS	0.50	0.22-1.12	.09
	DRFS	1.09	0.76-1.58	.6
	BCSS	1.22	0.80-1.85	.4
ER– and HER2– (n = 419)	LRRFS	Insufficient events		
	DRFS	0.70	0.46-1.08	.1
	BCSS	0.71	0.46-1.10	.1

Abbreviations: BCSS = breast cancer–specific survival; CF = conventional fractionation; DRFS = distant recurrence-free survival; ER– = estrogen receptor negative; HER2+ = HER2 overexpression; HER2– = HER2 not overexpressed; HF = hypofractionation; HR = hazard ratio; LN = lymph nodes positive; LRRFS = locoregional recurrence-free survival.

Conclusions: This large, population-based analysis with long-term follow-up after locoregional RT demonstrated that modest HF provides similar breast cancer-specific outcomes compared with CF. HF is an effective option for patients with stage I to III breast cancer receiving nodal RT.



After Breast reconstruction?

- All toxicities: same or better with hypofractionation
 - - skin retraction
 - - fibrosis
- What is the evidence for using 25 x 200cGy?



After Breast reconstruction?

Can Med Assoc J. 1938 May;38(5):467-9.

RADIOTHERAPY OF CANCER OF THE BREAST.

Brodeur P¹.



Acta Chir Belg. 1980 Mar-Apr;79(2):125-9.

Reconstruction of the breast.

Bostwick J.



After Breast reconstruction?

Moderately hypofractionated

Prospective Phase II Trial - USA

The total rate of implant loss or failure:

24% (9 of 38)

Khan AJ, et al. J Clin Oncol 2017; 35(18): 2037-43.

Convencional

*Swedish multicenter cohort study
725 patients*

5-year implant failure rates

10.4 % non-irradiated

28.2 % previously irradiated

25.2% postoperatively irradiated

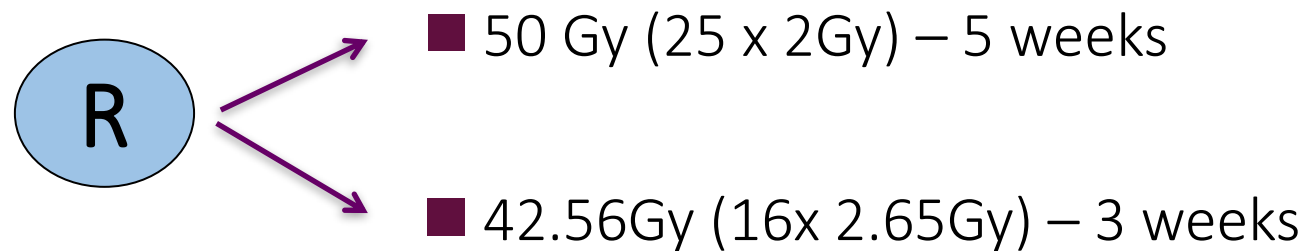
Eriksson M, et al. Breast Cancer Res Treat 2013; 142(3): 591-601.



After Breast reconstruction?

Patient-reported and toxicity results from the FABREC study: A multicenter randomized trial of hypofractionated vs. conventionally fractionated postmastectomy radiation therapy after implant-based reconstruction

400 patients; 16 U.S. health centers: mastectomies followed by immediate breast reconstruction using a tissue expander or implant.



Similar levels of physical well-being six months after treatment, the primary endpoint of the study (p=0.71)

Hypofractionated radiation:

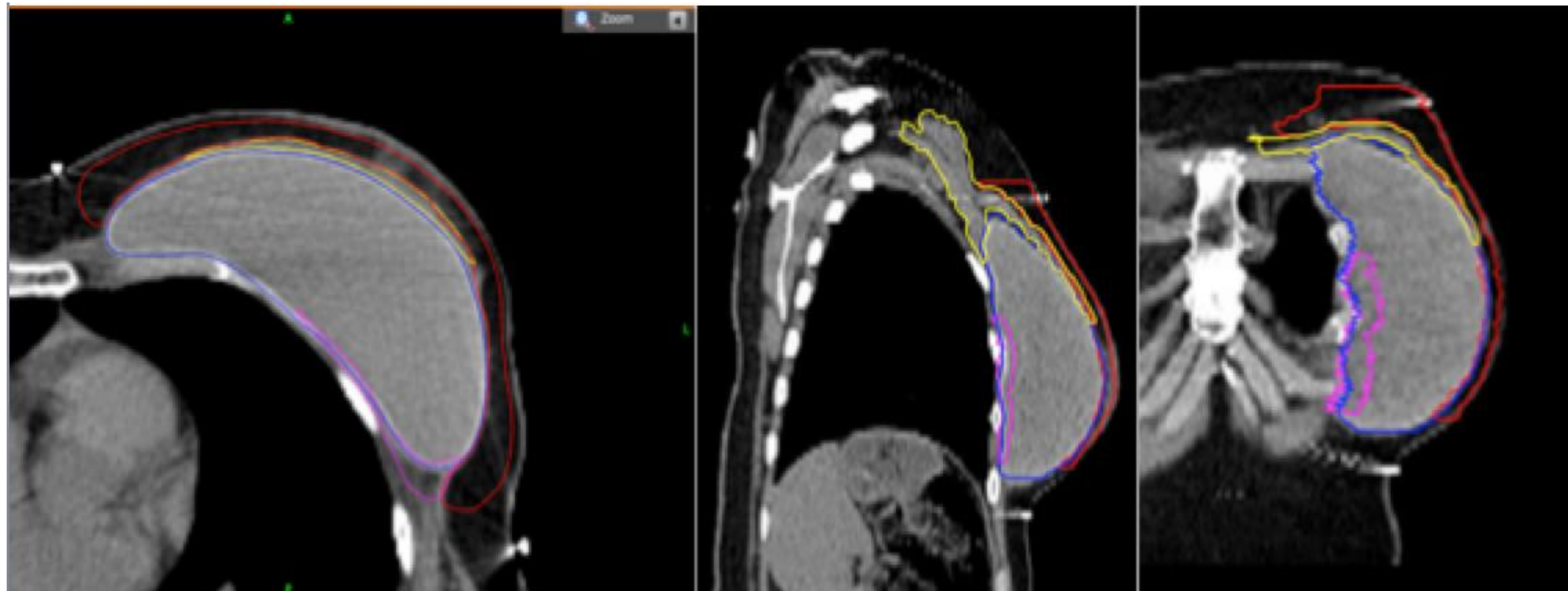
- Higher energy levels (p=0.02)
- Treatment breaks were significantly fewer (2.7% vs. 7.7% p=0.03)
- Improvements in QOL scores among younger patients (p=0.045)

No differences in the rates of recurrence or side effects between the two groups!

