V ZOOM Journal Club 2015

Bologna, 19 Febbraio 2016

Ca in situ e ormonoterapia

RAPPORTEUR : SARA FALIVENE

Original article The Breast 24 (2015) 673–679

How different terminology for ductal carcinoma in situ (DCIS) impacts women's concern and management preferences: A qualitative study

Brooke Nickel [a, b], Alexandra Barratt [a, b], Jolyn Hersch [a, b], Ray Moynihan [c], Les Irwig [a], Kirsten McCaffery [a, b, *]

Aumento di mastectomie bilaterali per DCIS

26 donne australiane

Reactions to DCIS and suggested alternative terminology.

DCIS terminology
"The word carcinoma jumps out at me. And I'd be fearful." (ID3, age 57, LE[a])
"Er … the only one that I sort of recognise … as it were is carcinoma. And carcinoma is a frightening word." (ID23, age 78, LE)
DIN terminology
"I guess my feelings would be, um, just guided by a fear of the unknown … my feelings are definitely more apprehensive, um, than if, er, the cells were referred to as abnormal" (ID4, age 25, HE)
"Um, it's better than the last one[DCIS]. It doesn't have carcinoma in it." (ID15, age 47, HE)
"… less concerning because it doesn't have carcinoma in it." (ID17, age 64, HE)
IDLE terminology
" … that sounds a bit like jargon." (ID3, age 57, LE)
"IDLE makes it sound like it's still, or no, no real problem. Well, that might make people feel quite calm about it. " (ID25, age 62, HE)
Abnormal cells in the milk duct of the breast that have not spread
"Well once they say has not spread into other … breast, breast tissues that sort of reduces my concern about the abnormal cells." (ID17, age 64, HE)
"Oh, that helps in terms of it's more precise and exact and provides a location, and it … more information about it which then I would explain when talking to other people, I'd be summarizing it back down to abnormal cells. Or I'd be comfortable having it discussed as abnormal cells being given that … definition in the first place." (ID5, age 32, HE)
"That one I understand … it's just a lot easier to understand. At, at least they're explaining exactly what it is." (ID13, age 50, LE)
"I really wouldn't know whether it can move out of the milk duct easily … to anywhere else. I have no idea." (ID11, age 80, LE, previous breast cancer diagnosis)

Viewpoints and debate The Breast xxx (2015) 1–4

Eliminating "ductal carcinoma in situ" and "lobular carcinoma in situ" (DCIS and LCIS) terminology in clinical breast practice: The cognitive psychology point of view

Gabriella Pravettoni [a, b, *], Whitney R. Yoder [c], Silvia Riva [a], Ketti Mazzocco [a, b], Paola Arnaboldi [b], Viviana Galimberti [d]

- ✓ Non invasivo
- ✓ DIN e LIN
  (ductal/lobular intraepitelial neoplasia)
- ✓ Impatto emozionale (pesantezza del termine-leggerezza cure… aspettative deluse… dubbio sottotrattamento)
- ✓ Impatto sul processo cognitivo (CHIARA comunicazione medico paziente)
- ✓ False percezioni, ansia, tristezza

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Annals of
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ORIGINAL ARTICLE – BREAST ONCOLOGY

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

Ductal carcinoma in situ (DCIS) accounts for over 20 % of all breast cancer diagnosed in the US annually.[1] A 500 % increase in the incidence of DCIS between 1983 and 2003 was observed for women 50 years of age and older, likely due to screening mammography.[2]

Reported recurrence rates for DCIS treated with breast-conserving surgery (BCS) from four prospective randomized trials of radiation range from 26 to 36 % for those treated without radiation therapy, and from 9 to 23 % for those treated with radiation at 13–20 years of follow-up.[3–6] These rates are higher than the 12-year ipsilateral breast tumor recurrence rates of 5–8 % for node-negative invasive breast cancer treated with radiation and systemic therapy.[7]

TABLE 1 Characteristics of the entire population ($n = 2996$) and patients treated between 1978 and 1998, and 1999 and 2010

Characteristic	Entire population ($n = 2996$)		1978–1998 ($n = 785$)		1999–2010 ($n = 2211$)		p value*
	N	%	*N*	%	*N*	%	
Age, years							
≤50	845	28.2	237	30.2	608	27.5	0.1
>50	2151	71.8	548	69.8	1603	72.5	
Number of excisions							
≤2	2775	92.6	738	94.0	2037	92.1	0.04
≥3	217	7.2	44	5.6	173	7.8	
Unknown	4	0.1	3	0.4	1	0.04	
Margin status							
Positive/close (≤2 mm)	553	18.5	185	23.6	368	16.6	<0.0001
Negative (>2 mm)	2235	74.6	440	56.1	1795	81.2	
Unknown	208	6.9	160	20.4	48	2.2	
Radiation therapy							
No	1374	45.9	458	58.3	916	41.4	<0.0001
Yes	1588	53.0	310	39.5	1278	57.8	
Unknown	34	1.1	17	2.2	17	0.8	
Endocrine therapy							
No	2321	77.4	642	81.8	1679	76.0	<0.0001
Yes	628	20.9	121	15.4	507	22.9	
Unknown	47	1.7	22	2.8	25	1.1	
Treatment period							
1978–1998	785	26.2	785	100	–		
1998–2010	2211	73.8	–		2211	100	

Ca in situ e ormonoterapia

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

Predictors of Recurrence in Patients Diagnosed with Ductal Carcinoma In Situ

GLORIA R. SUE, M.A., ANEES B. CHAGPAR, M.D.

From the Department of Surgery, Yale University School of Medicine, New Haven, Connecticut

205 pz DCIS
14 recidive

- Età
- Dimensioni
- Razza
- Caratteristiche istopatologiche

NON correlano con recidiva

G3 pare possa essere fattore predittivo

TABLE 1. *Comparison of Clinicopathologic Factors between Patients with DCIS with Recurrence and Those without Recurrence*

Factor	Recurrence	No Recurrence	*P* Value
Median patient age (years)	55.5	55.5	0.283
Median size of DCIS (mm)	10	10	0.942
Race			0.775
White	12 (85.7%)	163 (85.3%)	
Black	2 (14.3%)	21 (11.0%)	
Hispanic	0 (0%)	1 (0.5%)	
Grade of DCIS			0.032
1	0 (0%)	16 (9.9%)	
2	3 (27.3%)	88 (54.7%)	
3	8 (72.7%)	57 (35.4%)	
Solid histologic subtype	7 (50.0%)	82 (42.9%)	0.781
Comedo histologic subtype	9 (64.3%)	90 (47.1%)	0.272
Cribriform histologic subtype	3 (21.4%)	58 (30.4%)	0.562
Micropapillary histologic subtype	2 (14.3%)	60 (31.4%)	0.236
Presence of necrosis	8 (57.1%)	105 (55.0%)	1.000
Presence of possible microinvasion	3 (21.4%)	48 (25.1%)	1.000
Presence of microcalcifications	13 (92.9%)	140 (73.3%)	0.124

DCIS, ductal carcinoma *in situ*.

Co-Expression of p16, Ki67 and COX-2 Is Associated with Basal Phenotype in High-Grade Ductal Carcinoma In Situ of the Breast

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Table 5. Expression of Biomarkers COX-2, p16, Ki67 and Molecular Phenotypes in High-Grade Ductal Carcinoma In Situ.

	Molecular Phenotypes										
	Luminal A		Luminal B		HER2		Basal		"Not classified"		
Biomarker	N	%	N	%	N	%	N	%	N	%	p Value
COX-2[a]											0.475
Negative	49	72%	07	47%	09	69%	04	67%	11	69%	
Positive	19	28%	08	53%	04	31%	02	33%	05	31%	
Total	68	100%	15	100%	13	100%	06	100%	16	100%	
p16[a]											0.000
Negative	64	93%	12	80%	11	85%	01	17%	14	88%	
Positive	05	7%	03	20%	02	15%	05	83%	02	12%	
Total	69	100%	15	100%	13	100%	06	100%	16	100%	
Ki67[a]											0.274
Low Prolif index	22	34%	04	27%	01	9%	00	0%	05	31%	
High Prolif index	42	66%	11	73%	10	91%	05	100%	11	69%	
Total	64	100%	15	100%	11	100%	05	100%	16	100%	

COX-2, cyclooxygenase-2; p16, tumor suppressor protein p16; Ki67, nuclear antigen Ki67; Prolif, proliferation. Luminal A: ER$^+$/HER2$^-$; Luminal B: ER$^+$/HER2$^+$; HER2: ER$^-$/HER2$^+$; Basal: ER$^-$/HER2$^-$/EGFR$^+$ and/or CK5$^+$; "Not classified": ER$^-$/HER2$^-$/EGFR$^-$/CK5$^-$
p, significance level using [a]Pearson's Chi-squared test.

Table 6. High-Grade Ductal Carcinoma In Situ: Associations between Molecular Phenotype and Biomarker(s) Expression (COX-2, p16, Ki67).

Biomarker Co-Expression	Luminal A (*n*=70)	Luminal B (*n*=15)	HER2 (*n*=13)	Basal (*n*=6)	NC (*n*=17)	p Value[a]
COX2$^+$	19 (27%)	8 (53%)	4 (31%)	2 (33%)	5 (29%)	0.4634
Ki67$^+$	42 (60%)	11 (73%)	10 (77%)	5 (83%)	11 (65%)	0.3192
p16$^+$	**5 (7%)**	**3 (20%)**	**2 (15%)**	**5 (83%)**	**2 (12%)**	**0.0004**
COX2$^-$/p16$^-$/Ki67$^-$	12 (17.1%)	2 (13.3%)	0 (0%)	0 (0%)	2 (11.8%)	0.6483
COX2$^+$/p16$^+$/Ki67$^-$	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	*
COX2$^-$/p16$^-$/Ki67$^+$	30 (42.9%)	4 (26.7%)	6 (46.2%)	0 (0%)	7 (41.2%)	0.1679
COX2$^+$/Ki67$^+$/p16$^-$	9 (12.9%)	4 (26.7%)	2 (15.4%)	0 (0%)	1 (5.9%)	0.5536
COX2$^-$/Ki67$^-$/p16$^+$	2 (2.9%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	*
p16$^+$/Ki67$^+$/COX2$^+$	**1 (1.4%)**	**2 (13.3%)**	**1 (7.7%)**	**2 (33.3%)**	**1 (5.9%)**	**0.0106**
p16$^+$/Ki67$^+$/COX2$^-$	**2 (2.9%)**	**1 (6.7%)**	**1 (7.7%)**	**3 (50%)**	**1 (5.9%)**	**0.0049**
p16$^-$/Ki67$^-$/ COX2$^+$	8 (11.4%)	2 (13.3%)	1 (7.7%)	0 (0%)	3 (17.6%)	0.8721

COX2, cyclooxygenase-2; Ki67, nuclear antigen Ki67; p16, tumor suppressor protein p16. Luminal A: ER$^+$/HER2$^-$; Luminal B: ER$^+$/HER2$^+$; HER2: ER$^-$/HER2$^+$; Basal: ER$^-$/HER2$^-$/EGFR$^+$ and/or CK5$^+$; NC, "Not classified": ER$^-$/HER2$^-$/EGFR$^-$/CK5$^-$
p, significance level using [a]Exact Fisher's test; *test not performed due low frequency of biomarker. Note: eleven cases were not evaluated because there was no available information about one of the biomarkers.

