



**SÍRIO-LIBANÊS**

*Novas perspectivas em radioterapia:  
hipofracionamento? Omissão da radioterapia?*

**Gustavo Nader Marta**

*Médico titular do Departamento de Radioterapia do Hospital Sírio-Libanês*



1. Radioterapia hipofracionada moderada
2. Ultrahipofracionamento
3. Omissão da radioterapia
4. Considerações finais



1. Radioterapia hipofracionada moderada
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# Radioterapia hipofracionada moderada

	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			
<b>Moderate Hypofractionation</b>									
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 post-operative radiation therapy for breast cancer: Systematic review and meta-analysis of randomized clinical trials

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

12,139 breast cancer patients

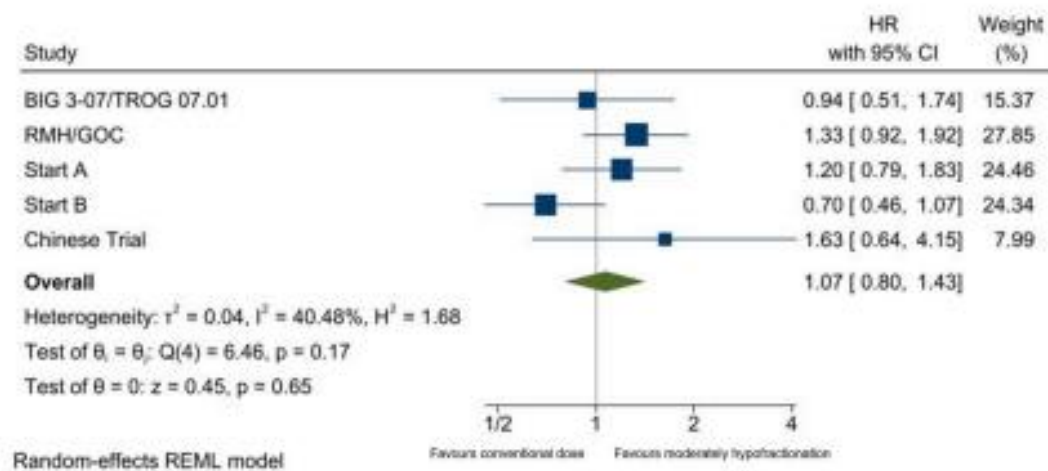


Fig. 1. Local recurrence.

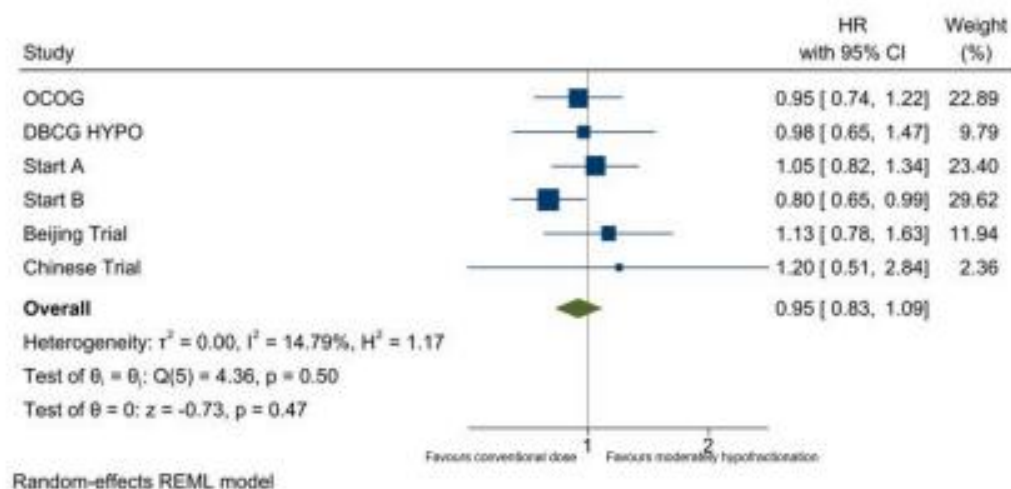


Fig. 4. Overall survival.