ESTRO ACROP consensus guideline for target volume delineation in the setting of postmastectomy radiation therapy after implant-based immediate reconstruction for early stage breast cancer



Orit Kaidar-Person^{a,*1}, Birgitte Vrou Offersen^{b,1}, Sandra Hol^c, Meritxell Arenas^d, Cynthia Aristei^e, Celine Bourcier^f, Maria Joao Cardoso^g, Boon Chua^h, Charlotte E. Colesⁱ, Tine Engberg Damsgaard^j, Dorota Gabrys^k, Reshma Jagsi^l, Rachel Jimenez^m, Anna M. Kirbyⁿ, Carine Kirkove^o, Youlia Kirova^p, Vassilis Kouloulis^q, Tanja Marinko^r, Icro Meattini^s, Ingvil Mjaaland^t, Gustavo Nader Marta^{u,v}, Petra Witt Nystrom^w, Elzbieta Senkus^x, Tanja Skyttä^y, Tove F. Tvedskov^z, Karolien Verhoeven^{aa}, Philip Poortmans^{ab}





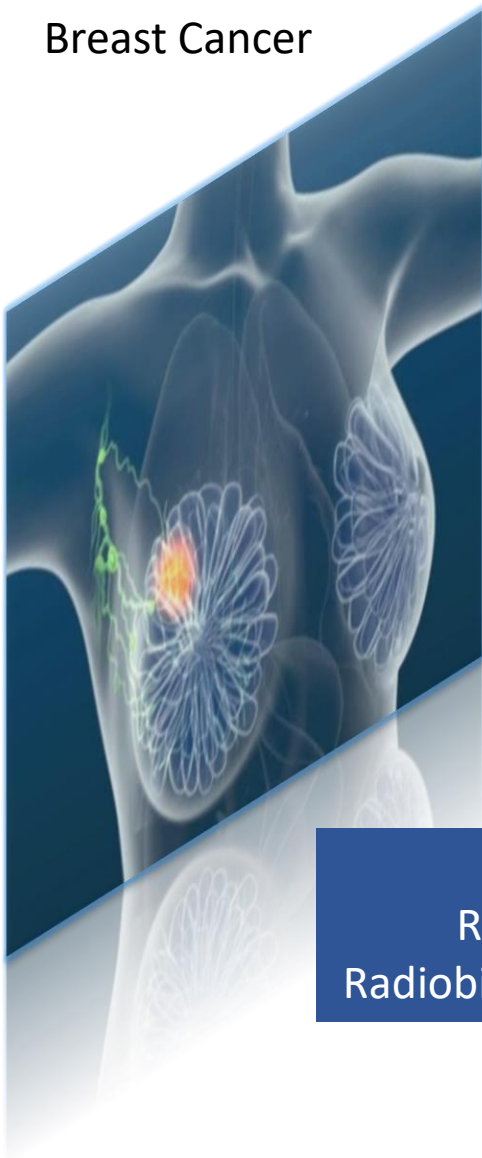
THE LANCET **Oncology**

Moderately hypofractionated breast radiation therapy: is more evidence needed?

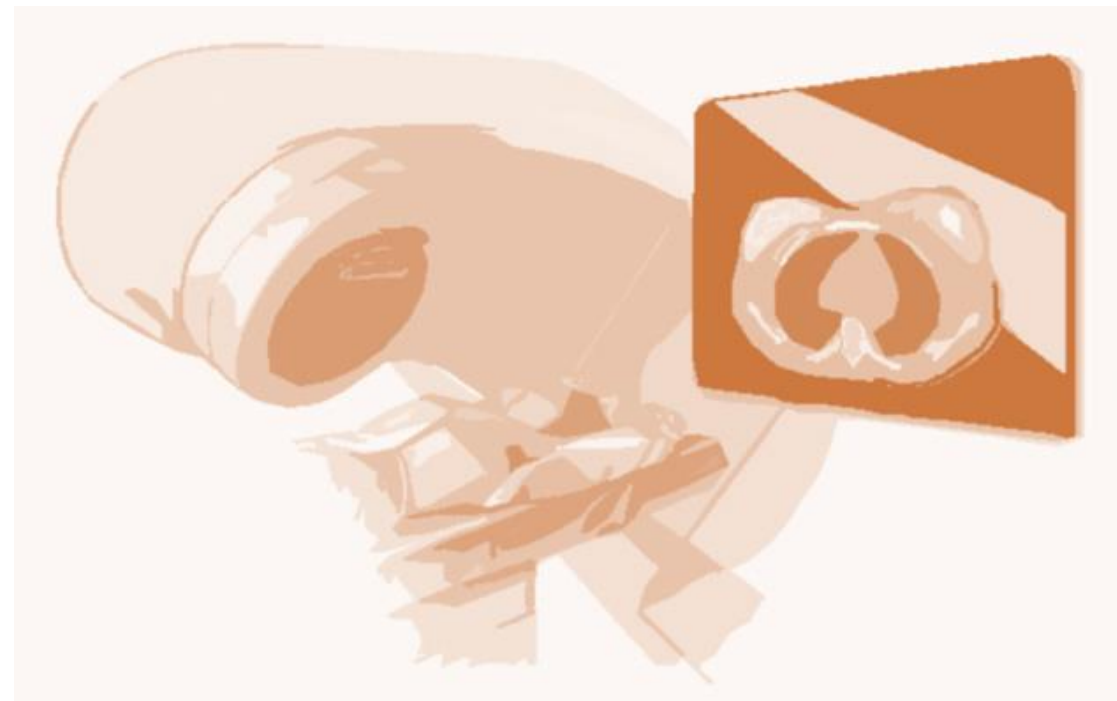
Gustavo N Marta and Philip Poortmans



Breast Cancer



Post-operative Radiation Therapy



Clinical trials
Retrospective data
Radiobiological considerations



Moderately Hypofractionated Radiation Therapy

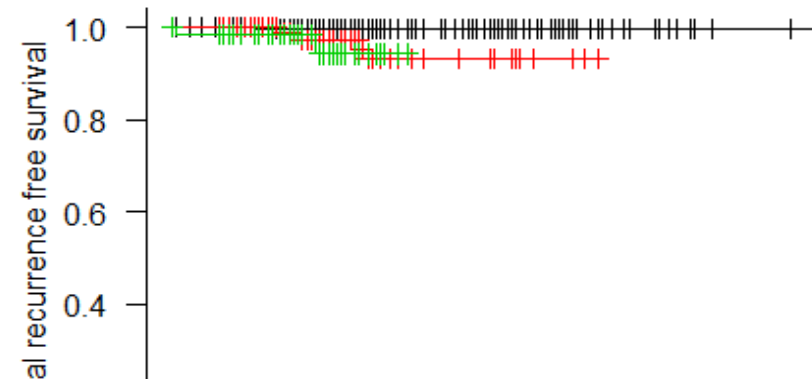
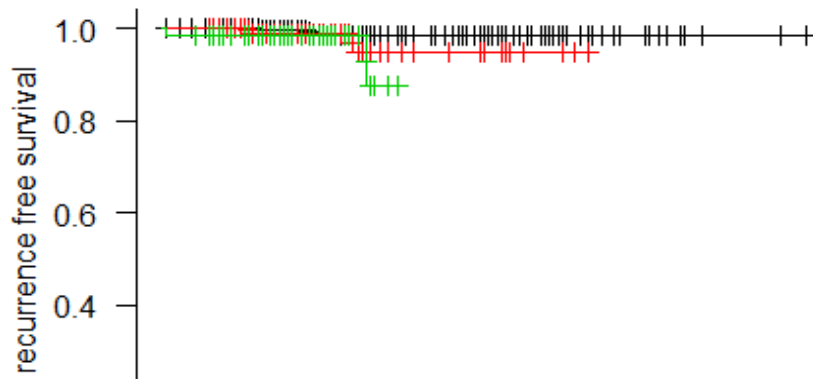
Efficient, convenient and safe for all indications
including regional nodal irradiation and chest wall with or
without breast reconstruction



Moderately hypofractionated radiation therapy for breast cancer: A Brazilian cohort study

Gabriela S.M. de Siqueira,^a Samir A. Hanna,^a Larissa F. de Moura,^a Fabiana Accioli Miranda,^a Heloísa de Andrade Carvalho,^{a,b} and Gustavo Nader Marta^{a,b*}

670 patients (stages I-III with RT of drainages and reconstruction and chemotherapy)



Acute and late side effects profile were mild and only 2.9% of patients developed grade 3 dermatitis. Among patients with breast implants 11.4% had capsular contracture.