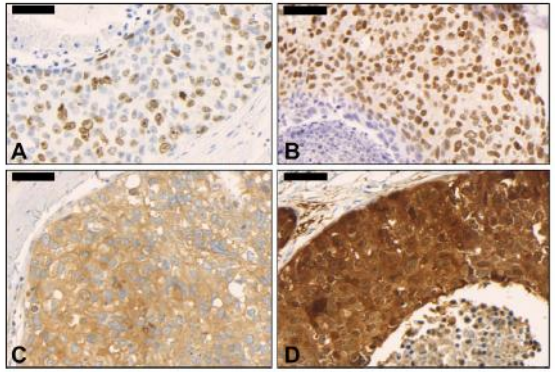

Figure 1. High-grade ductal carcinoma in situ of the breast. (A) High Ki67 proliferation index (400×); (B) Estrogen receptor positivity (400×); (C) Cyclooxygenase-2 (COX-2) positivity (400×); D: p16 positivity (400×). Scale, 50 µm.

In conclusion, p16 expression, alone or in combination with Ki67 and COX-2, is associated with a basal phenotype among patients with high-grade DCIS. It is possible that these biomarkers could be incorporated into routine clinical practice of DCIS evaluation and that this "triple test" could be useful in guiding the choice for a more aggressive treatment plan in patients with high-grade DCIS and/or to develop new targeted therapies in chemoprevention. It would be interesting to follow-up these cases to confirm the value of p16, Ki67 and COX-2, and to validate the co-expression of these putative biomarkers as prognostic and/or predictive factors for DCIS of the breast.

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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

higher risk of LIR.

Rischio DCIS rec senza diminuire rischio LIR (non è però un fattore indipendente)

Non significativo

Table 2 Risk estimates of associations between biomarkers, tumor characteristics, or modes of detection and the risk of local invasive recurrence

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	–	–	0.74 (0.36–1.12)/3	0.0	0.74 (0.36–1.12)/3	0.0
PR (positive vs. negative)	1556	–	–	0.89 (0.47–1.31)/3	0.0	0.89 (0.47–1.31)/3	0.0
HER2/neu (positive vs. negative)	1771	–	–	1.25 (0.70–1.81)/4	0.0	1.25 (0.70–1.81)/4	0.0
Tumor characteristics							
Nuclear grade							
High/low	52 635	1.33 (0.86–1.79)/4	0.0	0.97 (0.75–1.19)/8	0.0	1.04 (0.84–1.24)/12	0.0
Intermediate/low	45 360	1.27 (0.82–1.72)/3	0.0	1.38 (0.86–1.89)/3	0.0	1.32 (0.98–1.66)/6	0.0
Comedonecrosis (yes vs. no)	45 442	0.9 (0.62–1.19)/2	0.0	**1.41 (1.15–1.68)/**3	0.0	1.18 (0.98–1.37)/5	47.2
Margins (positive vs. negative)	10 021	1.15 (0.72–1.59)/3	68.4	**1.62 (1.14–2.10)/**4	0.0	**1.36 (1.04–1.69)/**7	39.7
Tumor size (large vs. small)	54 939	0.97 (0.66–1.27)/2	0.0	1.00 (0.92–1.08)/8	9.6	1.00 (0.92–1.08)/10	0.0
Focality (multifocality/ multicentric vs. unifocal)	1963	–	–	1.34 (0.82–1.87)/3	0.0	1.34 (0.82–1.87)/3	0.0
Mode of detection (nonscreening detection vs. screening detection)	10 866	**1.40 (1.06–1.75)/**2	0.0	1.36 (0.95–1.74)/4	68.5	**1.38 (1.12–1.63)/**6	48.2

CI, confidence interval; ER, estrogen receptor; HER2/neu, epidermal growth factor receptor-2; PR, progesterone receptor; RCT, randomized clinical trial.
Bold indicates P <0.05.

Clinicopathological predictive factors for ipsilateral and contralateral events following initial surgery to treat ductal carcinoma in situ

Nobuko Tamura · Hitoshi Tsuda · Masayuki Yoshida · Takashi Hojo · Sadako Akashi-Tanaka · Takayuki Kinoshita · Kenichi Sugihara

Of 301 consecutive DCIS patients,
179 → mastectomy
122 → **partial resection**

Results Of the 122 patients who underwent partial breast resection, IBTR occurred in 7 (5.7 %). The risk of IBTR was higher or tended to be higher in younger patients or those with lower NG tumors, but did not change significantly with respect to margin status or irradiation.

Table 5 Cox multivariate analysis to identify clinicopathological parameters that are independent risk factors for CBT in situ patients

Parameter	Total (n = 301)	CBTR (n = 18)			
		No. of cases (%)	p	Hazard ratio	95 % CI
Surrogate intrinsic subtype					
HR+/HER2−	222	17 (7.7)	*0.04*	5.1	1.0–92.6
Others	79	1 (1.3)			
Family history					
Yes	46	6 (13.0)	*0.07*	2.7	0.9–7.2
No	255	12 (4.7)			

CBTR contralateral breast tumor recurrence, *HER2* human epidermal growth factor receptor 2, *HR* hormone receptor, *CI* confidence interval

Conclusions The local recurrence rate was low following partial resection of DCIS. Younger age was a risk factor for IBTR, whereas the HR+/HER2− tumor subtype and a FH of breast cancer were risk factors for CBTR.

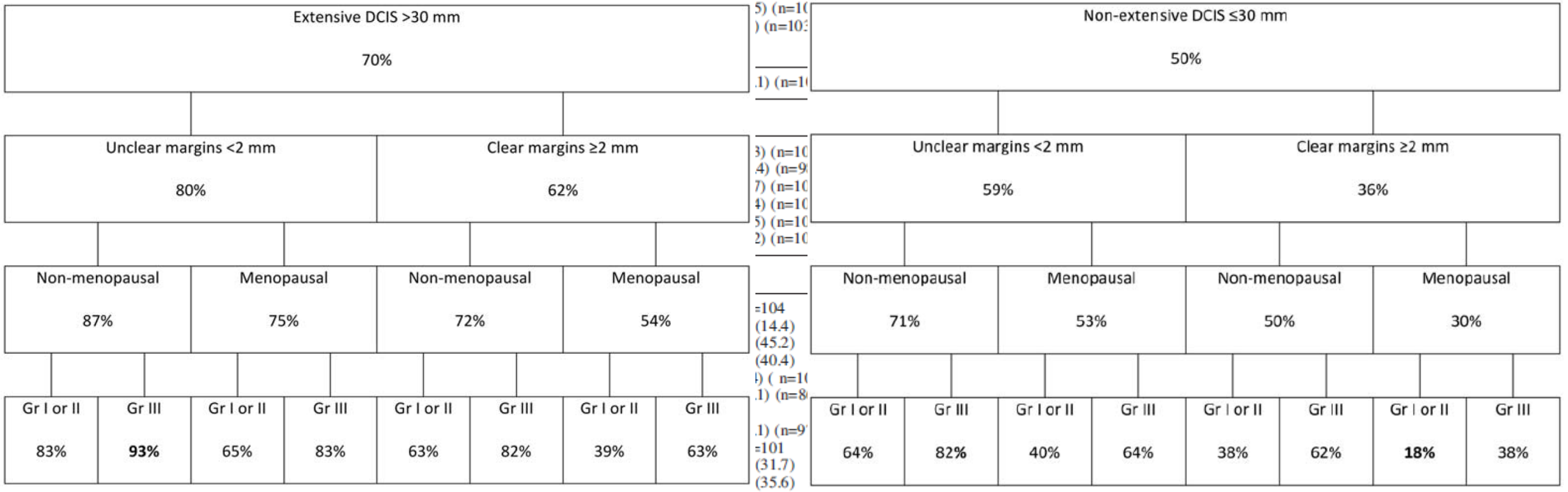
Non-menopausal Status, High Nuclear Grade, Tumor Size >30 mm and Positive Resection Margins Are Predictors of Residual Tumor After Lumpectomy for Ductal Carcinoma *In Situ* of the Breast

MARINE JOSTE[1], VANDA MENDES[2], SARAH TIXIER[3], CLEMENT PALPACUER[4], BRUNO LAVIOLLE[4], JEAN LEVEQUE[1] and LOBNA OULDAMER[2]

ANTICANCER RESEARCH *35*: 3471-3478 (2015)

Four factors predicting positive surgical re-excision after conservative treatment for DCIS of the breast resulted from the multivariate analysis. These were lesion size, high nuclear grade, unclear margins and the non-menopausal status of patients. Combined use of these four factors could enable surgeons to provide patients with precise probability of the risk of residual tumor and hence the need for a repeat operation.

	Re-excision			
	Total (n=285)	Negative (n=105)	Positive (n=180)	*p*-Value
Clinical [n(%)]				
Age (years)	55.96±10.22 (n=284)	57.73±9.02 (n=105)	54.92±10.75(n=179)	0.025*
Family history of breast cancer	111 (39.6) (n=280)	42 (41.2) (n=102)	69 (38.8) (n=178)	0.71



≥1 mm	61 (22.8)	33 (32.7)	28 (16.8)	0.0005*b
Positive margins (at margin *vs.* not at margin)	118 (44.0) (n=268)	32 (31.7) (n=101)	86 (51.5) (n=167)	0.0016*
Size of operative specimen (mm)	61.80±24.93 (n=264)	61.82±25.72 (n=98)	61.80±24.54 (n=166)	0.99

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Original Article

Large palpable ductal carcinoma in situ is Her-2 positive with high nuclear grade

Ahmad Monabati[1], Ali-Reza Sokouti[1], Sadat Noori Noori[1], Akbar Safaei[1], Abd-Rasul Talei[2], Shapoor Omidvari[3], Negar Azarpira[4]

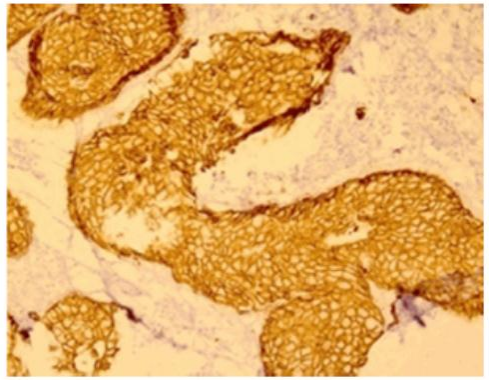


Figure 3. Her-2 positive malignant cells (3+) (IHC, × 400).

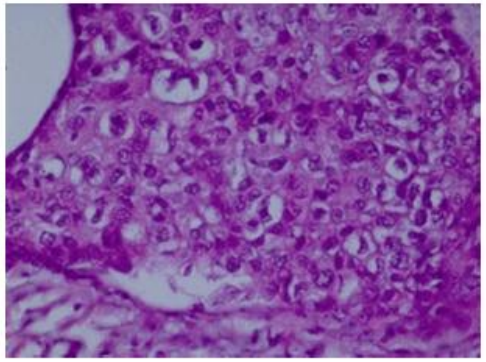


Figure 2. DCIS with high nuclear grade (Grade III), (H&E × 400).

