Bologna
19 Febbraio 2016
NH Hotel De La Gare

Associazione Italiana Radioterapia Oncologica
Gruppo di Studio per la Patologia Mammaria

V Zoom
Journal Club 2015

Ca in situ e ormonoterapia

Discussant : LORENZA MARINO

rem radioterapia s.r.l.

Ca in situ e ormonoterapia

- Quali fattori di rischio?
- Radioterapia?
- Ormonoterapia?

Ann Surg Oncol (2015) 22:3273–3281
DOI 10.1245/s10434-015-4740-8

Annals of
SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

CrossMark

ORIGINAL ARTICLE – BREAST ONCOLOGY

BCS

Decreasing Recurrence Rates for Ductal Carcinoma In Situ: Analysis of 2996 Women Treated with Breast-Conserving Surgery Over 30 Years

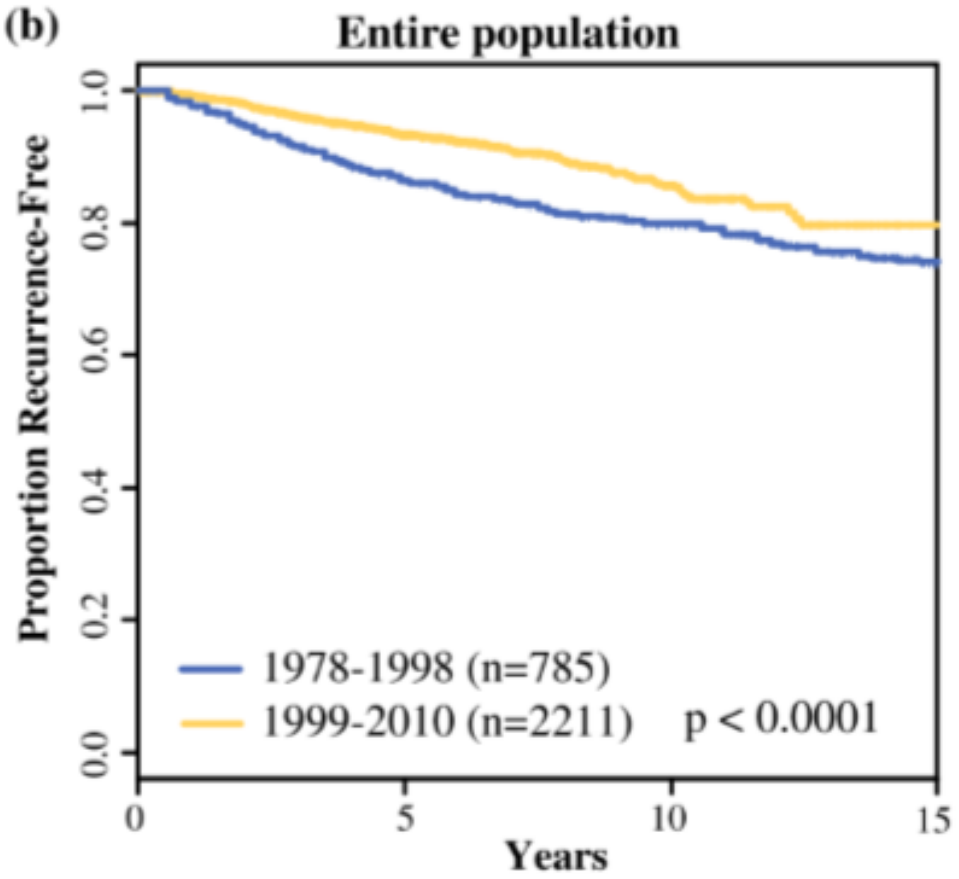
Recurrence rates
(FUP 13-20y)

Cuzick, Lancet Oncol.2011; 12(1): 21-9
Donker, JCO . 2013; 31(32): 4054-9
Wapnir, JNCI. 2011;103(6): 478-88
Wamberg, JCO. 2014; 32(32): 3613-18

BCS: 26-36%

BCS + RT : 9-23%

	Recurrence rate (95% confidence interval)			
Time period	5-year	10-year	HR	P‡
1978-1998	13.6% (11.3-16.3%)	20% (17.3-23.3%)	1.0	-----
1999-2010	6.6% (5.5-7.9%)	14% (12.1-16.9%)	0.62	<0.0001



J Natl Cancer Inst Monogr 2010;41:162–177

The Breast 24 (2015) 608–612

Contents lists available at ScienceDirect

The Breast

journal homepage: www.elsevier.com/brst

Original article

The locoregional recurrence post-mastectomy for ductal carcinoma in situ: Incidence and risk factors

Sahar Bannani [a, *], Sophie Rouquette [a, b], Cecile Bendavid-Athias [a], Patrick Tas [a], Jean Levêque [a, b]

MASTECTOMY

LRR a 3.2 anni: 3.67%

High grade disease 62.50%

LRR

Al Mushawah, J Surg Res 2012; 173: 10-5
Altintas S., Brest J 2009; 15(2): 120-32
Bijker N, JCO 2001; 19: 2263-71
Chadha M, Int J Surg Onc 2012; 2012: 423-520

→ **1 - 4.7%**

Young age (< 40 years)

Vargas C, IJROBP 2005; 63(5): 1514-21
Carlson GW, J Am Coll Surg 2007;204: 1074-8
Fitzsullivan E, Ann Sur Oncol 2013; 20: 4103-12

→ **5 - 8.1%**

Rashtian A, IJROBP 2008; 72: 1016-20

→ **16 %** *(margins < 2mm,high grade disease and/or comedonecrosis)*

Original Investigation

Breast Cancer Mortality After a Diagnosis of Ductal Carcinoma In Situ

Steven A. Narod, MD, FRCPC; Javaid Iqbal, MD; Vasily Giannakeas, MPH; Victoria Sopik, MSc; Ping Sun, PhD

***Breast cancer-specific mortality 10 years*: 1.1%**

***20 years*: 3.3%**

- Diagnosis before age 35 years: **7.8% vs 3.2%** (HR,2.58 [95%CI,1.85-3.60];P<.001) **at 20 years**.
- Black women *vs* white, non-Hispanic : **7.0% vs 3.0%**

Risks factors:

- ✓ Tumor size
- ✓ Grade
- ✓ ER status
- ✓ Comedonecrosis

Women with DCIS who developed an ipsilateral invasive in-breast recurrence were 18.1 times more likely to die of breast cancer than women who did not.

JAMAOncol.2015;1(7):888-896

Predictors for local invasive recurrence of ductal carcinoma *in situ* of the breast: a meta-analysis

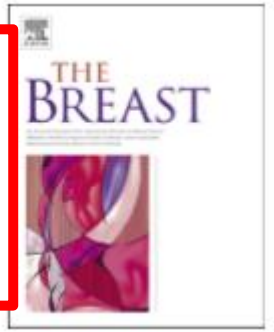
Xining Zhang, Hongji Dai, Ben Liu, Fengju Song and Kexin Chen

Characteristics	Number of cases	RCT [risk estimate (95% CI)/number of studies]	I^2 (%)	Observational studies [risk estimate (95% CI)/number of studies]	I^2 (%)	Combined studies [risk estimate (95% CI)/number of studies]	I^2 (%)
Biomarkers							
ER (positive vs. negative)	1556						
PR (positive vs. negative)	1556						
HER2/neu (positive vs. negative)	1771						
Tumor characteristics							
Nuclear grade							
High/low	52 635						
Intermediate/low	45 360						
Comedonecrosis (yes vs. no)	45 442						
Margins (positive vs. negative)	10 021						
Tumor size (large vs. small)	54 939						
Focality (multifocality/ multicentric vs. unifocal)	1963						
Mode of detection (nonscreening detection vs. screening detection)	10 866						

- ✓ The number of elegible studies in this meta-analysis was relatively small (different study types and patient selection criteria..)
- ✓ Different definitions of tumor predictors, such as tumor size, nclear grade and detection of margin, hampered our synthesis of the association between tumor characteristics and invasive outcomes.
- ✓ The expression levels of biomarkers are often correlated; it is therefore difficult to assess multiple markers simultaneously in a multivariable model

European Journal of Cancer Prevention 2015,

Conclusion: In addition to high grade, administered treatment and younger age at diagnosis, high Ki-67 expression seems to be independently associated with increased likelihood of recurrence in patients with DCIS. Future studies with additional molecular markers seem necessary to further improve the identification of high-risk patients for DCIS recurrence.