# Questões

## Radioterapia hipofracionada moderada

*Mastectomia?*

*Drenagens?*

*Reconstrução?*

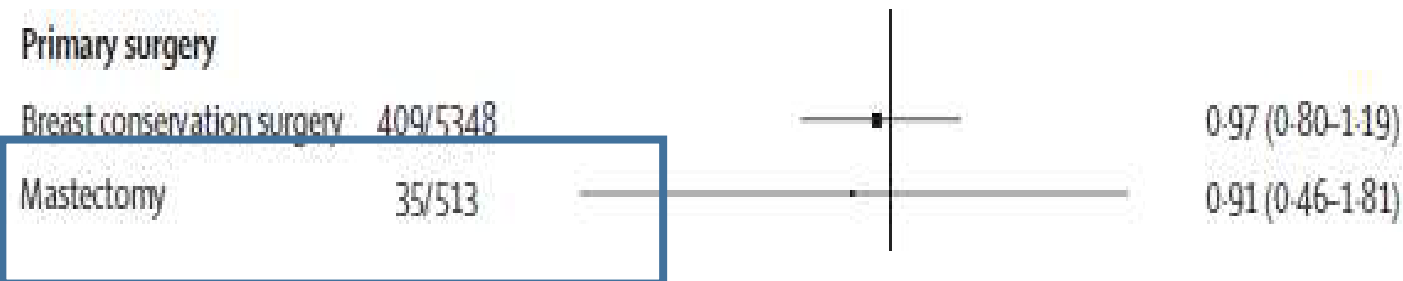


# Start A e B

## Mastectomia versus Cirurgia conservadora

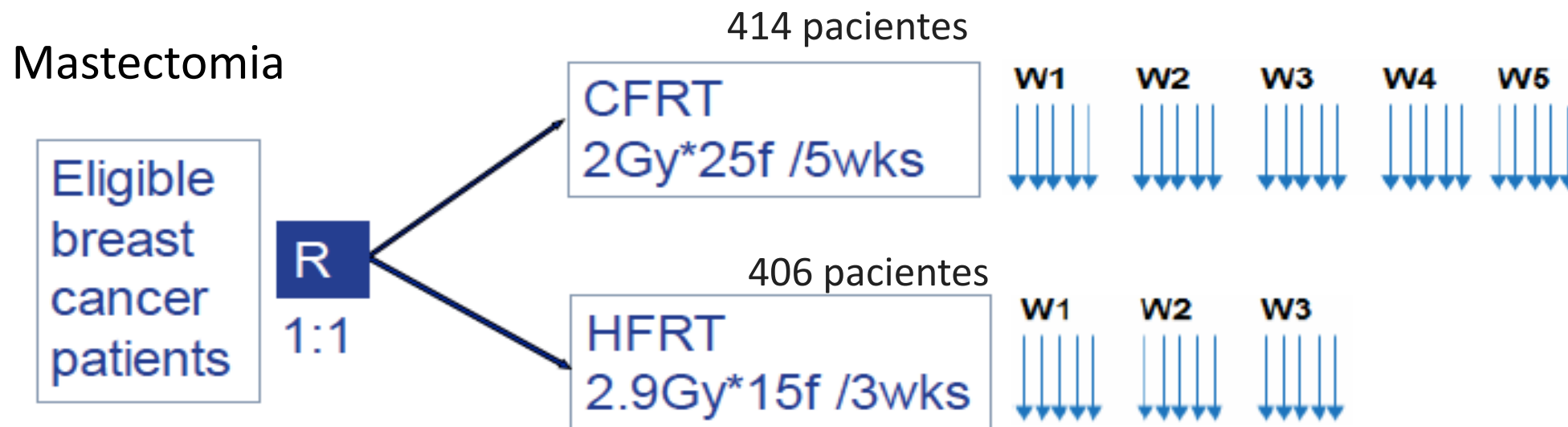
Sem diferença

- Controle local
- Toxicidade



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

# Estudo fase 3 de não inferioridade



- T3-T4 e/ ou  $\geq 4$  LN +

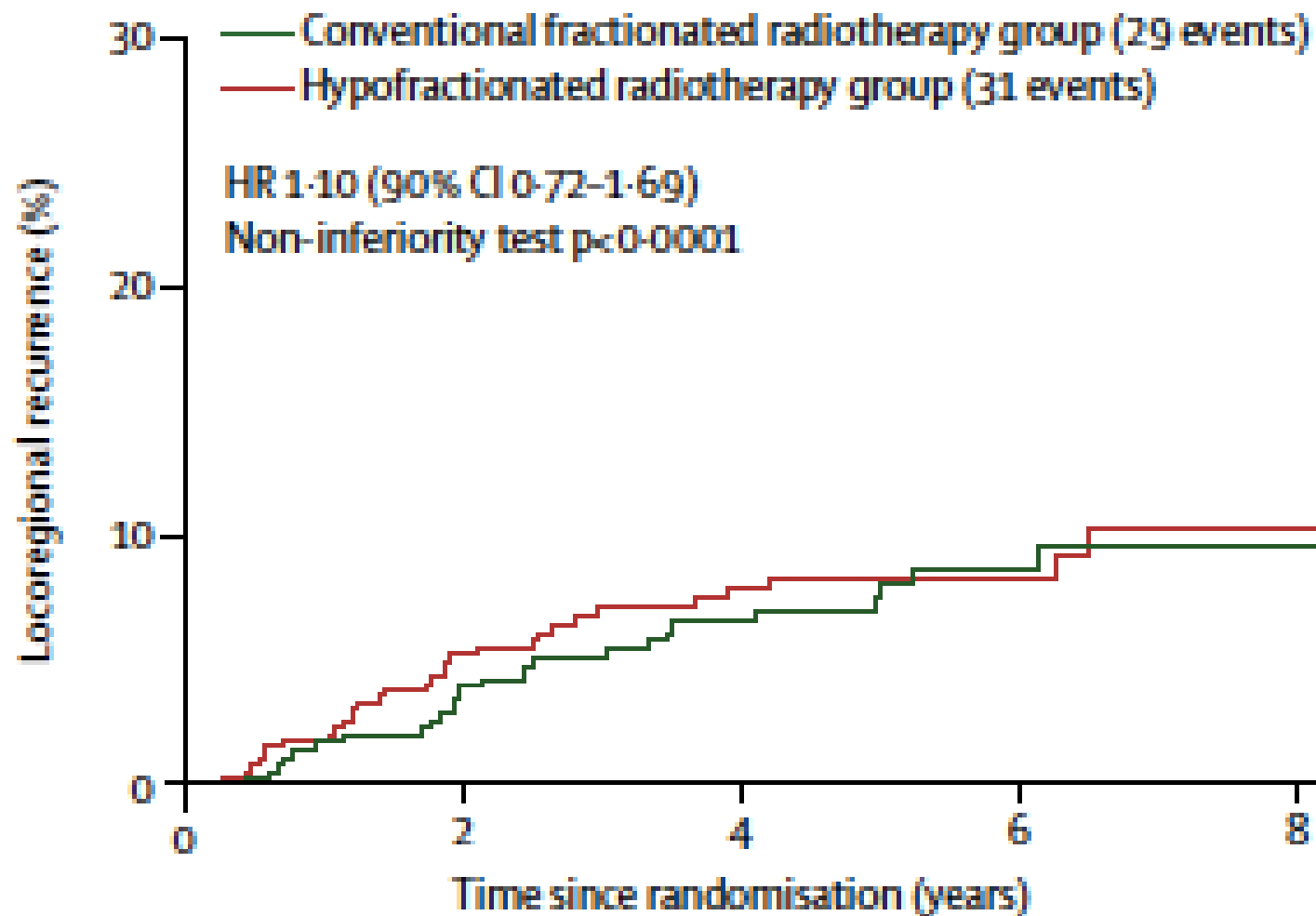
- Parede torácica + drenagem

Desfecho primário: Recorrência locorregional em 5 anos



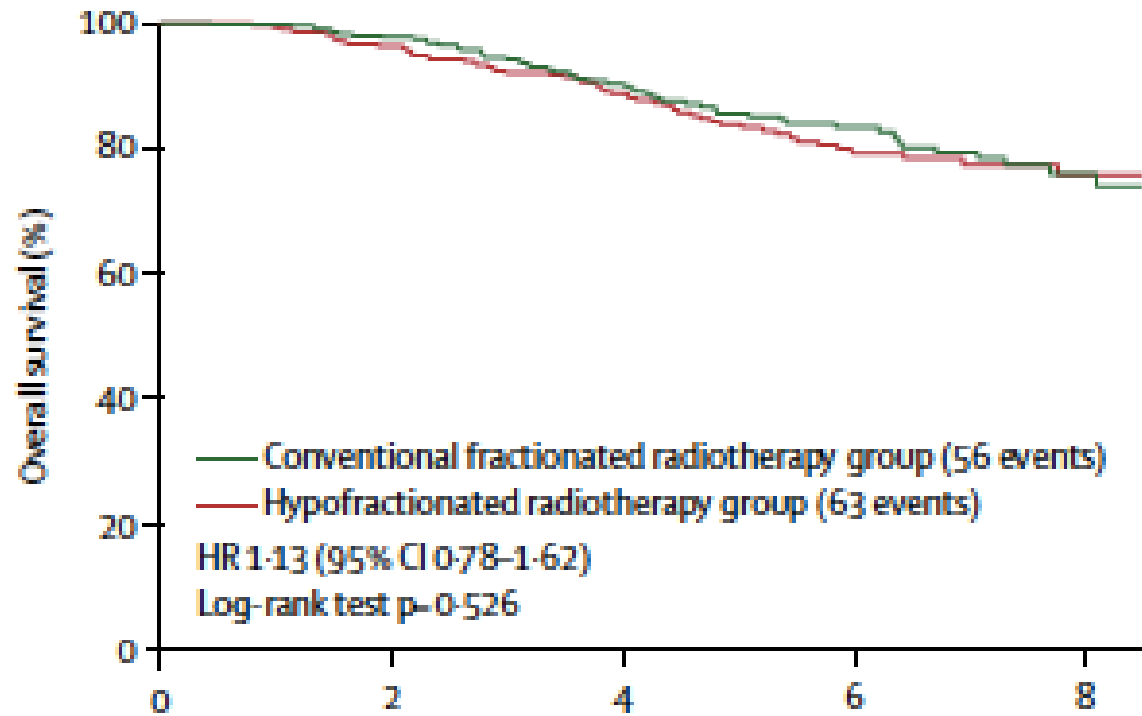


# Recorrência locorregional

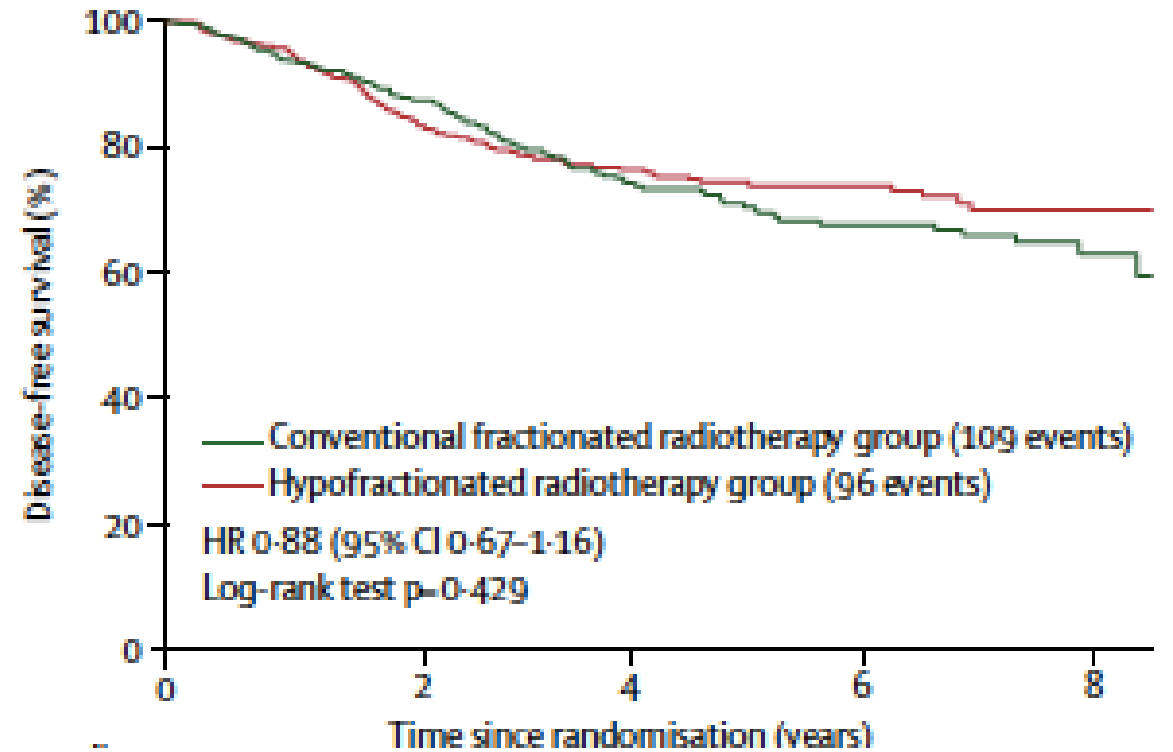




## Sobrevida Global



## Sobrevida Livre do Doença





# Eventos adversos

	Conventional fractionated radiotherapy group (n=409)	Hypofractionated radiotherapy group (n=401)	p value
<b>Acute toxicity</b>			
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	--	--	--
<b>Late toxicity</b>			
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  $\chi^2$  test was used to calculate p values. No grade 4 events or deaths due to adverse effects were reported.

**Table 2: Adverse events**



ELSEVIER

Contents lists available at [ScienceDirect](#)

## Radiotherapy and Oncology

journal homepage: [www.thegreenjournal.com](http://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<sup>a,\*</sup>, Mariella Mannino<sup>b</sup>, Clare Griffin<sup>a</sup>, Nuria Porta<sup>a</sup>, Mark Sydenham<sup>a</sup>, Judith M. Bliss<sup>a,1</sup>, John R. Yarnold<sup>c,1</sup>, 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) <sup>1</sup>	P-value <sup>2</sup>	Prevalence of moderate/ marked events at 5 years, n/total (%)	P-value <sup>3</sup>
<b>Arm/shoulder pain</b>						
<b>START-A</b>						
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
<b>START-B</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
<b>Swelling in arm or hand</b>						
<b>START-A</b>						
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
<b>START-B</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
<b>Difficulty in raising arm</b>						
<b>START-A</b>						
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
<b>START-B</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
<b>Shoulder stiffness</b>						
<b>START-A</b>						
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
<b>START-B</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)	

- 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 <sup>1</sup>	Prevalence of moderate/ marked events at 5 years, n/total (%)	P-value <sup>2</sup>	Prevalence of moderate/ marked events at 10 years, n/total (%)	P-value <sup>2</sup>
<b>Arm oedema</b>									
<b>START-pilot</b>									
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
<b>START-A</b>									
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
<b>START-B</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)	-
<b>Shoulder stiffness</b>									
<b>START-pilot</b>									
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
<b>START-A</b>									
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
<b>START-B</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



## RT hipofracionada moderada após reconstrução?

- Todas as toxicidades: igual ou melhor com hipofracionamento
  - *Retração de pele*
  - *fibrose*
  - *Atrofia*
- Qual a evidência de usar 25 x 200cGy?





# RT hipofracionada moderada após reconstrução?

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

## **RADIOTHERAPY OF CANCER OF THE BREAST.**

Brodeur P<sup>1</sup>.



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

## **Reconstruction of the breast.**

Bostwick J.



# RT hipofracionada moderada após reconstrução?

## Hipofracionamento

*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**

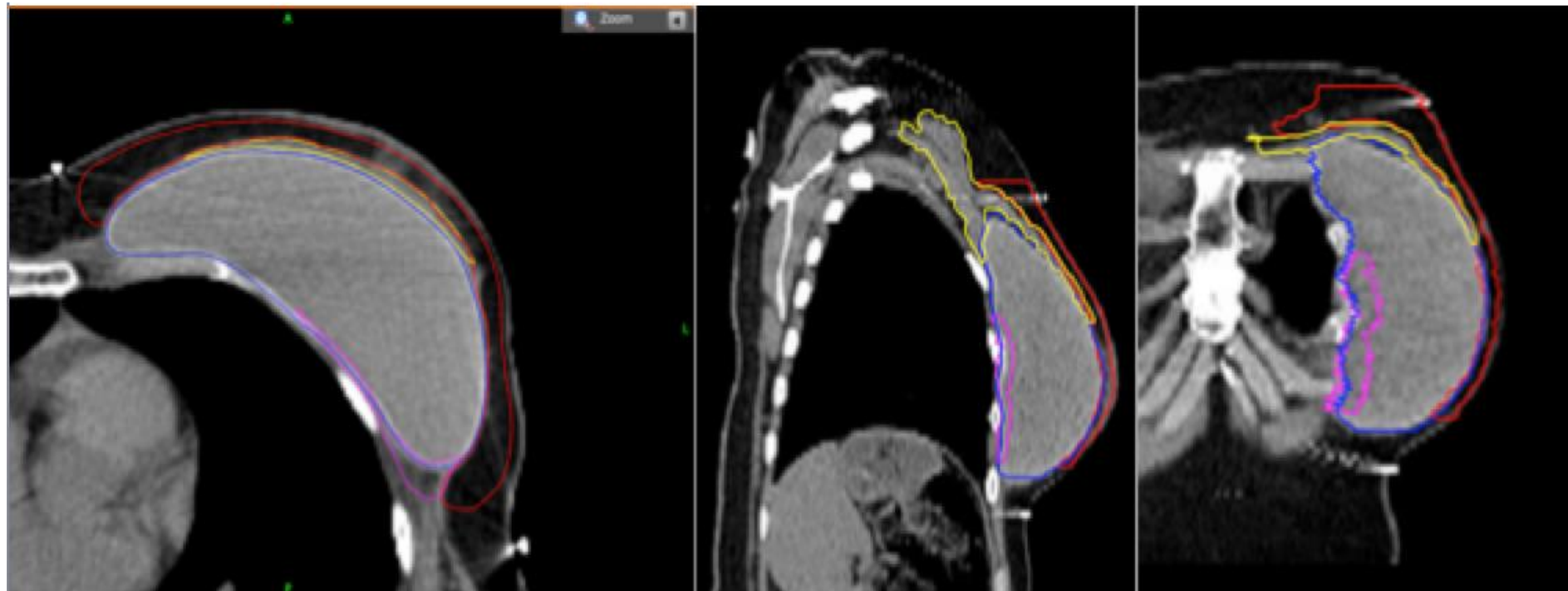
**25.2% postoperatively irradiated**

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

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



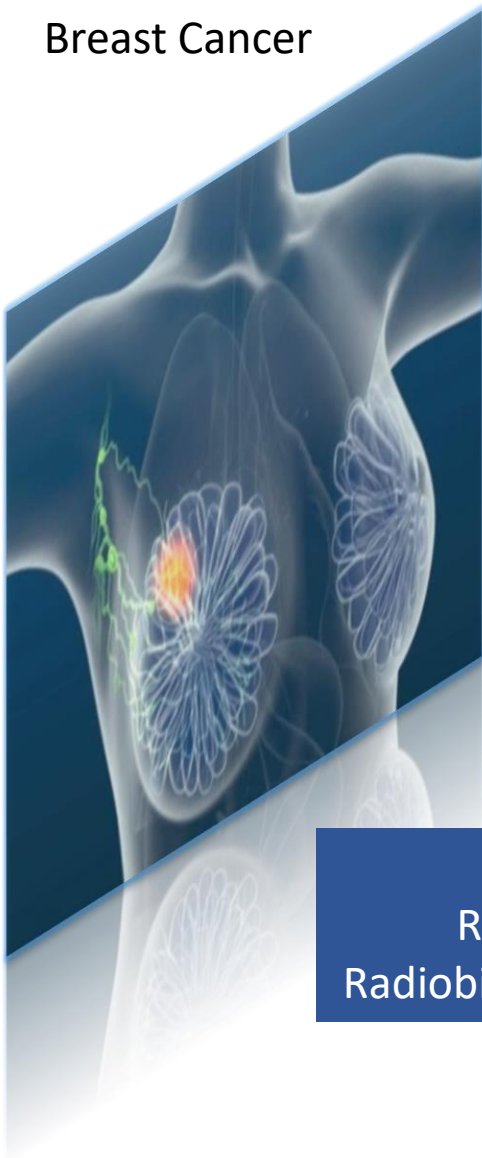


# THE LANCET **Oncology**

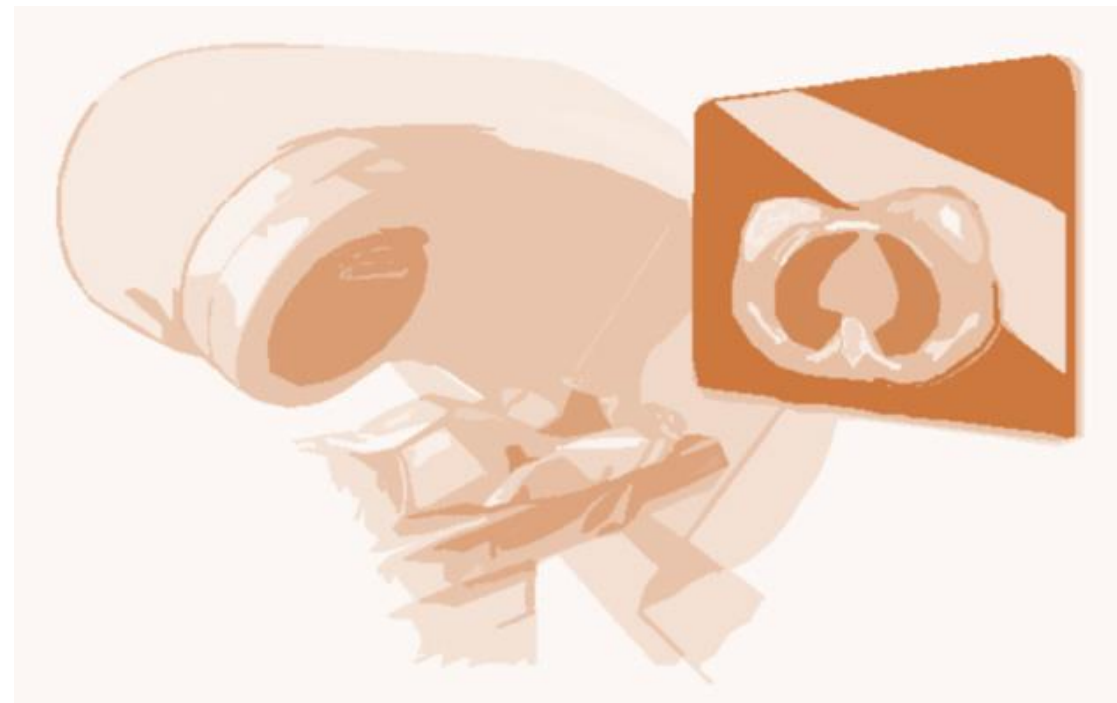
## **Moderately hypofractionated breast radiation therapy: is more evidence needed?**