Table 4. Comparison of DCIS nuclear grade and hormone receptor (n = 54)

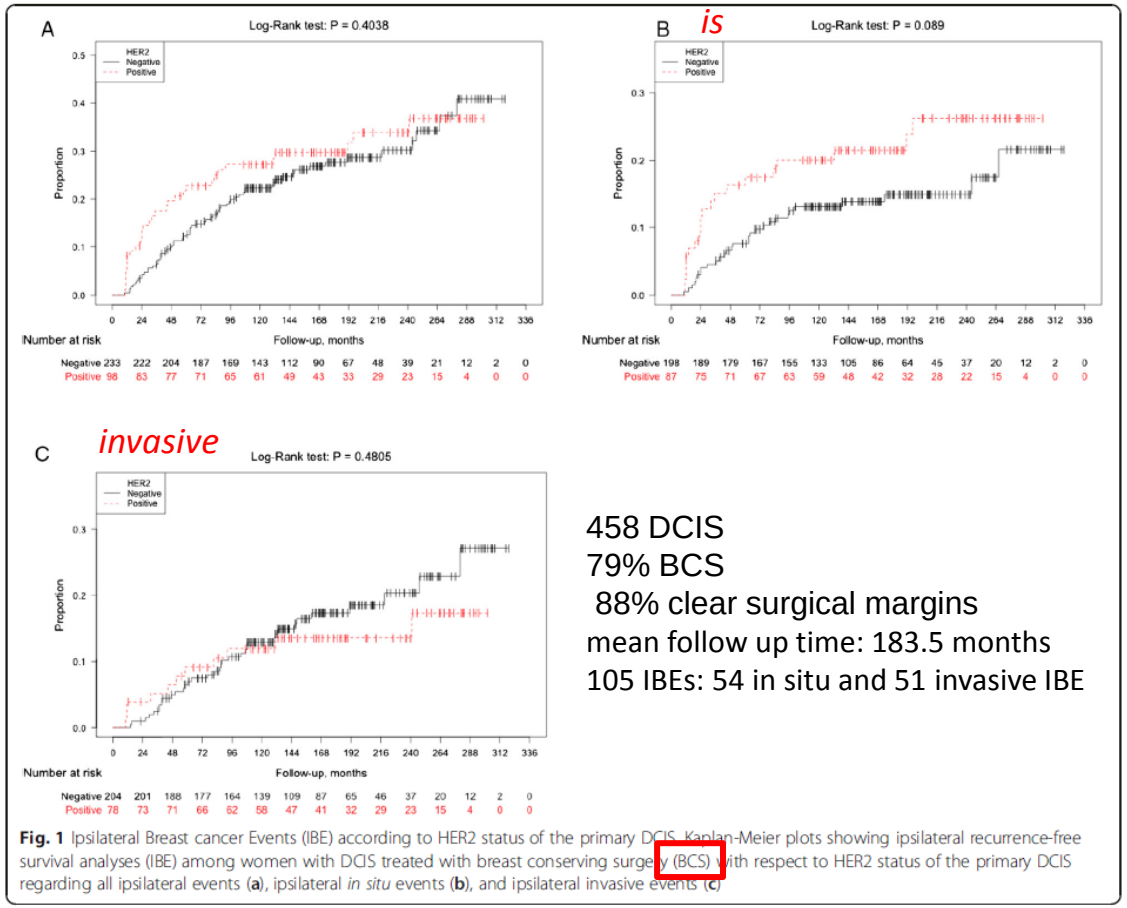
	Grade III (n = 39)	Grade II (n = 15)	Grade I (n = 0)	*p*-value
Her2/neu				
Positive	36 (92)	14 (93)	0	1.000
Negative	3 (8)	1 (7)	0	1.000
ER				
Positive	11 (28.2)	15 (100)	0	0.001*
Negative	28 (71.8)	0 (0)	0	0.001*
PR				
Positive	7 (17.9)	14 (93)	0	0.001*
Negative	32 (82.1)	1 (7)	0	0.001*

*P<0.05 is consider significant.

Palpable DCIS lesions were significantly more HER-2 positive (92%). The DCIS cases were more likely to be of high nuclear grade (grade III) and Her-2 positive cases were more likely to be of high nuclear grade than intermediate grade. All ER negative tumors had high nuclear grade. The Her-2 positivity is suggested as the most important factor responsible for marked in situ proliferation and production of palpable mass.

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]



458 DCIS
79% BCS
88% clear surgical margins
mean follow up time: 183.5 months
105 IBEs: 54 in situ and 51 invasive IBE

Fig. 1 Ipsilateral Breast cancer Events (IBE) according to HER2 status of the primary DCIS. Kaplan-Meier plots showing ipsilateral recurrence-free survival analyses (IBE) among women with DCIS treated with breast conserving surgery (BCS) with respect to HER2 status of the primary DCIS regarding all ipsilateral events (**a**), ipsilateral *in situ* events (**b**), and ipsilateral invasive events (**c**)

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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,†]

Divisions of [1]Experimental Therapeutics; [2]Epidemiology and Biostatistics; [3]Department of Pathology and Laboratory Medicine; [4]School of Medicine, University of Milano, Milan; Divisions of [5]Cancer Prevention and Genetics; [6]Senology; [7]Department of Medical Imaging and Radiation Sciences; [8]Breast Health Program, European Institute of Oncology, Milan, Italy

Conclusion: HER2 overexpression predicts an increased risk of *is*BCR. Radiotherapy reduces local failure rates in HER2-positive DCIS.

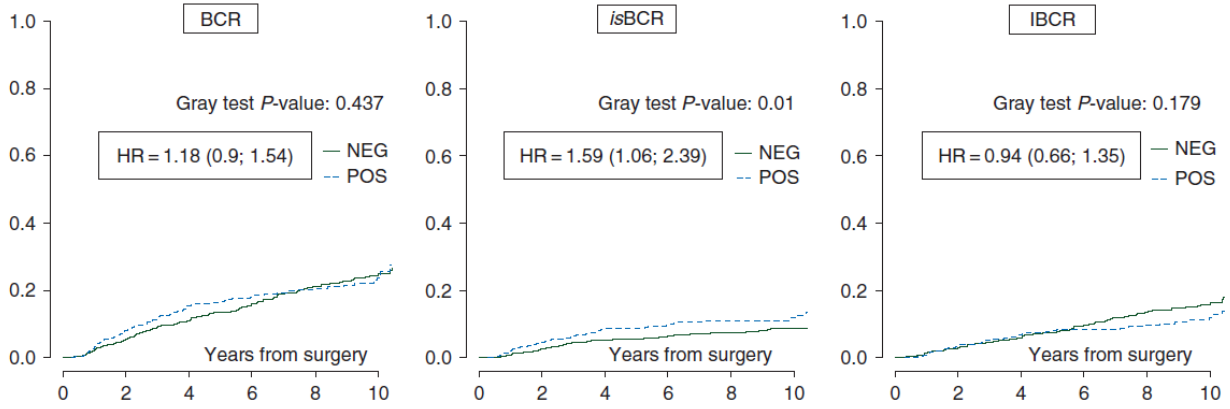

Figure 1. Cumulative incidence of any breast cancer recurrence (BCR), *in situ* breast cancer recurrence (*is*BCR) and INvasive breast cancer recurr (IBCR), by HER2 status. Hazard ratio adjusted for: ER/PgR, hormone therapy, type of surgery, radiotherapy, menopausal status, and grade.

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ORIGINAL ARTICLE – BREAST ONCOLOGY

Microcalcifications in 1657 Patients with Pure Ductal Carcinoma in Situ of the Breast: Correlation with Clinical, Histopathologic, Biologic Features, and Local Recurrence

Gaiane M. Rauch, MD, PhD[1], Brian P. Hobbs, PhD[2], Henry M. Kuerer, MD, PhD[3], Marion E. Scoggins, MD[4], Ana P. Benveniste, MD[5], Young Mi Park, MD[5], Abigail S. Caudle, MD[3], Patricia S. Fox, MS[2], Benjamin D. Smith, MD[6], Beatriz E. Adrada, MD[4], Savitri Krishnamurthy, MD[7], and Wei T. Yang, MD[8]

Increased LR risk was seen in patients with dense breast tissue ($p < 0.05$) and larger DCIS size ($p < 0.01$). Radiation therapy was associated with a 2.8-fold decrease in the LR risk. Fine linear (branching) microcalcifications were associated with 5.2-fold increase in LR. Extremely dense breast tissue was associated with positive/close margins ($p = 0.04$) and multicentricity ($p < 0.01$). Younger women were more likely to have extremely dense breast tissue ($p < 0.0001$), multicentric disease ($p < 0.0004$), and undergo mastectomy ($p < 0.0001$).

Conclusions. Dense breast tissue, large DCIS size, and fine linear (branching) microcalcifications were associated with increased LR, yet overall LR rates remained low. Extremely dense breast tissue was a risk factor for multicentricity and positive margins in DCIS.

TABLE 3 Multivariate analysis of associations between grade, comedonecrosis, multicentricity with mammographic features and ER status in 1657 patients with pure DCIS

Feature	Grade 3 ($N = 854$)		Comedonecrosis ($N = 855$)		Multicentricity ($N = 663$)	
	Odds ratio (95 % CI)	p value	Odds ratio (95 % CI)	p value	Odds ratio (95 % CI)	p value
Breast density						
Fatty/scattered	1 (–)	–	1 (–)	–	1 (–)	–
Heterogeneously dense	1.2 (0.8–1.6)	0.37	1.1 (0.8–1.5)	0.57	1.1 (0.6–1.8)	0.8
Extremely dense	1.0 (0.5–1.9)	0.98	0.9 (0.5–1.6)	0.62	3.1 (1.3–7.0)	**<0.01**
Microcalcification morphology						
Punctate/amorphous	1 (–)	–	1 (–)	–	1 (–)	–
Coarse heterogeneous/fine pleomorphic	2.3 (1.5–3.3)	**<0.0001**	1.4 (1.0–2.0)	0.08	1.4 (0.8–2.6)	0.25
Fine linear (branching)	3.4 (1.9–6.1)	**<0.0001**	1.7 (1.0– 2.9)	**<0.05**	0.7 (0.3–1.7)	0.44
Microcalcification distribution						
Clustered/grouped	1 (–)	–	1 (–)	–	1 (–)	–
Linear/segmental	1.3 (0.8–1.9)	0.27	1.6 (1.1–2.4)	**<0.02**	0.9 (0.5–1.8)	0.83
Regional/diffuse	1.0 (0.6–1.7)	0.97	1.4 (0.8–2.2)	0.21	1.6 (0.8–3.1)	0.15
Mammographic size	1.1 (1.0–1.2)	**0.02**	1.2 (1.1–1.3)	**<0.0001**	1.4 (1.3–1.5)	**<0.0001**
ER–negative status	30.8 (12.4–76.6)	**<0.0001**	3.2 (2.1–4.7)	**<0.0001**	1.4 (0.8–2.4)	0.21

