IV ZOOM Journal Club 2014

Bologna, 20 Febbraio 2015
Hotel NH De La Gare

Innovazioni tecnologiche e applicazioni nel trattamento radioterapico dei tumori mammari.

Discussant:

Marco Trovò

CRO - Aviano

Outline

- Cardiac dose-sparing techniques
- Proton beam
- Targit-A trial

The NEW ENGLAND JOURNAL of MEDICINE

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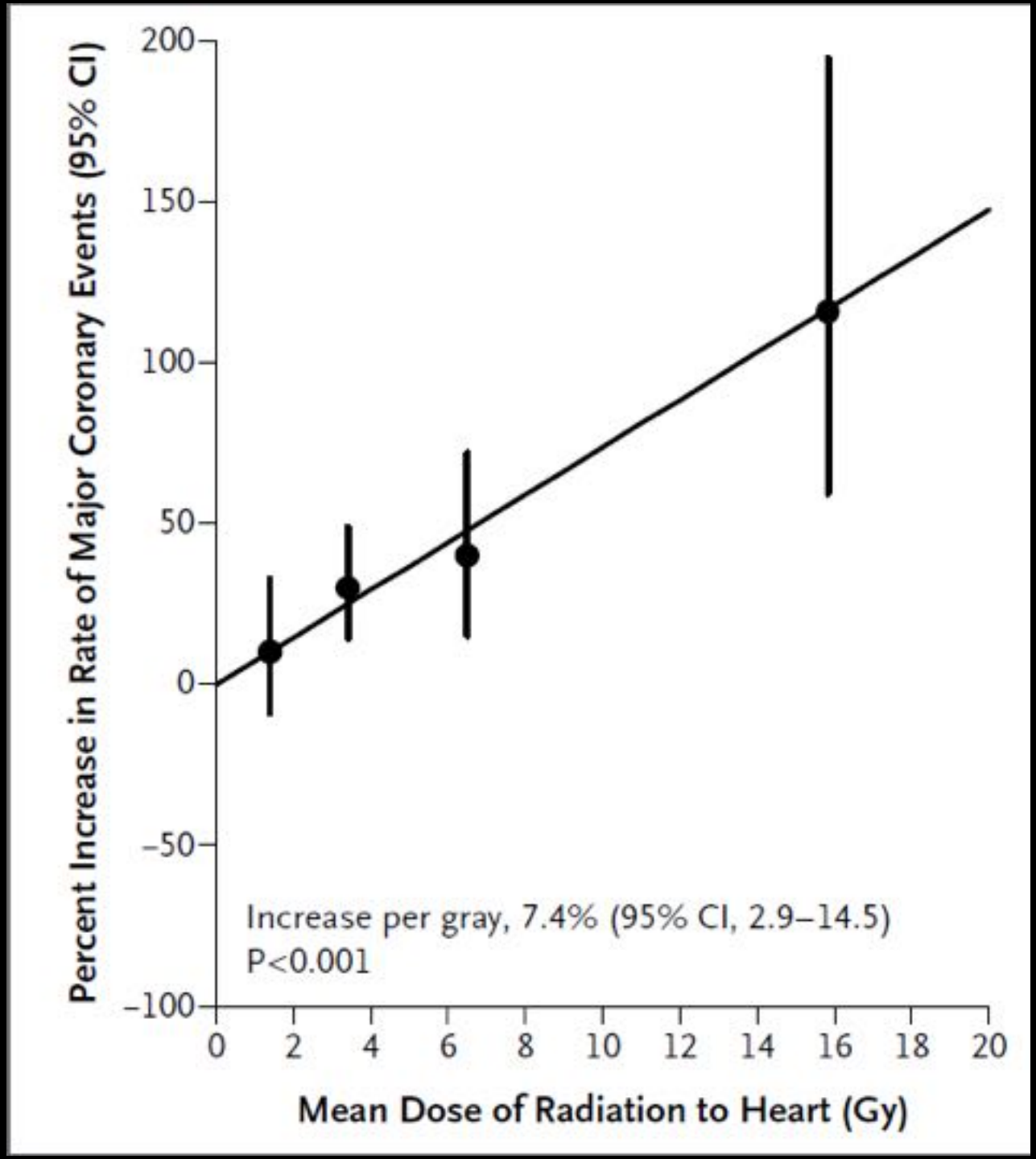
Risk of Ischemic Heart Disease in Women after Radiotherapy for Breast Cancer

Sarah C. Darby, Ph.D., Marianne Ewertz, D.M.Sc., Paul McGale, Ph.D., Anna M. Bennet, Ph.D., Ulla Blom-Goldman, M.D., Dorthe Brønnum, R.N., Candace Correa, M.D., David Cutter, F.R.C.R., Giovanna Gagliardi, Ph.D., Bruna Gigante, Ph.D., Maj-Britt Jensen, M.Sc., Andrew Nisbet, Ph.D., Richard Peto, F.R.S., Kazem Rahimi, D.M., Carolyn Taylor, D.Phil., and Per Hall, Ph.D.


Percent Increase in Rate of Major Coronary Events (95% CI)
200
150
100
50
0
−50
−100
0
2
4
6
8
10
12
14
16
18
20
Mean Dose of Radiation to Heart (Gy)
Increase per gray, 7.4% (95% CI, 2.9–14.5)
P<0.001

Radiation-related mortality from heart disease and lung cancer more than 20 years after radiotherapy for breast cancer

K E Henson*[,1], P McGale[1], C Taylor[1] and S C Darby[1]

[1]Clinical Trial Service Unit (CTSU), University of Oxford, Richard Doll Building, Old Road Campus, Roosevelt Drive, Oxford OX3 7LF, UK

558.000 breast cancer patients

SEER database 1973-2008

Cardiac mortality left-sided vs. right-sided

British Journal of Cancer 2012

Radiation-related mortality from heart disease and lung cancer more than 20 years after radiotherapy for breast cancer

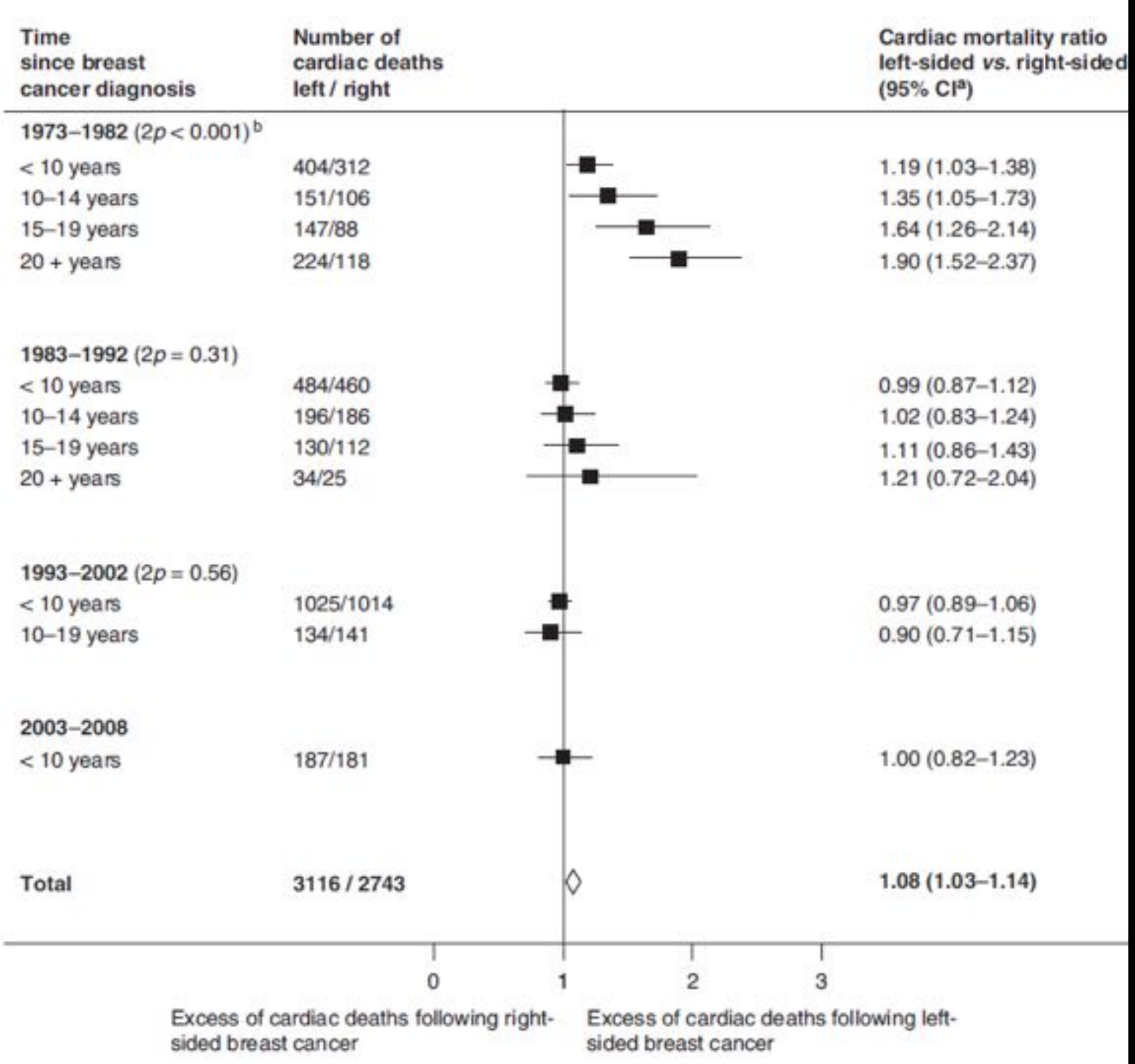
K E Henson*[,1], P McGale[1], C Taylor[1] and S C Darby[1]