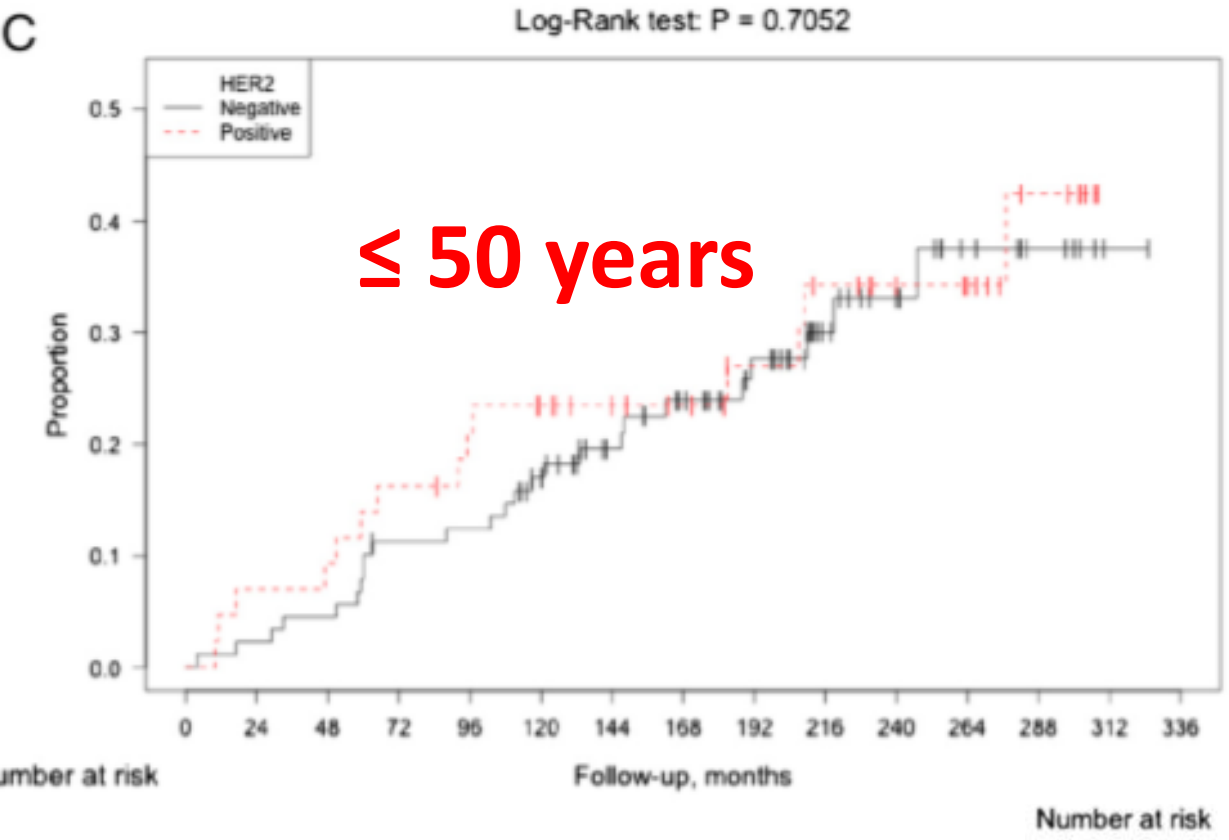
Variables	Category or increment	Univariable analysis		Multivariable analysis	
		Univariable HR (95%CI)	p	Multivariable HR (95%CI)	p
Age at diagnosis	10 years increase	**0.69 (0.51–0.93)**	**0.015**	**0.60 (0.43–0.83)**	**0.002**
Grade	1 level increase	**1.83 (1.15–2.93)**	**0.011**	**1.72 (1.06–2.78)**	**0.028**
ER expression	Positive vs. Negative	1.39 (0.68–2.83)	0.368	1.13 (0.51–2.53)	0.764
PR expression	Positive vs. Negative	1.44 (0.77–2.70)	0.260	1.42 (0.70–2.89)	0.331
HER2 expression	Positive vs. Negative	0.83 (0.40–1.75)	0.633	1.04 (0.48–2.24)	0.930
Ki-67 expression	Intermediate/High vs. Low	**3.04 (1.40–6.61)**	**0.005**	**1.78 (1.11–2.88)**	**0.017**
Treatment	Lumpectomy plus radiotherapy vs. Lumpectomy alone	**0.47 (0.24–0.95)**	**0.035**	**0.34 (0.16–0.73)**	**0.005**
	Mastectomy vs. Lumpectomy alone	**0.57 (0.38–0.87)**	**0.009**	**0.38 (0.24–0.61)**	**<0.001**

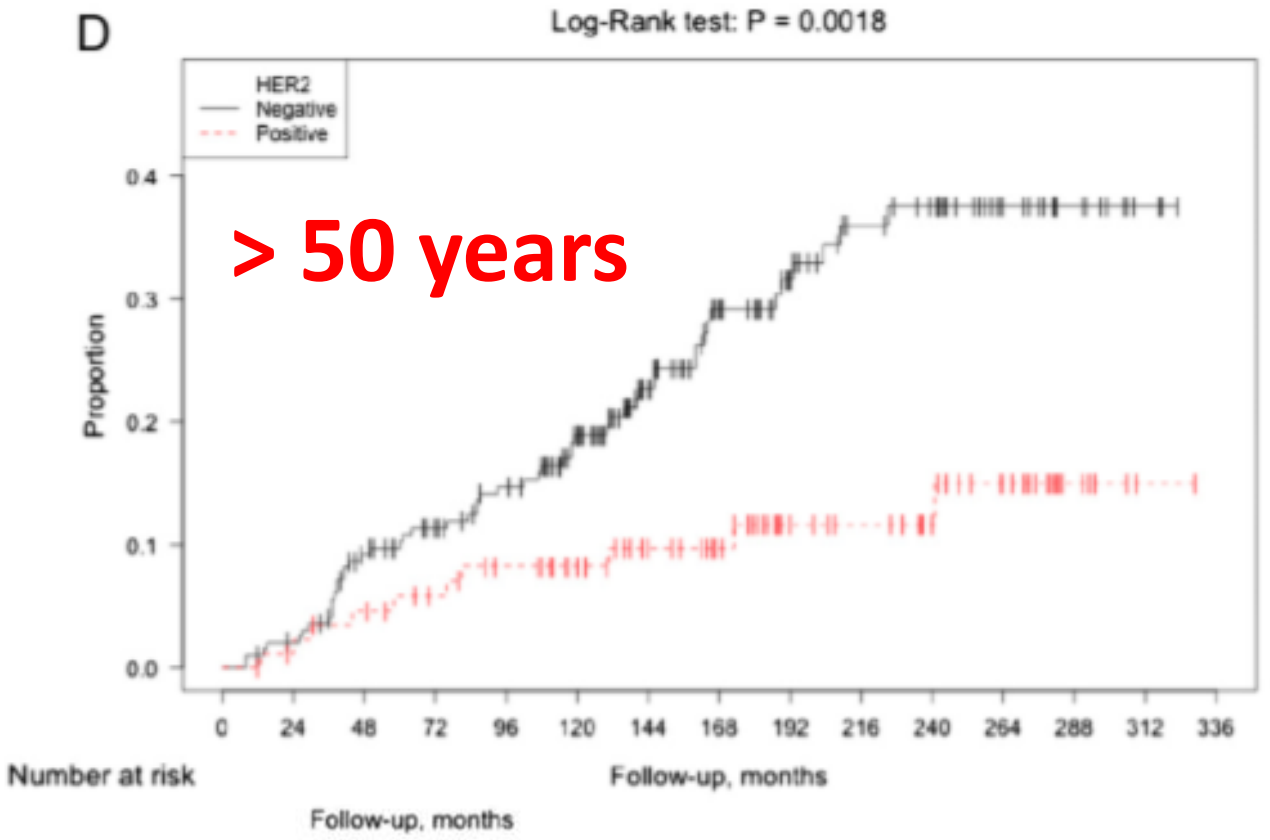
- Study restricted to patients with negative margins
- 1D5 antibody for the assessment of ER
- No Bcl-2 anti-apoptotic protein and the mitotic index
- Small number

The Breast 2015; 1-5

The prognostic role of HER2 expression in ductal breast carcinoma *in situ* (DCIS); a population-based cohort study

Signe Borgquist[1*], Wenjing Zhou[2], Karin Jirström[1], Rose-Marie Amini[3], Thomas Sollie[4], Therese Sørlie[5], Carl Blomqvist[6], Salma Butt[7] and Fredrik Wärnberg[2]





Borgquist *et al. BMC Cancer* (2015) 15:468

The prognostic role of HER2 expression in ductal breast carcinoma *in situ* (DCIS); a population-based cohort study

Signe Borgquist[1*], Wenjing Zhou[2], Karin Jirström[1], Rose-Marie Amini[3], Thomas Sollie[4], Therese Sørlie[5], Carl Blomqvist[6], Salma Butt[7] and Fredrik Wärnberg[2]

- Large sample size
- Long-term FUP (> 15 years)
- Unequal recurrence…. ➡ no sistemic endocrine treatment

- TMAs ➡ may have limited the assessment of heterogenous expression vs whole section
- Trastuzumab in DCIS ➡ no significant effects (proliferation and apoptosis)
- SISH ed IHC: concordance 89.2%,