Multiple logistic regression analysis was implemented using the set of independent variables (breast density, microcalcification morphology, microcalcification distribution, mamı grade 3, comedonecrosis, and multicentricity)

p values for the partial odds ratios deri tor levels, the partial odds ratio for observing the dependent variable is mographic size, the partial odds ratio is provided per unit increase in c

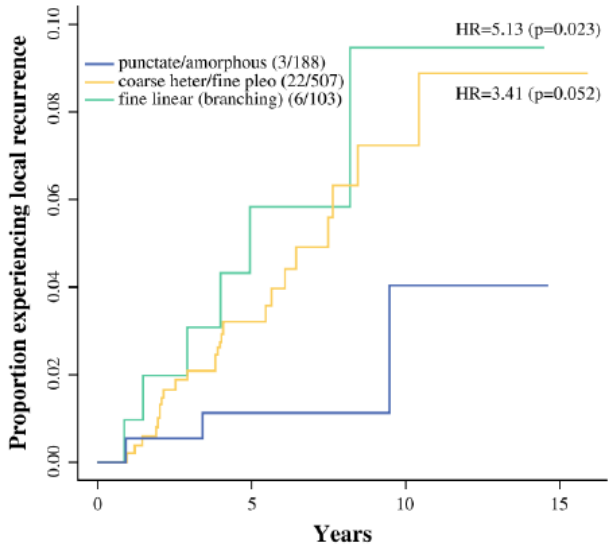


FIG. 1 Cumulative incidence curves for time to LR stratified by microcalcification morphology in patients with pure DCIS who underwent segmentectomy

Ca in situ e ormonoterapia

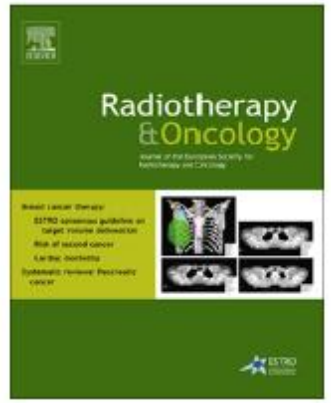
- Quali fattori di rischio?
- Radioterapia?
- Ormonoterapia?

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,*]

[a] Center for Clinical Research, Västmanlands County Hospital, Västerås; and [b] Centre for Clinical Research Sörmland, Uppsala University, Eskilstuna, Sweden



Analisi di 13 tirals

Sono in corso TCR i cui risultati sono attesi tra 10 anni *(TROG 07.01trials; the BONBIS trial)*

Ad oggi l'evidenza si basa su studi osservazionali retrospettivi

Outcome	No of studies (patients)	Quality assessment					Summary of findings			Quality of evidence
		Study limitations	Consistency	Directness	Precision	Publication bias	Odds Ratio (95% CI)	Heterogeneity I^2, %	Heterogeneity p value	
Local recurrence (boost vs. no boost)	12 (6943)	Moderate	Presence of inconsistency	Direct	Imprecision	Undetectable	0.91 (0.77–1.08)	0	0.47	Very low
Local recurrence (boost vs. no boost) positive margins	6 (811)	Moderate	Presence of inconsistency	Direct	Imprecision	Undetectable	0.56 (0.36–0.87)	43	0.12	Very low
Local recurrence (boost vs. no boost) Age < 50 years old	7 (1345)	Moderate	Presence of inconsistency	Direct	Imprecision	Undetectable	0.83 (0.62–1.11)	28	0.22	Very low
Local recurrence (hypofractionated RT vs. standard RT)	4 (2534)	Moderate	No inconsistency	Direct	Imprecision	Undetectable	0.78 (0.58–1.03)	0	0.89	Low

Breast Cancer Res Treat (2015) 151:199–208
DOI 10.1007/s10549-015-3389-0

EPIDEMIOLOGY

Accelerated partial breast irradiation through brachytherapy for ductal carcinoma in situ: factors influencing utilization and risks of second breast tumors

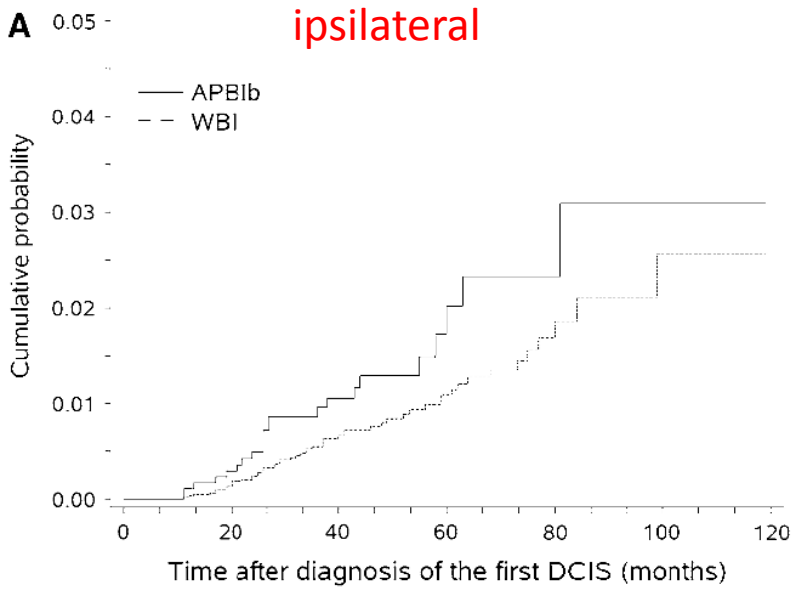
Ying Liu[1] · Derek T. Schloemann[1] · Min Lian[2,3] · Graham A. Colditz[1,3]

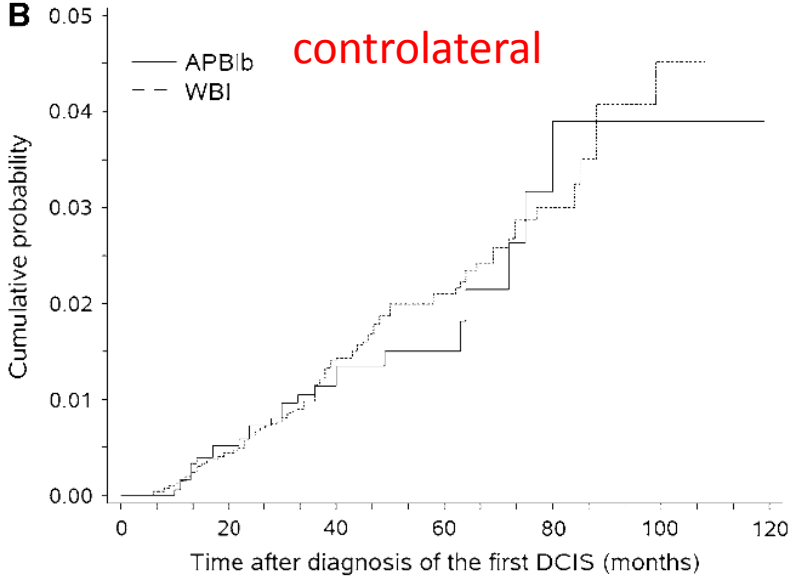
Little is known about clinical outcomes after APBIb for ductal carcinoma in situ (DCIS), a precancerous breast lesion with treatment options similar to early invasive breast cancer. APBIb is not considered suitable for DCIS according to the American Society for Radiation Oncology (ASTRO) guidelines [9]. However, 6.5 % of DCIS patients from the Commission on Cancer (CoC)-accredited hospitals received APBIb following BCS. APBIb use was as-

Table 3 Hazard ratios (HRs) of second breast tumors in the ipsilateral and contralateral breasts in DCIS patients receiving breast-conserving surgery and radiation therapy

	No. of patients	Ipsilateral breast tumors			Contralateral breast tumors		
		No. of events	HR (95 % CI)	*P*	No. of events	HR (95 % CI)	*P*
Propensity score matching							
WBI	7203	52	1.00 (reference)		106	1.00 (reference)	–
APBIb	1962	22	1.74 (1.06, 2.85)	0.03	25	0.91 (0.59, 1.41)	0.68
Propensity score adjustment							
WBI	36,471	539	1.00 (reference)		837	1.00 (reference)	–
APBIb	2043	23	1.68 (1.13, 2.49)	0.01	25	0.87 (0.65, 1.15)	0.32

WBI whole breast irradiation, *APBIb* accelerated partial breast irradiation through brachytherapy, *95 % CI* 95 % confidence interval





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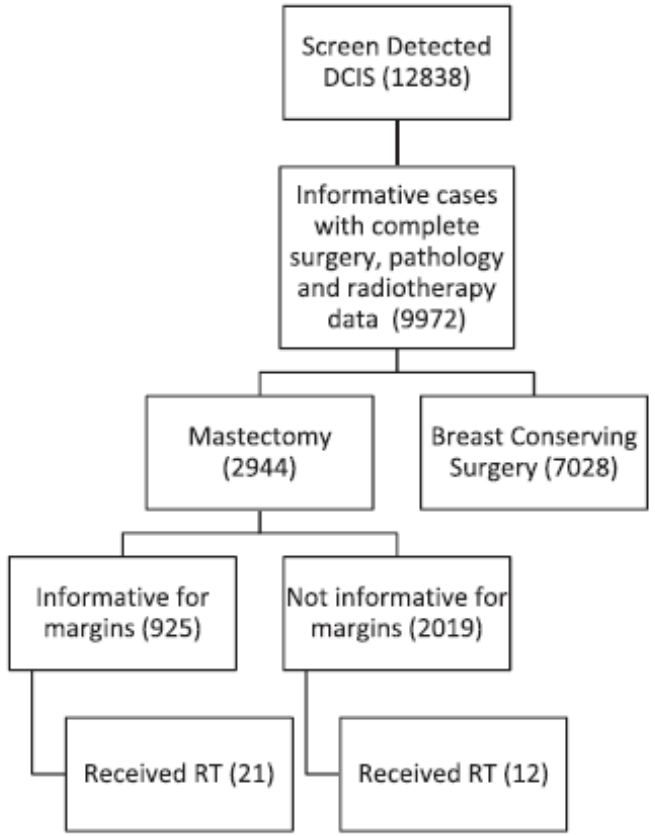
Radiotherapy after mastectomy for screen-detected ductal carcinoma *in situ*

K. Clements [a], D. Dodwell [b,*], G. Lawrence [a], G. Ball [c], A. Francis [d], S. Pinder [e], E. Sawyer [e], M. Wallis [f], A.M. Thompson [g], on behalf ofthe Sloane Project Steering Group