[1]Clinical Trial Service Unit (CTSU), University of Oxford, Richard Doll Building, Old Road Campus, Roosevelt Drive, Oxford OX3 7LF, UK

Patients receiving NO RT: mortality for hearth disease did not differ between left-sided vs. right sided

Patients receiving RT: excess of cardiac deaths in left-sided:
Cardiac mortality ratio = 1.08 (CI 1.03 – 1.14) (p=0.002)

British Journal of Cancer 2012


Time since breast cancer diagnosis
Number of cardiac deaths left / right
Cardiac mortality ratio left-sided vs. right-sided (95% CI[a])
1973–1982 (2p < 0.001)[b]
< 10 years
404/312
1.19 (1.03–1.38)
10–14 years
151/106
1.35 (1.05–1.73)
15–19 years
147/88
1.64 (1.26–2.14)
20 + years
224/118
1.90 (1.52–2.37)
1983–1992 (2p = 0.31)
< 10 years
484/460
0.99 (0.87–1.12)
10–14 years
196/186
1.02 (0.83–1.24)
15–19 years
130/112
1.11 (0.86–1.43)
20 + years
34/25
1.21 (0.72–2.04)
1993–2002 (2p = 0.56)
< 10 years
1025/1014
0.97 (0.89–1.06)
10–19 years
134/141
0.90 (0.71–1.15)
2003–2008
< 10 years
187/181
1.00 (0.82–1.23)
Total
3116 / 2743
1.08 (1.03–1.14)
0
1
2
3
Excess of cardiac deaths following right-sided breast cancer
Excess of cardiac deaths following left-sided breast cancer

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Breast radiotherapy

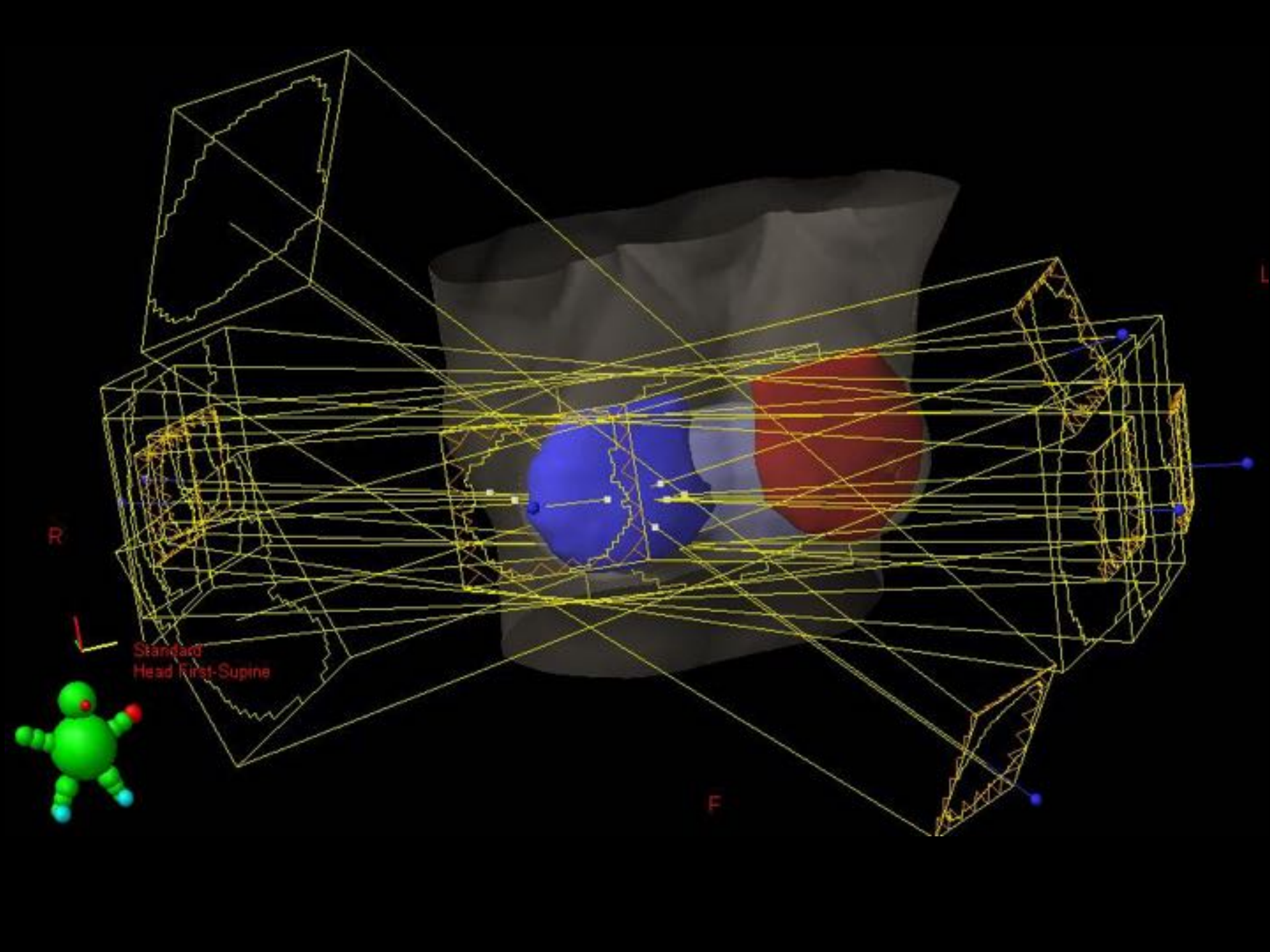
Volumetric modulated arc therapy and breath-hold in image-guided locoregional left-sided breast irradiation

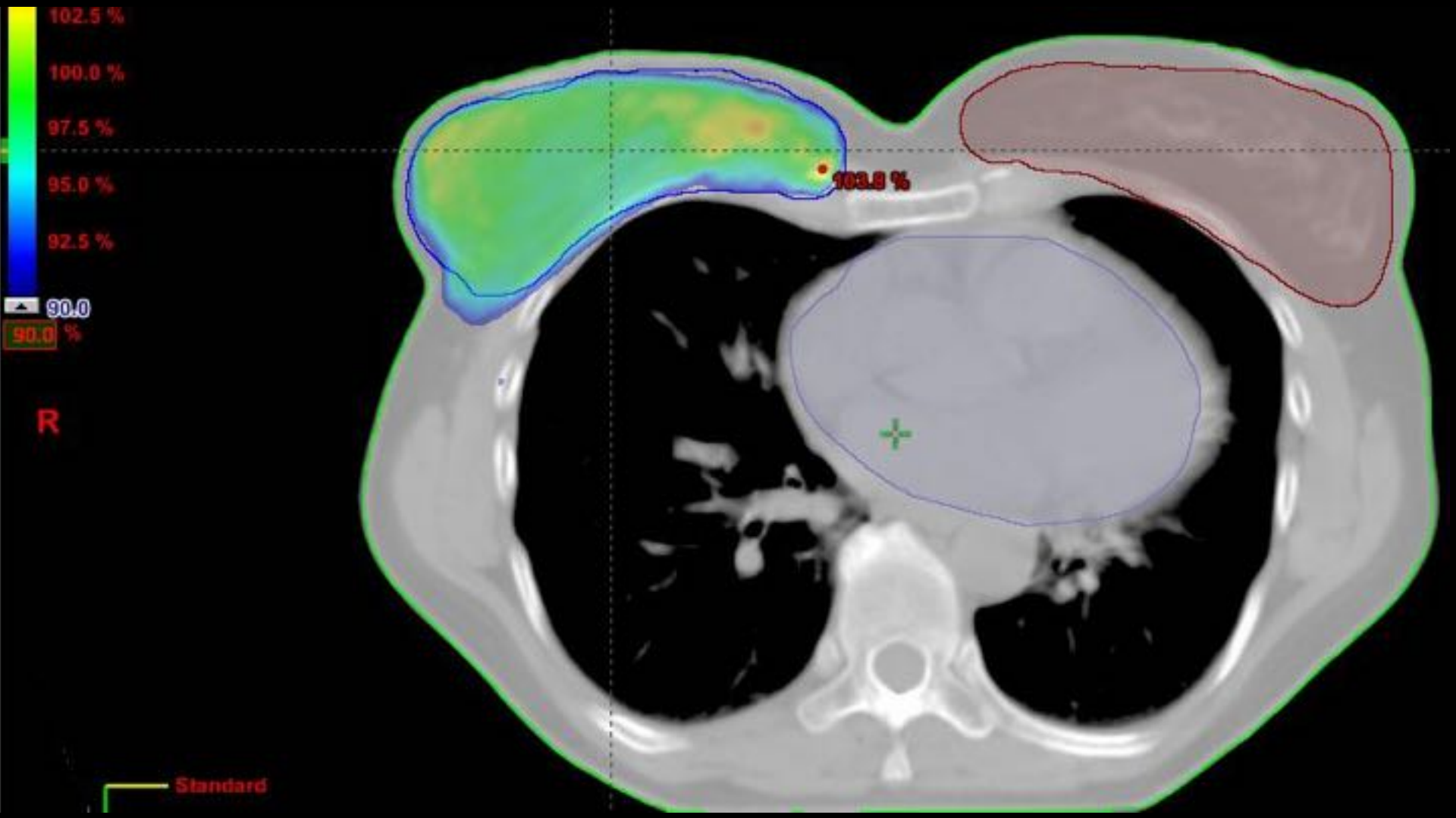
Sarah O.S. Osman, Sandra Hol, Philip M. Poortmans, Marion Essers *