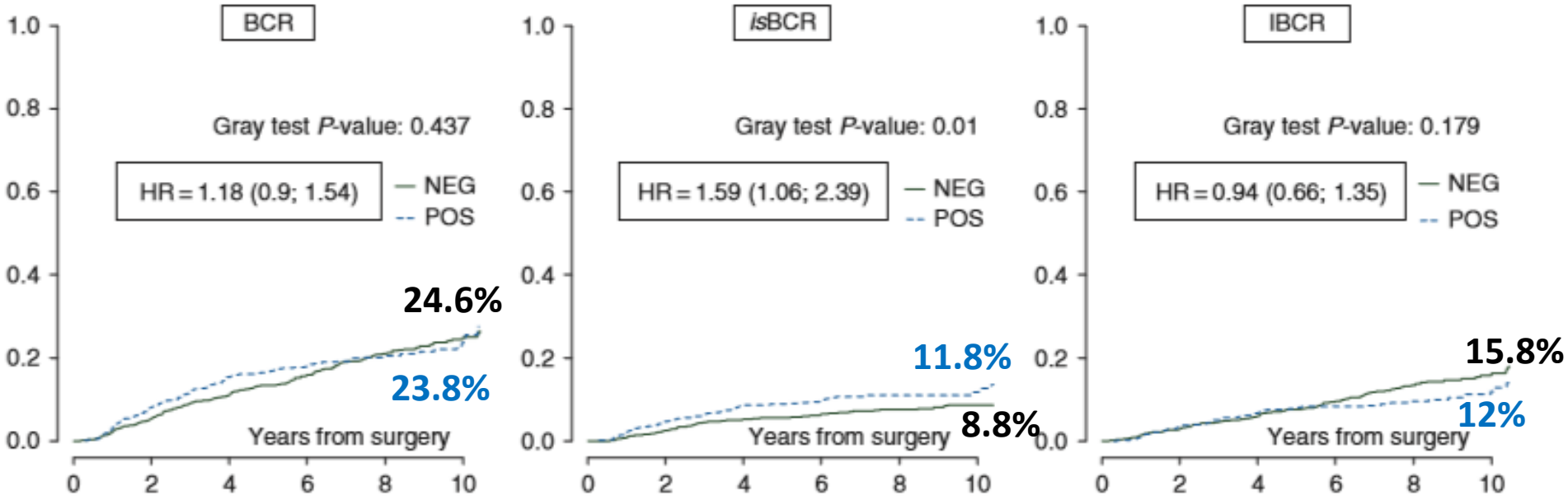
Estévez et al. Breast Cancer Research 2014, 16:R76: Molecular effects of lapatinib in patients with HER2 positive ductal carcinoma in situ

Cancer . 2011 January 1; 117(1): 39–47 **Biologic and Immunologic Effects of Preoperative Trastuzumab for Ductal Carcinoma in Situ of the Breast**

Risk of subsequent *in situ* and invasive breast cancer in human epidermal growth factor receptor 2-positive ductal carcinoma *in situ*

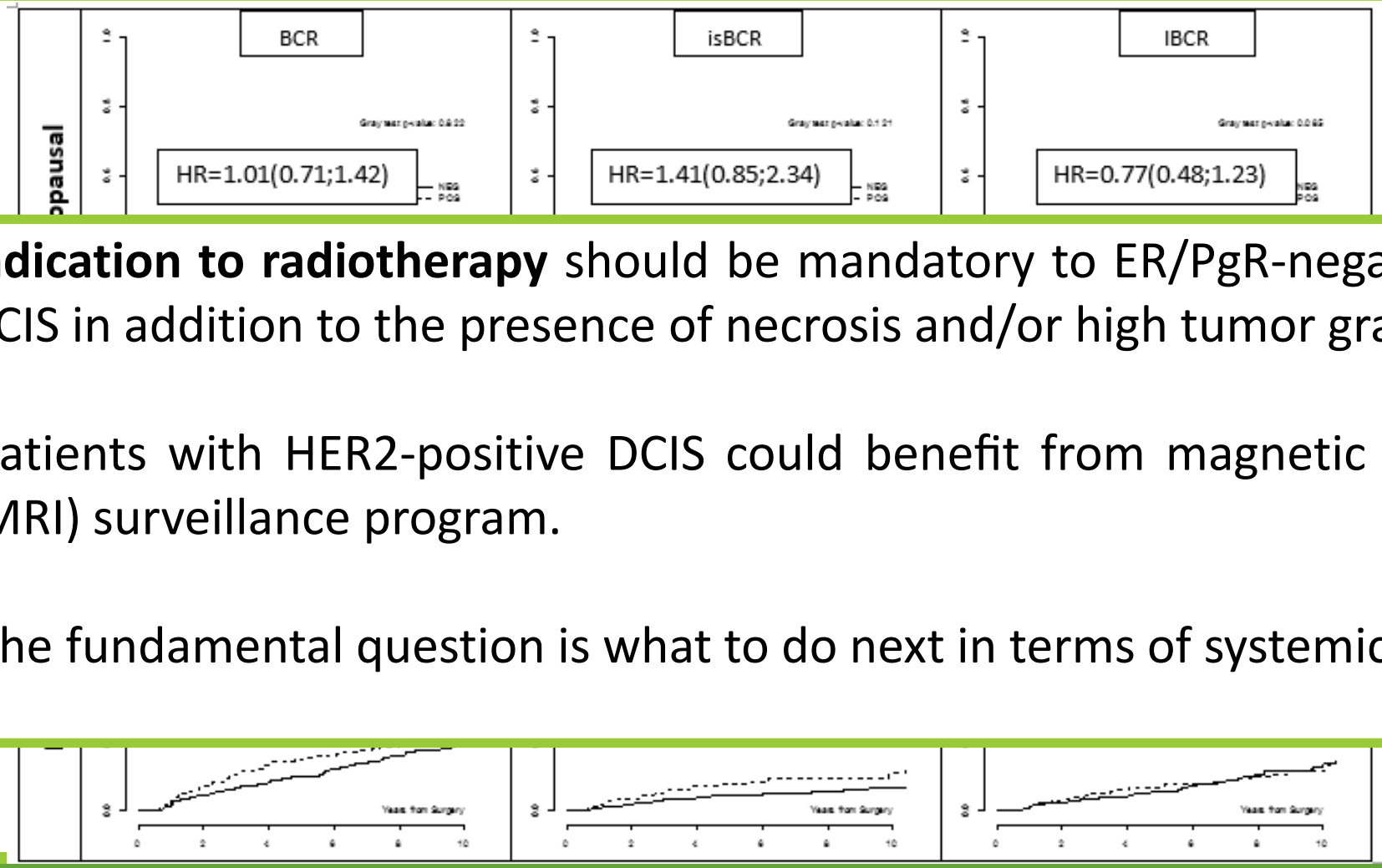
G. Curigliano[1*], D. Disalvatore[2], A. Esposito[1], G. Pruneri[3,4], M. Lazzeroni[5], A. Guerrieri-Gonzaga[5], A. Luini[6], R. Orecchia[4,7], A. Goldhirsch[8], N. Rotmensz[2,†], B. Bonanni[5,†] & G. Viale[3,4,†]

1667 pz: 560 (33.5%) HER2+



Annals of Oncology 26: 682–687, 2015

In the adjuvant treatment of invasive breast cancer, HER-2 overexpression may predict resistance to tamoxifen. In premenopausal patients, we observed no difference in BCR, isBCR and IBCR while in postmenopausal patients we observed a significant difference in BCR and isBCR. Postmenopausal women with HER2-positive DCIS were more frequently ER/PgR negative, thus taking no tamoxifen.



- **Indication to radiotherapy** should be mandatory to ER/PgR-negative, HER2-positive DCIS in addition to the presence of necrosis and/or high tumor grade.
- Patients with HER2-positive DCIS could benefit from magnetic resonance imaging (MRI) surveillance program.
- The fundamental question is what to do next in terms of systemic therapy.