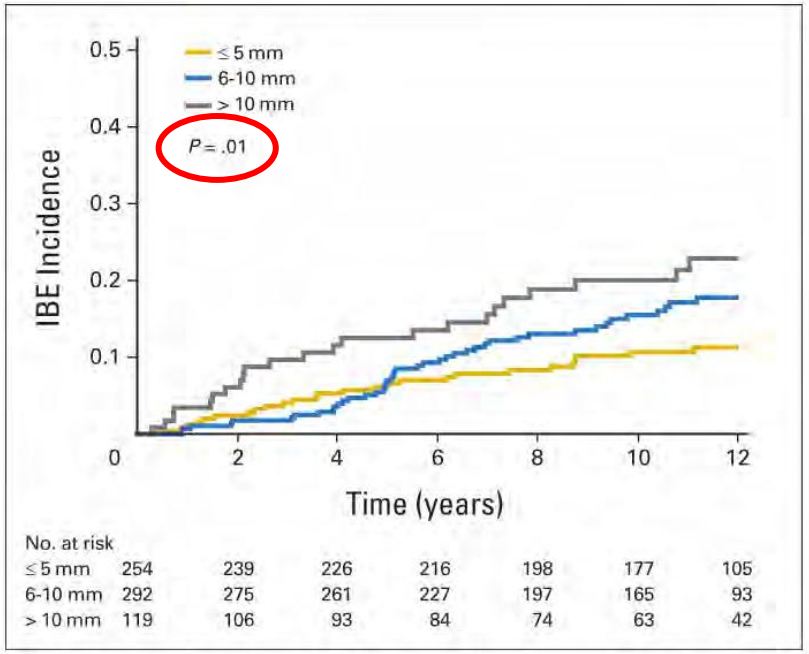


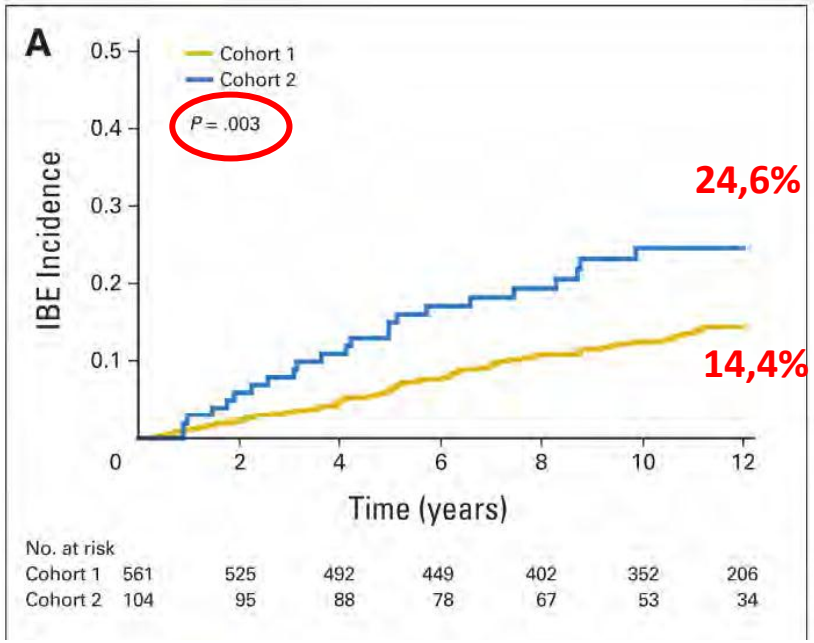
Results: Use of post mastectomy radiotherapy was significantly associated with a close (<1 mm) pathology margin (χ^2(1) 95.81; $p < 0.00001$), DCIS size (χ^2 (3) 16.96; $p < 0.001$) and the presence of microinvasion (χ^2(1) 3.92; $p < 0.05$). At a median follow up 61 months, no woman who received radiotherapy had an ipsilateral further event, and only 1/33 women (3.0%) had a contralateral event. Of the women known not to have had radiotherapy post mastectomy, 45/2894 (1.6%) had an ipsilateral further event and 83 (2.9%) had a contralateral event. *Conclusion*: Recurrence following mastectomy for DCIS is rare. A close (<1 mm) margin, large tumour size and microinvasion, may merit radiotherapy to reduce ipsilateral recurrence.

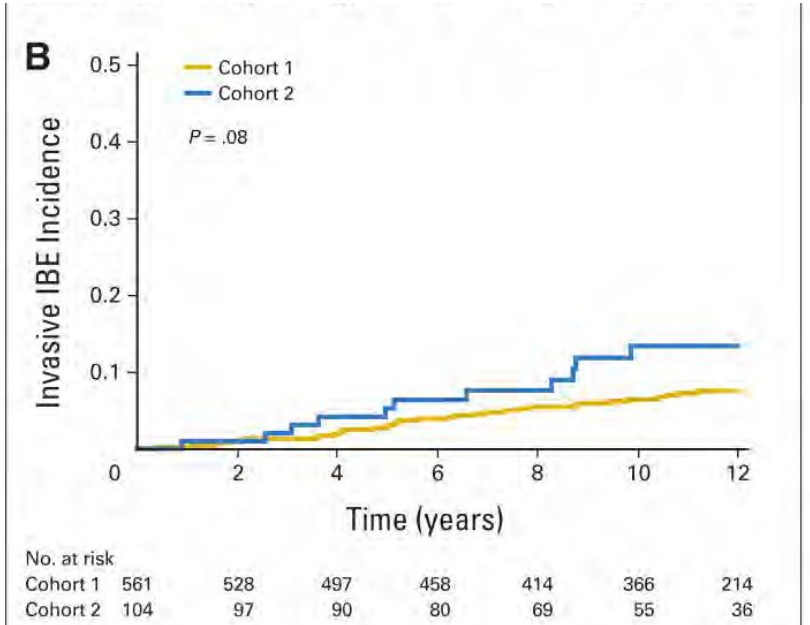
JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

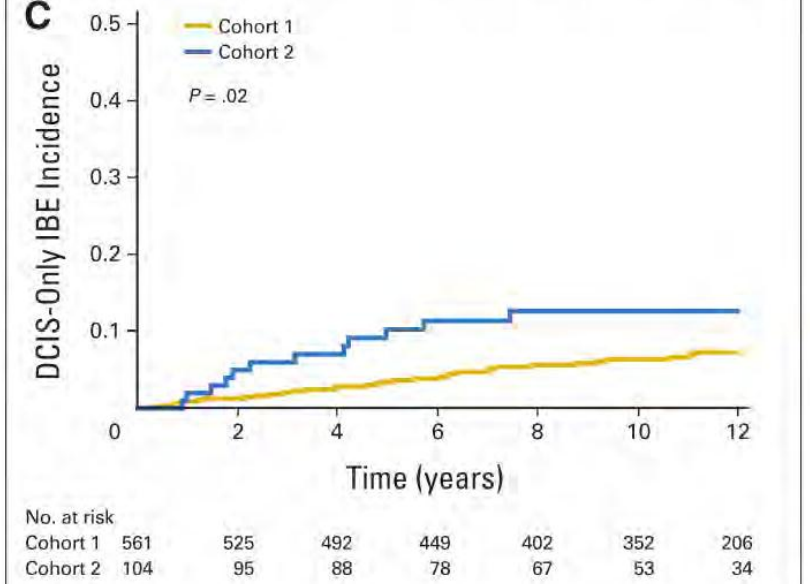
Surgical Excision Without Radiation for Ductal Carcinoma in Situ of the Breast: 12-Year Results From the ECOG-ACRIN E5194 Study

Lawrence J. Solin, Robert Gray, Lorie L. Hughes, William C. Wood, Mary Ann Lowen, Sunil S. Badve, Frederick L. Baehner, James N. Ingle, Edith A. Perez, Abram Recht, Joseph A. Sparano, and Nancy E. Davidson









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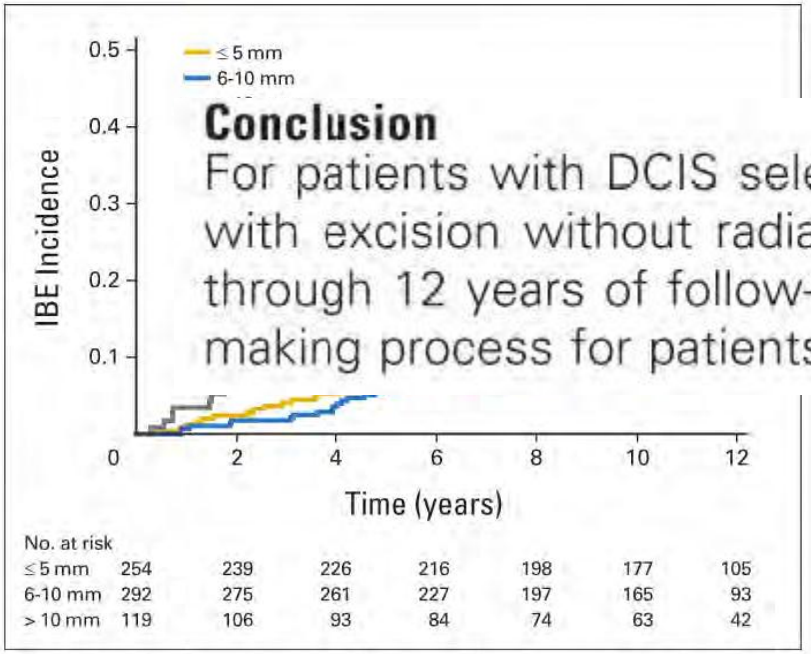