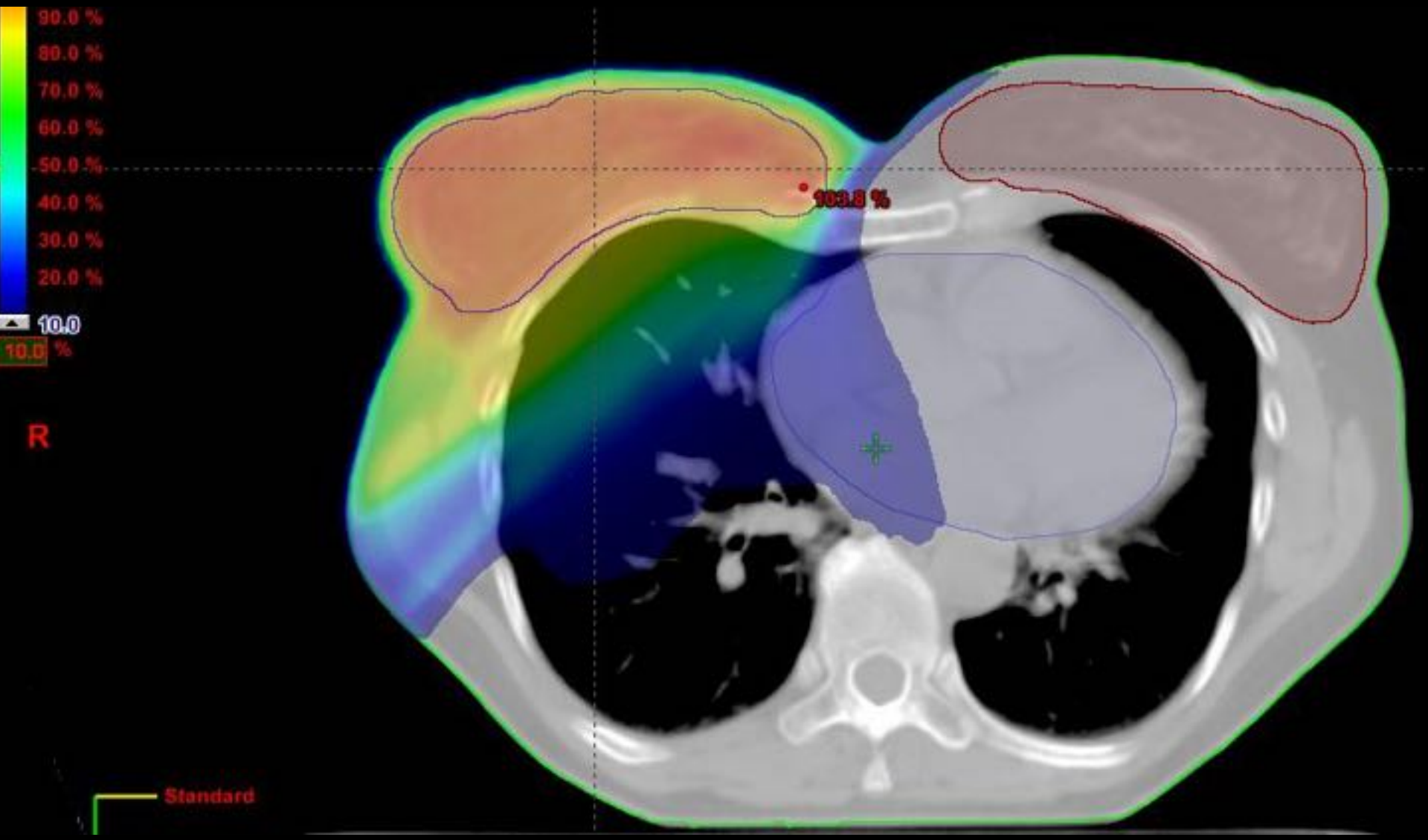
Department of Radiation Oncology, Institute Verbeeten, Tilburg, The Netherlands

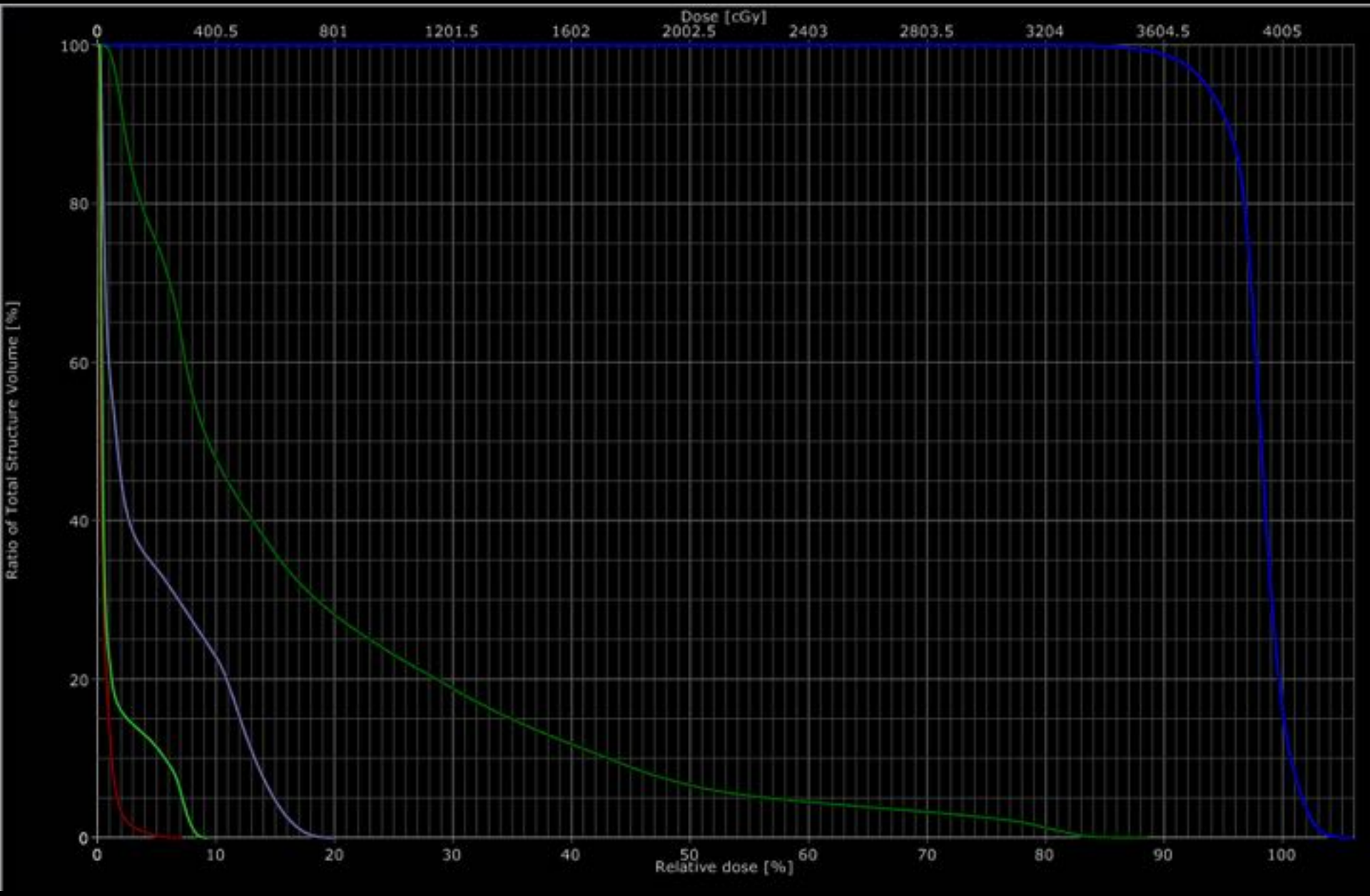
4 treatment techniques were compared in 13 patients