I	392	91	20	0
II	112	15	0	0
III	60	2	0	0

I	392	91	20	0
II	111	15	0	0
III	60	2	0	0



The Early Breast Cancer Trialists' Collaborative Group (EBCTCG)



MRC Population
Health Research
Unit

The list of writing committee members external to EBCTCG is below:

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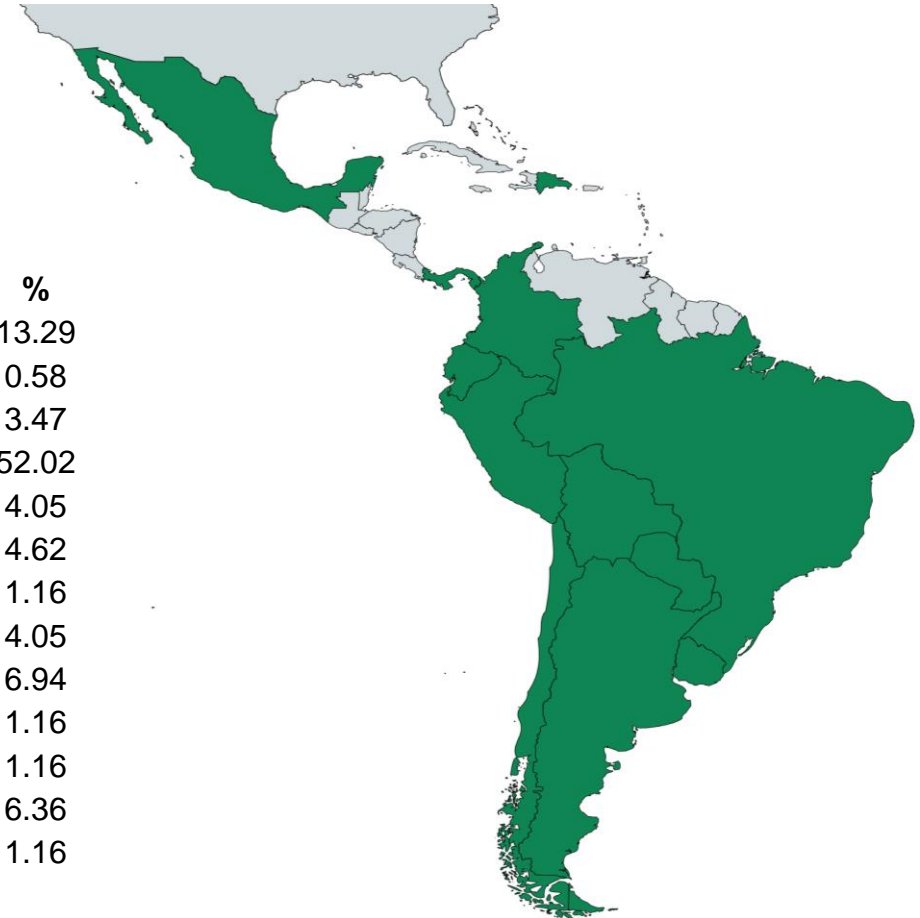
Jo Haviland - UK



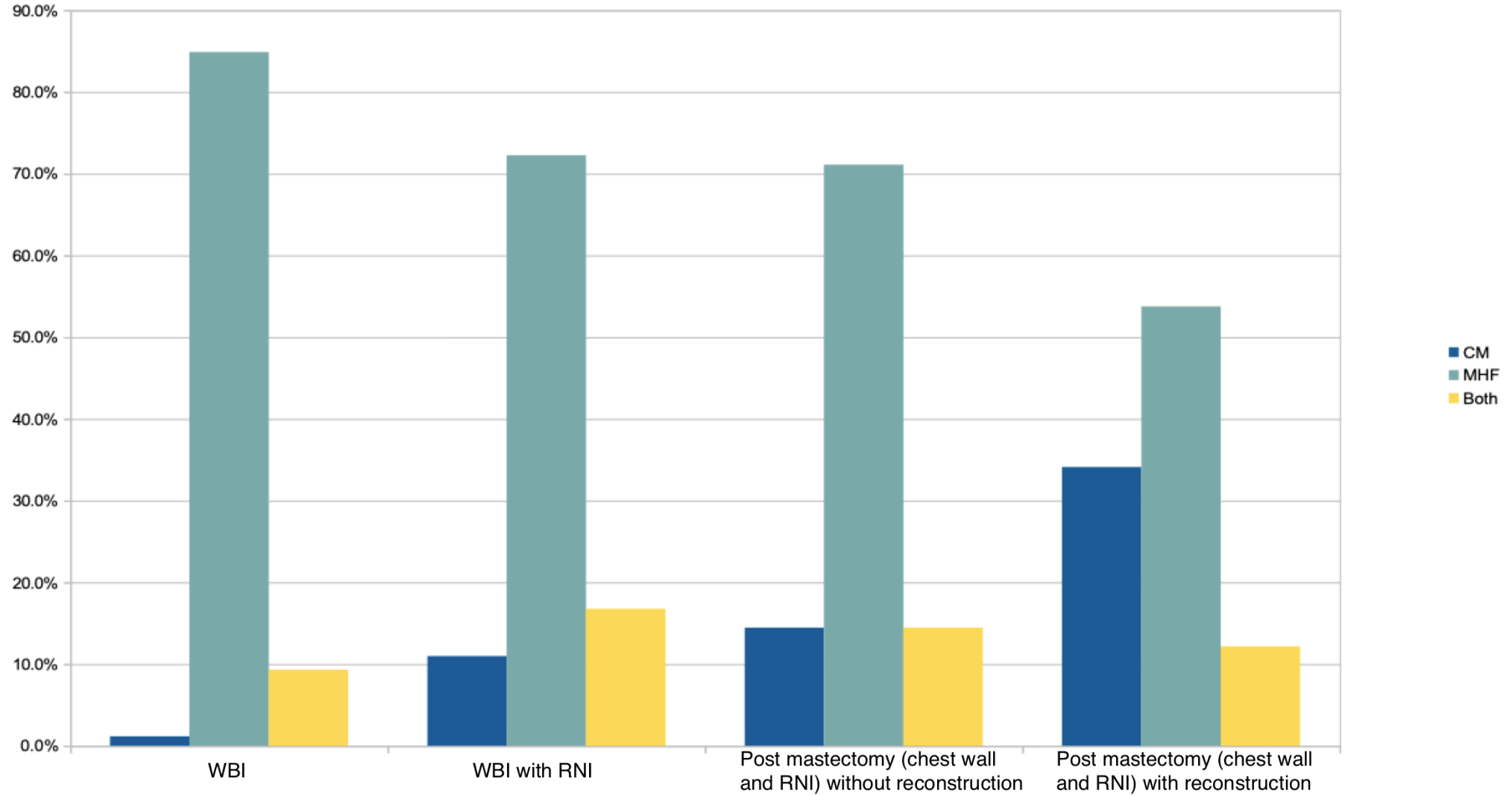
Moderately hypofractionated post-operative radiation therapy for breast cancer: Preferences amongst radiation oncologists from countries in Latin and Central Americas

173 radiation oncologists
13 countries

Country	N	%
Argentina	23	13.29
Aruba	1	0.58
Bolivia	6	3.47
Brazil	90	52.02
Chile	7	4.05
Colombia	8	4.62
Dominican Republic	2	1.16
Ecuador	7	4.05
Mexico	12	6.94
Panama	2	1.16
Paraguay	2	1.16
Peru	11	6.36
Uruguay	2	1.16