Gustavo N Marta and Philip Poortmans

## Breast Cancer



## Post-operative Radiation Therapy



Clinical trials  
Retrospective data  
Radiobiological considerations



### Moderately Hypofractionated Radiation Therapy

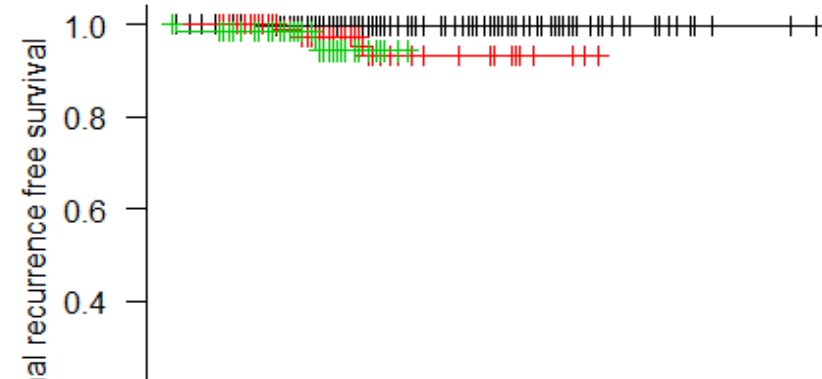
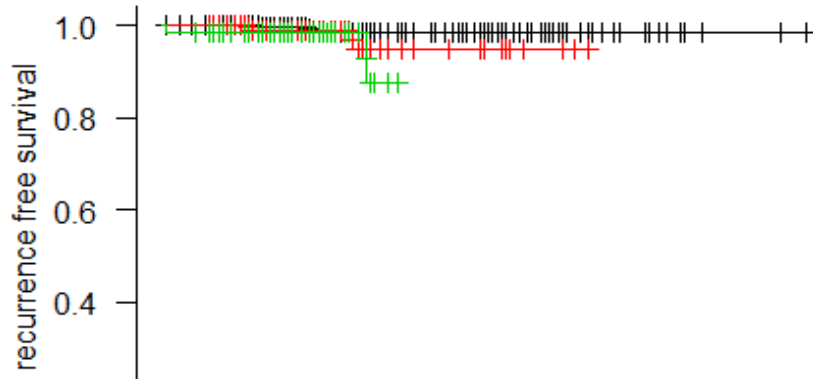
Efficient, convenient and safe for all indications  
including regional nodal irradiation and chest wall with or  
without breast reconstruction



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

Gabriela S.M de Siqueira, Samir A. Hanna, Larissa F. de Moura, Fabiana Accioli Miranda, Heloísa de Andrade Carvalho, Gustavo Nader Marta

670 pacientes (estádios I-III com RT de drenagens e reconstrução e quimioterapia)



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:

Tim Whelan - Canada

Murray Brunt - UK

Philip Poortmans - Belgium

Birgitte Offerson - Denmark

Gustavo Marta - Brazil

Charlotte Coles - UK

Soren Bentzen - USA

Shiroma de Silva Minor - UK

John Yarnold - UK

Judith Bliss - UK

Jo Haviland - UK



1. Radioterapia hipofracionada moderada
- 2. Ultrahipofracionamento**
3. Omissão da radioterapia
4. Considerações finais

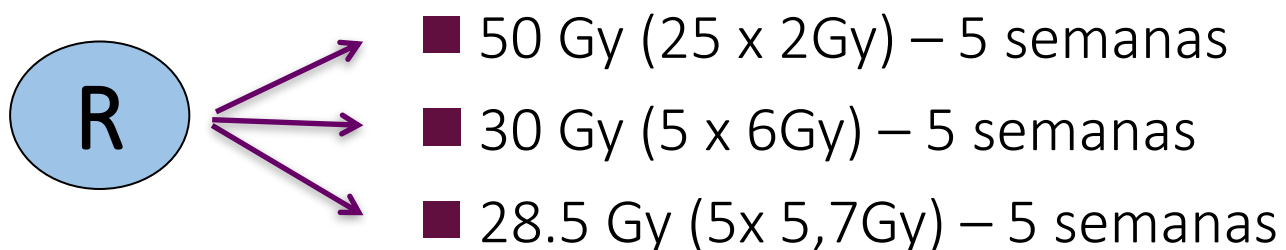


# FAST - CRUKE/04/015

## 915 pacientes

- $\geq 50$  anos
- pT1-2 pN0 (<3.0 cm)
- Cirurgia conservadora
- Câncer de mama invasivo

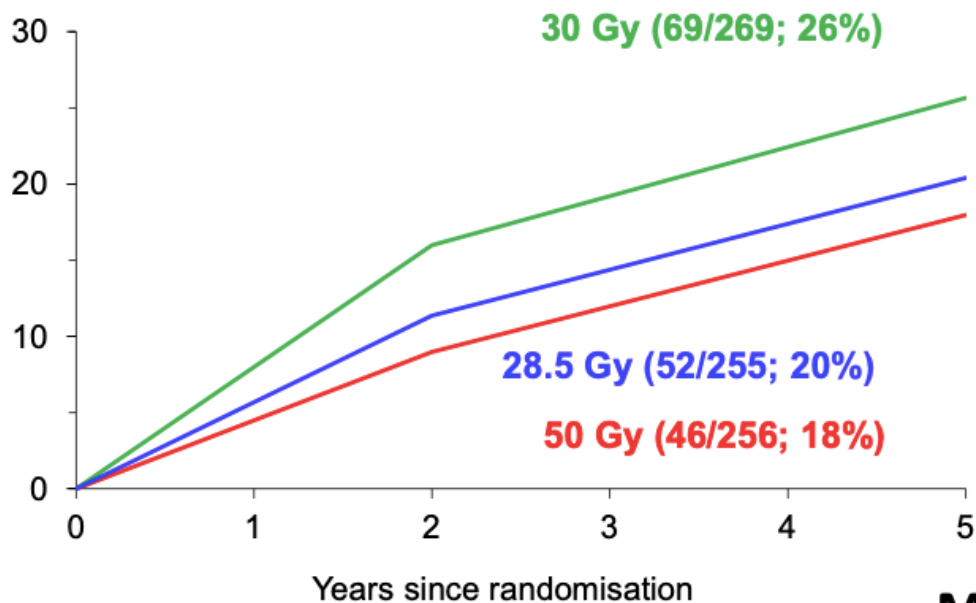
Exclusão: mastectomia; RT drenagens, boost, QT neoadjuvante



# FAST - CRUKE/04/015

## Alteração na aparência fotográfica da mama

% 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

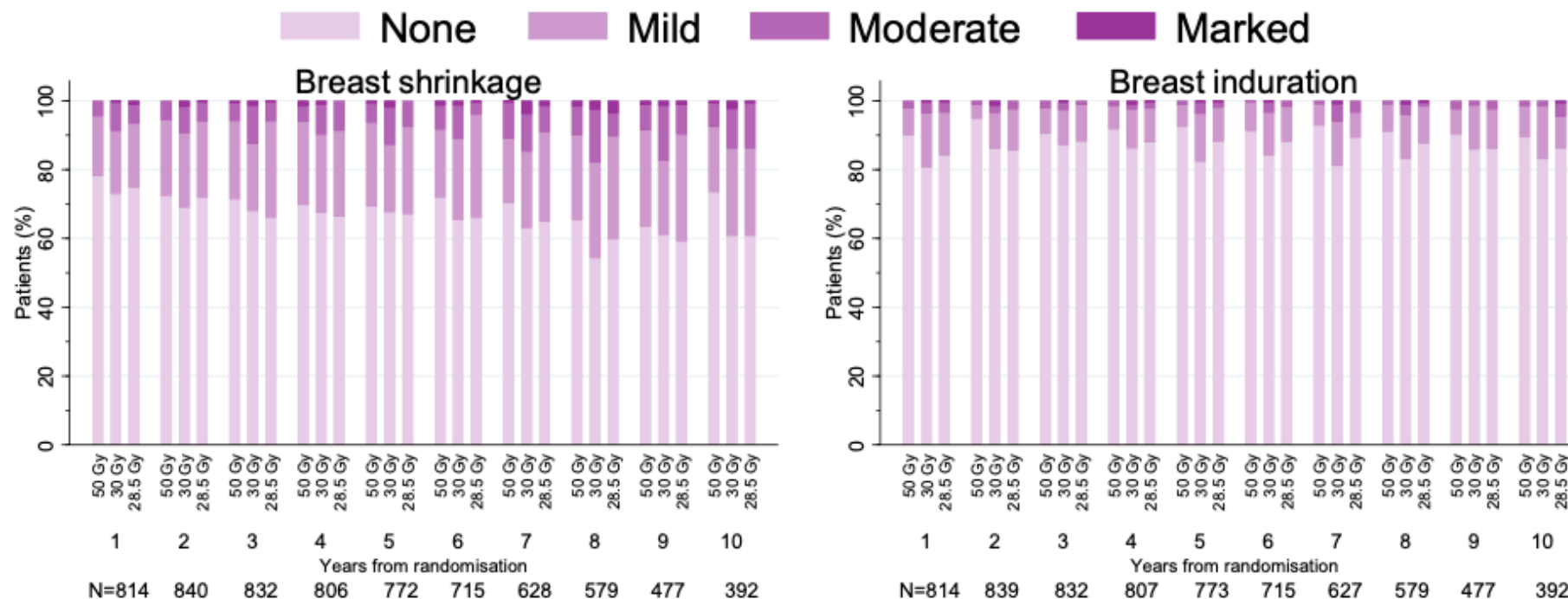
+2.4% (-3.8, 10.8)  
p=0.47

Marked changes: 2%, 4%, 2%



# FAST - CRUKE/04/015

## Efeitos colaterais



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

## Controle local

### Relapse and survival at median 10 years' follow-up

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

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





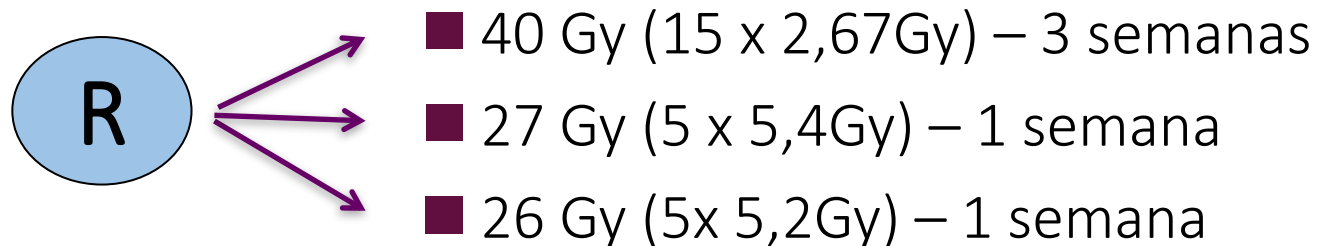
# UK FAST-FORWARD

## 4110 Pacientes (97 hospitais)

- $\geq 18$  anos
- pT1-3 pN0-1, M0
- Cirurgia conservadora ou mastectomia
- Câncer de mama invasivo
- Reconstrução e boost permitidos

15/02/2013:

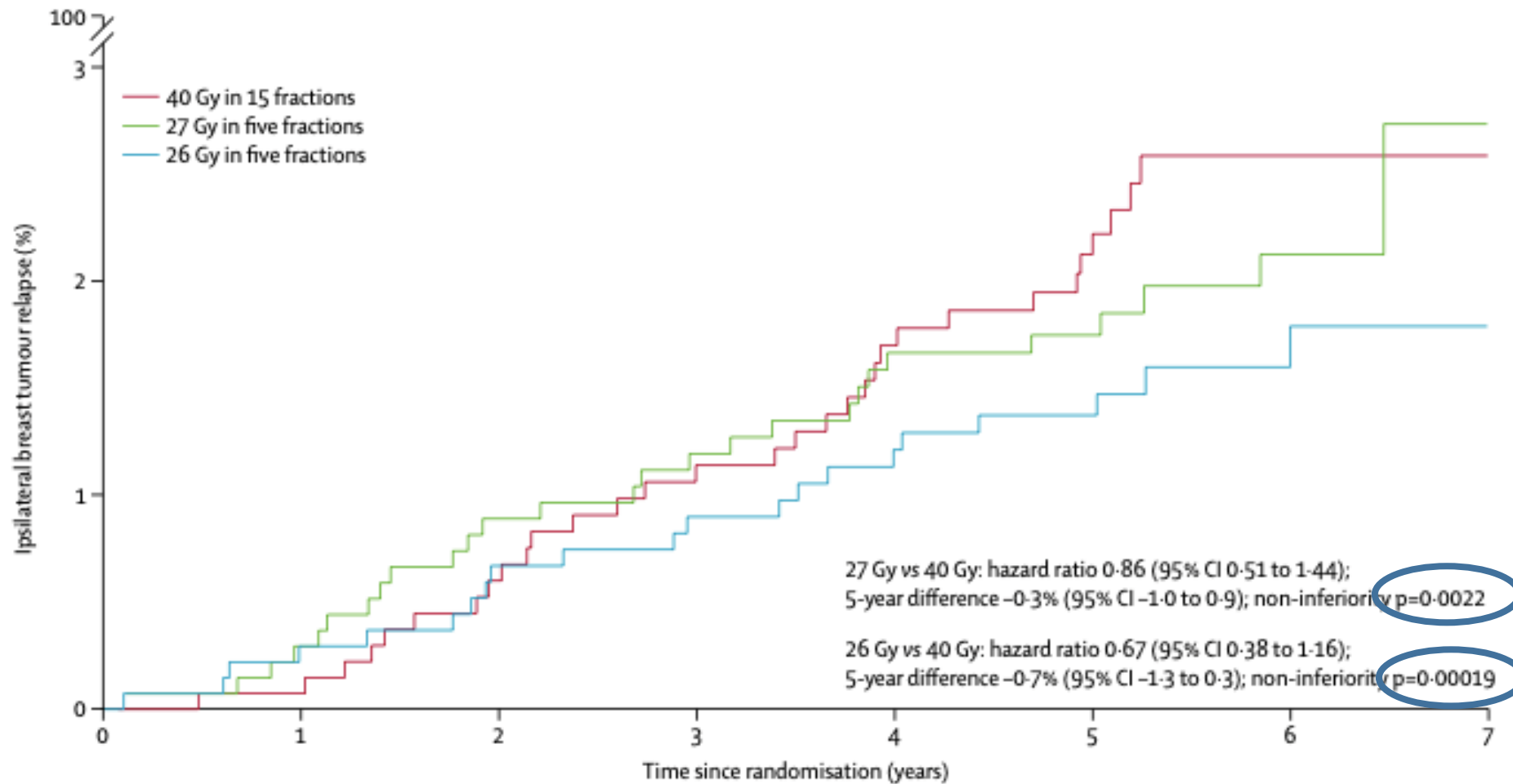
Exclusão de pacientes de baixo risco ( $\geq 65$  anos, pT1, graus 1 ou 2, RE +, HER 2 -, pN0)