Structure	Parameter	3D-CRT FB	3D-CRT vmDIBH	VMAT FB	VMAT vmDIBH
	#MU	589 (559–618)	594 (564–624)	682 (649–732)	549 (528–569)
PTV	Volume	812 (524–1191)	786 (527–1156)	812 (524–1191)	786 (527–1156)
	$V_{95\%}$ (%)	95.3 ± 2.5 (89.3–98.3)	95.3 ± 2.7 (90.3–98.3)	95.4 ± 1.2 (94.0–98.1)	96.0 ± 1.5 (93.6–99.1)
	$D_{1\%}$ (%)	116.6 ± 4.4**	117.3 ± 4.4**	111.4 ± 3.2	111.2 ± 2.4
	CI	0.4 ± 0.1 (0.3–0.6)**	0.4 ± 0.1 (0.3–0.5)**	0.7 ± 0.1 (0.6–0.8)	0.7 ± 0.1 (0.6–0.8)
IMN	$V_{95\%}$ (%)	89.2 ± 7.7 (76.2–99.5)**	93.3 ± 5.3 (85.5–100)**	98.8 ± 1.8 (95.0–100)	99.1 ± 1.6 (95.0–100)
Periclav	$V_{95\%}$ (%)	97.2 ± 3.8 (87.7–100)	97.8 ± 4.4 (87.1–100)	98.7 ± 2.0 (94.6–100)	99.2 ± 1.4 (96.2–100)
Heart	V_{30Gy} (%)	12.8 ± 7.7 (2.6–23.7)**	4.9 ± 4.7 (0.0–14.6)**	1.0 ± 1.2 (0–4.2)	0.5 ± 0.9 (0.0–2.8)
	V_{20Gy} (%)	16.6 ± 7.2 (6.7–29.4)**	7.9 ± 7.3 (0.3–25.9)*	3.9 ± 2.5 (0.0–7.7)*	2.1 ± 2.4 (0.0–6.8)
	V_{5Gy} (%)	39.1 ± 14.0 (14.2–60.7)*	24.3 ± 15.0 (7.8–61.0)*	33.6 ± 16.3 (6.3–70.3)*	18.7 ± 11.1 (7.7–43.7)
	V_{2Gy} (%)	57.3 ± 9.2 (34.7–69.3)**	42.3 ± 13.7(20.0–70.8)**	87.1 ± 13.5(52.7–100)*	68.3 ± 11.4 (51.2–87.2)
	D_{mean} (Gy)	9.0 ± 2.2 (4.1–12.8)**	5.0 ± 2.1 (2.0–8.9)*	5.8 ± 1.6 (2.7–8.4)*	4.1 ± 1.4 (2.6–6.5)
IL lung	Volume	1238(810–1840)*	2009 (1292–2853)*	1238 (810–1840)*	2009 (1292–2853)
	V_{20Gy} (%)	44.2 ± 9.1 (31.2–57.1)**	38.7 ± 6.7 (25.8–51.2)**	27.9 ± 11.5 (11.4–55.0)	26.5 ± 8.9 (16.1–44.0)
	V_{5Gy} (%)	69.4 ± 16.8 (42.6–95.6)	65.5 ± 13.3 (45.0–94.2)	67.5 ± 13.6 (42.0–92.7)	66.2 ± 10.6 (50.4–86.5)
	D_{mean} (Gy)	19.0 ± 3.5 (13.3–23.8)**	17.1 ± 2.4 (13.0–21.9)**	14.0 ± 3.4 (8.4–21.3)	13.3 ± 3.1 (9.6–18.8)
CL lung	V_{20Gy} (%)	0.0 ± 0.0 (0.0)	0.0 ± 0.0 (0.0)	0.2 ± 0.4 (0.0–1.6)	0.0 ± 0.0 (0.0–0.1)
	V_{5Gy} (%)	0.0 ± 0.0 (0.0)**	0.1 ± 0.2 (0.0–0.9)**	17.8 ± 13.6 (5.7–57.7)	11.2 ± 6.7 (1.2–27.6)
	D_{mean} (Gy)	0.4 ± 0.1 (0.3–0.4)**	0.4 ± 0.1 (0.2–0.7)**	3.4 ± 1.2 (2.2–6.9)*	2.6 ± 0.6 (1.5–3.6)
Lungs	Volume	2811(1990–3864)*	4438 (3167–6066)*	2811(1990–3864)*	4439 (3167–6066)
	V_{20Gy} (%)	20.1 ± 3.9 (13.4–27.2)**	17.3 ± 2.3 (12.7–20.9)**	12.4 ± 5.2 (5.4–26.2)	11.6 ± 3.9 (7.3–19.5)
	D_{mean} (Gy)	8.7 ± 1.5 (6.1–11.3)*	7.8 ± 0.8 (6.2–9.0)	8.3 ± 1.8 (5.5–12.2)*	7.5 ± 1.4 (5.5–10.0)
CL breast	V_{20Gy} (%)	0.4 ± 0.7 (0.0–2.2)	0.6 ± 1.0 (0.0–2.5)	0.1 ± 0.1 (0.0–0.4)	0.1 ± 0.1 (0.0–0.3)
	V_{5Gy} (%)	1.6 ± 1.9 (0.0–5.4)**	1.7 ± 2.2 (0.0–6.0)**	12.9 ± 7.4 (1.8–24.0)*	10.3 ± 6.4 (1.0–18.0)
	V_{2Gy} (%)	5.6 ± 5.8 (0.1–20.7)**	5.8 ± 6.1 (0.1–21.4)**	51.3 ± 24.8 (13.6–82.6)	40.7 ± 28.2 (8.7–88.9)
	D_{mean} (Gy)	0.7 ± 0.4 (0.1–1.4)**	0.7 ± 0.6 (0.2–1.7)**	2.8 ± 0.9 (1.3–3.9)	2.5 ± 1.0 (1.0–3.7)
Non-target tissue	V_{5Gy} (%)	21.4 ± 4.3 (14.6–29.2)*	20.9 ± 4.3 (15.9–30.7)*	28.2 ± 6.5 (9.5–33.8)	28.3 ± 3.9 (23.2–34.5)
	D_{mean} (Gy)	6.0 ± 0.8 (4.8–7.6)	6.0 ± 0.6 (5.3–7.0)	5.9 ± 1.2 (2.5–6.9)*	5.8 ± 0.6 (4.9–6.7)


R
L
Standard
Head First-Supine
F


102.5 %
100.0 %
97.5 %
95.0 %
92.5 %
90.0
90.0 %
R
103.8 %
Standard


90.0 %
80.0 %
70.0 %
60.0 %
50.0 %
40.0 %
30.0 %
20.0 %
10.0
10.0 %
R
103.8 %
Standard


Dose [cGy]
0
400.5
801
1201.5
1602
2002.5
2403
2803.5
3204
3604.5
4005
100
80
60
40
20
0
Ratio of Total Structure Volume [%]
0
10
20
30
40
50
60
70
80
90
100
Relative dose [%]

Randomised trial of standard 2D radiotherapy (RT) versus intensity modulated radiotherapy (IMRT) in patients prescribed breast radiotherapy

Ellen Donovan[a], Natalie Bleakley[a], Erica Denholm[b], Phil Evans[a], Lone Gothard[c], Jane Hanson[c], Clare Peckitt[b], Stephanie Reise[a], Gill Ross[d], Grace Sharp[c], Richard Symonds-Tayler[a], Diana Tait[c], John Yarnold[c,*], on behalf of the Breast Technology Group

Radiotherapy and Oncology 82 (2007) 254–264

Table 2
Percent of breast volume receiving dose >105% prescribed, based on data from 190 patients for whom DVH data were accessible

Percentage volume of breast receiving >105% of prescribed dose	Standard (2D) $n = 145$		IMRT (3D) $n = 145$	
	Number of patients	Percentage (%)	Number of patients	Percentage (%)
<1%	134	92.4	27	18.6
>1% and <5%	35	24.1	16	11.0
>5% and <10%	32	22.1	9	6.2
>10% and <15%	29	20.0	2	1.4
>15% and <20%	17	11.7	0	0.0
>20%	21	14.5	0	0.0

The dosimetric parameter used is the percentage volume of the breast receiving 105% of the prescribed dose for each patient. The minimum volume is defined at 1%. The data are banded into five further volume categories.

Randomised trial of standard 2D radiotherapy (RT) versus intensity modulated radiotherapy (IMRT) in patients prescribed breast radiotherapy

Ellen Donovan[a], Natalie Bleakley[a], Erica Denholm[b], Phil Evans[a], Lone Gothard[c], Jane Hanson[c], Clare Peckitt[b], Stephanie Reise[a], Gill Ross[d], Grace Sharp[c], Richard Symonds-Tayler[a], Diana Tait[c], John Yarnold[c,*], on behalf of the Breast Technology Group

Radiotherapy and Oncology 82 (2007) 254–264

Table 5
Proportion of patients with any clinician-assessed breast induration (a little, quite a bit or very much) within number of assessments performed according to randomisation arm, standard 2D dosimetry or 3D intensity modulated radiotherapy (IMRT)

	Year 2 assessment		Year 5 assessment		*P*-value (from GEE)
	Standard 2D	IMRT 3D	Standard 2D	IMRT 3D	
Centre of the breast	33/122 (27%)	19/117 (16%)	37/117 (32%)	25/118 (21%)	0.02
Pectoral fold	32/119 (27%)	13/113 (12%)	34/118 (29%)	26/119 (22%)	0.006
Inframammary fold	35/121 (29%)	18/113 (16%)	28/116 (24%)	20/117 (17%)	0.009
Boost site	65/120 (54%)	44/118 (37%)	70/114 (61%)	43/115 (37%)	<0.001

VOLUME 26 · NUMBER 13 · MAY 1 2008

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

A Multicenter Randomized Trial of Breast Intensity-Modulated Radiation Therapy to Reduce Acute Radiation Dermatitis

Jean-Philippe Pignol, Ivo Olivotto, Eileen Rakovitch, Sandra Gardner, Katharina Sixel, Wayne Beckham, Thi Trinh Thuc Vu, Pauline Truong, Ida Ackerman, and Lawrence Paszat