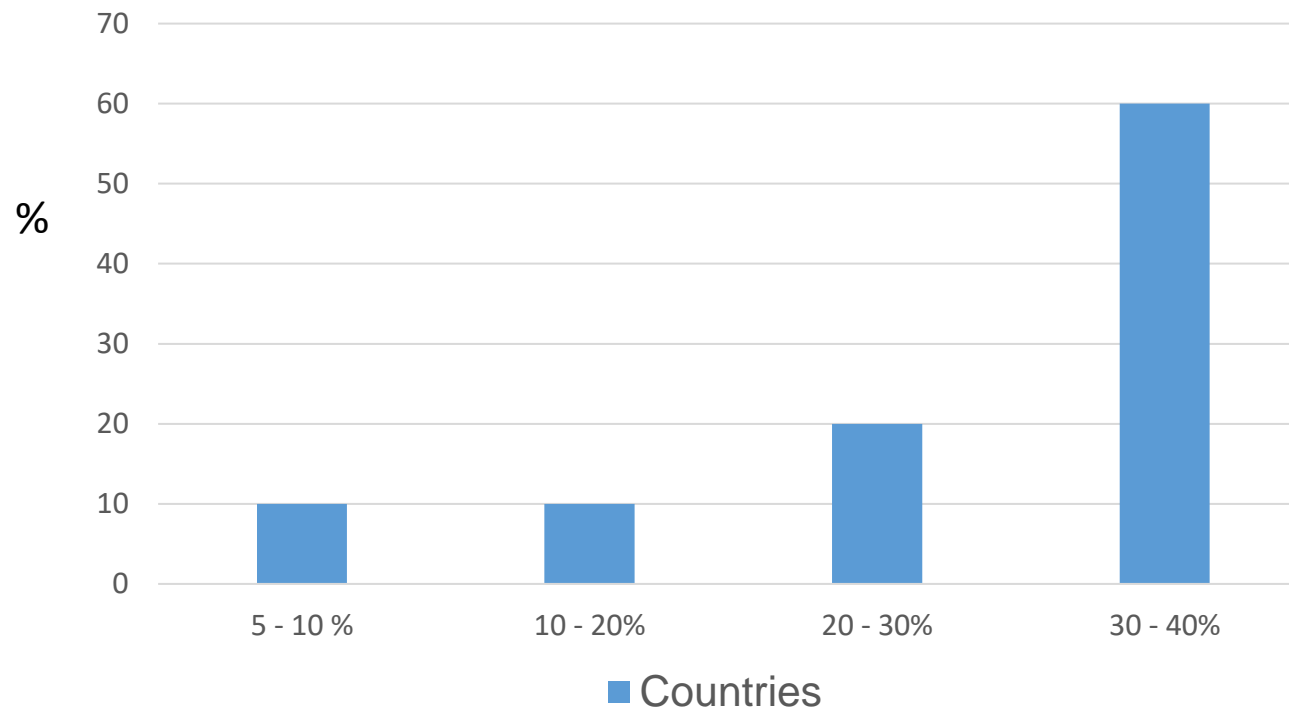
Moderately hypofractionated post-operative radiation therapy for breast cancer: Preferences amongst radiation oncologists from countries in Latin and Central Americas





The financial impact on reimbursement of moderately hypofractionated postoperative radiation therapy for breast cancer: An International Consortium report

13 countries from all populated continents was collected (Europe: Denmark, France, Italy, Netherlands, Spain, United Kingdom; North America: Canada, United States; South America: Brazil; Africa: South Africa; Oceania: Australia; Asia: Israel, Taiwan)



The decrease in remuneration generated by the reduction in per-patient income from applying a hypofractionation-based schedule

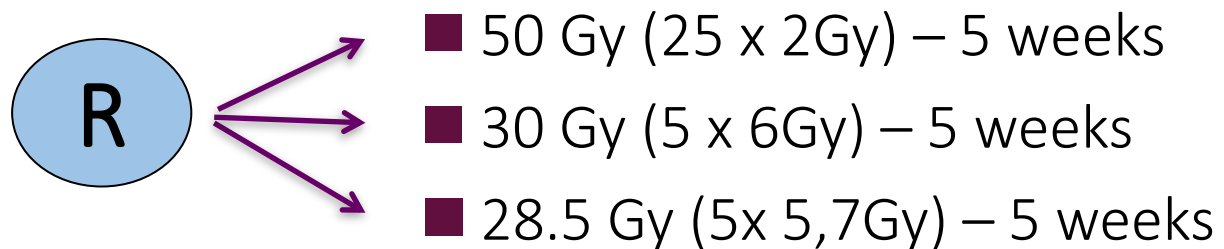


Ultra hypofractionated radiation therapy

FAST - CRUKE/04/015

915 patients

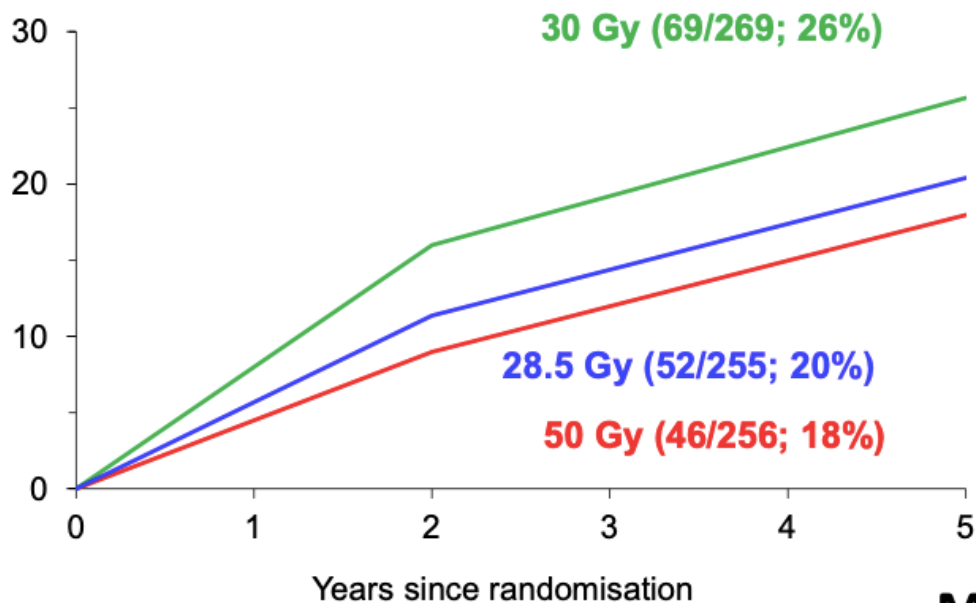
- ≥ 50 years
- pT1-2 pN0 (<3.0 cm)
- Breast conservation surgery
- Invasive breast cancer



FAST - CRUKE/04/015

Change in breast appearance

% with mild / severe change in breast appearance



Difference (95%CI)