Relationship Between Margin Width and Recurrence of Ductal Carcinoma In Situ

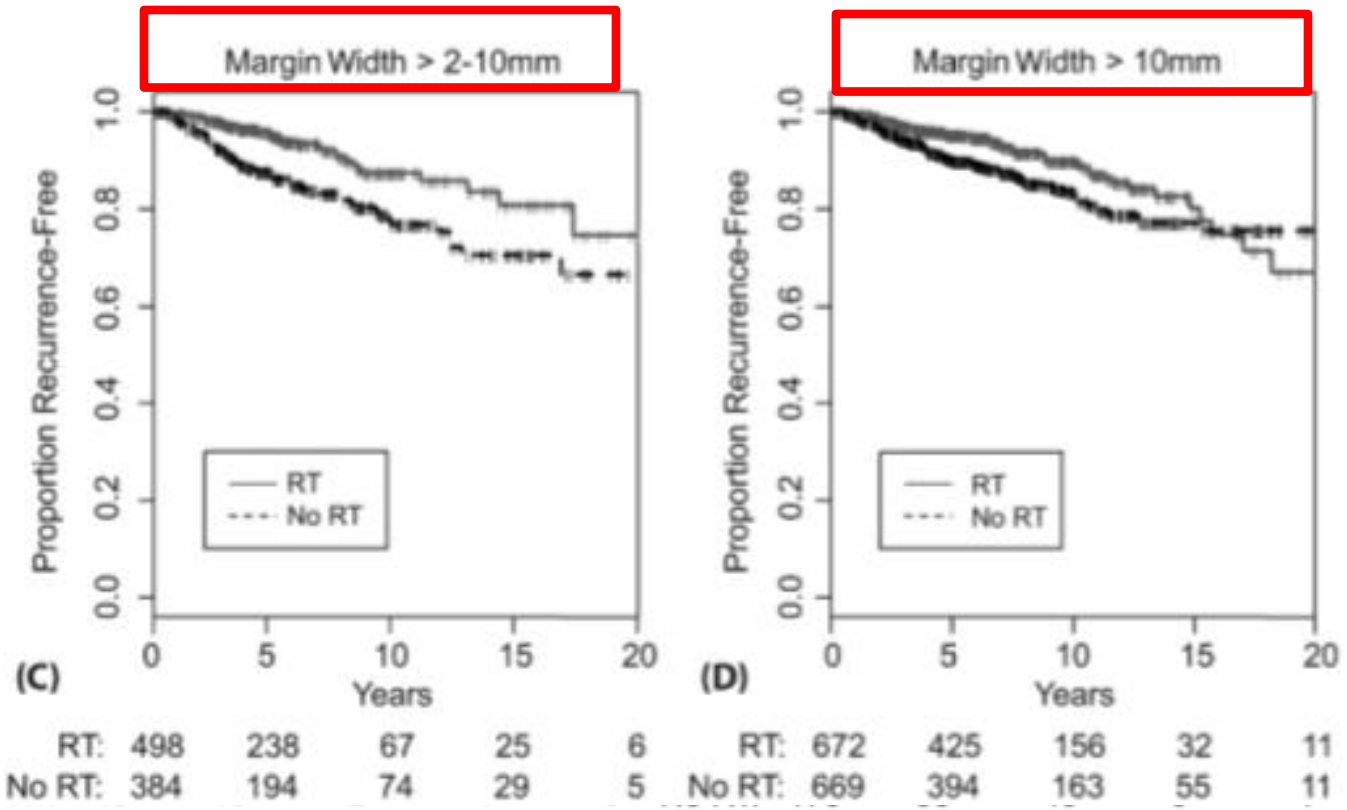
Analysis of 2996 Women Treated With Breast-conserving Surgery for 30 Years

Kimberly J. Van Zee, MS, MD, FACS, Preeti Subhedar, MD,* Cristina Olcese, BS,* Sujata Patil, PhD,† and Monica Morrow, MD, FACS**

1978-2010: **2996 pz**

Margin Width	Entire Population With Known Margin Width (N = 2788)*	No Radiation (N = 1266)†	Radiation (N = 1500)†	HR‡ for Radiation	*P*§ for Radiation	Adjusted HR for Radiation¶	*P*‖ for Radiation
Positive	31	41	23	0.22	0.0026	0.10	0.0036
Close (≤2 mm)	17	27	12	0.32	<0.0001	0.29	<0.0001
>2–10 mm	18	23	13	0.46	0.0002	0.42	0.0006
>10 mm	13	16	10	0.66	0.0132	0.54	0.0013
P# for margin width	=0.087	=0.0003	=0.99				

- ✓ Large cohort (n=2996 pz)
- ✓ Long FUP (~ 10 years)
- ✓ Pathologic and treatment chararacteristics



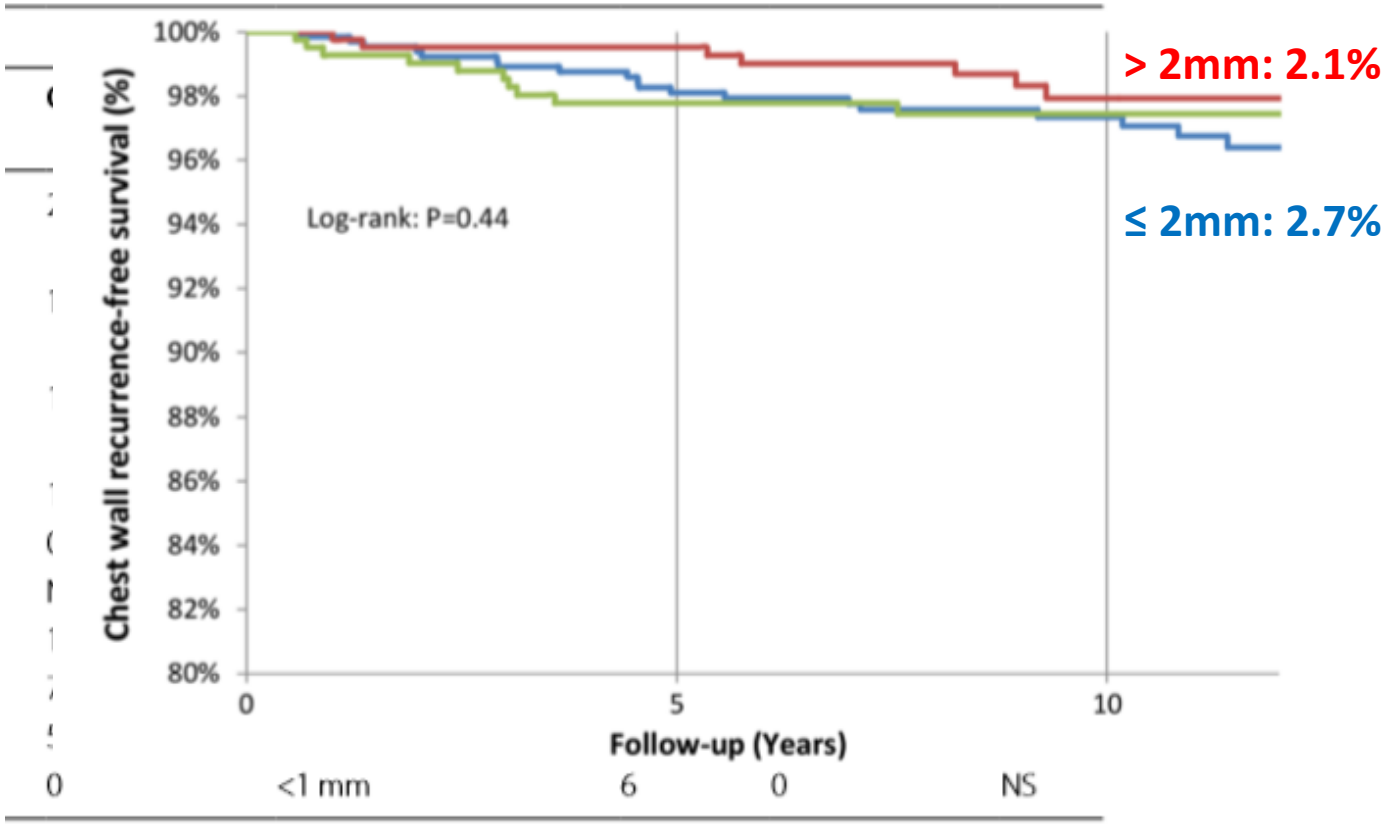
- ✓ Very few positive margins (dermis, pectoralis fascia…)

Margins	
Positive	104
Close (≤2 mm)	449
>2–10 mm	888
>10 mm	1347
Unknown	208

Underestimate recurrence rate

- ✓ The cumulative rate of chest wall recurrence may be underestimated.
- ✓ No data RT
- ✓ No information on all pathological features.

Parameter		Reference	Chest wall recurrence HR (95% CI)	p value
Age	Continuous	-	0.98 (0.95-1.01)	0.19
	<45	>50	1.29 (0.55-3.02)	0.72
	45-50	>50	1.3 (0.58-3.16)	0.7
Nuclear Grade	High	Low	3.0 (0.4-23.1)	0.29
	Intermediate	Low	1.4 (0.16-12.60)	0.76
	Unreported	Low	2.3 (0.31-17.53)	0.41
Margin Width	≤2 mm	>2 mm	2.1 (0.86-5.1)	0.10
	Unreported		1.59 (0.54, 4.37)	0.35
Multifocality	Present	Absent	0.7 (0.28-1.62)	0.36
Necrosis	Present	Absent	1.7 (0.23-13.1)	0.60
Histological Subtype	Cribriform	Solid	0.5 (0.17-1.37)	0.16
	Other	Solid	0	0.98
	Unreported	Solid	0.48 (0.18-1.24)	0.13
Breast Surgeon Volume (quintile)	1	5	2.6 (0.89-7.37)	0.08
	2	5	1.1 (0.31-3.70)	0.91
	3	5	1.80 (0.59-5.49)	0.30
	4	5	1.4 (0.43-4.26)	0.61
Year of Diagnosis	1997-1999	1994-1996	0.60 (0.28-1.29)	0.13
	2000-2002	1994-1996	0.43 (0.19-1.00)	0.13