Table 2. χ^2 Analysis Between the True Arms

End Point	BIMRT (%) (n = 170)	Standard RT* (%) (n = 161)	*P*
Skin toxicity grade 3-4 (NCI CTC 2.0)	27.1	36.7	.06
Moist desquamation, all breast	31.2	47.8	.002
Moist desquamation, inframammary crease	26.5	43.5	.001
Pain grade 2-4 (NCI CTC 2.0)	23.5	25.5	.68

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Table 4. Logistic Multivariate Analysis for Moist Desquamation Anywhere in the Breast

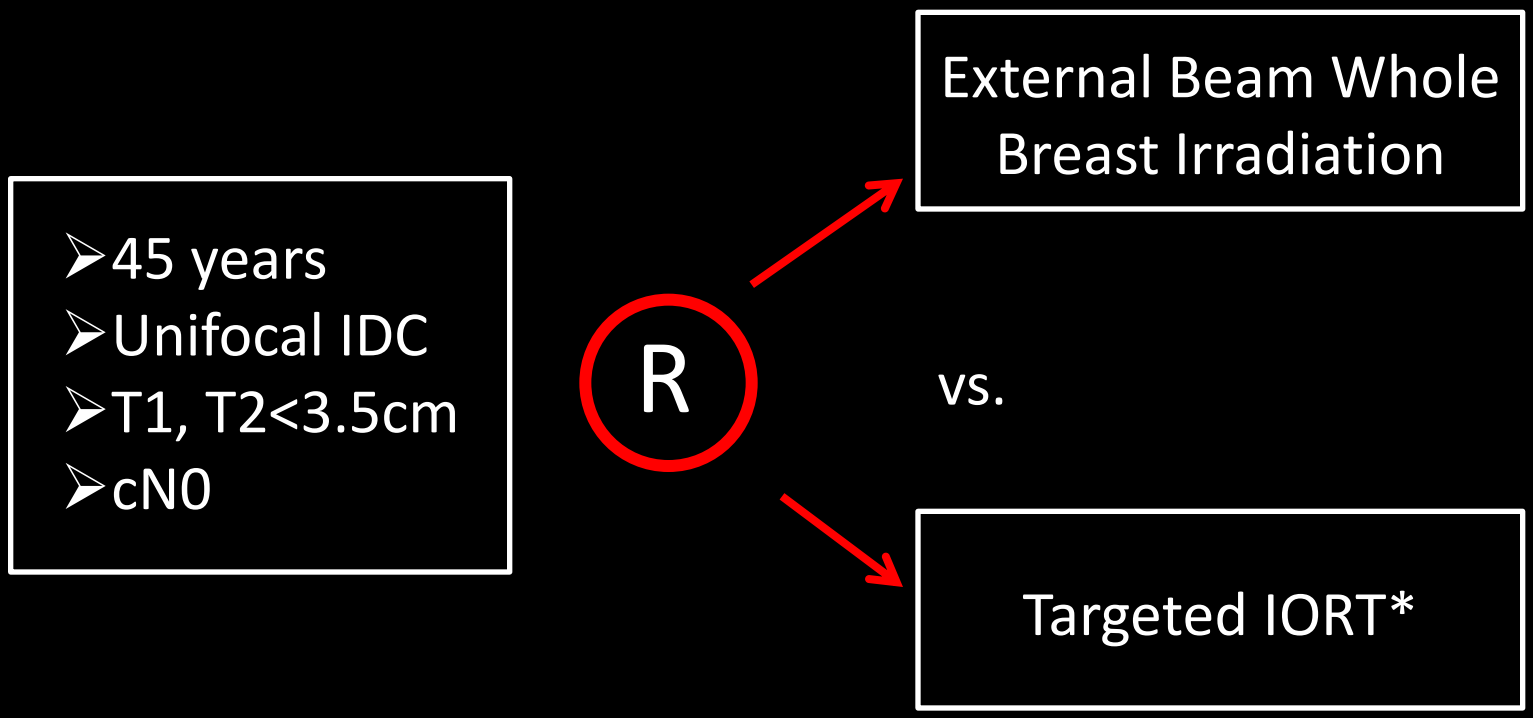
Factor	Odds Ratio	95% CI	*P*
BIMRT technique	0.418	0.232 to 0.753	.0034
Breast size (per 100 cm^3)	1.236	1.157 to 1.321	< .0001
6-MV energies	1.299	0.733 to 2.304	.3703
V_{110} (0 $v >$ 0%)	0.773	0.441 to 1.355	.3691
Boost	1.162	0.677 to 1.993	.5856

Risk-adapted targeted intraoperative radiotherapy versus whole-breast radiotherapy for breast cancer: 5-year results for local control and overall survival from the TARGIT-A randomised trial

Jayant S Vaidya, Frederik Wenz, Max Bulsara, Jeffrey S Tobias, David J Joseph, Mohammed Keshtgar, Henrik L Flyger, Samuele Massarut, Michael Alvarado, Christobel Saunders, Wolfgang Eiermann, Marinos Metaxas, Elena Sperk, Marc Sütterlin, Douglas Brown, Laura Esserman, Mario Roncadin, Alastair Thompson, John A Dewar, Helle M R Holtveg, Steffi Pigorsch, Mary Falzon, Eleanor Harris, April Matthews, Chris Brew-Graves, Ingrid Potyka, Tammy Corica, Norman R Williams, Michael Baum, on behalf of the TARGIT trialists' group

Lancet 2014; 383: 603–13

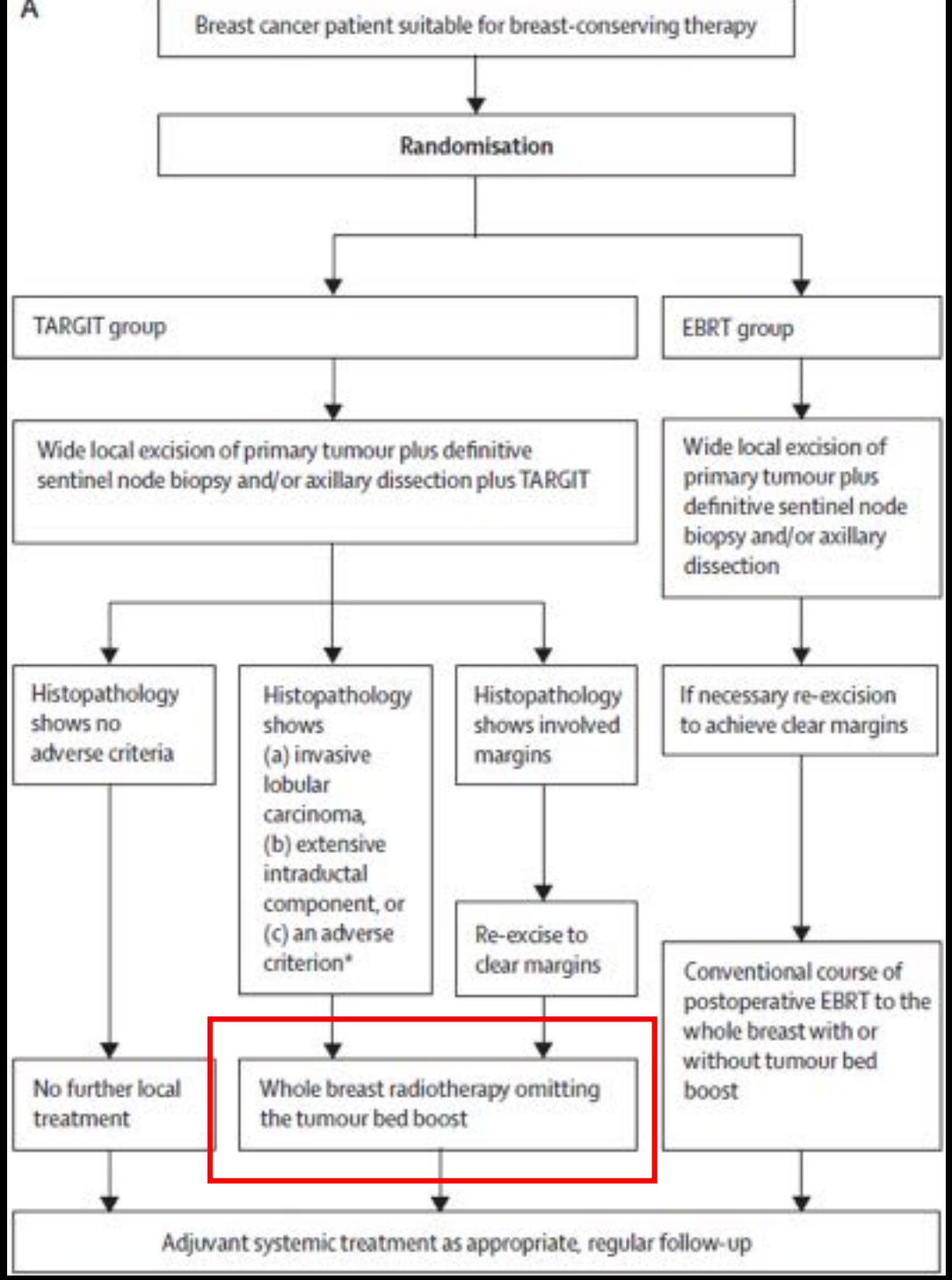
TARGIT-A RANDOMIZATION SCHEMA



* Post- patholgy discovery of predefined factors trigged the addition of EB-WBRT to IORT