**30Gy vs
50Gy**

**+7.4% (0.3, 16.7)
p=0.03**

**28.5Gy vs
50Gy**

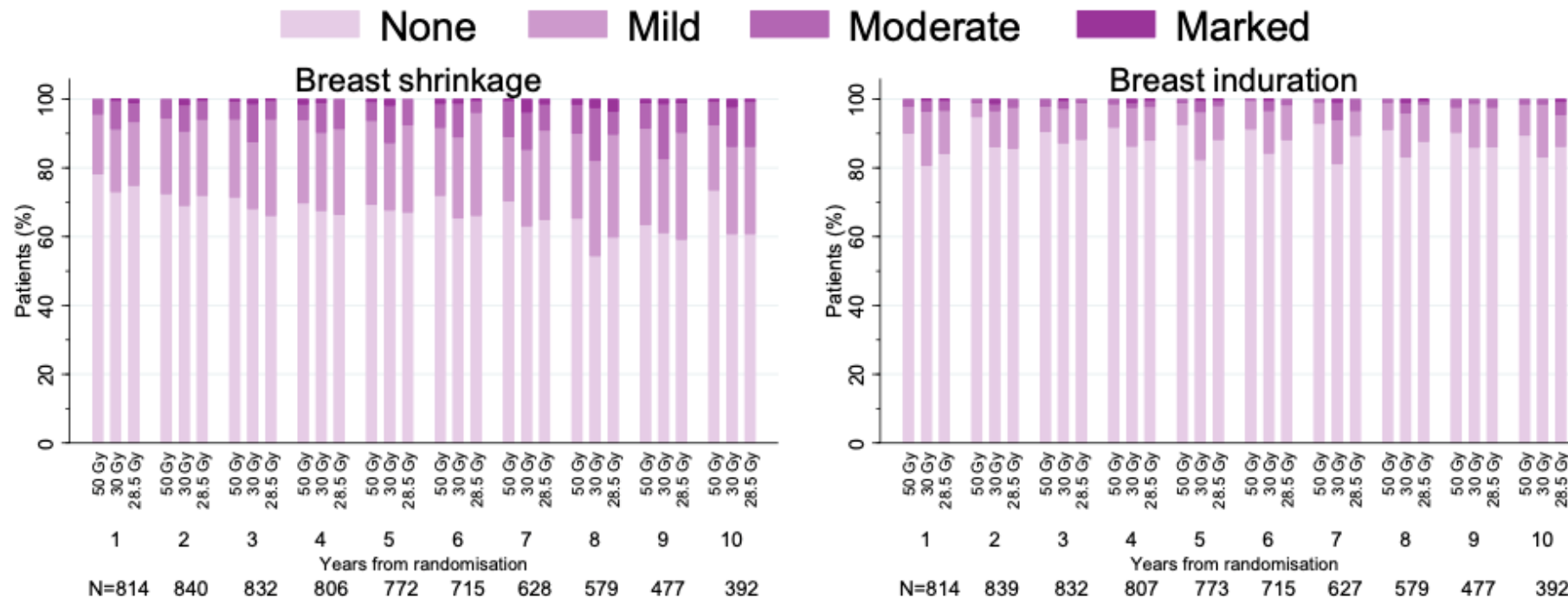
**+2.4% (-3.8, 10.8)
p=0.47**

Marked changes: 2%, 4%, 2%



FAST - CRUKE/04/015

Side effects



OR for moderate/marked shrinkage (95%CI)

OR for moderate/marked induration (95%CI)

30Gy vs 50Gy	1.88 (1.32, 2.67), p<0.001	2.39 (1.31, 4.35), p=0.004
28.5Gy vs 50Gy	1.11 (0.76, 1.64), p=0.59	1.67 (0.89, 3.16), p=0.11

FAST - CRUKE/04/015

Local Control

Relapse and survival at median 10 years' follow-up

	50Gy/25# N=302	30Gy/5# N=308	28.5Gy/5# N=305	Total N=915
Local relapse	3	4	4	11
Regional relapse	2	0	3	5
Distant relapse	17	15	15	47
Death (breast cancer)	30 (7)	33 (8)	33 (10)	96 (25)

Estimate of 10-year local relapse rate: 1.3% (95%CI 0.7, 2.3%)



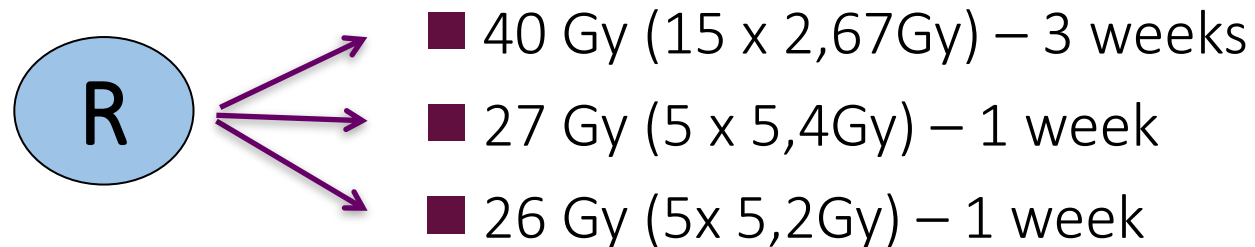
UK FAST-FORWARD

4110 Patients (97 Hospitals)

- ≥ 18 years
- pT1-3 pN0-1, M0
- Breast conservation surgery or mastectomy
- Invasive cancer
- Breast reconstruction and boost were permitted

15/Fev/2013:

Exclusion of low-risk patients (≥ 65 years, pT1, grades 1 or 2, ER +, HER 2 -, pN0)



Target: Breast or chest wall



UK FAST-FORWARD

	40 Gy in 15 fractions (n=1361)	27 Gy in five fractions (n=1367)	26 Gy in five fractions (n=1368)
Age, years			
Median (IQR)	60 (53-66)	61 (53-67)	61 (52-66)
Range	29-89	25-90	25-89
<40	12 (0.9%)	16 (1.2%)	28 (2.0%)
40-49	186 (13.7%)	173 (12.7%)	189 (13.8%)
50-59	440 (32.3%)	423 (30.9%)	414 (30.3%)
60-69	506 (37.2%)	511 (37.4%)	524 (38.3%)
70-79	175 (12.9%)	197 (14.4%)	172 (12.6%)
≥80	42 (3.1%)	47 (3.4%)	41 (3.0%)
Sex			
Female	1355 (99.6%)	1365 (99.9%)	1362 (99.6%)
Male	6 (0.4%)	2 (0.1%)	4 (0.3%)
Unknown	0	0	2 (0.1%)
Tumour grade			
1	315 (23.1%)	315 (23.0%)	300 (21.9%)
2	660 (48.5%)	663 (48.5%)	690 (50.4%)
3	386 (28.4%)	389 (28.5%)	378 (27.6%)
Risk group			
Low (age ≥50 and grade 1 or 2)	843 (61.9%)	854 (62.5%)	854 (62.4%)
High (age <50 or grade 3, or both)	518 (38.1%)	513 (37.5%)	514 (37.6%)



UK FAST-FORWARD

Primary surgery			
Breast conservation surgery	1270 (93.3%)	1278 (93.5%)	1284 (93.9%)
Breast conservation surgery with oncoplastic technique	42 (3.1%)	33 (2.4%)	42 (3.1%)
Mastectomy			
Mastectomy with immediate reconstruction	91 (6.7%)	89 (6.5%)	84 (6.1%)
Autologous reconstruction	8 (0.6%)	11 (0.8%)	7 (0.5%)
Implant-based reconstruction	5/8 (62.5%)	7/11 (63.6%)	3/7 (42.9%)
Reconstruction type not specified	2/8 (25.0%)	4/11 (27.3%)	4/7 (57.1%)
	1/8 (12.5%)	0	0
Side of primary tumour			
Left	726 (53.3%)	674 (49.3%)	662 (48.4%)
Right	635 (46.7%)	693 (50.7%)	704 (51.5%)
Unknown	0	0	2 (0.1%)
Maximal extent of axillary staging			
Sentinel node biopsy or guided axillary sampling	1157 (85.0%)	1184 (86.6%)	1164 (85.1%)
Axillary clearance	200 (14.7%)	181 (13.2%)	201 (14.7%)
Other	4 (0.3%)	2 (0.1%)	1 (0.1%)
Unknown	0	0	2 (0.1%)
Pathological node status			
Positive	257 (18.9%)	243 (17.8%)	256 (18.7%)
Negative	1103 (81.0%)	1124 (82.2%)	1110 (81.1%)
Unknown	1 (0.1%)	0	2 (0.1%)



UK FAST-FORWARD

	40 Gy in 15 fractions (n=1361)	27 Gy in five fractions (n=1367)	26 Gy in five fractions (n=1368)
(Continued from previous page)			
Pathological T stage			
T1mi	4 (0.3%)	5 (0.4%)	6 (0.4%)
T1a	69 (5.1%)	68 (5.0%)	51 (3.7%)
T1b	258 (19.0%)	270 (19.8%)	256 (18.7%)
T1c	612 (45.0%)	601 (44.0%)	602 (44.0%)
T2	394 (28.9%)	389 (28.5%)	424 (31.0%)
T3	21 (1.5%)	30 (2.2%)	25 (1.8%)
Unknown	3 (0.2%)	4 (0.3%)	4 (0.3%)
ER and HER2 status			
ER positive HER2 positive	103 (7.6%)	103 (7.5%)	93 (6.8%)
ER positive HER2 negative	1108 (81.4%)	1130 (82.7%)	1097 (80.2%)
ER negative HER2 positive	32 (2.4%)	34 (2.5%)	42 (3.1%)
ER negative HER2 negative	111 (8.2%)	96 (7.0%)	128 (9.4%)
Not known	7 (0.5%)	4 (0.3%)	8 (0.6%)
Progesterone receptor status			
Positive	577 (73.1%)†	541 (70.3%)†	566 (69.8%)†
Negative	212 (26.9%)†	229 (29.7%)†	245 (30.2%)†
Not done	571 (42.0%)	596 (43.6%)	555 (40.6%)
Missing on form	1 (0.1%)	1 (0.1%)	2 (0.1%)