*Radioterapia da mama ou plastrão*

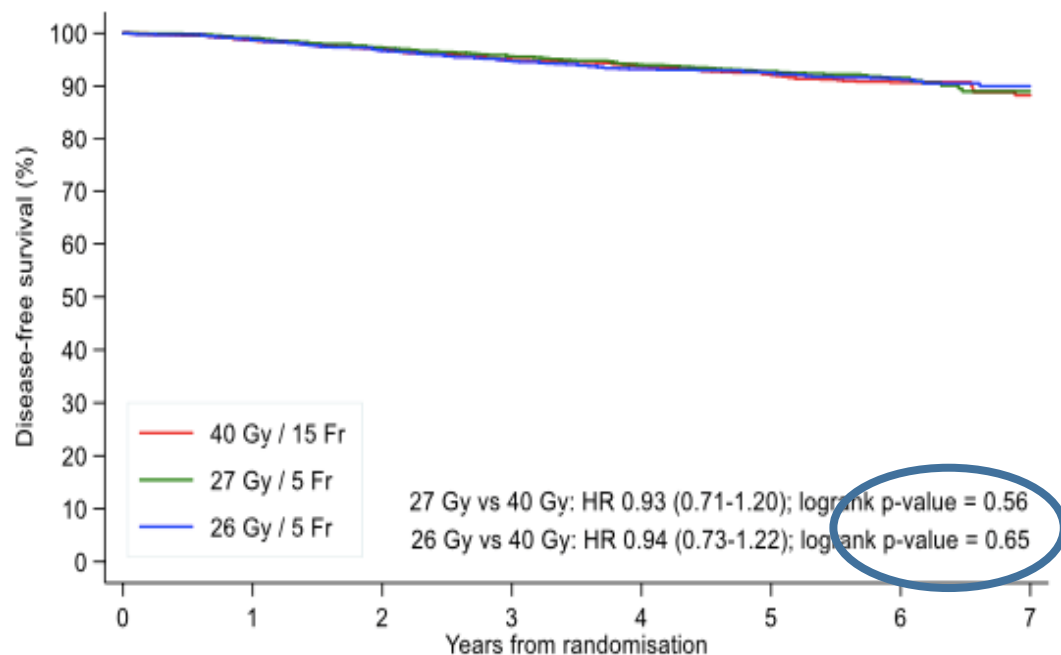
# UK FAST-FORWARD

## Recorrência ipsilateral

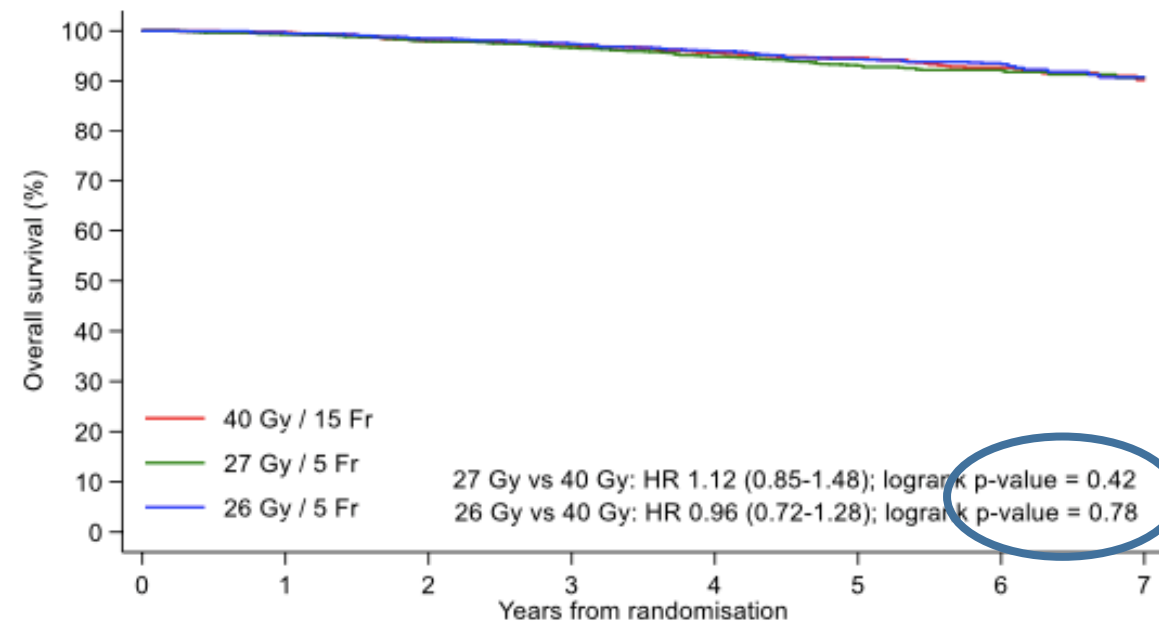


# UK FAST-FORWARD

## Sobrevida livre de doença



## Sobrevida global





# UK FAST-FORWARD

## Eventos adversos

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 > toxicidade





## EDITORIAL

<https://doi.org/10.1590/1806-9282.67.02.20200801>

### Possible impact of adopting extreme hypofractionation after FAST Forward trial publication

Gustavo Nader Marta<sup>1,2\*</sup> 

## **FAST – Forward 26Gy (5x5,2Gy)**

- RT de mama e plastrão (*pT1-3 pN0-1, M0*) -> *ductal in situ*
- Sem drenagens



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

Normal tissue effects (NTE) in arm or shoulder <sup>1</sup>	40Gy/15Fr  All randomised (%)	26Gy/5Fr (%)	40Gy/15Fr  Randomised concurrently with 27Gy/5Fr (%)	27Gy/5Fr (%)
<b>Patient assessments at 2 years</b>				
<b>Swollen arm or hand; N</b>	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)
<b>Pain in arm or shoulder; N</b>	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)
<b>Difficulty raising arm or moving it sideways; N</b>	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)
<b>Shoulder stiffness; N</b>	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)
<b>Clinician assessments at 3 years</b>				
<b>Arm lymphoedema; N</b>	130	123	80	85
Yes	11 (8)	15 (12)	7 (9)	9 (11)
No	119 (92)	108 (88)	73 (91)	76 (89)

- 467 pacientes pT1-3 pN1-3a
- Cirurgia conservadora ou mastectomia

Radioterapia drenages FSC e axila



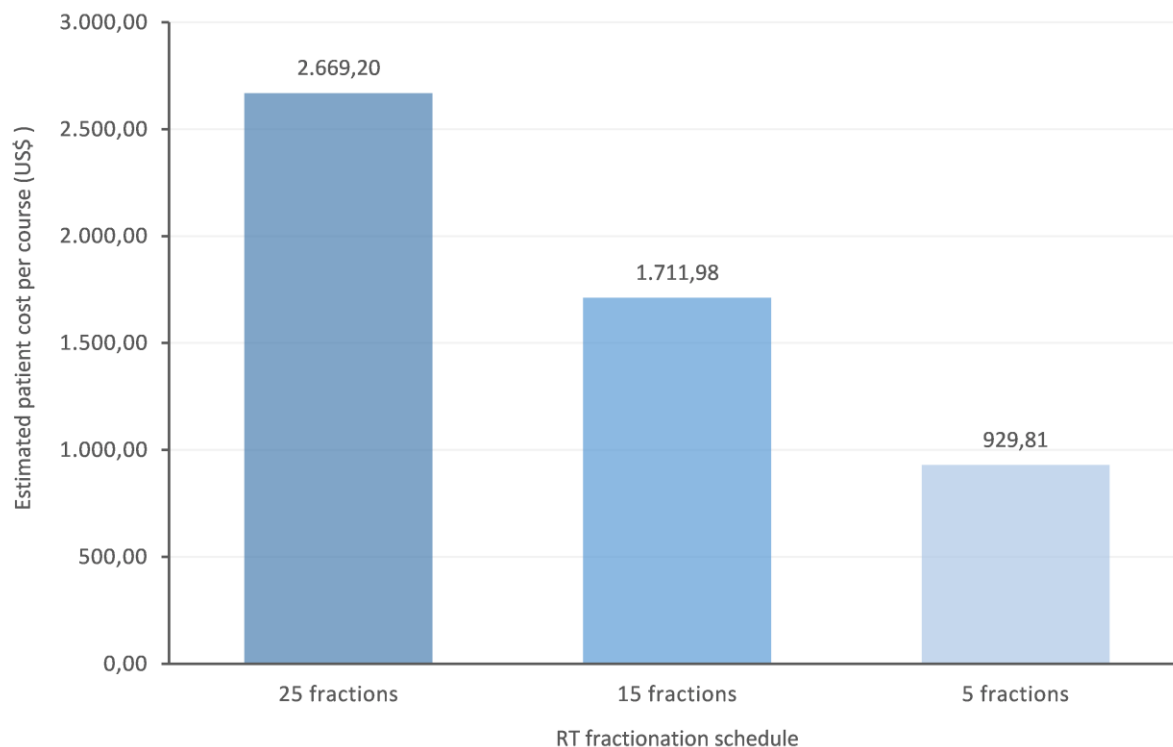
06 May 2022 - 10 May 2022  
Copenhagen, Denmark

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

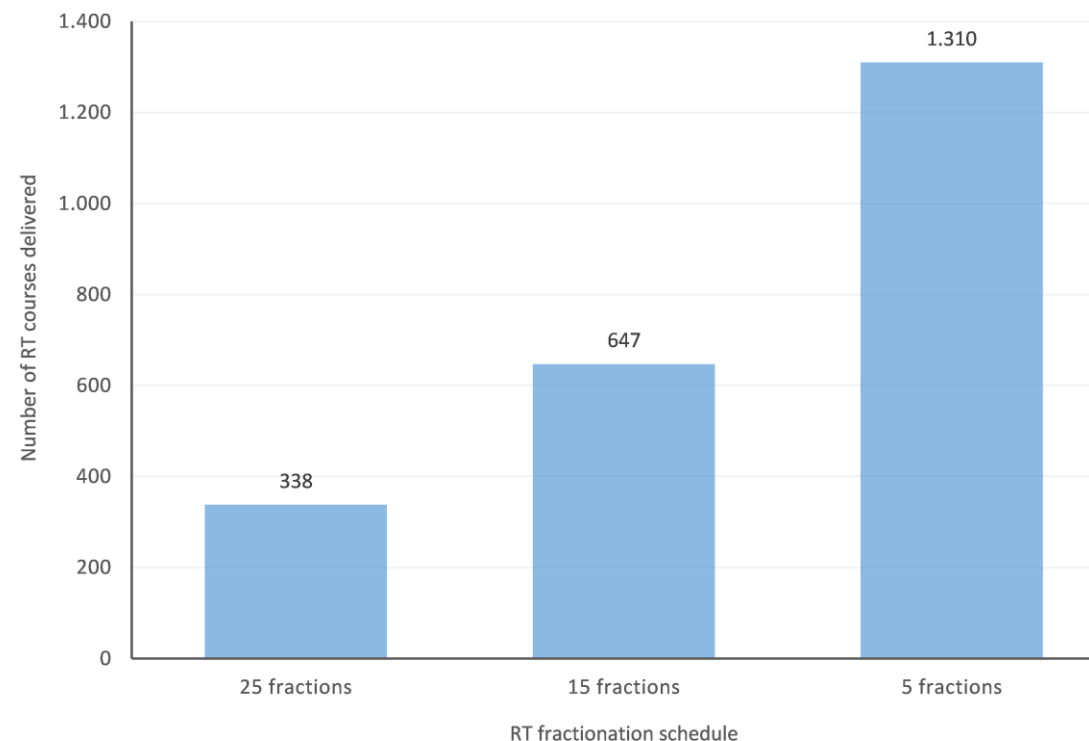


Prince Taylor,<sup>ab</sup> Marcus Simões Castilho,<sup>c</sup> and Gustavo Nader Marta<sup>d,e\*</sup>

Estimated Patient Cost per RT Schedule



Estimated annual RT productivity of 1 LINAC machine per EBRT regimen





# Radioterapia parcial da mama

Breast J. 2019 Jan;25(1):124-128. doi: 10.1111/tbj.13164. Epub 2018 Dec 7.

## **Accelerated partial breast irradiation: Current status with a focus on clinical practice.**

Miranda FA<sup>1</sup>, Teixeira LAB<sup>1,2</sup>, Heinzen RN<sup>3</sup>, de Andrade FEM<sup>3</sup>, Hijal T<sup>4</sup>, Buchholz TA<sup>5</sup>, Moraes FY<sup>1,6</sup>, Poortmans P<sup>7</sup>, Marta GN<sup>1,2</sup>.

*The Breast Journal*

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Lancet Oncol. 2021 Jul;22(7):e297. doi: 10.1016/S1470-2045(21)00260-6.

THE LANCET  
Oncology

## **Partial breast irradiation with intraoperative radiotherapy in the ELIOT trial**

Marta GN and Meattini I



# THE LANCET Oncology

## 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

[Icro Meattini, MD](#)   • [Carlotta Becherini, MD](#) • [Prof Liesbeth Boersma, MD](#) • [Orit Kaidar-Person, MD](#) • [Gustavo Nader Marta, MD](#) • [Angel Montero, MD](#) • [Prof Birgitte Vrou Offersen, MD](#) • [Marianne C Aznar, PhD](#) • [Prof Claus Belka, MD](#) • [Prof Adrian Murray Brunt, FRCR](#) • [Samantha Dicuonzo, MD](#) • [Pierfrancesco Franco, MD](#) • [Mechthild Krause, MD](#) • [Mairead MacKenzie, MD](#) • [Tanja Marinko, MD](#) • [Livia Marrazzo, MSc](#) • [Ivica Ratoso, MD](#) • [Astrid Scholten, MD](#) • [Elżbieta Senkus, MD](#) • [Hilary Stobart](#) • [Philip Poortmans, MD](#) \* • [Prof Charlotte E Coles, FRCR](#) \* • [Show less](#) • [Show footnotes](#)





# ESTRO 2022- Radioterapia parcial da mama

- $\geq$  Idade 50 anos
- Doença invasiva (não lobular) até 3 cm – grau 1 ou 2.
- Margens livres ( $> 2$  mm)
- Ausência de invasão angiolinfática
- Perfil luminal
- Tumor unicêntrico e unifocal
- Linfonodos axilares negativos (incluindo células tumorais isoladas)
- Sem tratamento sistêmico neoadjuvante
- Carcinoma ductal *in situ* de risco favorável (tamanho  $\leq 2,5$ cm com margens cirúrgicas livres de  $\geq 3$  mm)



1. Radioterapia hipofracionada moderada
2. Ultrahipofracionamento
- 3. Omissão da radioterapia**
4. Considerações finais



# Evidências sobre omissão da RT

- **Opção padrão**
  - Pacientes selecionadas com CDIS de mama após cirurgia conservadora
  - Doença invasiva estágio I RE+ em idosas
- **Em investigação**
  - Biologia favorável doença invasiva com RE+ em idade mais ampla (não idosas)





# Carcinoma *in situ* (*CDIS*)



# CDIS

## Cirurgia exclusiva

Author	Ref.	Period	n	FU [months]	LR %	Invasive LR %
Guerrieri-Gonzaga (2010)	[23]	1999-05	338	66	14.5	43
Kerlikowske (2010)	[24]	1983-94	1162	98	27.9	52
Rakovitch (2013)	[25]	1994-03	1867	120	19.5	51

LR: local recurrence, CBC: contralateral breast cancer, NR: not reported.