ISIORT
INTERNATIONAL SOCIETY of INTRAOPERATIVE RADIATION THERAPY

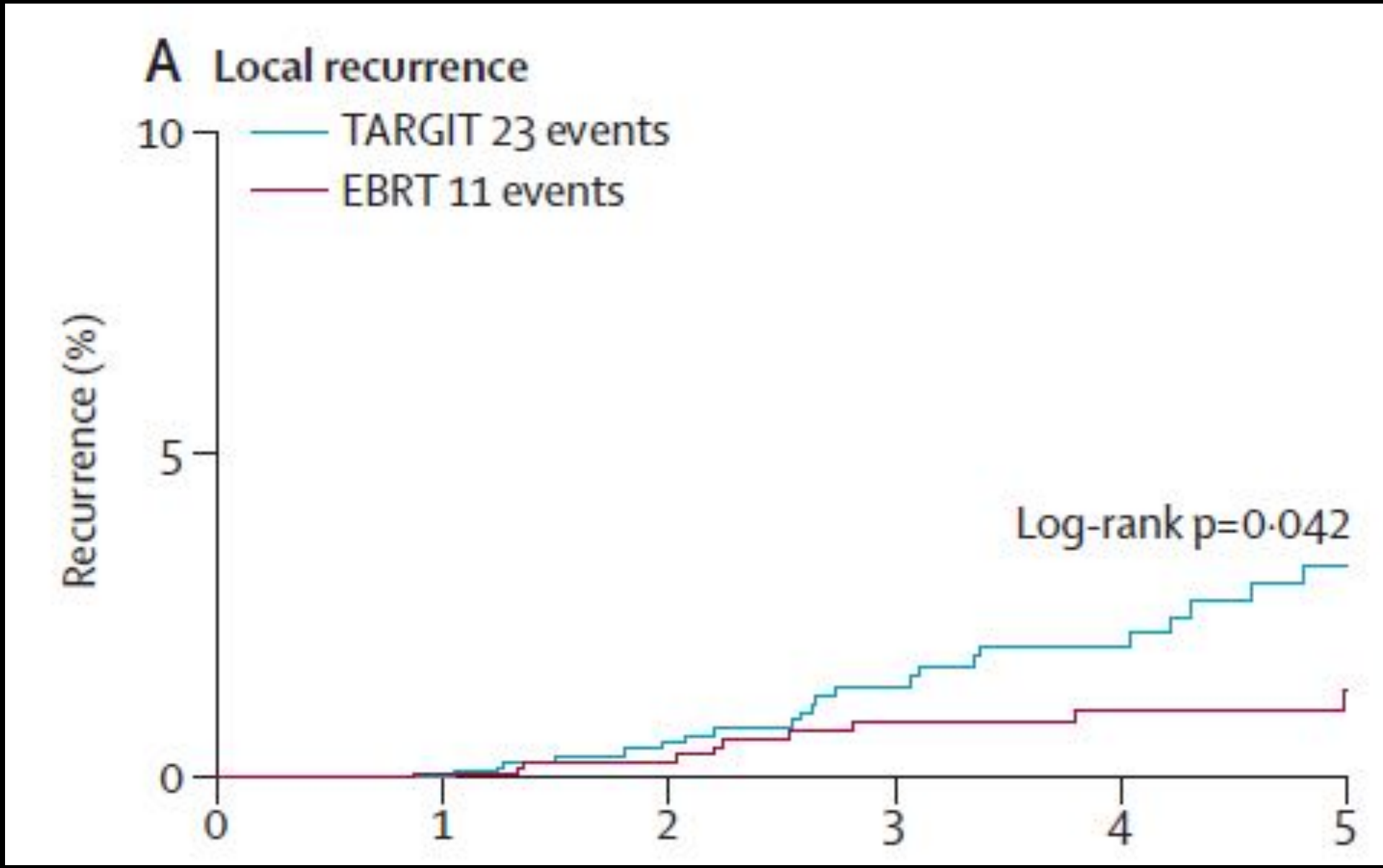
PRE-PATHOLOGY RANDOMIZATION SCHEMA

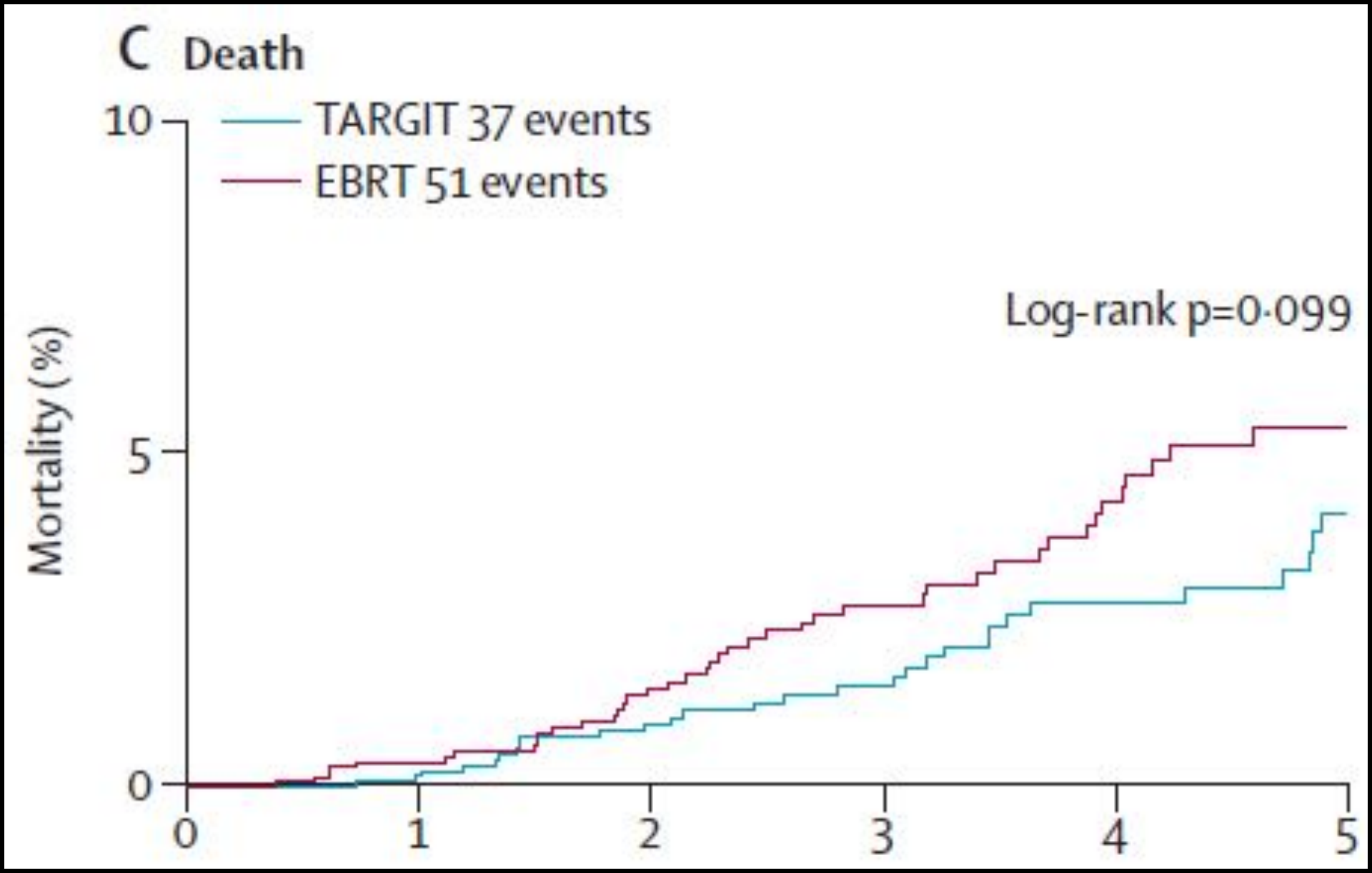


High risk post-pathology features should trig the addition of EB-WBRT to IORT.

and must be *pre-defined* features !