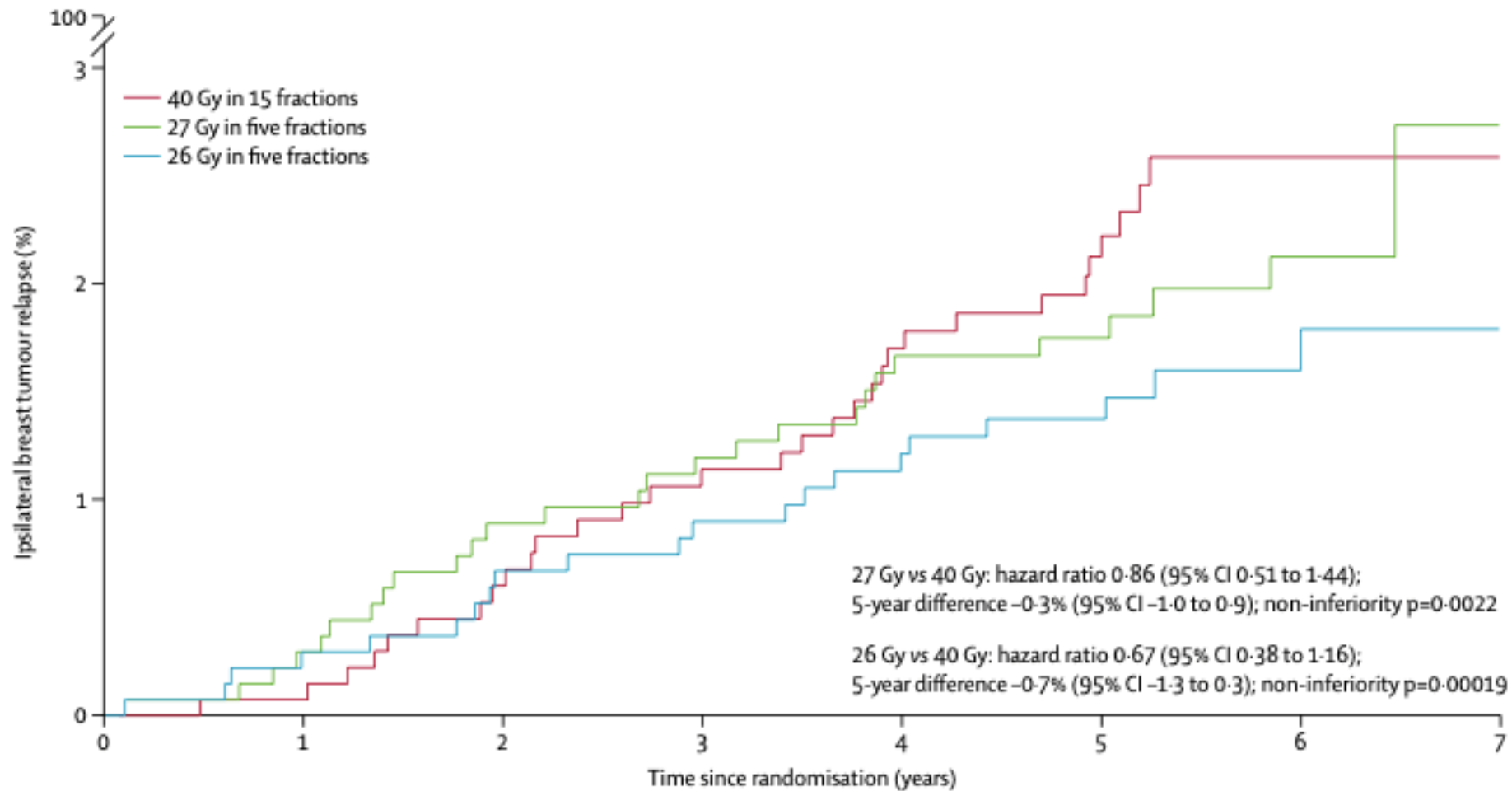


UK FAST-FORWARD

Lymphovascular invasion			
Present	186 (13.7%)	178 (13.0%)	202 (14.8%)
Absent	1085 (79.7%)	1084 (79.3%)	1055 (77.1%)
Uncertain	34 (2.5%)	40 (2.9%)	51 (3.7%)
Unknown	56 (4.1%)	65 (4.8%)	60 (4.4%)
Neoadjuvant chemotherapy received‡			
Yes	48 (3.5%)	56 (4.1%)	43 (3.1%)
No	1312 (96.4%)	1311 (95.9%)	1323 (96.7%)
Unknown	1 (0.1%)	0	2 (0.1%)
Adjuvant therapy received: all patients			
Chemotherapy§	333/1360 (24.5%)	324/1367 (23.7%)	370/1366 (27.1%)
Adjuvant therapy received:‡ HER2-positive patients			
Chemotherapy and trastuzumab	84/135 (62.2%)	85/137 (62.0%)	100/135 (74.1%)
Trastuzumab, no chemotherapy	16/135 (11.9%)	13/137 (9.5%)	13/135 (9.6%)
Chemotherapy, no trastuzumab	2/135 (1.5%)	2/137 (1.5%)	0
No chemotherapy, no trastuzumab	33/135 (24.4%)	37/137 (27.0%)	22/135 (16.3%)
Adjuvant therapy received:‡ ER-positive patients			
Endocrine therapy	1169/1216 (96.1%)	1186/1237 (95.9%)	1157/1196 (96.7%)
Boost given			
Yes	342 (25.1%)	337 (24.7%)	332 (24.3%)
No	1017 (74.7%)	1027 (75.1%)	1031 (75.4%)
Not known	2 (0.1%)	3 (0.2%)	5 (0.4%)
Boost dose			
10 Gy in five fractions	260/342 (76.0%)	273/337 (81.0%)	257/332 (77.4%)
16 Gy in eight fractions	80/342 (23.4%)	64/337 (19.0%)	75/332 (22.6%)
Unknown	2/342 (0.6%)	0	0