# CDIS

Estudo	Recorrência local (%)						Sobrevida global (%)	
	Total		Invasiva		In situ			
	Sem RT	Com RT	Sem RT	Com RT	Sem RT	Com RT	Sem RT	Com RT
<b>NSABP B-17</b>	35	19,8	19,6	10,7	15,5	9	86	87
<b>EORTC 10853</b>	30	17	15	9,5	15	7,5	90	88
<b>UK/ANZ DCIS</b>	19,4	7	9,1	3,3	9,7	3,8	97,9	96,2
<b>SweDCIS</b>	20	32	-	-	-	-	77,7	73
<b>RTOG 9804</b>	15,1	7,1	9,5	5,4	-	-	81,9	81,2

# CDIS

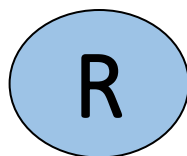
## NRG Oncology/RTOG 9804

### 636 pacientes – “*good-risk ductal*”

- > 26 anos
- CDIS (<2,5 cm)
- Margem > 3 mm
- Unicêntrico
- Grau nuclear: 1 e 2
- Detecção incidental / mamografia

Cirurgia

conservadora



■ 50 Gy (25 x 2Gy) – 5 semanas +/- Tamoxifeno

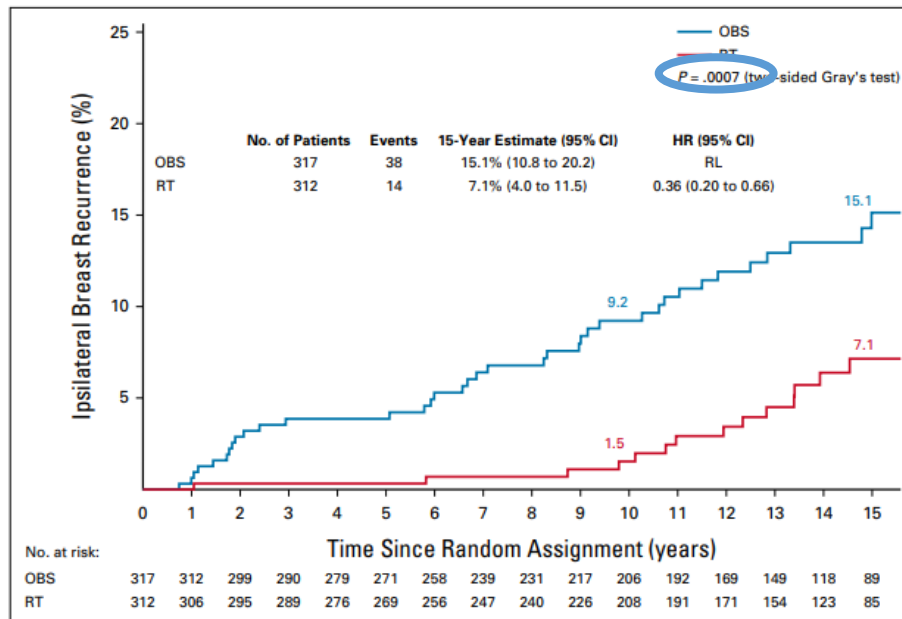
■ Observação (+/- Tamoxifeno)



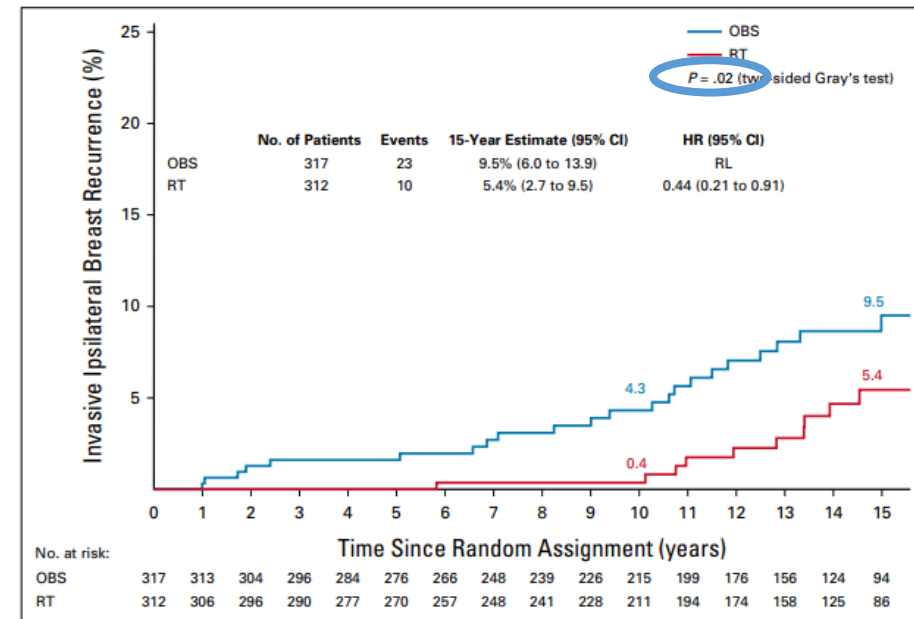
# CDIS

## NRG Oncology/RTOG 9804

### Recorrência ipsilateral



### Recorrência ipsilateral invasiva





# CDIS – Controle local

	Local resection	Local resection + PORT	2p
Age			
<50 y	29.1	18.5	0.007
≥50 y	27.8	10.8	<0.00001
Surgery type			
Local excision	27	12.5	<0.00001
Sector excision	30.4	13.7	<0.00001

**Subgrupo 291 pacientes com CDIS baixo risco**

*T ≤ 20 mm*

*Margens livres*

*Grau I*

**RT = redução do risco de recidiva absoluta de 18%**  
*(12% versus 30%, 2p = 0.002)*

Present	36.5	16.6	<0.00001
Absent	25.5	12	0.0003
Tumour size [pT]			
1-20 mm	28.9	13.1	<0.00001
21-50 mm	39	13	0.0001



## *SEER data*

- 32.144 *pacientes*

*RT: 20.329 (63%)*

*Sem RT: 11.815 (37%)*

- 304 *mortes por CA mama (96 meses)*

### Ganho de sobrevida no grupo da RT

- Alto grau nuclear
  - Jovens
- Tumor volumoso

# CDIS

	Age (years)	Size (mm)	Histology	Score
Points				
0	61+	< 16	Low grade	0
1	40-60	16-40	Intermediate grade	
2	< 40	41+	High grade	6

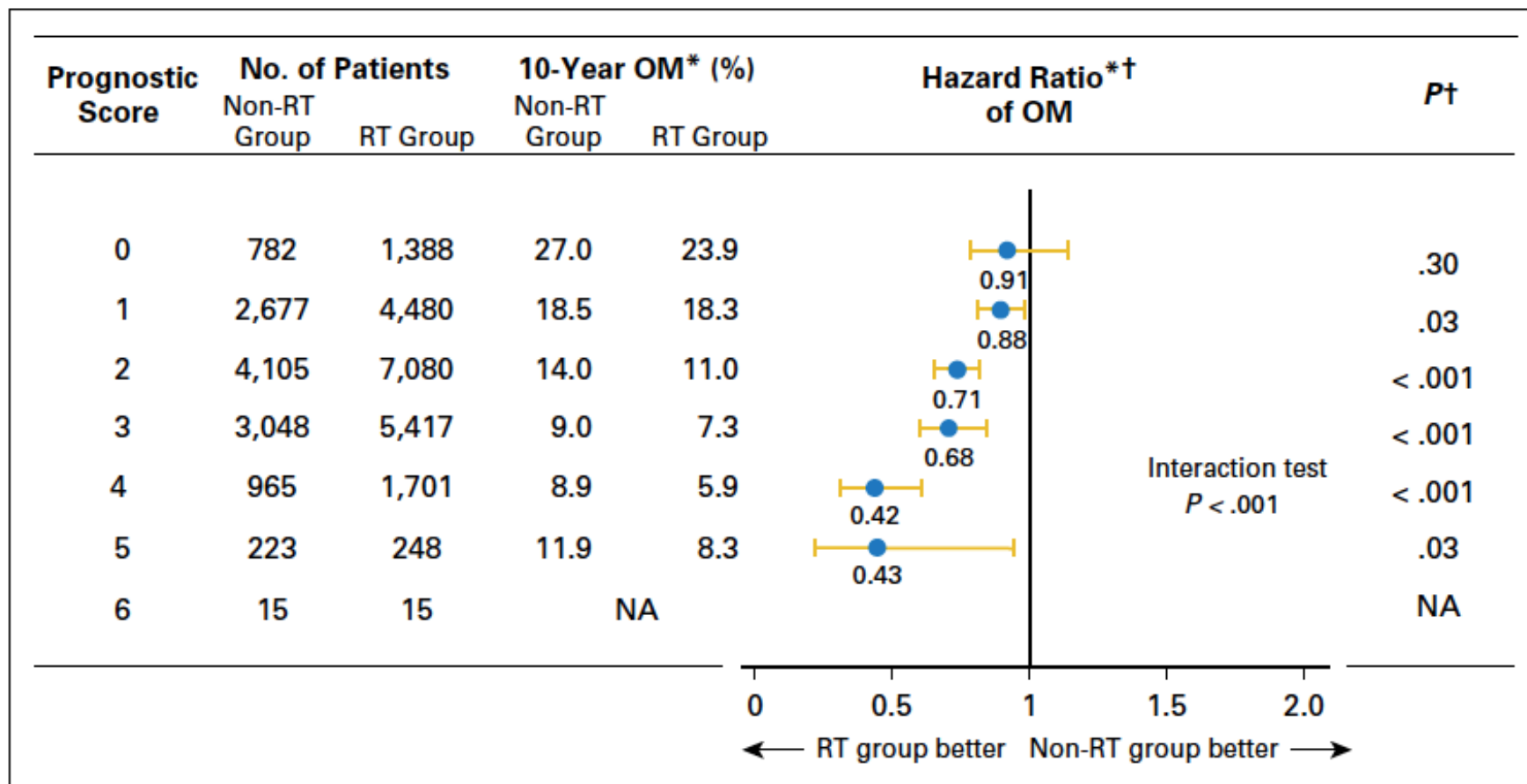
A large blue arrow points downwards from the 'Score' column, indicating that the score increases from 0 at the top to 6 at the bottom.

**Fig 1.** Patient prognostic score: risk stratification. Modified from Smith et al.<sup>20</sup>





## Mortalidade Global





# CDIS



National  
Comprehensive  
Cancer  
Network®

## NCCN Guidelines Ductal Carcinoma in Situ (DCIS)

### DIAGNOSIS

### WORKUP

### PRIMARY TREATMENT

DCIS  
Tis,N0,M0

- History and physical exam
- Diagnostic bilateral mammogram
- Pathology review<sup>a</sup>
- Determination of tumor estrogen receptor (ER) status
- Genetic counseling for patients at risk<sup>b</sup> of hereditary breast cancer
- Breast MRI<sup>c,d</sup> as indicated

Breast-conserving surgery<sup>e</sup> (BCS) without lymph node surgery<sup>f</sup>

Total mastectomy with or without sentinel lymph node biopsy (SLNB)<sup>f,h</sup> + reconstruction (optional)<sup>k</sup>

Whole breast radiation therapy (WBRT) (category 1) with or without boost to tumor bed<sup>g,h,i,j</sup>

or  
Accelerated partial breast irradiation (APBI)<sup>g,h,i,j</sup>

or  
No RT<sup>g,h,i,j</sup> (category 2B)