- Lobular Histology
- EIC
- Positive Margins
- LVI
- Gross N+


A Local recurrence
TARGIT 23 events
EBRT 11 events
Recurrence (%)
10
5
0
Log-rank p=0·042
0
1
2
3
4
5


C Death
TARGIT 37 events
EBRT 51 events
Log-rank p=0·099
Mortality (%)
10
5
0
0
1
2
3
4
5

Discussion points:

1. 5-year LF: 1.3% for EBRT vs. 3.3% for Targit, p=0.04

   the predetermined 2.5% non-inferiority threshold was met…

Discussion points:

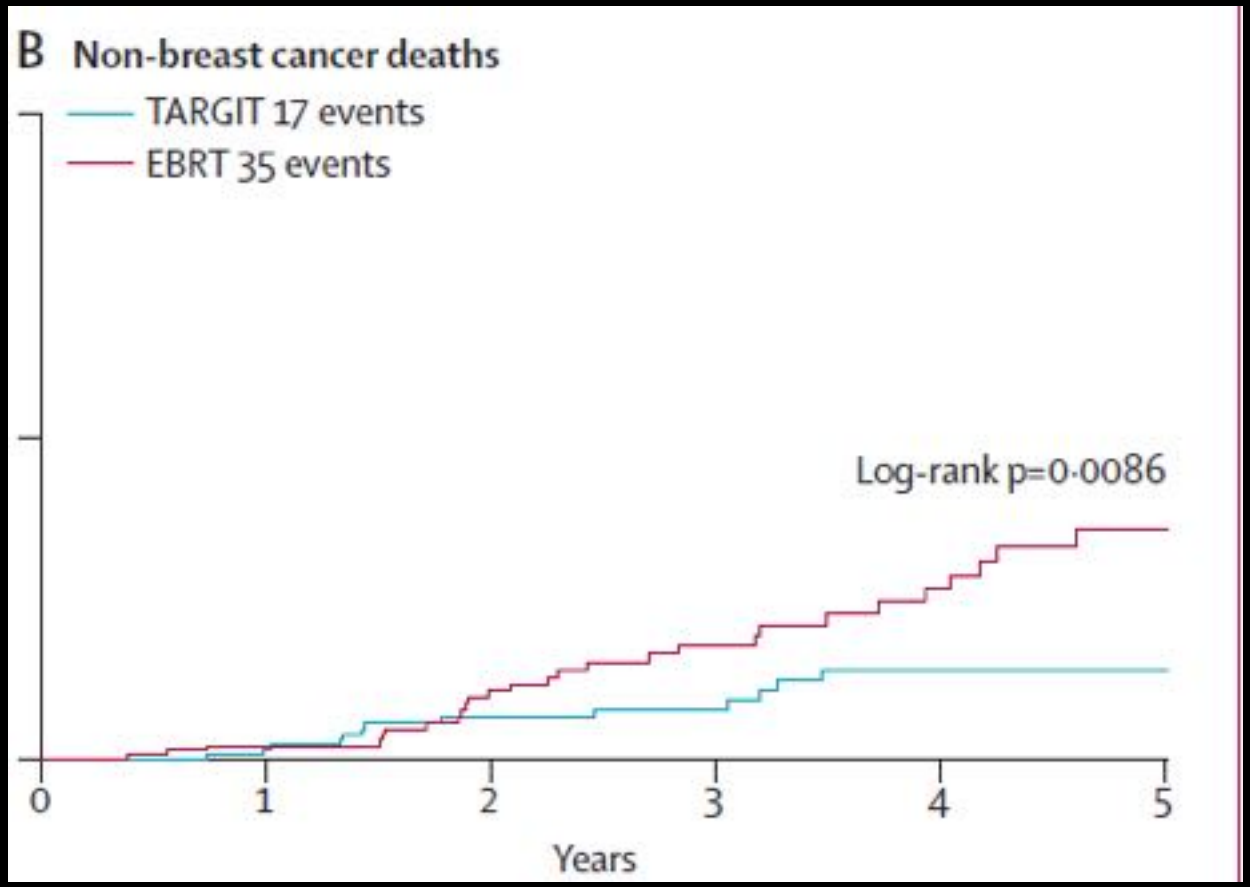
2. Only 20% of patients have a follow-up > 5 years.

Median follow-up of 2 years.

1. Statistical flaw
2. Majority of recurrence in low-risk Luminal A patients will develop after 5 years

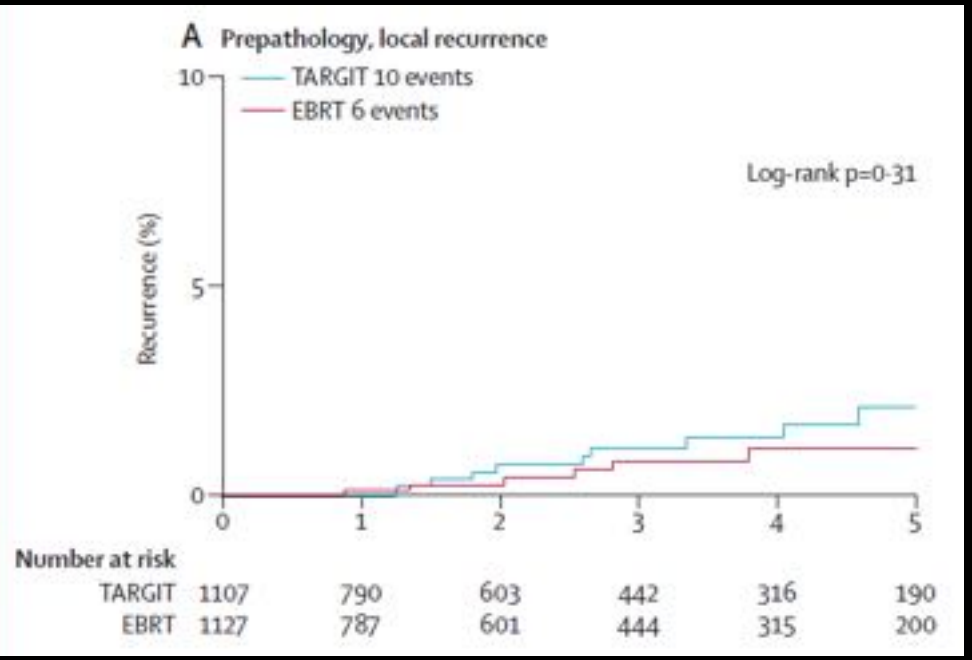
Discussion points:

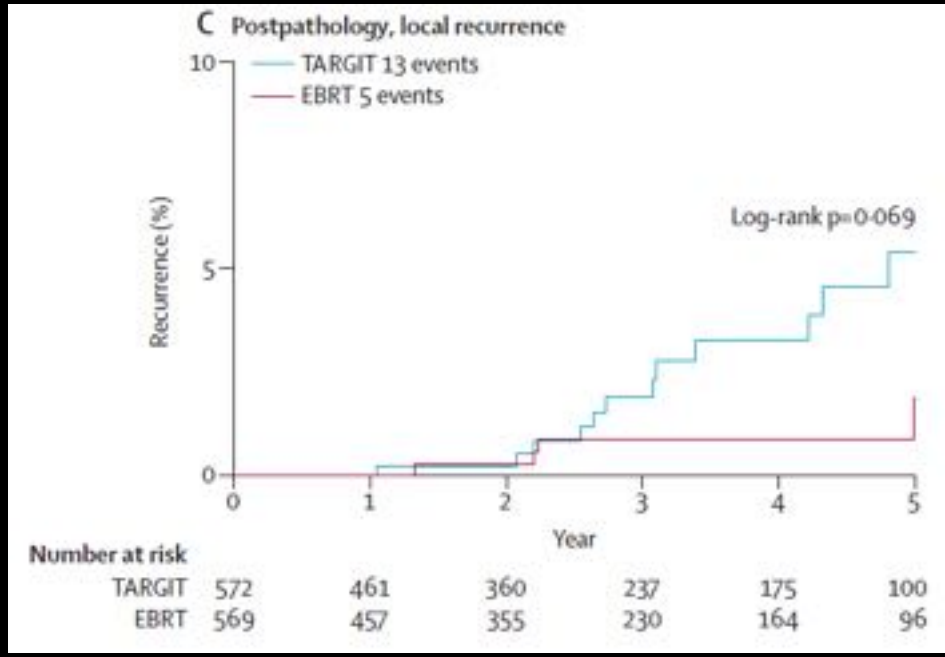
3. Non breast cancer deaths



Discussion points:

4. Pre- vs. Post-pathology





Discussion points:

5. Low-risk patients

	TARGIT (1721)	
Age (years)		
<=50	150	9%
51-60	527	31%
61-70	781	45%
>70	263	15%
Pathological tumour size		
<=1cm	611	39%
1.1-2cm	751	48%
>2cm	190	12%
Unknown	169	10 %
Grade		
1	528	35%
2	757	50%
3	232	15%
Unknown	194	11%
Lymphovascular invasion		
Absent	1348	87%
Present	194	13%
Unknown	179	10%
Nodes involved		
0	1307	83%
1-3	219	14%
>3	43	3%
Unknown	152	9%
ER status		
ER +ve	1441	92%
ER -ve	120	8%
ER Unknown	160	9%