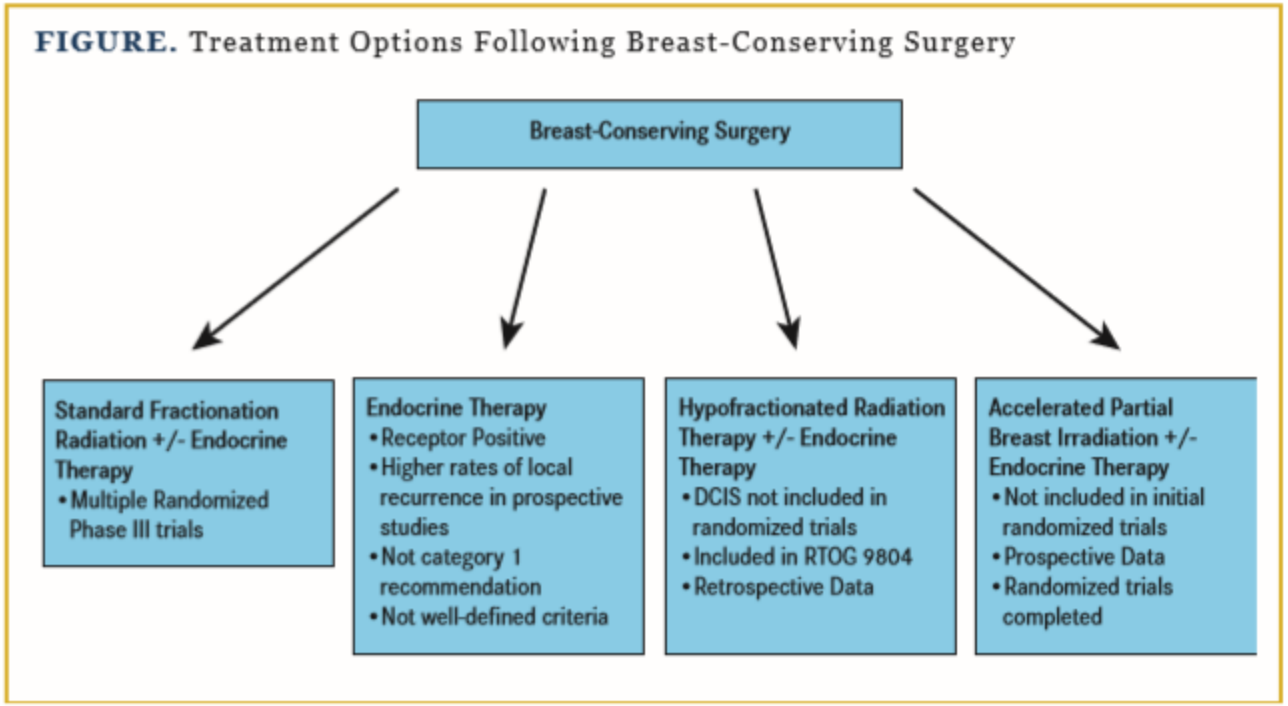
Klein *et al. SpringerPlus (2015) 4:335*
DOI 10.1186/s40064-015-1032-5

Ca in situ e ormonoterapia

- Quali fattori di rischio?
- Radioterapia?
- Ormonoterapia?

Ductal Carcinoma In Situ: Review of the Role of Radiation Therapy and Current Controversies

FIGURE. Treatment Options Following Breast-Conserving Surgery



always receive adjuvant RT due to
nd distance to treatment facilities.

At this time, there is no standard as to what defines acceptable local recurrence rates, and some patients may accept a 10-year recurrence rate of 10%

Future studies are required before the concept of surveillance represents an appropriate standard for women with DCIS; at this time, the standard of care remains surgery (mastectomy or BCS) with or without RT.

Effect of radiotherapy on survival of women with locally excised ductal carcinoma in situ of the breast: a Surveillance, Epidemiology, and End Results population-based analysis

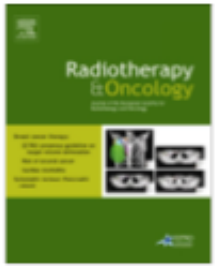
- ✓ Retrospective analysis with clinicopathological variables were not well balanced
- ✓ The SEER database did not provide complete tumor characteristics (eg, HER2/neu status, breast subtype, and tumor size), cancer therapy (chemotherapy, endocrine therapy, and RT types), and clinical outcome (recurrence and metastasis) variables.
- ✓ The SEER database did not provide surgery information on patients diagnosed before 1998, so DCIS patients who underwent BCS before 1998 were omitted, leading to limited sample size for our analysis.

OncoTargets and Therapy 2015:8 1407–1418

Systematic review

The role of boost and hypofractionation as adjuvant radiotherapy in patients with DCIS: A meta-analysis of observational studies

Cecilia Nilsson [a], Antonis Valachis [b,*]



- ✓ Level of evidence very low
- ✓ The evidence of hypofractionation in DCIS is scarce

- ✓ The randomized trials of RT in DCIS did not evaluate the role of boost since they either did not recommend boost or permitted boost in the discretion of the investigator which led to a limited number of patients who received boost.
- ✓ Retrospective studies
- ✓ The number of patients in the subgroups of margin status and age are relatively low and the stability of the statistical results questionable
- ✓ The median FUP was relatively shorter (~ 60 months)

Radiotherapy and Oncology 114 (2015) 50–55

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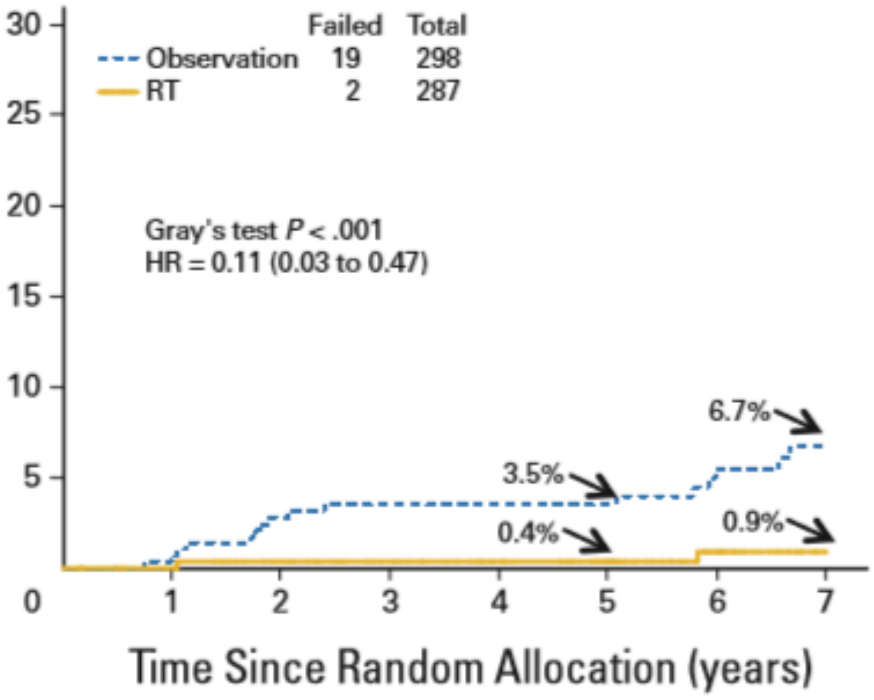
JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

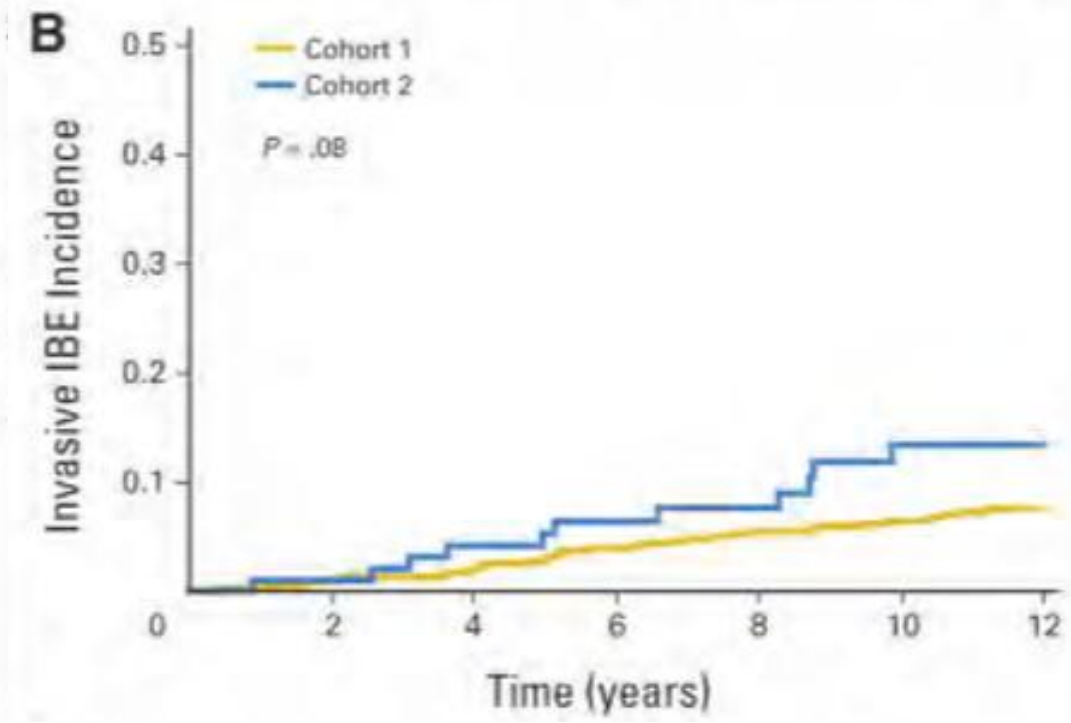
RTOG 9804: A Prospective Randomized Trial for Good-Risk Ductal Carcinoma In Situ Comparing Radiotherapy With Observation