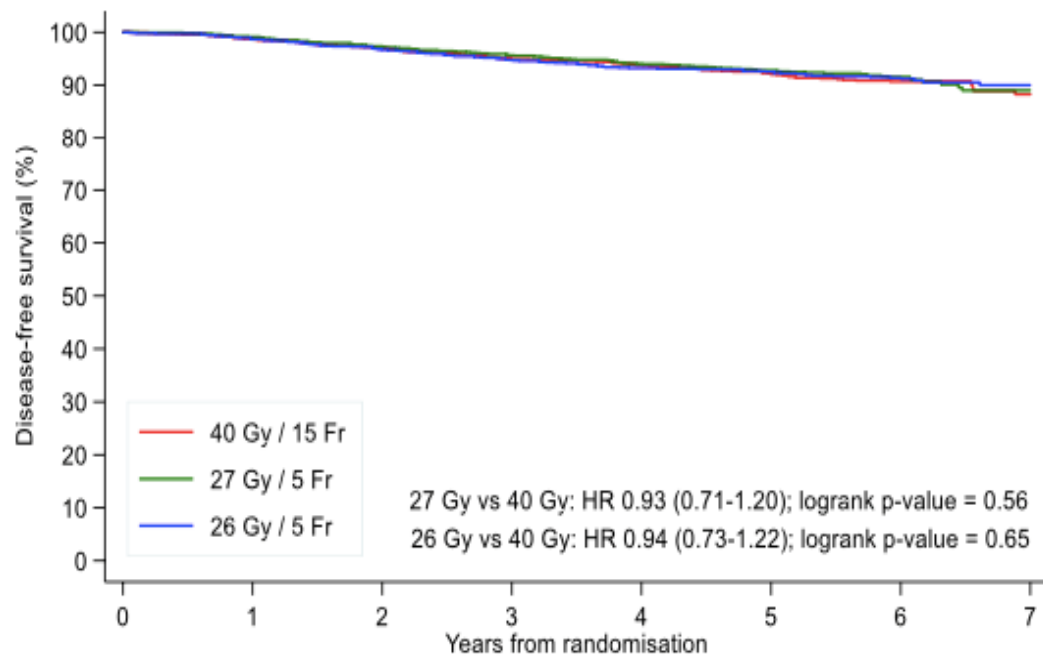
UK FAST-FORWARD

Ipsilateral Breast Recurrence

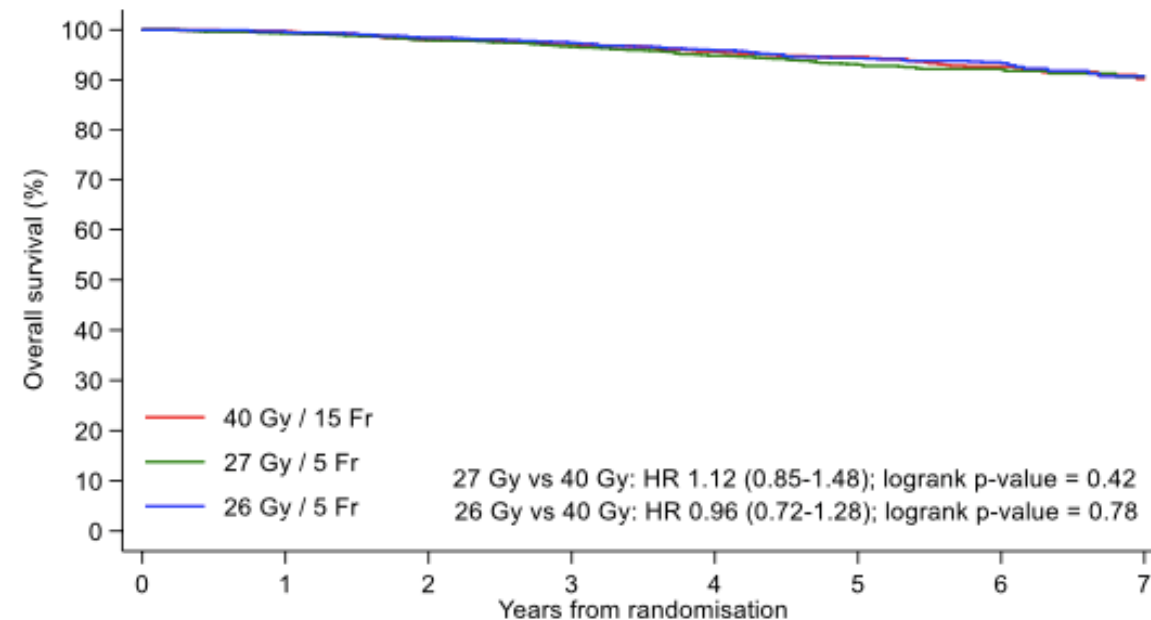


UK FAST-FORWARD

Disease-Free Survival



Overall Survival





UK FAST-FORWARD

Side effects

Any adverse event in the breast or chest wall*	--	--	--	--	0.98 (0.96-1.00); 0.055
40 Gy	651/6121 (10.6%)	1 (ref)	--	--	--
27 Gy	1004/6303 (15.9%)	1.55 (1.32-1.83)	<0.0001	--	--
26 Gy	774/6327 (12.2%)	1.12 (0.94-1.34)	0.20	0.0001	--
Breast distortion†	--	--	--	--	0.99 (0.95-1.02); 0.38
40 Gy	232/5724 (4.0%)	1 (ref)	--	--	--
27 Gy	363/5953 (6.1%)	1.51 (1.15-1.97)	0.0028	--	--
26 Gy	299/5945 (5.0%)	1.20 (0.91-1.60)	0.19	0.083	--
Breast shrinkage‡	--	--	--	--	1.03 (1.00-1.06); 0.023
40 Gy	330/5728 (5.8%)	1 (ref)	--	--	--
27 Gy	503/5944 (8.5%)	1.50 (1.20-1.88)	0.0004	--	--
26 Gy	369/5943 (6.2%)	1.05 (0.82-1.33)	0.71	0.0018	--
Breast induration (tumour bed)†	--	--	--	--	1.00 (0.96-1.04); 0.95
40 Gy	185/5713 (3.2%)	1 (ref)	--	--	--
27 Gy	304/5948 (5.1%)	1.56 (1.19-2.05)	0.0013	--	--
26 Gy	236/5937 (4.0%)	1.19 (0.90-1.59)	0.23	0.047	--
Breast induration (outside tumour bed)†	--	--	--	--	0.96 (0.90-1.02); 0.17
40 Gy	45/5712 (0.8%)	1 (ref)	--	--	--
27 Gy	137/5943 (2.3%)	2.79 (1.74-4.50)	<0.0001	--	--
26 Gy	97/5930 (1.6%)	1.90 (1.15-3.14)	0.013	0.059	--
Telangiectasia	--	--	--	--	1.21 (1.14-1.29); <0.0001
40 Gy	63/6087 (1.0%)	1 (ref)	--	--	--
27 Gy	100/6272 (1.6%)	1.68 (1.07-2.65)	0.025	--	--
26 Gy	102/6300 (1.6%)	1.53 (0.96-2.43)	0.070	0.65	--
Breast or chest wall oedema	--	--	--	--	0.73 (0.69-0.78); <0.0001
40 Gy	89/6097 (1.5%)	1 (ref)	--	--	--
27 Gy	217/6287 (3.4%)	2.18 (1.57-3.03)	<0.0001	--	--
26 Gy	155/6318 (2.4%)	1.47 (1.03-2.09)	0.032	0.0097	--
Breast or chest wall discomfort	--	--	--	--	0.93 (0.89-0.97); 0.0003
40 Gy	234/6086 (3.8%)	1 (ref)	--	--	--
27 Gy	269/6285 (4.3%)	1.10 (0.86-1.40)	0.44	--	--
26 Gy	250/6309 (4.0%)	0.98 (0.76-1.26)	0.86	0.35	--

• 40Gy ~ 26Gy

• 27Gy > Toxicities



First results of FAST-Forward phase 3 RCT nodal substudy: 3-year normal tissue effects