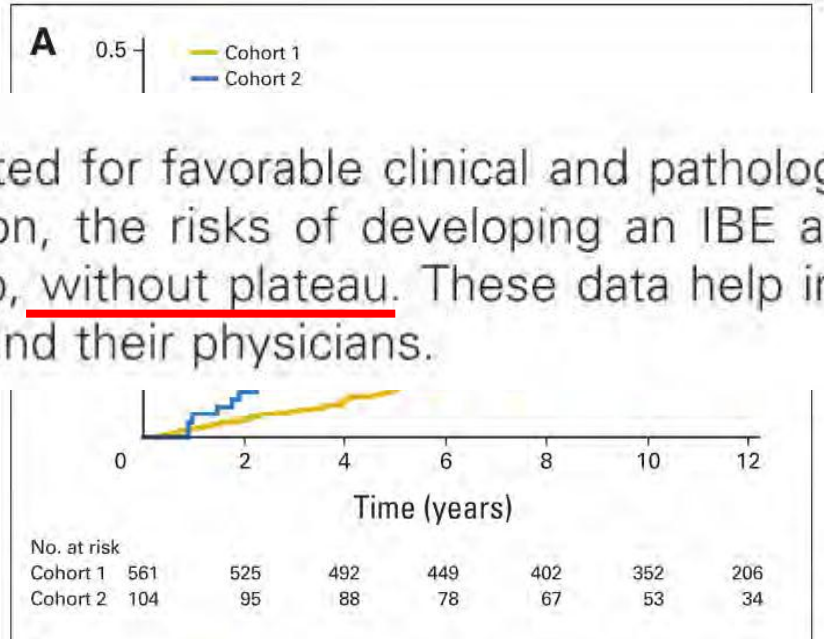

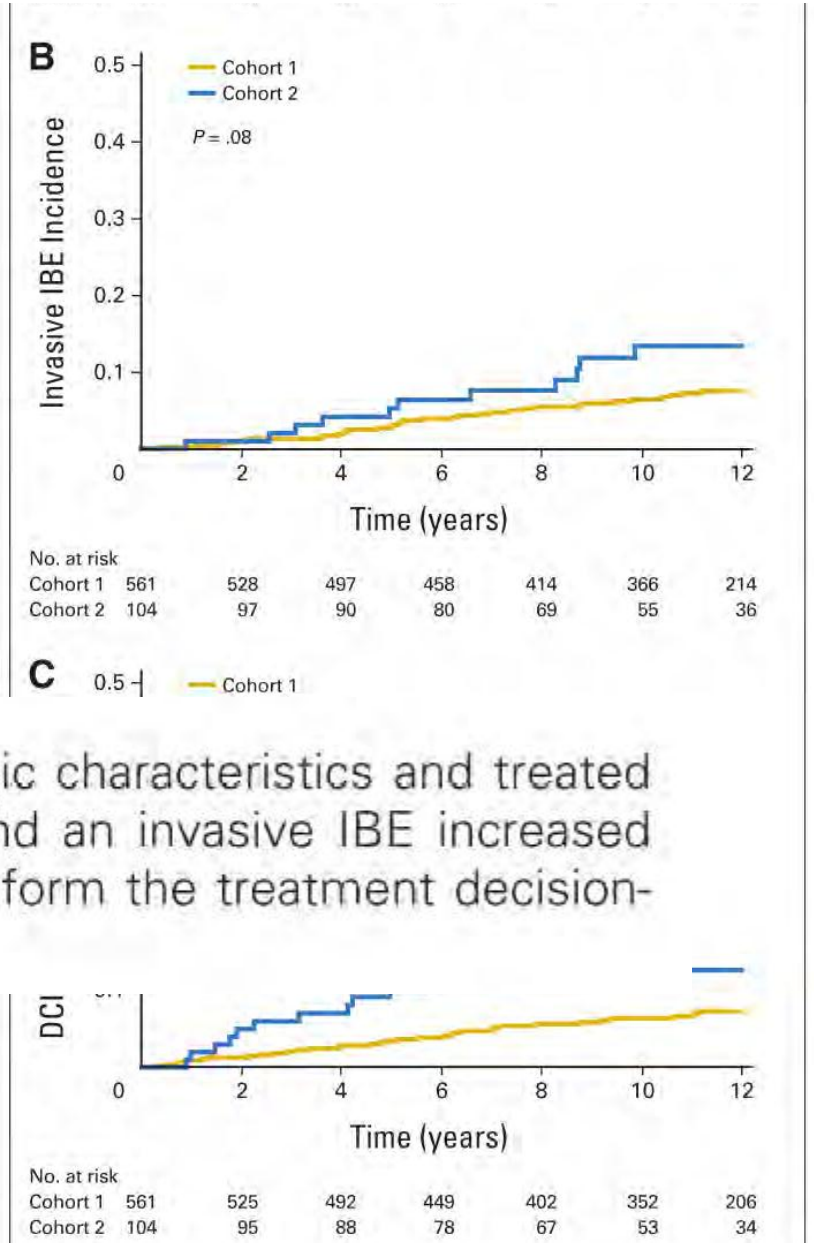

Conclusion

For patients with DCIS selected for favorable clinical and pathologic characteristics and treated with excision without radiation, the risks of developing an IBE and an invasive IBE increased through 12 years of follow-up, without plateau. These data help inform the treatment decision-making process for patients and their physicians.

VOLUME 33 · NUMBER 7 · MARCH 1 2015

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

This prospective randomized trial (1998 to 2006) in women with mammographically detected low or intermediate-grade DCIS, measuring less than 2.5 cm with margins 3 mm, compared RT with observation after surgery.

The study was designed for 1,790 patients but was closed early because of lower than projected accrual.

636 pazienti arruolate
62% tamoxifene

Stratify	Randomize
Age 1. < 50 2. ≥ 50 Final Path Margins 1. Negative (re-excision) 2. 3-9 mm 3. ≥ 10 mm Mammographic/Pathologic Size of Primary 1. ≤ 1 cm 2. > 1 cm to ≤ 2.5 cm Nuclei Grade 1. Low 2. Intermediate Tamoxifen Use 1. No 2. Yes	Arm 1 Observation with or without tamoxifen 20 mg per day for 5 years Arm 2 Radiation therapy* to the whole breast, with or without tamoxifen 20 mg per day for 5 years

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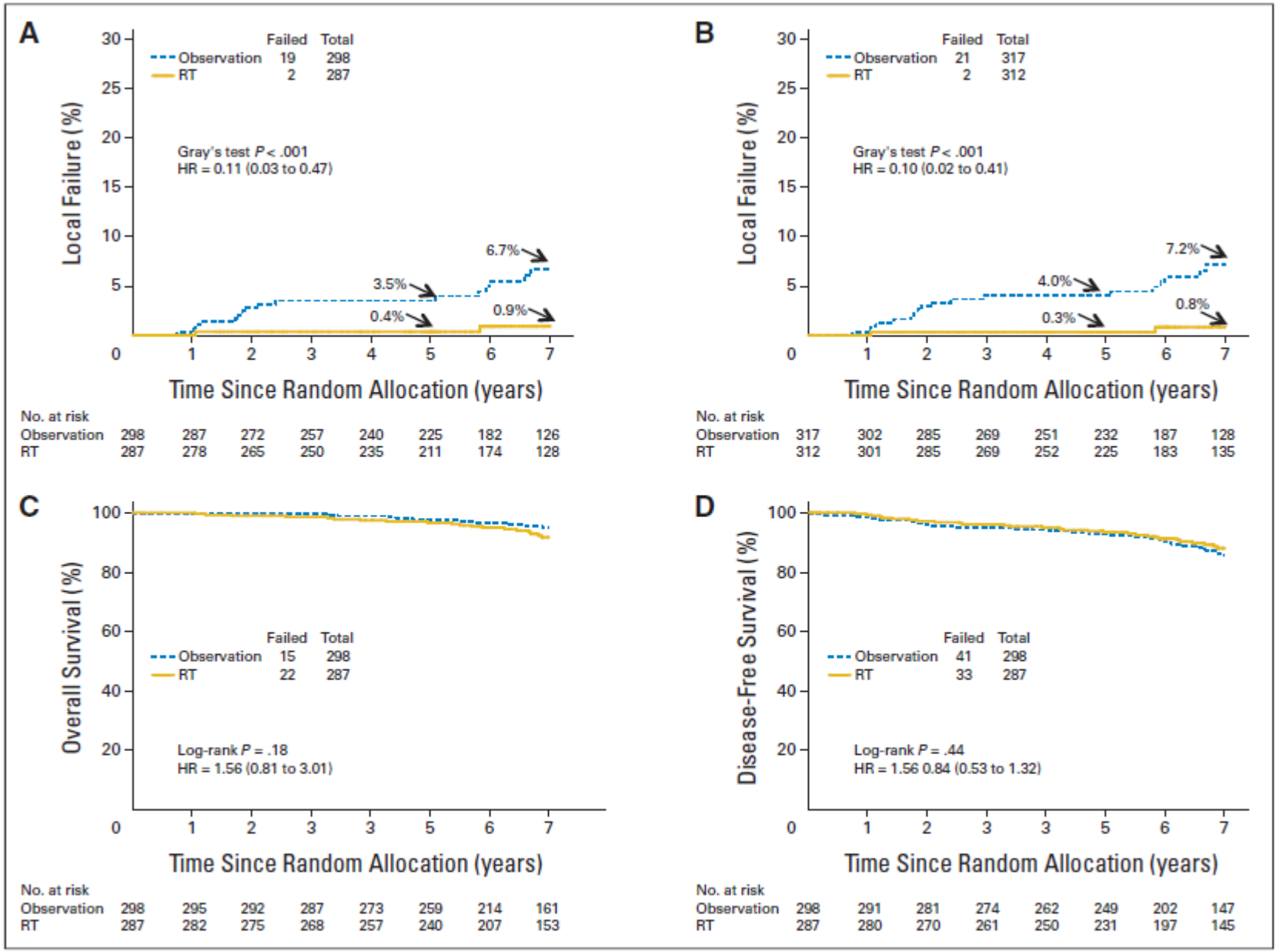

Fig 2. (A) Local failure in ipsilateral breast for all eligible patients (n = 585). (B) Local failure in ipsilateral breast for all accrued patients with follow-up (n = 629). (C) Disease-free survival (n = 585). (D) Overall survival (n = 585). HR, hazard ratio; RT, radiation therapy.

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636 pazienti arruola
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ut tamoxifen (n = 314)

(n = 312)

(n = 287)

then 20 mg per day for 5 years

east, with or without tamoxifen

Ca in situ e ormonoterapia

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

Population-based analysis of the impact and generalizability of the NSABP-B24 study on endocrine therapy for patients with ductal carcinoma *in situ* of the breast†

A. C. Lo[1,5], P. T. Truong[2,3,5], E. S. Wai[2,3,5], A. Nichol[1,3,5], L. Weir[1,3,5], C. Speers[3], M. M. Hayes[4,5], C. Baliski[5,6] & S. Tyldesley[1,3,5*]

- 1999 NSABP B24 trial dimostra vantaggio del tam in aggiunta a RT per DCIS sottoposte a QUAD
- 2001 Cuzick et al dimostrano che il tam non riduce BCE in pazienti trattati con RT per DCIS dopo QUAD
- Dic 2002 Allred dimostra vantaggio del Tam nel sottogruppo di pazienti ER +

Our primary objective was to determine the impact and generalizability of the NSABP-B24 study and ER subgroup analysis at a population level. Secondary objectives were to assess the degree to which the trial results [1, 4, 5] were incorporated into clinical practice, and the ET continuation rates in patients with DCIS treated with BCS + RT.