Beryl McCormick, Kathryn Winter, Clifford Hudis, Henry Mark Kuerer, Eileen Rakovitch, Barbara L. Smith, Nour Sneige, Jennifer Moughan, Amit Shah, Isabelle Germain, Alan C. Hartford, Afshin Rashtian, Eleanor M. Walker, Albert Yuen, Eric A. Strom, Jeannette L. Wilcox, Laura A. Vallow, William Small Jr, Anthony T. Pu, Kevin Kerlin, and Julia White

- ✓ It is recognized that this study closed early, with 636 patients accrued of the original planned 1,790 women and approximately 20% of the planned events
- ✓ The LF rate in the RT arm is less than 1%, yielding a statistically significant difference between the two arms as a result of the much larger than anticipated hazard reduction (HR, 0.11).
- ✓ Follow-up is continuing, and future analyses with longer follow-up will determine the reliability of this proportional reduction.



Variable	No. of Patients	5 Years %	5 Years 95% CI	10 Years %	10 Years 95% CI	12 Years %	12 Years 95% CI	P
Cohort 1	561	2.7	1.3 to 4.1	6.4	4.2 to 8.6	7.5	5.1 to 10.0	.08
Cohort 2	104	5.3	0.8 to 9.7	13.4	5.9 to 20.9	13.4	5.9 to 20.9	



- ✓ The trial design was a nonrandomized cohort study
- ✓ Tamoxifen was administered to approximately 30% of patients in a nonrandomized fashion
- ✓ The number of patients in cohort 2 was relatively small (n=104), limiting the statistical power in this group of patients

Ca in situ e ormonoterapia

- Quali fattori di rischio?
- Radioterapia?
- Ormonoterapia?

Long-term outcomes of ductal carcinoma in situ of the breast: a systematic review, meta-analysis and meta-regression analysis

Kirsty E. Stuart[1,2,3*], Nehmat Houssami[4], Richard Taylor[1,5], Andrew Hayen[5] and John Boyages[1,6]

				Meta-analysis[a]				Meta-regression[b]			
								Unadjusted	Adjusted for weighted mean age & period, & 10-year follow-up		
Treatment	Groups	DCIS cases	Local recurrence or death	Rate (%) & 95%CI	Model	*P* heterog	I^2 heterog[c]	Rate (%) & 95 % CI	Rate (%) & 95 % CI	OR	*P*
Invasive local recurrence											
Model *P*-value								*P* = 0.0005	*P* < 0.0001	*P* < 0.0001	
CS(alone)	10	2038	241	11.4	R	<0.05	60.1	11.2	11.3	2.61	0.001
				8.8–14.1				8.8–13.7	8.9–13.8	1.71–3.97	
CS + TAM(no RT)	1	567	49	8.6	-	-	-	8.6	11.0	2.52	0.001
				3.0–5.6				2.2–6.0	3.0–6.4	-	

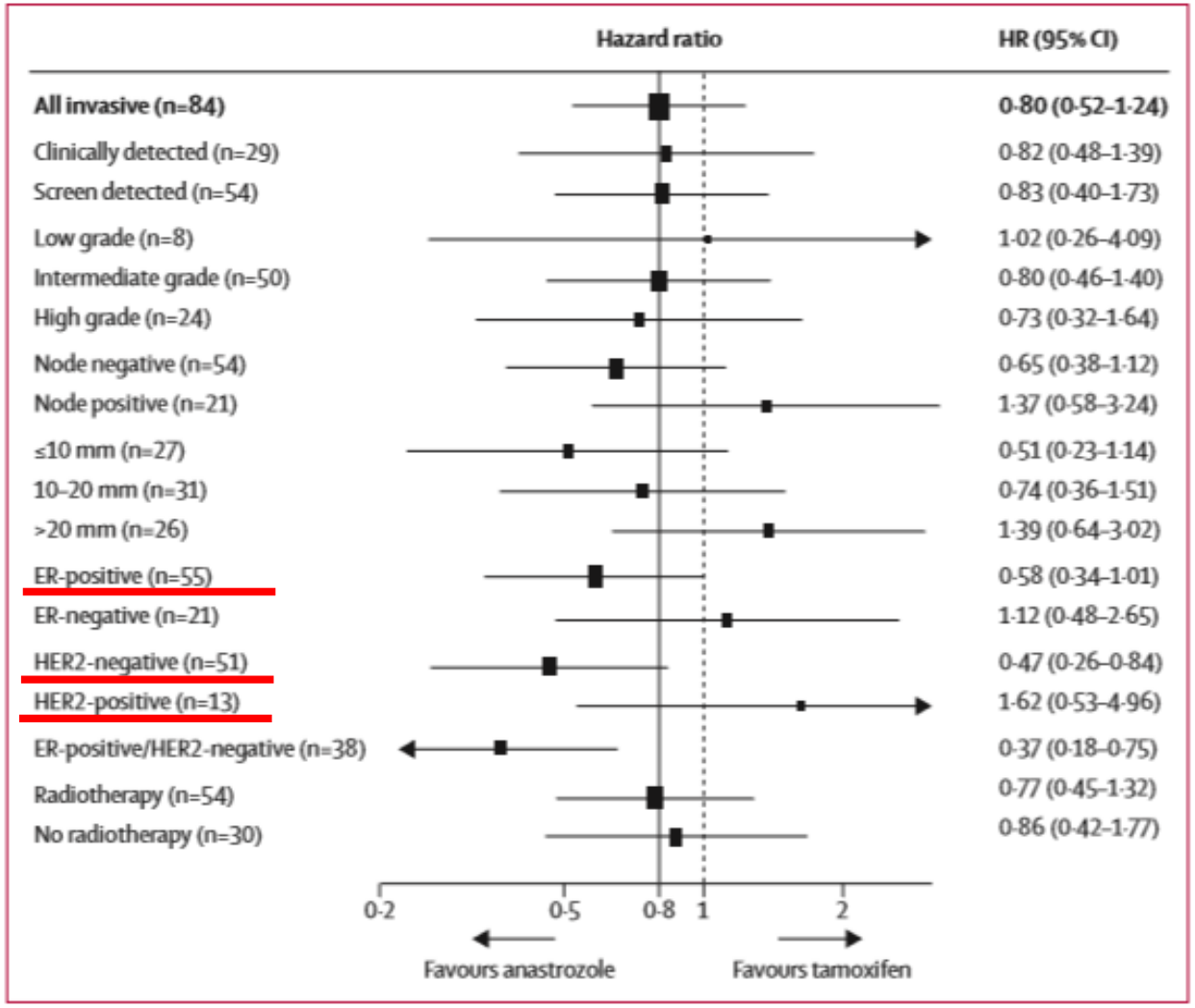
The results suggest that TAM does very little to prevent invasive recurrence on the same side over and above CS alone.

The ipsilateral LR rate was reduced when TAM was added to CS+RT. RT not only sterilizes residual cancer cells within the breast, but could additionally have a synergistic effect when combined with TAM

Anastrozole versus tamoxifen for the prevention of locoregional and contralateral breast cancer in postmenopausal women with locally excised ductal carcinoma in situ (IBIS-II DCIS): a double-blind, randomised controlled trial

John F Forbes, Ivana Sestak, Anthony Howell, Bernardo Bonanni, Nigel Bundred, Christelle Levy, Gunter von Min
Patrick Neven, Michael Stierer, Chris Holcombe, Robert E Coleman, Louise Jones, Ian Ellis, Jack Cuzick, on behalf o

- ✓ The major limitation of this trial was the lower-than-expected event rate, which adds uncertainty about the lack of significance of some of the small differences seen.
- ✓ It is too early to assess the effect of these treatments on mortality and long-term follow-up; a full meta-analysis of all major endpoints with the B-35 study is planned to study these issues.
- ✓ Anastrozole offers another treatment option for postmenopausal women with hormone-receptor-positive DCIS, which may be more appropriate for some women with contraindications for tamoxifen.