- 467 patients pT1-3 pN1-3a Breast conservation surgery or mastectomy

Radiation therapy: Regional lymph nodes



06 May 2022 - 10 May 2022
Copenhagen, Denmark

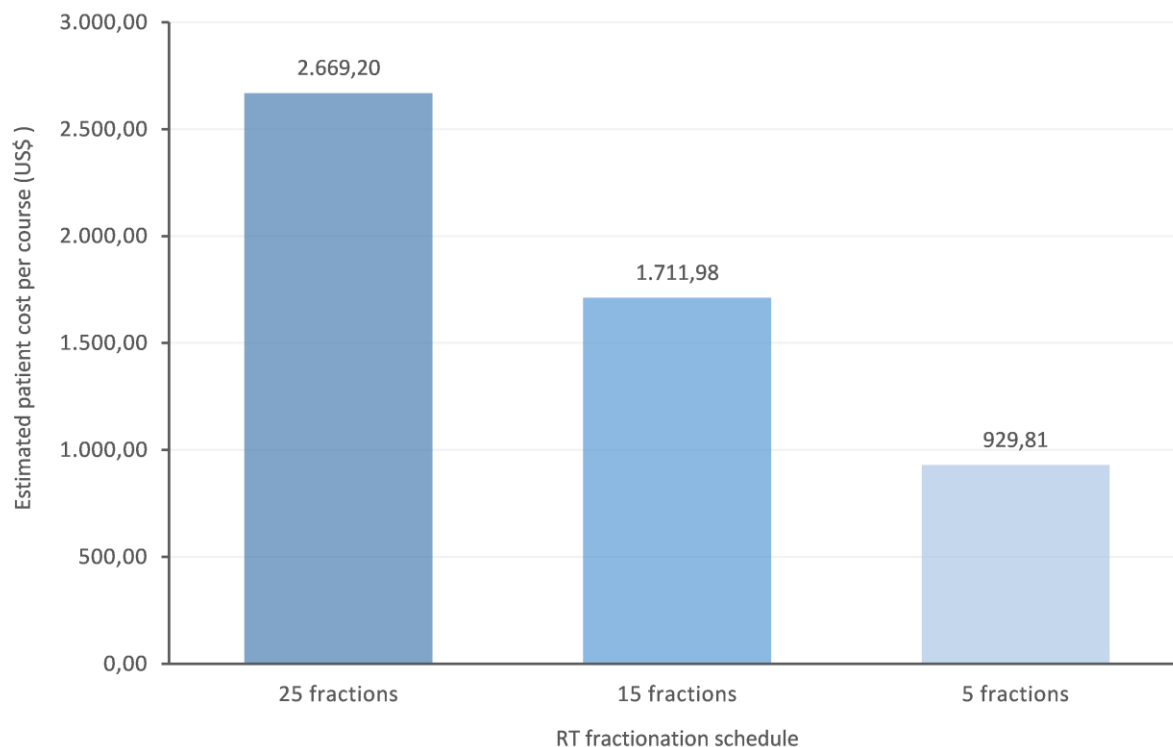
Normal tissue effects (NTE) in arm or shoulder ¹	40Gy/15Fr All randomised (%)	26Gy/5Fr (%)	40Gy/15Fr Randomised concurrently with 27Gy/5Fr (%)	27Gy/5Fr (%)
Patient assessments at 2 years				
Swollen arm or hand; N	127	134	72	89
Not at all	93 (73)	102 (76)	53 (74)	59 (66)
A little	21 (16)	22 (16)	13 (18)	18 (20)
Quite a bit	7 (6)	7 (5)	3 (4)	8 (9)
Very much	6 (5)	3 (2)	3 (4)	4 (5)
Pain in arm or shoulder; N	127	134	72	89
Not at all	50 (39)	53 (40)	26 (36)	29 (33)
A little	54 (43)	61 (45)	32 (44)	38 (43)
Quite a bit	14 (11)	15 (11)	8 (11)	15 (17)
Very much	9 (7)	5 (4)	6 (8)	7 (8)
Difficulty raising arm or moving it sideways; N	127	134	72	89
Not at all	78 (61)	74 (55)	38 (53)	51 (57)
A little	34 (27)	50 (37)	26 (36)	25 (28)
Quite a bit	8 (6)	6 (4)	5 (7)	8 (9)
Very much	7 (6)	4 (3)	3 (4)	5 (6)
Shoulder stiffness; N	125	129	71	88
Not at all	70 (56)	67 (52)	36 (51)	42 (48)
A little	43 (34)	46 (36)	27 (38)	31 (35)
Quite a bit	7 (6)	12 (9)	6 (8)	10 (11)
Very much	5 (4)	4 (3)	2 (3)	5 (6)
Clinician assessments at 3 years				
Arm lymphoedema; N	130	123	80	85
Yes	11 (8)	15 (12)	7 (9)	9 (11)
No	119 (92)	108 (88)	73 (91)	76 (89)

Cost containment analysis and access to treatment associated with adopting hypofractionated radiation therapy from the brazilian perspective

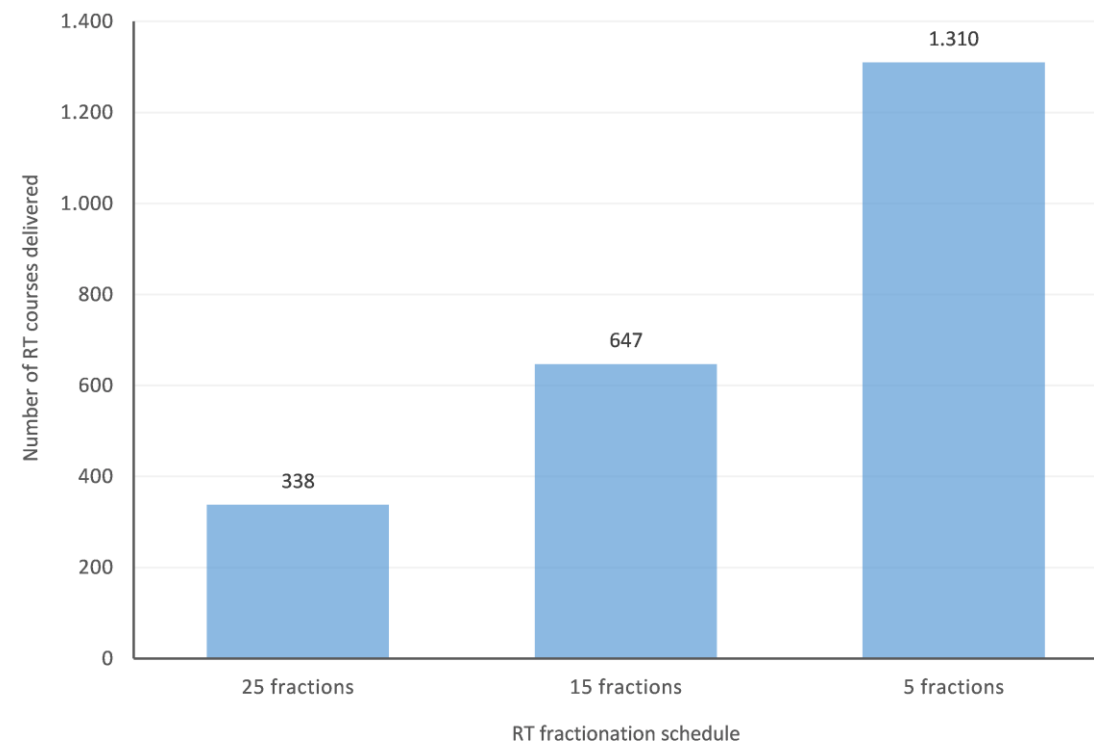


Prince Taylor,^{ab} Marcus Simões Castilho,^c and Gustavo Nader Marta^{d,e*}

Estimated Patient Cost per RT Schedule



Estimated annual RT productivity of 1 LINAC machine per EBRT regimen





European Society for Radiotherapy and Oncology Advisory Committee in Radiation Oncology Practice consensus recommendations on patient selection and dose and fractionation for external beam radiotherapy in early breast cancer

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Practice consensus state that **moderately hypofractionated radiotherapy** can be offered to any patient for whole breast, chest wall (with or without reconstruction), and nodal volumes. **Ultrafractionation (five fractions)** can also be offered for non-nodal breast or chest wall (without reconstruction) radiotherapy either as standard of care or within a randomised trial or prospective cohort.



Conclusions

Hypofractionated radiation therapy (moderate)

- All patients (including regional nodal irradiation and chest wall with or without breast reconstruction)

Hypofractionated radiation therapy (extreme)

- Patients over 50 years following with early-stage, node-negative disease
 - In situ, T1-2
 - Without regional nodal irradiation
 - Without breast reconstruction



SÍRIO-LIBANÊS

Thank you!

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