Table 1. Patient and tumor characteristics of entire study cohort

	No endocrine therapy, *N* (%)	Endocrine therapy, *N* (%)	*P* value
All patients	1657	404	
Age (years)			
Median	57	53	<0.0005
Mean	57	54	
SD	10	10	
Range	29–80	35–79	
Menopausal status			
Premenopausal	521 (31%)	183 (45%)	<0.0005
Postmenopausal	1082 (65%)	214 (53%)	
Unknown	54 (3%)	7 (2%)	
Tumor size (cm)			
Median	1.5	1.5	0.31
Mean	1.8	1.8	
SD	1.3	1.4	
Range	0.1–9.9	0.1–7.0	
Unknown	58 (4%)	8 (2%)	
Grade			
1	261 (16%)	62 (15%)	0.320
2	628 (38%)	162 (40%)	
3	700 (42%)	171 (42%)	
Unknown	68 (4%)	9 (2%)	
Estrogen receptor status			
Positive	434 (26%)	156 (39%)	0.0005
Negative	163 (10%)	8 (2%)	
Unknown	1060 (64%)	240 (59%)	
Final margin status			
Positive	95 (6%)	7 (2%)	0.001
Negative	1530 (92%)	395 (98%)	
Unknown	32 (2%)	2 (<1%)	

Annals of Oncology 26: 1898–1903, 2015
doi:10.1093/annonc/mdv251
Published online 10 June 2015

Population-based analysis of the impact and generalizability of the NSABP-B24 study on endocrine therapy for patients with ductal carcinoma *in situ* of the breast†

A. C. Lo[1,5], P. T. Truong[2,3,5], E. S. Wai[2,3,5], A. Nichol[1,3,5], L. Weir[1,3,5], C. Speers[3], M. M. Hayes[4,5], C. Baliski[5,6] & S. Tyldesley[1,3,5*]

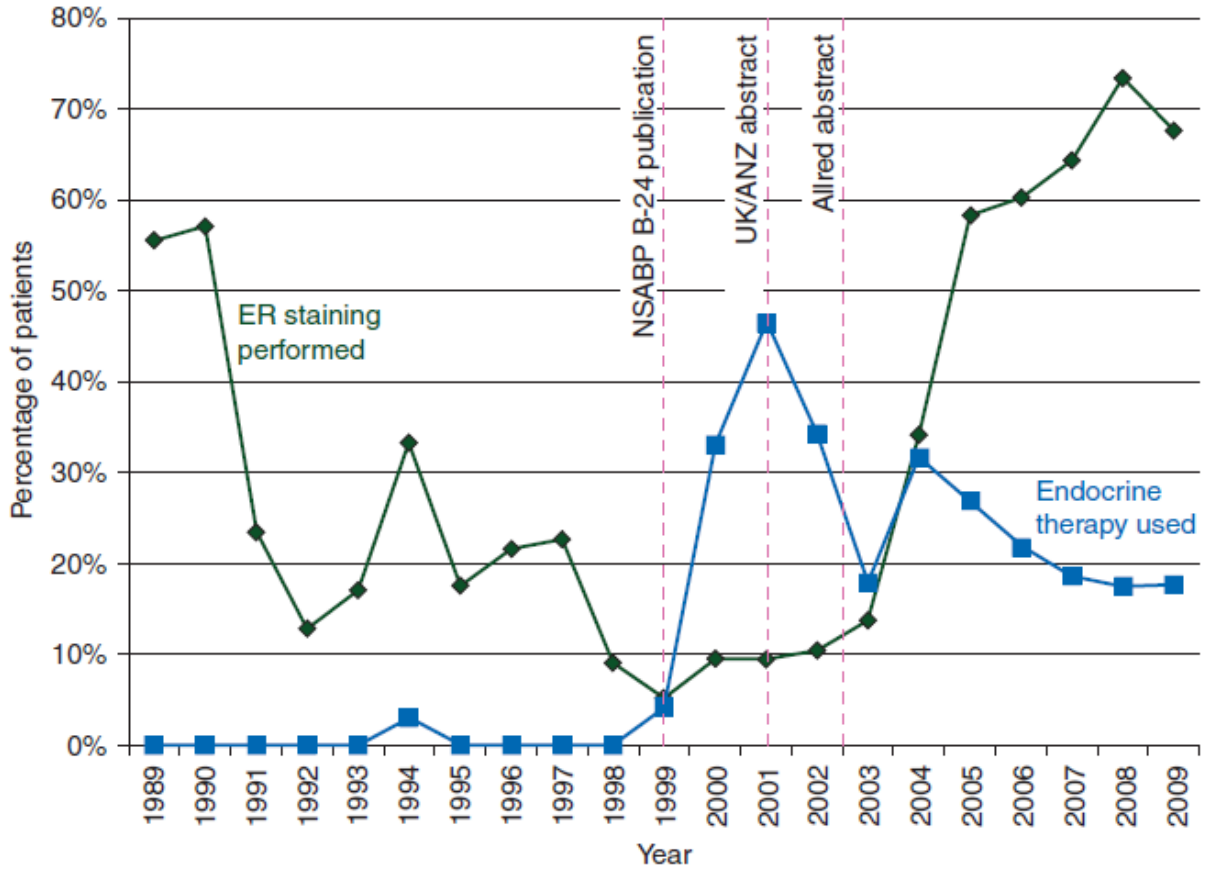


Table 3. Five-year Kaplan–Meier local relapse-free survival and event-free survival rates for endocrine versus no endocrine therapy in post-NSABP-B24 era (2000–2009)

	Endocrine therapy	No endocrine therapy	*P* value*
Ipsilateral event-free survival	98.9 ± 1.0%	97.3 ± 1.0%	0.03
Event-free survival	96.9 ± 1.8%	94.5 ± 1.4%	0.01
Breast cancer-specific survival	100%	99.3 ± 0.6%	0.53
Overall survival	98.0 ± 0.8%	99.5 ± 0.8%	0.01

conclusions

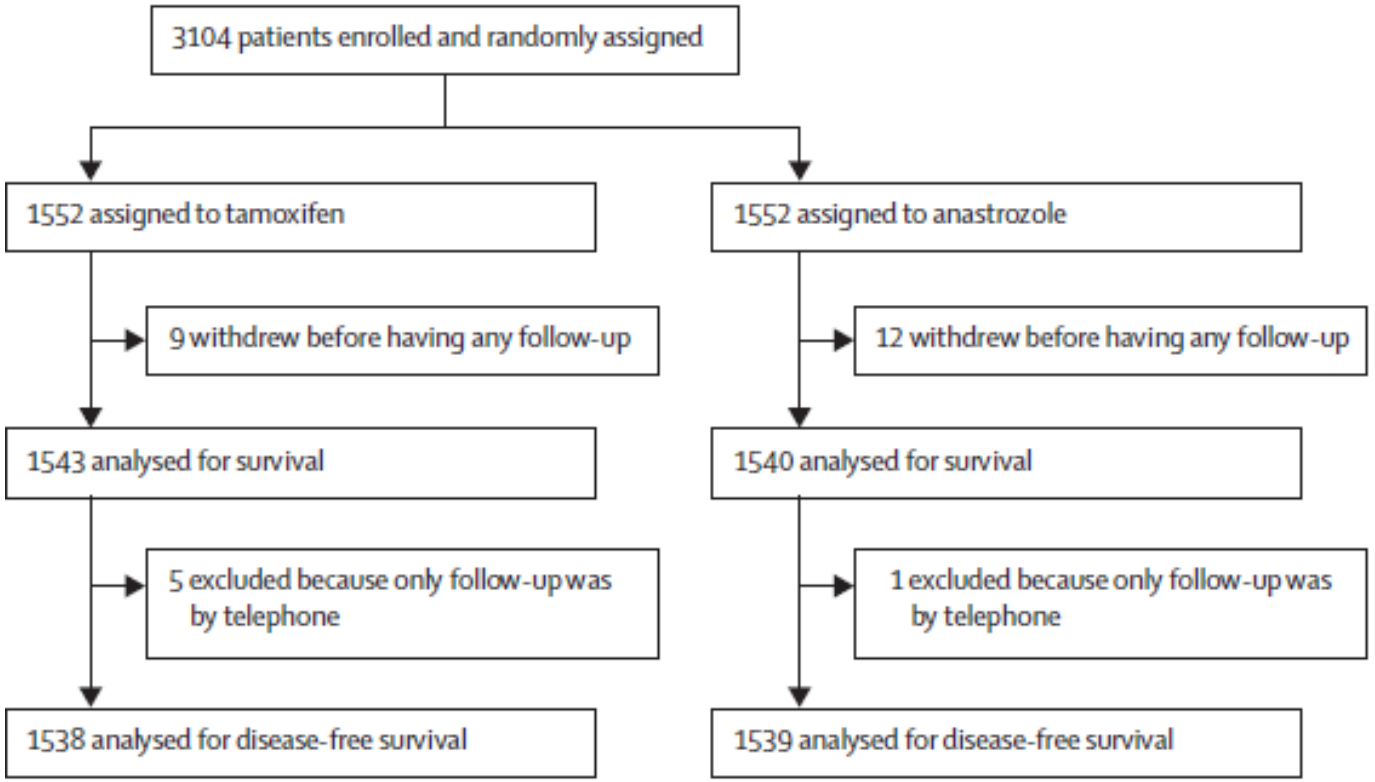
This study demonstrates that the NSABP-B24 trial had a clear impact on ET utilization in DCIS patients treated with BCS + RT in BC. The use of ET increased significantly to almost 50% after the publication of NSABP-B24 in 1999, and then decreased to ~20% with the use of ER assessment after Cuzick and Allred's publications. Factors associated with ET use were younger age and ER+ tumors. Adherence rate to ET was ~50%. Our study confirms that, in routine clinical practice, women with DCIS treated with BCS+RT are achieving benefits from ET that are expected based on randomized data.

Annals of Oncology 26: 1898–1903, 2015
doi:10.1093/annonc/mdv251
Published online 10 June 2015

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 Clanfrocca, 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

www.thelancet.com **Published online December 10, 2015 http://dx.doi.org/10.1016/S0140-6736(15)01168-X**



	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**

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 Clanfrocca, 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

www.thelancet.com **Published online December 10, 2015 http://dx.doi.org/10.1016/S0140-6736(15)01168-X**

Anastrozole treatment provided a significant improvement in breast cancer free interval, mainly in women younger than 60 years of age.