Anastrozole versus tamoxifen in postmenopausal women with ductal carcinoma in situ undergoing lumpectomy plus radiotherapy (NSABP B-35): a randomised, double-blind, phase 3 clinical trial

Richard G Margolese, Reena S Cecchini, Thomas B Julian, Patricia A Ganz, Joseph P Costantino, Laura A Vallow, Kathy S Albain, Patrick W Whitworth, Mary E Cianfrocca, Adam M Brufsky, Howard M Gross, Gamini S Soori, Judith O Hopkins, Louis Fehrenbacher, Keren Sturtz, Timothy F Wozniak, Thomas E Seay, Eleftherios P Mamounas, Norman Wolmark

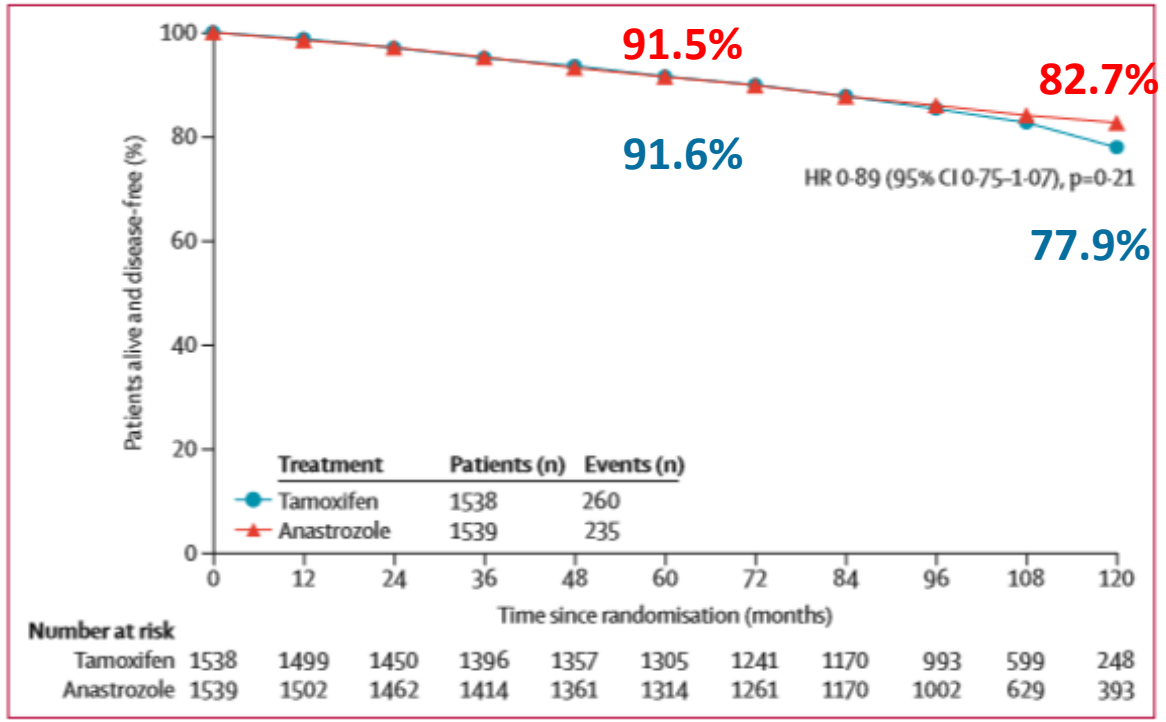
	Tamoxifen (n=1538)	Anastrozole (n=1539)	Hazard ratio (95% CI)	p value
All breast cancers				
Total	122	90	0·73 (0·56–0·96)	0·0234
Invasive	69	43	0·62 (0·42–0·90)	0·0123
Ductal carcinoma in situ	53	47	0·88 (0·59–1·30)	0·52
Ipsilateral recurrence				
Total	55	46	0·83 (0·56–1·22)	0·34
Invasive	22	17	0·76 (0·40–1·43)	0·39
Ductal carcinoma in situ	33	29	0·87 (0·53–1·43)	0·59
Contralateral breast cancer				
Total	60	39	0·64 (0·43–0·96)	0·0322
Invasive	40	21	0·52 (0·31–0·88)	0·0148
Ductal carcinoma in situ	20	18	0·90 (0·47–1·69)	0·73
Breast cancer at distant sites	7	4	0·57 (0·17–1·95)	0·37
Breast second primary cancer*	0	1	..	..

*Angiosarcoma in the ipsilateral breast.

Table 2: **Breast cancer first events**

	Patients (n)	Tamoxifen (n=1538)	Anastrozole (n=1539)	Hazard ratio (95% CI)	p value
Breast cancer-free interval events					
<60 years	1447	63	34	0·53 (0·35–0·80)	0·0026
≥60 years	1630	59	56	0·95 (0·66–1·37)	0·78
Disease-free survival events					
<60 years	1447	104	74	0·69 (0·51–0·93)	0·0151
≥60 years	1630	156	161	1·03 (0·83–1·28)	0·79

Table 3: **Breast cancer-free interval and disease-free survival events by age group**



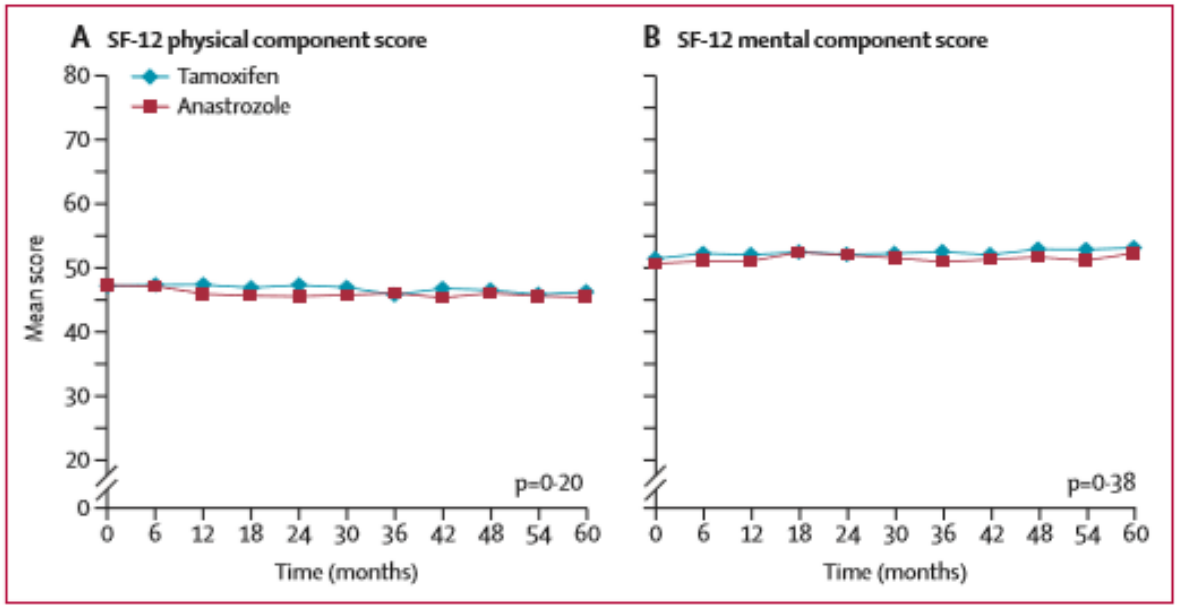
7·9% for the anastrozole group.
2·5% for the anastrozole group.