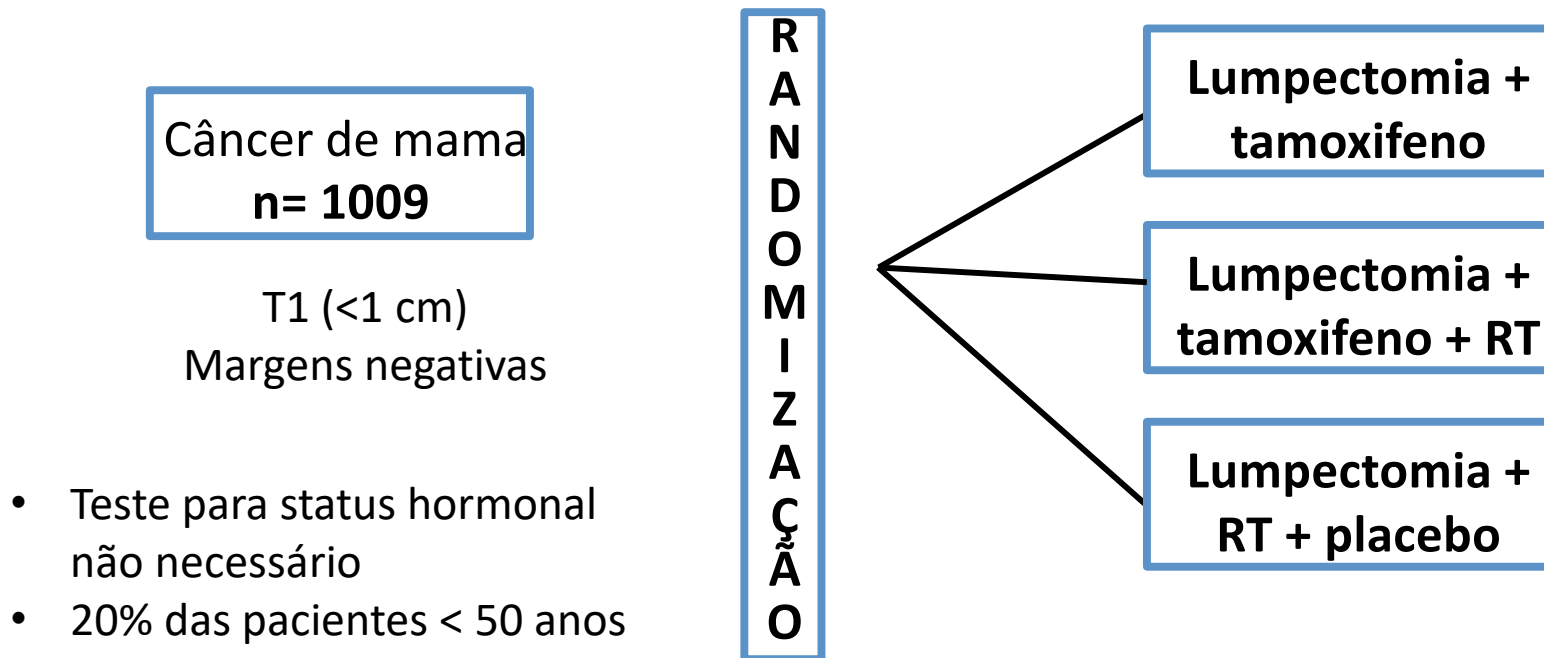


# Carcinoma invasivo



# NSABP B-21

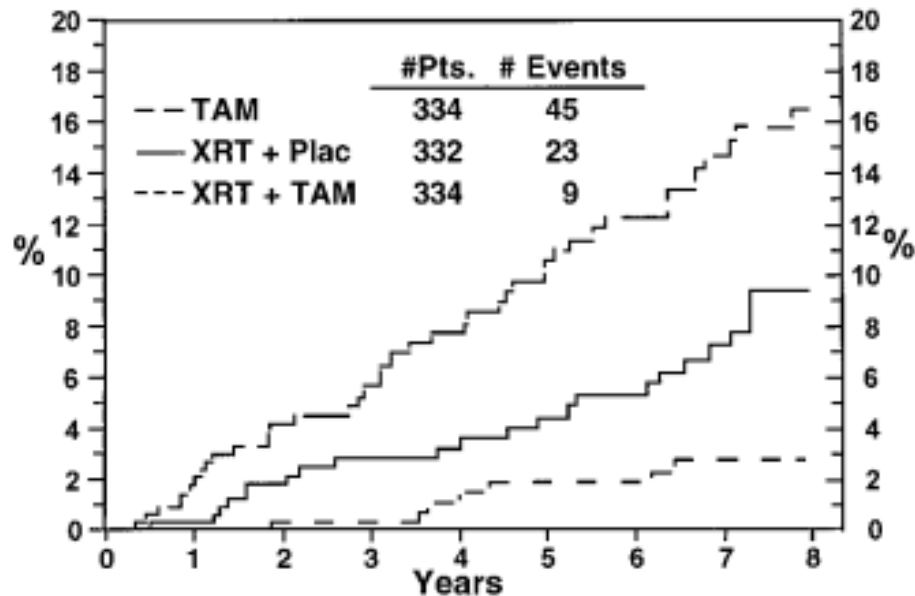
O tamoxifeno pode ser utilizado em vez da RT em pacientes selecionada?





# NSABP B-21

O tamoxifeno pode ser utilizado em vez da RT em pacientes selecionada?

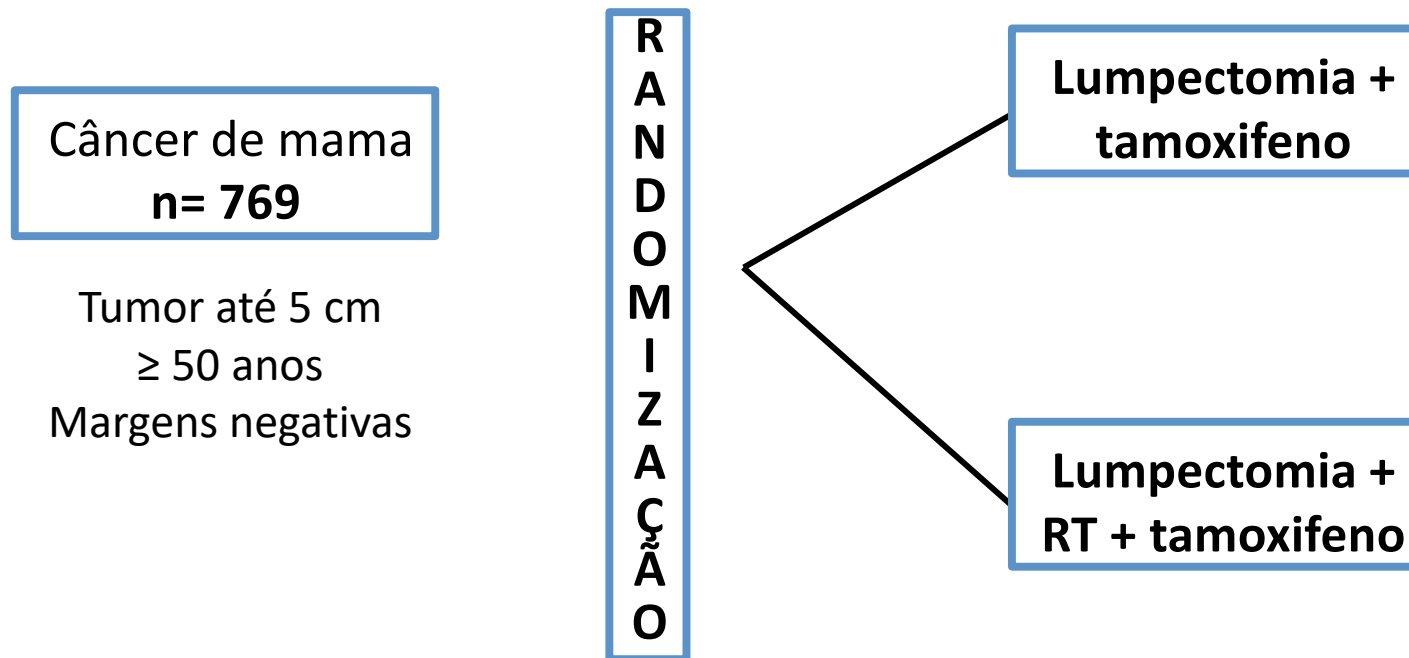


*Recorrência ipsilateral em 8 anos*

- 16,5% com TAM exclusivo
- 9,3% com RT
- 2,8 com RT + TAM

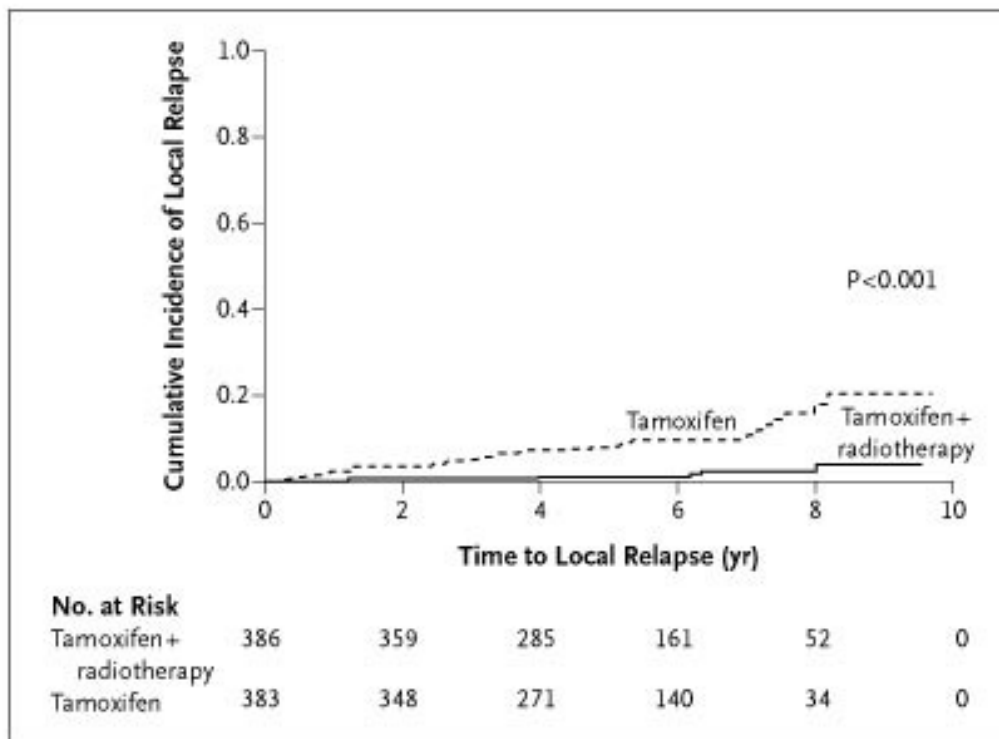


# Estudo Canadense





# Estudo Canadense



***Recorrência ipsilateral em 8 anos***

- **18% TAM exclusivo versus 4% RT + TAM**

Análise de subgrupo 611 pacientes T1, RE positivo:

***Recorrência ipsilateral em 8 anos***

- **15% TAM exclusivo versus 4% RT + TAM**



# CALGB 9343

Câncer de mama  
n= 636

**≥ 70 anos**

**Julho 1994 - Agosto 1996:** 4 cm (T1 / T2),  
independente do status receptor hormonal

**Agosto 1996:** Tumor até 2 cm  
RE - positivo ou desconhecido  
Margens negativas

R  
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O

Lumpectomia +  
tamoxifeno

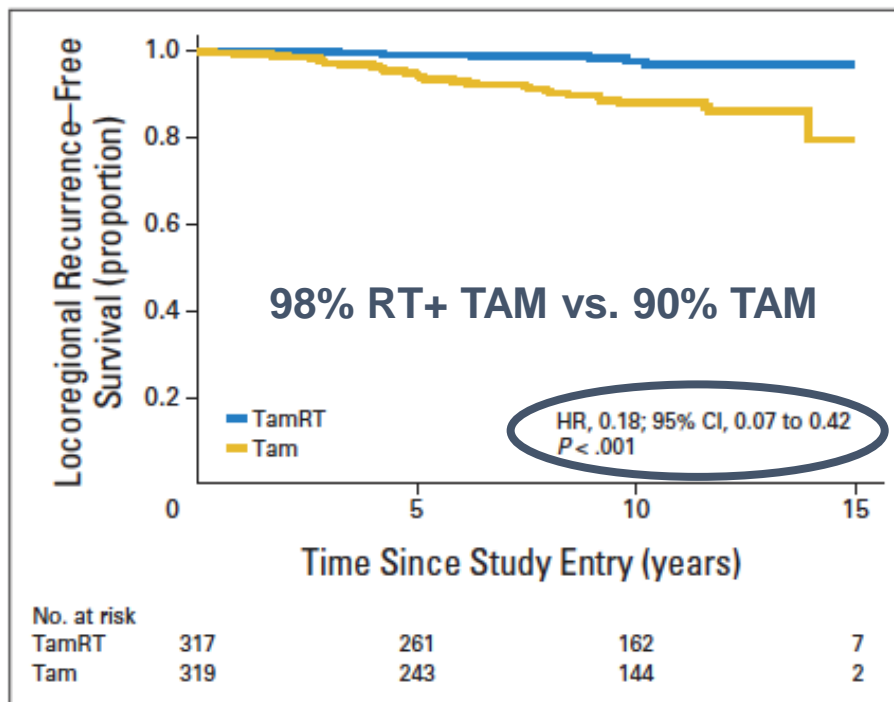
Lumpectomia +  
tamoxifeno + RT



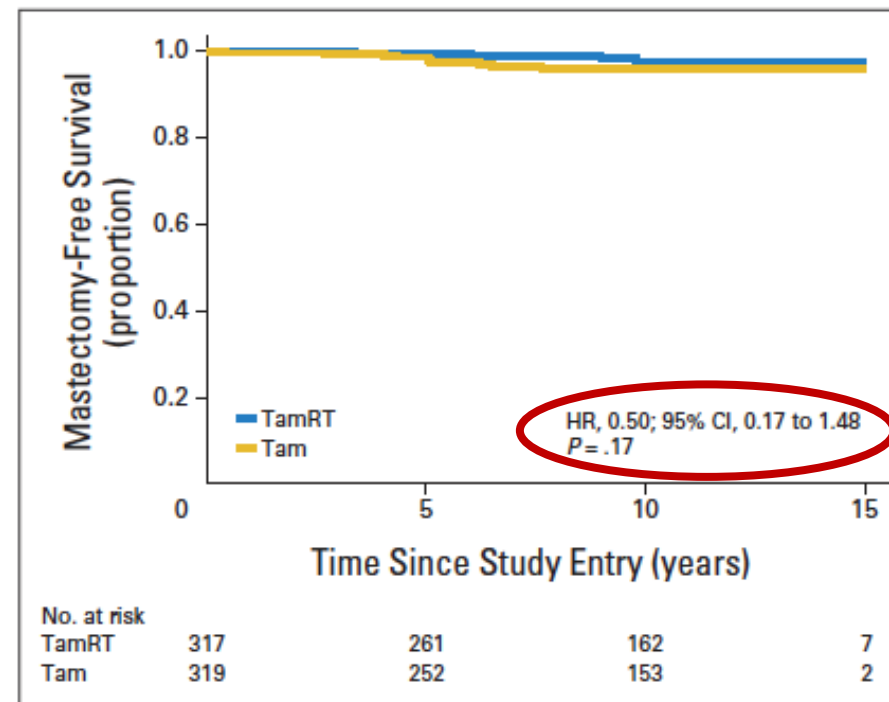


# CALGB 9343

### Recorrência locorregional



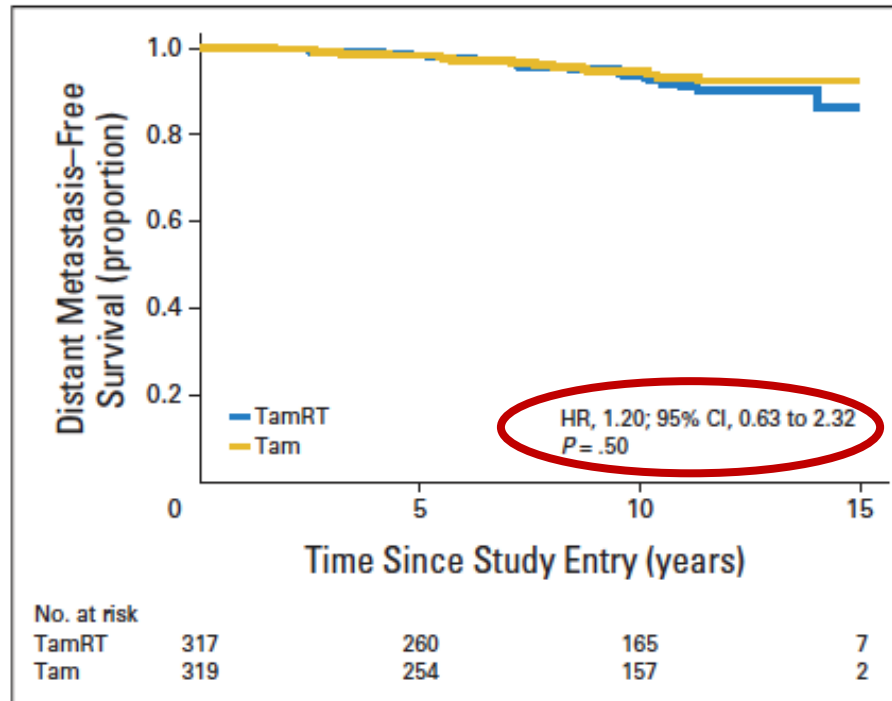
### Sobrevida livre de mastectomia



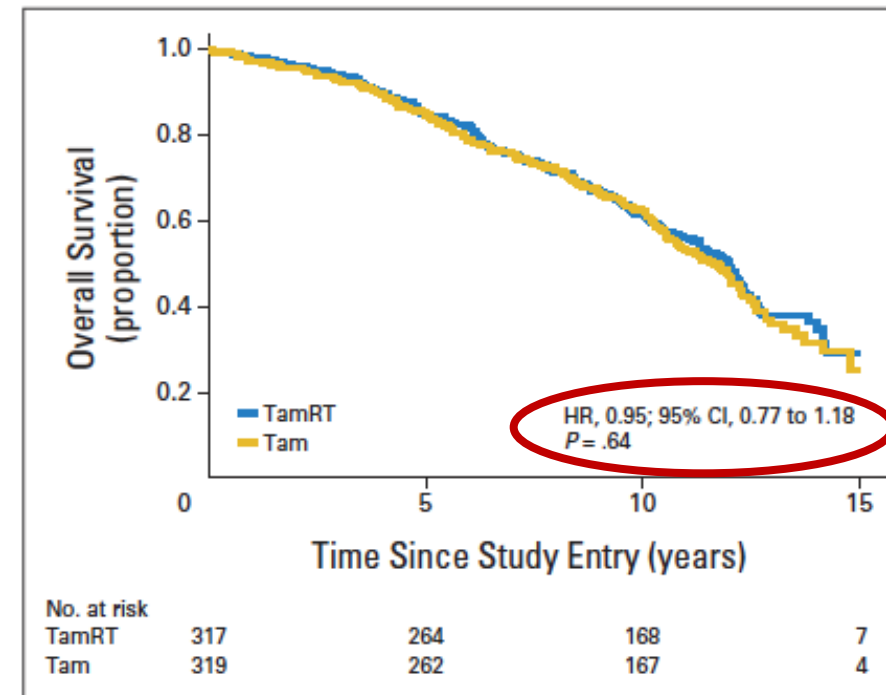


# CALGB 9343

### Sobrevida livre de doença à distância



### Sobrevida Global



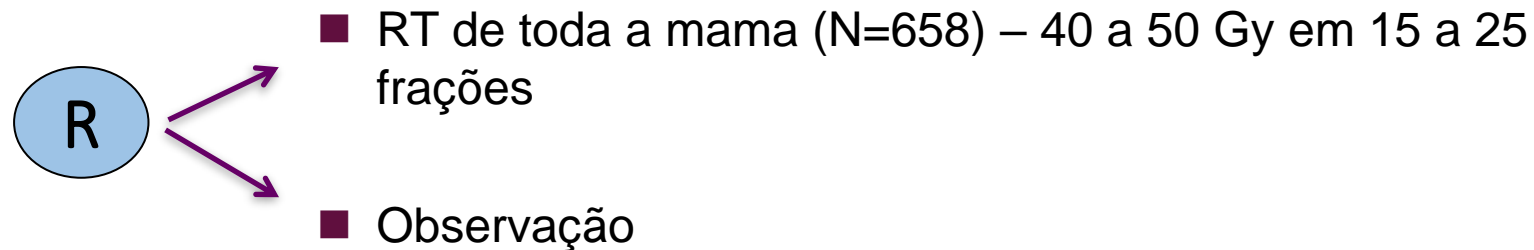


# PRIME II

## 1326 Pacientes (2003 - 2009)

- $\geq 65$  anos
- $T \leq 3$  cm, pN0
- Cirurgia conservadora
- RE / RP positivos
- Tratados com HT
- Margem cirúrgica  $\geq 1$  mm

Exclusão: grau 3, invasão angiolinfática e invasão perineural (1 fator isolado foi permitido)



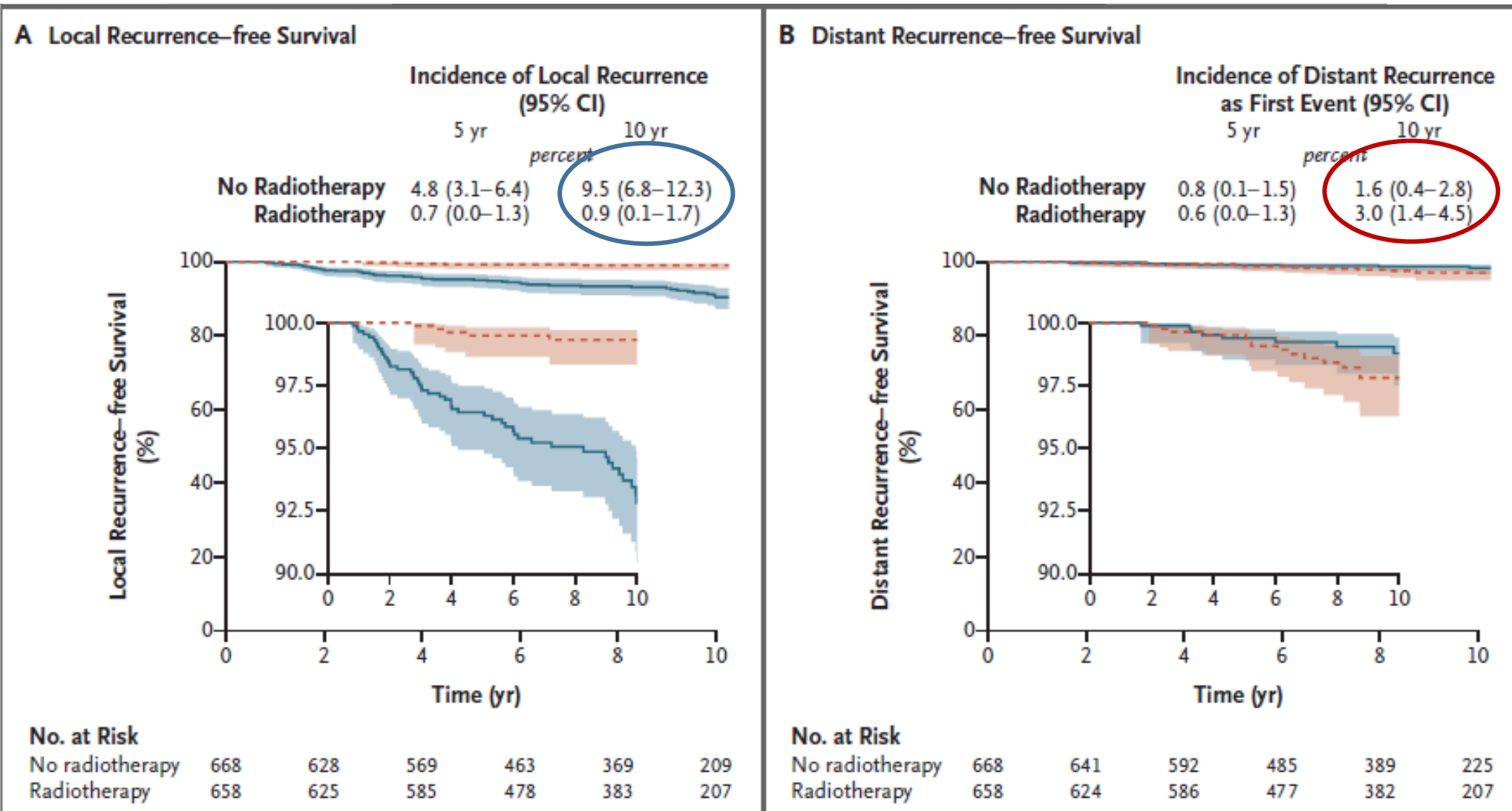
**Objetivo primário:** recorrência ipsilateral

**Objetivos secundários:** recorrências regional, contralateral e a distância, sobrevida livre de doença e sobrevida global



# PRIME II

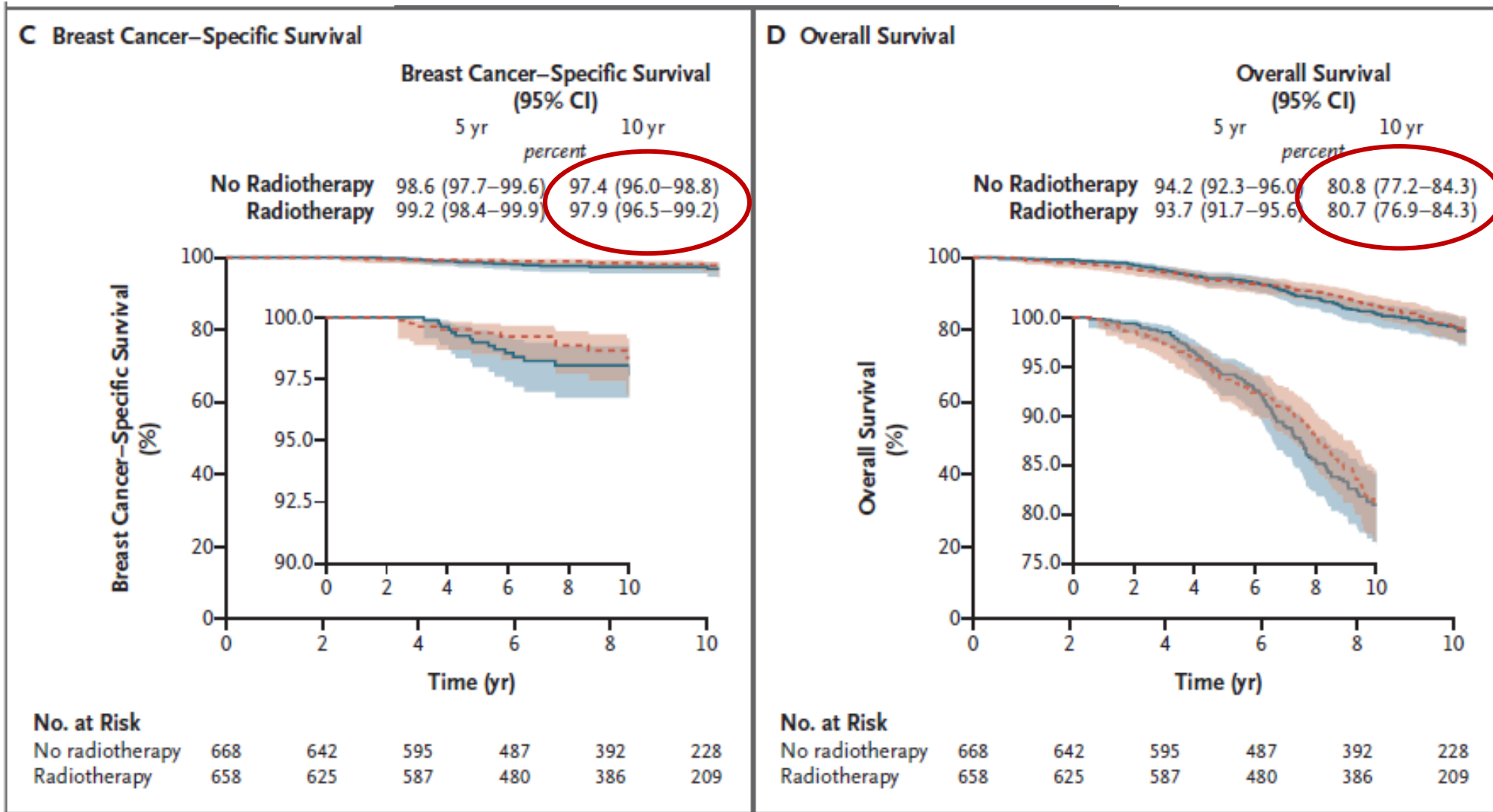
--- Radiotherapy    — No radiotherapy





# PRIME II

--- Radiotherapy    — No radiotherapy





# Estudos contemporâneos

- Características clínico-patológicas
- Características biológicas



2022 ASCO<sup>®</sup>  
ANNUAL MEETING

# LUMINA: A Prospective Trial Omitting Radiotherapy following Breast Conserving Surgery in T1N0 Luminal A Breast Cancer

T Whelan, S Smith, T Nielsen, S Parpia, A Fyles, A Bane, F Liu, L Grimard, C Stevens, J Bowen, S Provencher, E Rakovitch, V Théberge, A Mulligan, M Akra, D Voduc, T Hijal, I Dayes, G Pond, and M Levine

For the Ontario Clinical Oncology Group



2022 ASCO<sup>®</sup>  
ANNUAL MEETING

#ASCO22

PRESENTED BY:  
Timothy Whelan BM BCh

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CLINICAL ONCOLOGY  
KNOWLEDGE CONQUERS CANCER



## Specific Objective

- To determine if women with low risk clinical pathological factors ( $\geq 55$  years, T1N0, G1-2) and luminal A ( $ER \geq 1\%$ ,  $PR > 20\%$ , Her2 -ve and  $Ki67 \leq 13.25\%$ ), treated with BCS and endocrine therapy alone for 5 years without RT have an acceptable low risk of LR at 5 years ( $< 5\%$ )





## Results

Outcome	Events at 5 Years (total events)	5-Year Rate (90% CI)
<b>Local Recurrence</b>	<b>10</b>	<b>2.3 (1.3, 3.8)</b>
Contralateral Breast Cancer	8	1.9 (1.1, 3.2)
Any Recurrence	12	2.7 (1.6, 4.1)
Disease Free Survival	47 (23 second primary non-BCs)	89.9 (87.5, 92.2)
Overall Survival	13 (1 BC death)	97.2 (95.9, 98.4)

# Assinatura genética carcinoma invasivo

Table 1 Ongoing Trials of RT Omission.