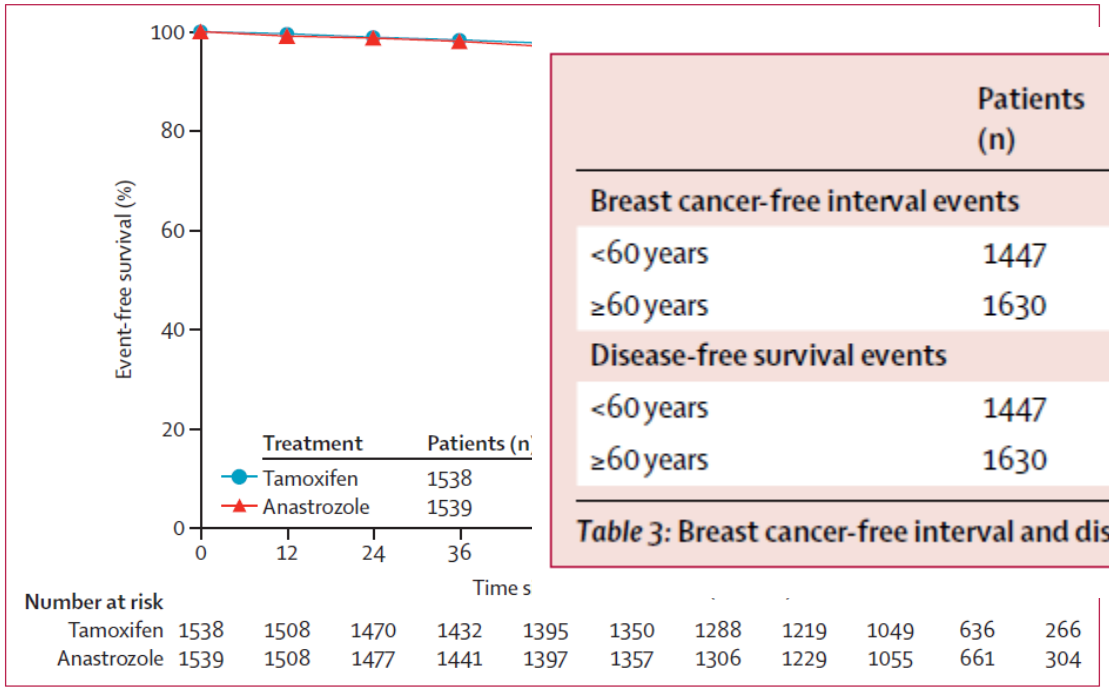
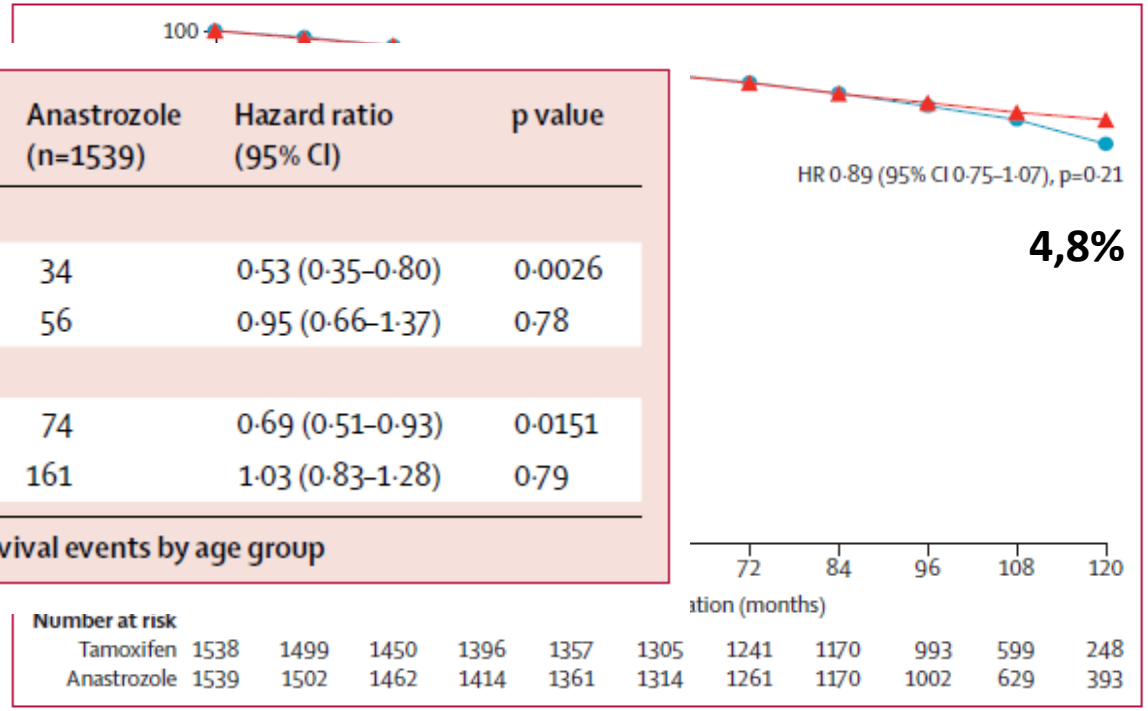


Figure 2: Breast cancer-free interval

	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



4,8%

Figure 3: Disease-free survival

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 Minckwitz, Wolfgang Eiermann, Patrick Neven, Michael Stierer, Chris Holcombe, Robert E Coleman, Louise Jones, Ian Ellis, Jack Cuzick, on behalf of the IBIS-II investigators*

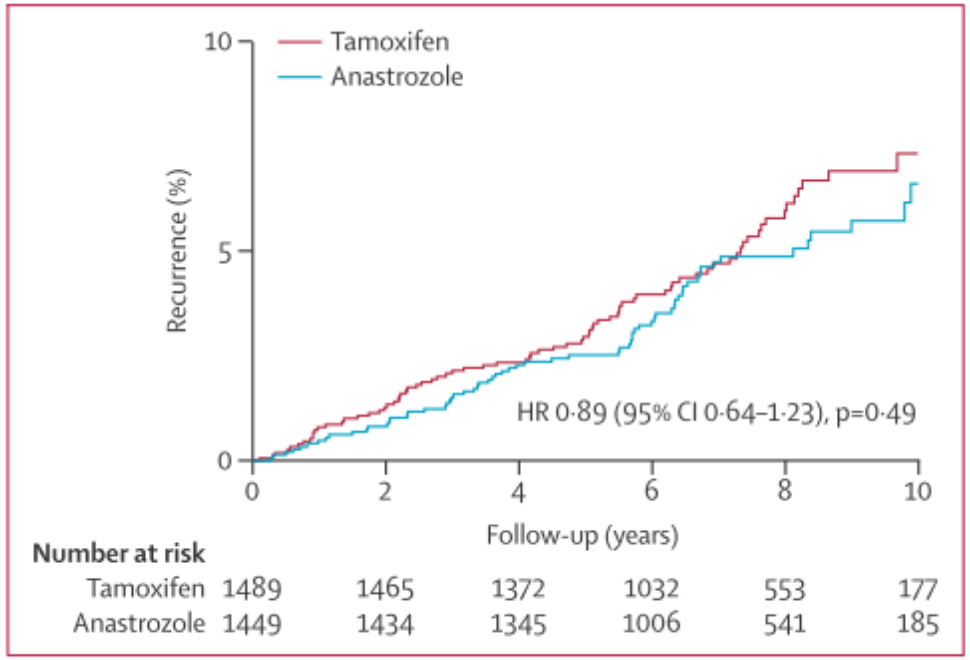


Figure 2: **Recurrence for all breast cancer according to treatment allocation**

2003-2012
236 centri in 14 paesi
2980 donne in post menopausa
DCIS OR+
Anastrozolo 1 mg (1449) VS Tamoxifene 20 mg (1489) per 5 anni
Median FU 7,2 anni

Conclusions No clear efficacy differences were seen between the two treatments. Anastrozole offers another treatment option for postmenopausal women with hormone-receptor-positive DCIS, which may be be more appropriate for some women with contraindications for tamoxifen. Longer follow-up will be necessary to fully evaluate treatment differences.

Ri
14
69

Numero simile di eventi avversi (1323 vs 1379)
Diverso profilo di tossicità *(fratture, eventi muscoloscheletrici, ipercolesterolemia e stroke VS spasmi muscolari, ca ginecologici, sintomi vasomotori, TVP)*

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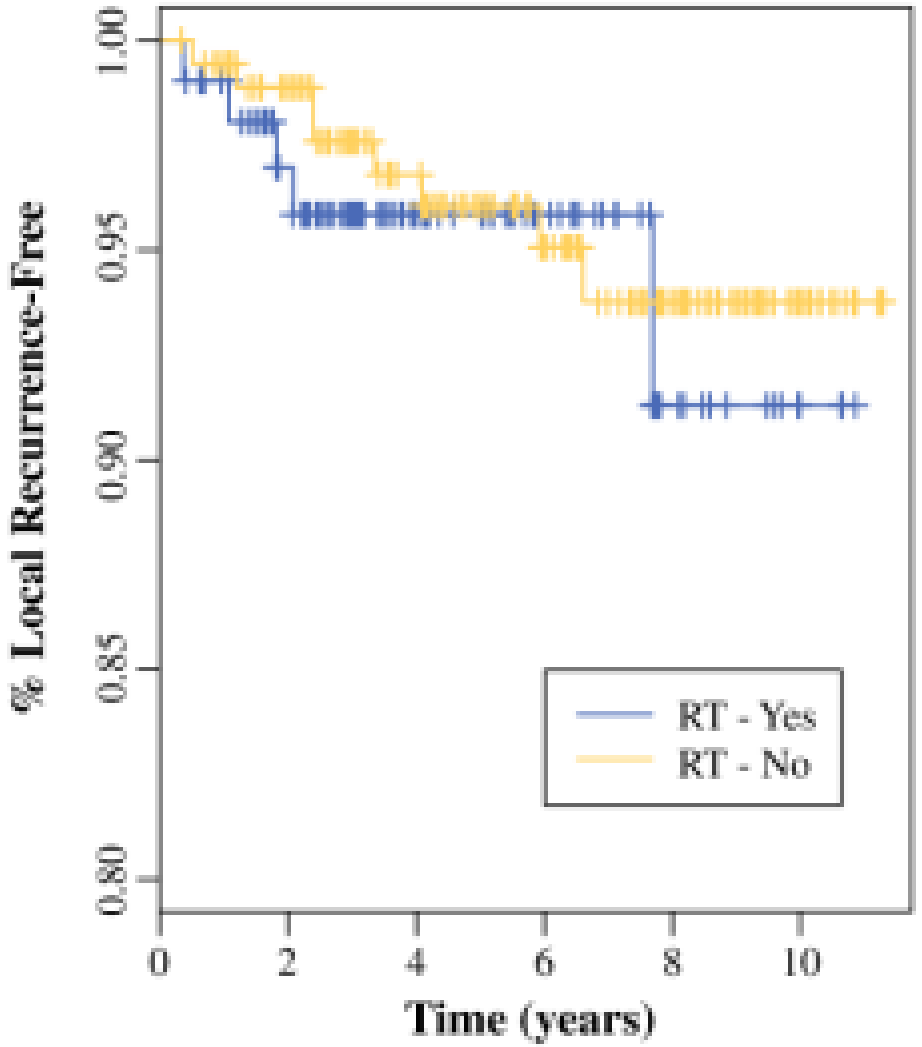
Annals of



RT = Radiation Therapy

FIG. 2 Local recurrence-free rates

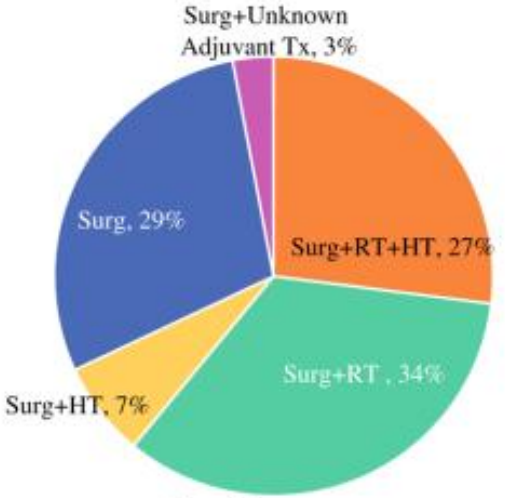
TABLE 2 Univariable logistical r

Factor	*p* value
Age (per 1-year increase)	0.004
Comedo necrosis (reference: not p	0.003
DCIS size (per 1-cm increase)	0.001
DCIS grade (reference: 1)	
2	0.007
3	
Margin width (mm) (reference: ne	
≤5	0.13
>5	
Multifocal DCIS (reference: not p	0.69
MRI (reference: not done)	0.97
Re-excision (reference: not done)	0.40
Period of surgery (reference: 2002	0.02

OR odds ratio, *CI* confidence inter

nagement

William Wong, MD[2],



Surg=Surgery,
RT=Radiation Therapy,
HT=Hormonal Therapy,
Tx=Treatment

3). Among all the BCT patients, 99 (33 %) underwent adjuvant HT, with the HT status of 6 patients (2 %) unknown. Of the 221 ER-positive BCT patients, 86 (39 %) underwent adjuvant HT, with the HT status of 4 patients (2 %) unknown. The treatment strategies used for the patients in the cohort are summarized in Fig. 1.