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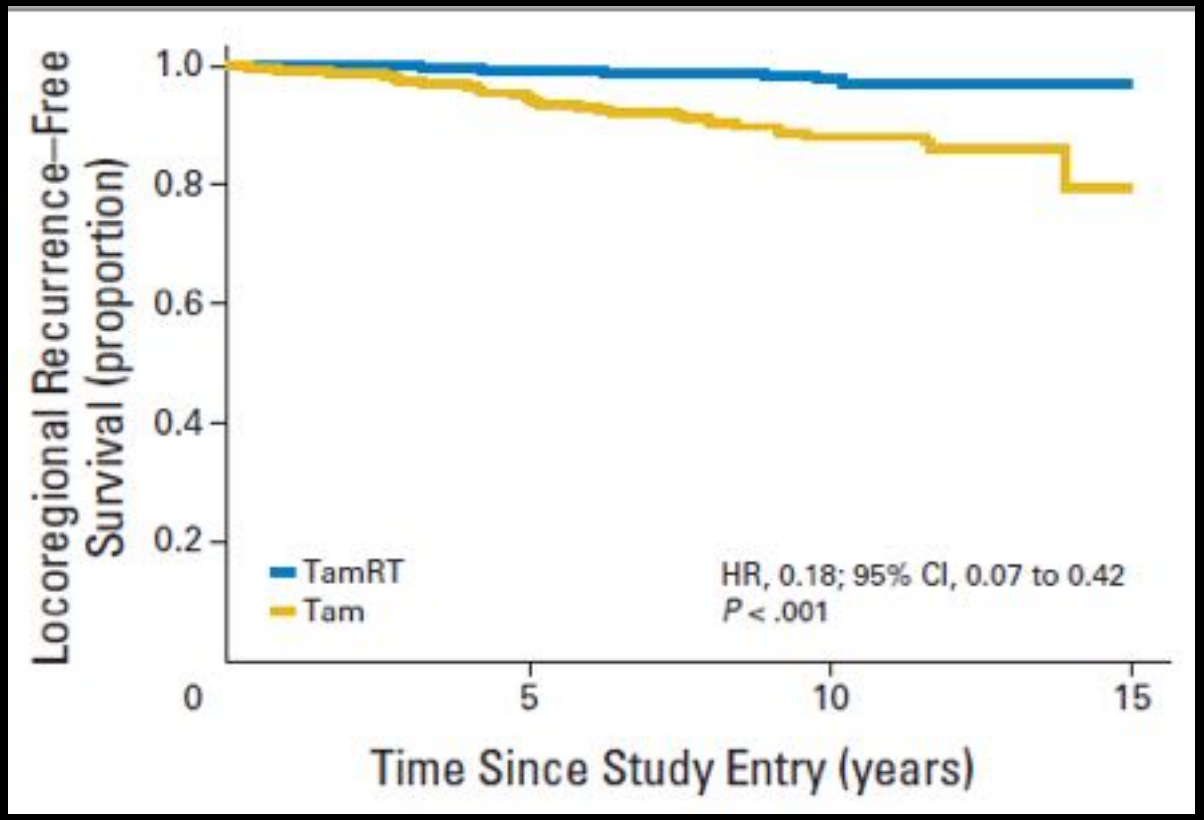
JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Lumpectomy Plus Tamoxifen With or Without Irradiation in Women Age 70 Years or Older With Early Breast Cancer: Long-Term Follow-Up of CALGB 9343

Kevin S. Hughes, Lauren A. Schnaper, Jennifer R. Bellon, Constance T. Cirrincione, Donald A. Berry, Beryl McCormick, Hyman B. Muss, Barbara L. Smith, Clifford A. Hudis, Eric P. Winer, and William C. Wood

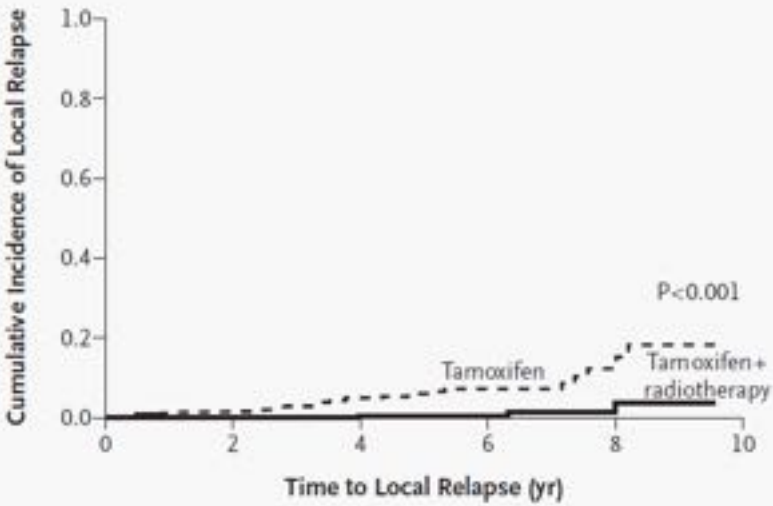


The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 SEPTEMBER 2, 2004 VOL. 351 NO. 10

Tamoxifen with or without Breast Irradiation in Women 50 Years of Age or Older with Early Breast Cancer

Anthony W. Fyles, M.D., David R. McCready, M.D., Lee A. Manchul, M.D., Maureen E. Trudeau, M.D., Patricia Merante, R.N., Melania Pintilie, M.Sc., Lorna M. Weir, M.D., and Ivo A. Olivotto, M.D.



No. at Risk						
Tamoxifen+ radiotherapy	306	289	224	125	39	0
Tamoxifen	305	282	218	112	26	0

Figure 4. Cumulative Incidence of Local Relapse among Women with a Good Prognosis.

Women with a good prognosis were defined as those with T1 tumors that either were positive for hormone receptors or had an unknown hormone-receptor status.

Accelerated partial breast irradiation using intensity modulated radiotherapy versus whole breast irradiation

5-year survival results of a phase 3 randomized trial

Lorenzo Livi

Icro Meattini, Livia Marrazzo, Stefania Pallotta, Gabriele Simontacchi, Calogero Saieva, Vieri Scotti, Carla De Luca Cardillo, Paolo Bastiani, Jacopo Nori, Lorenzo Orzalesi, Simonetta Bianchi

Department of Radiotherapy-Oncology
Florence University
Florence, Italy

PHASE 3 TRIAL DESIGN

ACCELERATED IMRT TO TREAT THE INDEX QUADRANT
30 Gy in 5 fractions (6 Gy/fr in 2 weeks)

versus

STANDARD WHOLE BREAST RADIOTHERAPY
50 Gy + boost 10 Gy in 30 fractions (2 Gy/fr in 6 weeks)

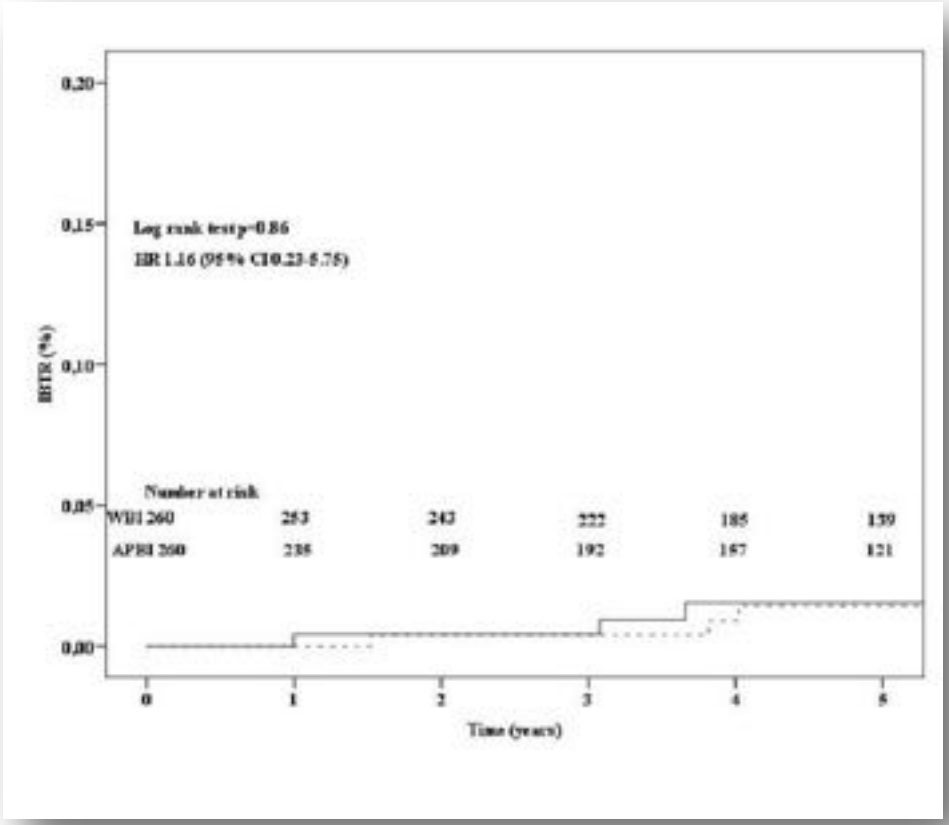
*AFTER CONSERVING SURGERY IN HIGHLY **SELECTED** EARLY BREAST CANCER **PATIENTS***

pT < 25 mm
surgical margins > 5 mm
aged > 40 year

Livi et al, IJROBP, 2010

Cumulative incidence of ipsilateral breast tumour recurrence

(intention-to-treat population)



5-year IBTR rate 1,5% in the APBI and 1,4%in the WBI group (log rank test p=0.86)

5-year event rate according to allocated group *(ITT population)*

	Total	Whole Breast (n=260) N	%	Partial Breast (n=260) N	%	Log-rank p value
Ipsilateral breast tumour recurrence	6	3	1·4	3	1·5	0·86
Local relapse	3	3	1·4	0	0	0·11
New ipsilateral BC	3	0	0	3	1·5	0·063
Locoregional tumour recurrence	7	4	1·9	3	1·5	0·86
Contralateral breast tumour	10	7	3·2	3	1·6	0·31
Distant metastasis*	7	4	1·8	3	1·5	0·87
Total deaths	8	7	3·4	1	0·6	0·057
Breast cancer	4	3	1·6	1	0·6	0·40
Other cause	4	4	1·8	0	0	0·065

*As first or secondary event.

Conclusions:

Cultural improvements have bigger impact than technological innovations.

Technological innovations allow for improvements in knowledge.

Grazie per l'attenzione !

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