Trial ClinicalTrials.gov Identifier, Trial Status	Design, Target Accrual	Demographics	Pathologic	Hormone Receptors (all require HER2 tumors)	Additional RT Omission Criteria	Primary Outcome	Other
<b>IDEA</b> <sup>26</sup> NCT02400190, Closed to accrual	Prospective single-arm cohort 200 eligible patients enrolled	Female Age 50-69 Postmenopausal	Unifocal pT1 pN0-pN0(i+) Margins $\geq 2$ mm No grade requirement	ER+ and PgR+	Oncotype DX Recurrence Score $\leq 18$	5-year LRR	
<b>LUMINA</b> <sup>27</sup> NCT01791829, Closed to accrual	Prospective single-arm cohort 500 patients in investigational cohort	Female Age $\geq 55$	Unifocal pT1 pN0 (i+ not specified) Margins $\geq 1$ mm Grade 1-2	ER $\geq 1\%$ and PgR $> 20\%$	Exclude if central Ki-67 staining $> 13.25\%$ (consistent with luminal B subtype) Prosigna PAM50 low Risk Of Recurrence score (ie, luminal A subtype)	5-year IBR	Non-lobular histologies only No EIC or LVI
<b>PRECISION</b> <sup>28</sup> NCT02653755, Closed to accrual	Prospective Phase II cohort 345 patients in investigational cohort	Female Age 50-75	Unicentric pT1 pN0-pN0(i+) No tumor on ink Grade 1-2 (cN0 allowed if $\geq 70$ )	ER $\geq 10\%$ or PgR+		5-year LRR	Optional survey component on decision comfort/regret
<b>PRIMETIME</b> <sup>29</sup> ISRCTN: 41579286, Open to accrual	Prospective cohort 1550 patients in RT omission cohort	Female Age $\geq 60$	Unifocal pT1 pN0-pN0(i+) Margins $\geq 1$ mm Grade 1-2	ER+  (PgR incorporated into IHC4+C score)	Central Ki-67 staining  IHC4+C risk category very low ( $< 5\%$ distant recurrence rate at 10 years)	5-year IBR	Postmenopausal women $< 60$ with comorbidities placing at significant risk of RT toxicity allowed
<b>EXPERT</b> <sup>30</sup> NCT02889874, Open to accrual	Randomized, non- inferiority, Phase III 1170 patients randomized	Female Age $\geq 50$	Unifocal pT1 pN0-pN0(i+) No tumor on ink Grade 1-2	ER $\geq 10\%$ and PgR $\geq 10\%$	Prosigna PAM50 Risk Of Recurrence $\leq 60$ and luminal A subtype	Non-inferiority of RT omission to adjuvant RT, followed up to 10 years	PRO, QALY, fear of recurrence assessment
<b>DEBRA</b> <sup>31</sup> NCT04852887, Open to accrual	Randomized, non- inferiority, Phase III 1670 patients randomized	Female or male Age 50-69	Unicentric pT1 pN0 (i+ not allowed) No tumor on ink No grade requirement	ER $\geq 1\%$ or PgR $\geq 1\%$	Oncotype DX Recurrence Score $\leq 18$	Non-inferiority of RT omission to adjuvant RT, followed up to 10 years	PRO, QoL, distress of recurrence assessment



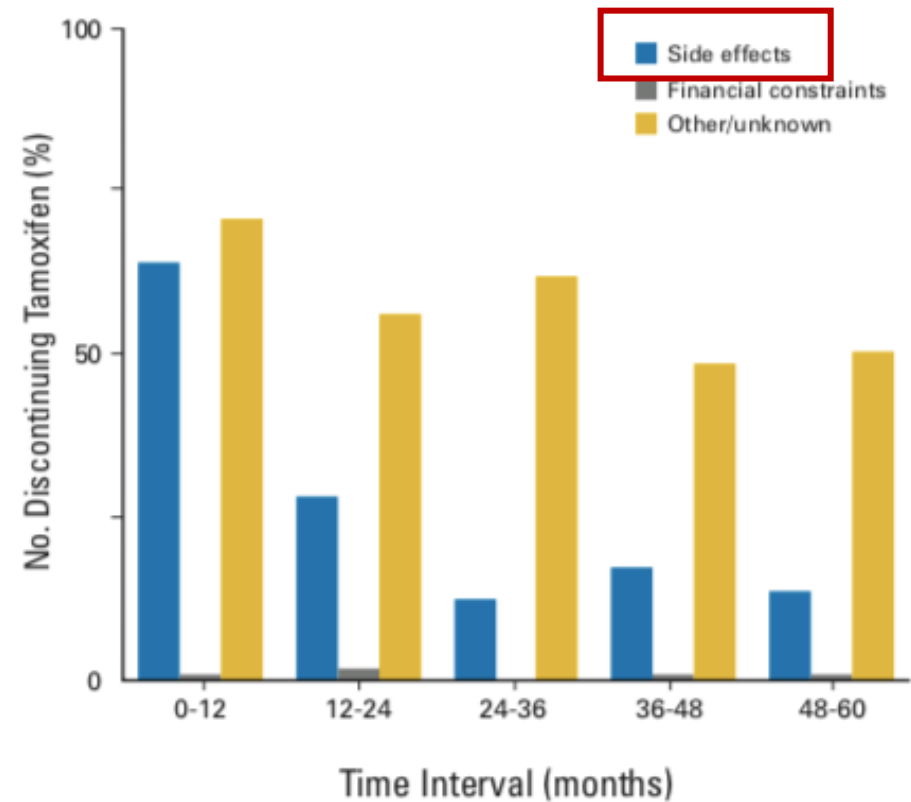
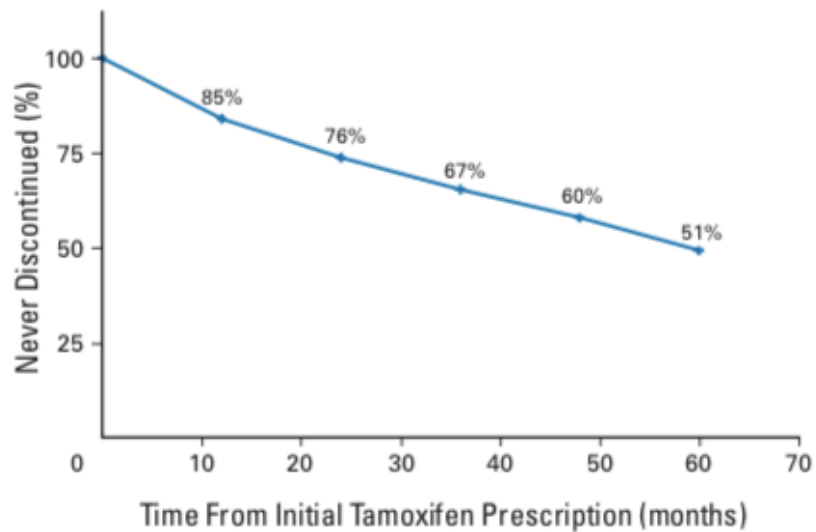
# Endocrinoterapia

- Duração: 5 anos
- **Efeitos colaterais**
- **Aderência**

# Endocrinoterapia

- Tamoxifen discontinuation among older women

49% discontinued tamoxifen before the completion of 5 years





# Endocrinoterapia

JAMA Oncology | Original Investigation

## Evaluation of the Quality of Adjuvant Endocrine Therapy Delivery for Breast Cancer Care in the United States

**eTable 1. Factors Related to Adjuvant Endocrine Therapy Underuse Among Patients With Hormone Receptor–Positive Breast Cancer**

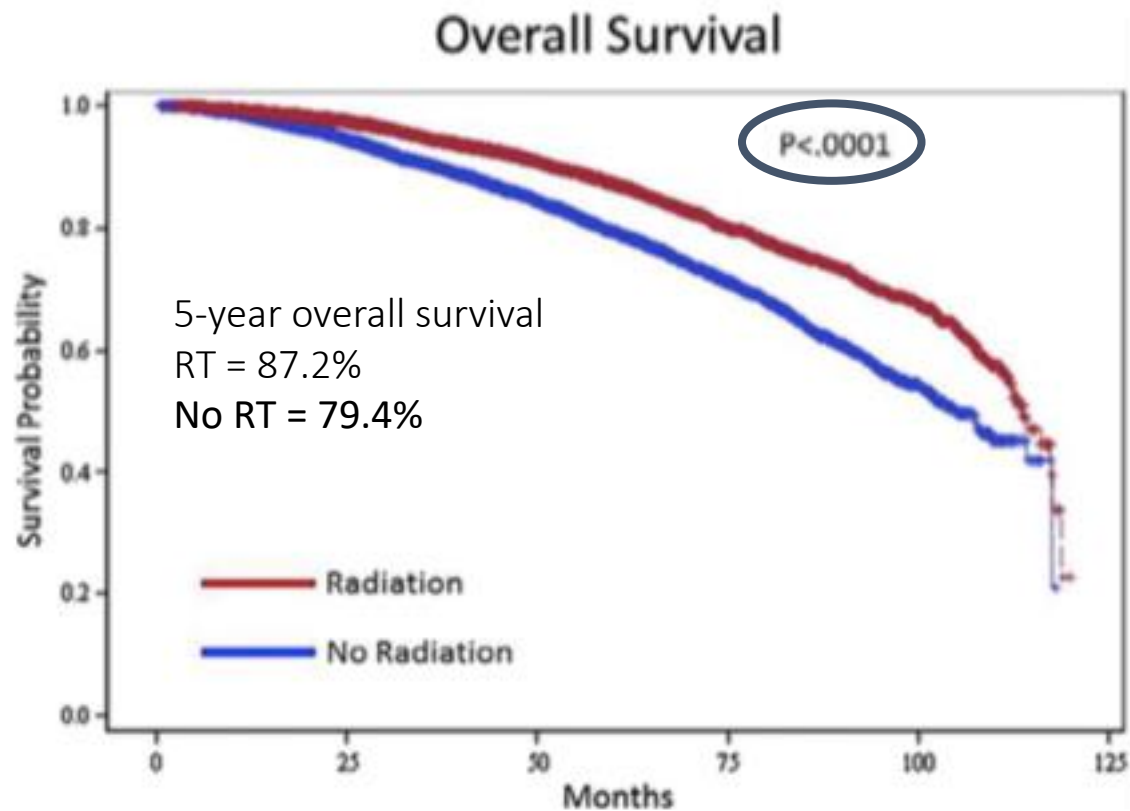
Characteristic	No. of Patients	No. (%) of AET Users	aOR (95% CI)*	$\chi^2$ Test †
Age at diagnosis				2572
<40	32,006	25,328 (79.1)	0.54 (0.52-0.57)	
40-49	141,697	115,245 (81.3)	0.90 (0.88-0.92)	
50-59	201,452	165,647 (82.2)	0.99 (0.97-1.01)	
60-69	214,687	175,712 (81.8)	1.0 (ref.)	
70-79	149,530	113,863 (76.1)	0.92 (0.90-0.93)	
80+	79,063	47,854 (60.5)	0.59 (0.58-0.61)	



# Real-world practice

- National Cancer Data Base (47,358 women)

Age  $\geq 70$  years  
Clinical stage I  
Estrogen receptor positive  
Negative margins





# Será que as pacientes idosas não preferem RT exclusiva?

- **BASO II Trial** (Blamey et al. Eur J. Cancer 2013)
  - Recorrência local (10 anos): 22% sem RT e HT; **8% RT; 8% HT;**  
**2% RT + HT**
- **Coorte de Ontário** (Goldberg et al. BCRT 2019)
  - Recorrência local **0,9% RT + HT;** **1,4% RT;** **3,1% HT;** 9,4% sem adjuvância
- **Trials em andamento**
  - **EUROPA:** *Exclusive endocrine therapy or partial breast irradiation for women aged  $\geq 70$  years with luminal A-like early stage breast cancer (NCT04134598 - EUROPA): Proof of concept of a randomized controlled trial comparing health related quality of life by patient reported outcome measures.*

Meattini I, et al. J Geriatr Oncol. 2021;12(2):182-189.



1. Radioterapia hipofracionada moderada
2. Ultrahipofracionamento
3. Omissão da radioterapia
4. **Considerações finais**





# Considerações finais

## Radioterapia

### Dose

*Esquema convencional -> **Hipofracionamento moderado (padrão)** ->*

***hipofracionamento extremo***

*(incluindo radioterapia parcial da mama)*

# Considerações finais

## Considerar omissão da RT

**CDIS:** detectado por imagem; Grau I ou II; T = 2,5 cm; margens negativas (3 mm)

### Invasivo

- Idade  $\geq 70$  anos ( $\geq 60$  anos *clinical trial*)
- T1N0
- Receptor hormonal positivo
- HER-2 negativo
- Grau 1-2
- HT por 5 anos

# Considerações finais

**Considerar omissão da RT**

**Omitir a RT = aumento da falha local**

**RT: segura, eficaz e muito rápida (hipofracionamento / RT parcial)**



**SÍRIO-LIBANÊS**

Obrigado

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