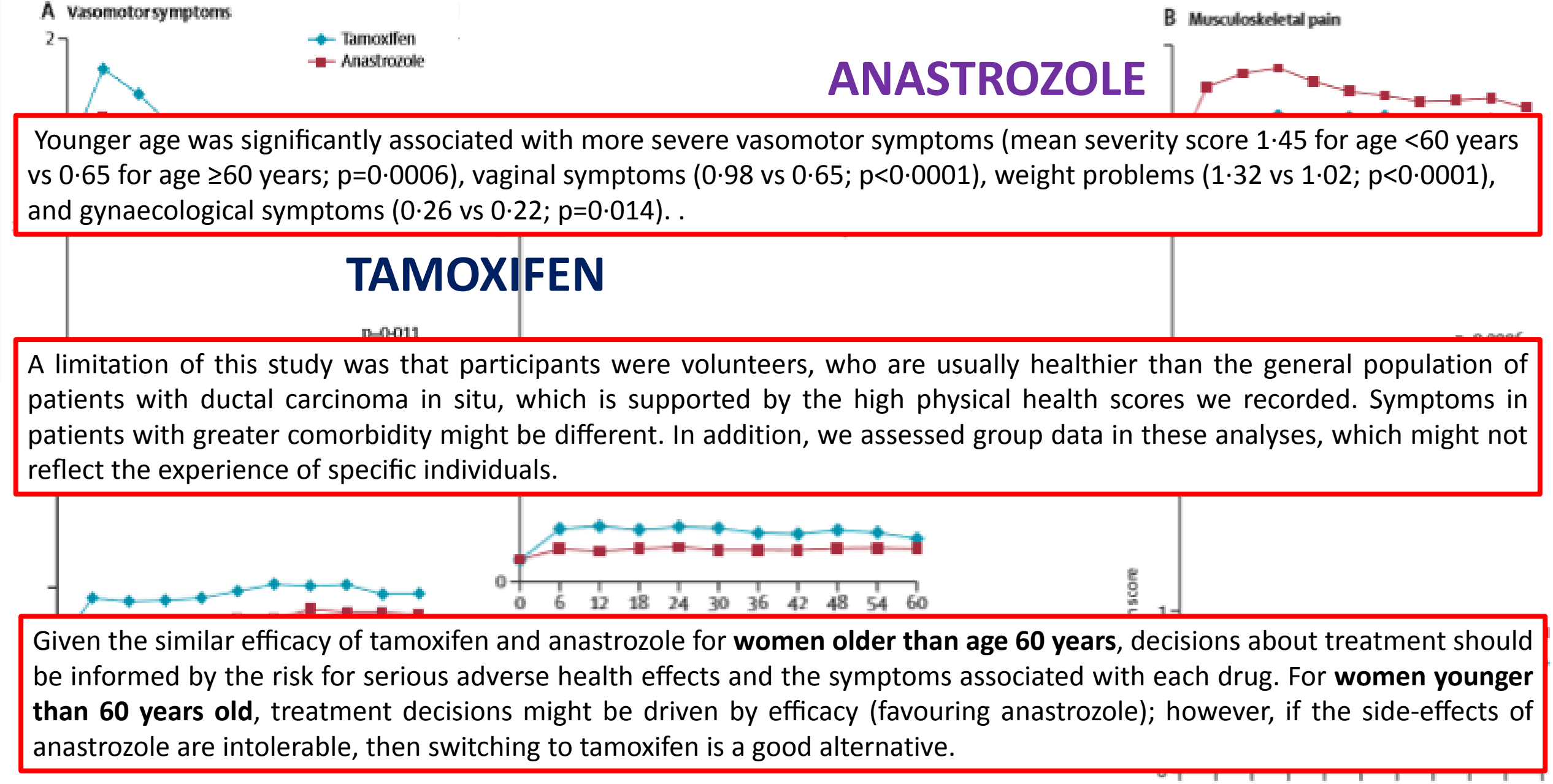
Patient-reported outcomes with anastrozole versus tamoxifen for postmenopausal patients with ductal carcinoma in situ treated with lumpectomy plus radiotherapy (NSABP B-35): a randomised, double-blind, phase 3 clinical trial

Patricia A Ganz, Reena S Cecchini, Thomas B Julian, Richard G Margolese, Joseph P Costantino, Laura A Vallow, Kathy S Albain, Patrick W Whitworth, Mary E Cianfrocca, Adam M Brufsky, Howard M Gross, Gamini S Soori, Judith O Hopkins, Louis Fehrenbacher, Keren Sturtz, Timothy F Wozniak, Thomas E Seay, Eleftherios P Mamounas, Norman Wolmark

Primary outcomes: **SF-12** physical and mental halth component scale scores
Vasomotor symptoms (**BCPT symptom scale**)

Secondary outcomes: **vaginal symptoms**
sexual functioning





ANASTROZOLE

Younger age was significantly associated with more severe vasomotor symptoms (mean severity score 1·45 for age <60 years vs 0·65 for age ≥60 years; p=0·0006), vaginal symptoms (0·98 vs 0·65; p<0·0001), weight problems (1·32 vs 1·02; p<0·0001), and gynaecological symptoms (0·26 vs 0·22; p=0·014). .

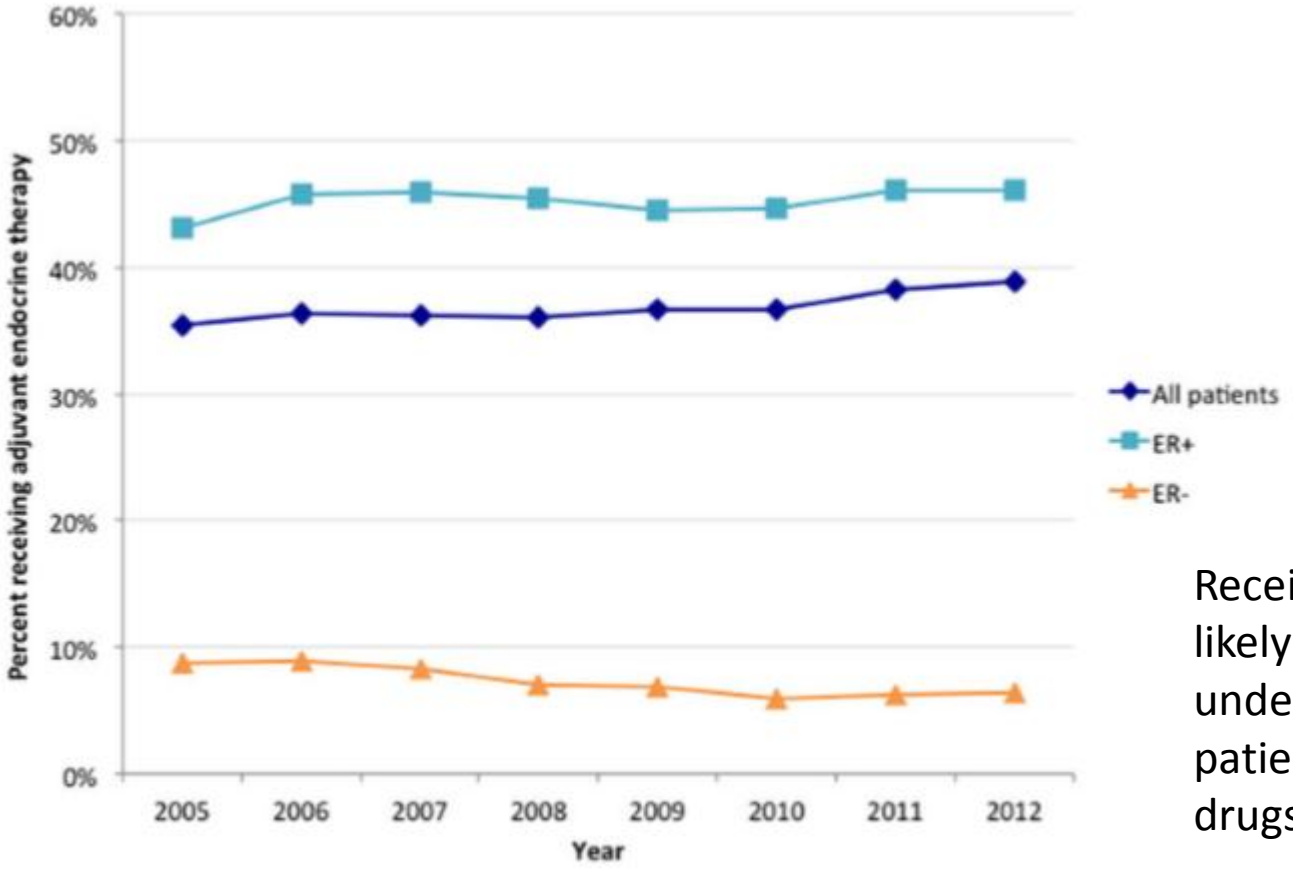
TAMOXIFEN

A limitation of this study was that participants were volunteers, who are usually healthier than the general population of patients with ductal carcinoma in situ, which is supported by the high physical health scores we recorded. Symptoms in patients with greater comorbidity might be different. In addition, we assessed group data in these analyses, which might not reflect the experience of specific individuals.

Given the similar efficacy of tamoxifen and anastrozole for **women older than age 60 years**, decisions about treatment should be informed by the risk for serious adverse health effects and the symptoms associated with each drug. For **women younger than 60 years old**, treatment decisions might be driven by efficacy (favouring anastrozole); however, if the side-effects of anastrozole are intolerable, then switching to tamoxifen is a good alternative.

Adjuvant endocrine therapy in patients with ductal carcinoma in situ: a population-based retrospective analysis from 2005-2012 in the National Cancer Database

Meghan R. Flanagan, MD[1], Mara H. Rendi, MD, PhD[2], Vijayakrishna K. Gadi, MD, PhD[3,4], Kristine E. Calhoun, MD[1], Kenneth W. Gow, MD[1,5], and Sara H. Javid, MD[1]



2005-2012

206255 pz

BCS (no RT): 23.7% *vs* 21.0%

BCS (+ RT): 49.9% *vs* 51.0%

Bilateral mastectomies: 5.2% *vs* 10.0%

AET: 33.1% *vs* 40.0%

Receipt of AET is relatively low in the group of women most likely to benefit from its use, namely ER+ patients who underwent BCS. Significant variation exists with respect to patient, tumor, site and treatment factors. More tolerable drugs or clearer guideline recommendations may increase use.

Ann Surg Oncol. 2015 October ; 22(10): 3264–3272

Grazie

……ma è altrettanto essenziale discernere per scegliere il trattamento adeguato…