

V ZOOM Journal Club 2015

Bologna, 19 Febbraio 2016

NH Hotel De La Gare



CA IN SITU E ORMONOTERAPIA

CASO CLINICO

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# ANAMNESI

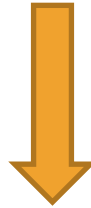
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- ✘ Paziente di 51 aa
- ✘ In anamnesi: appendicectomia, laparotomia per lisi di aderenze, endometriosi ovarica operata
- ✘ Nega altre comorbidità degne di nota

# ANAMNESI ONCOLOGICA

✓ Marzo 2009 intervento chirurgico di **QUADRANTECTOMIA SUPERO-ESTERNA SINISTRA e BLSN**

E.I.: Ca duttale infiltrante G1, con minore componente di ca duttale "in situ", varietà cribriforme, senza necrosi; pT1b N0(sn) Mx; ER e PgR +, Ki-67 5%, HER2 negativo



✓ **RADIOTERAPIA POST-OPERATORIA:** 50 Gy (2Gy/fr) su mammella sinistra residua + 10 Gy (2,5 Gy/fr) su letto tumorale

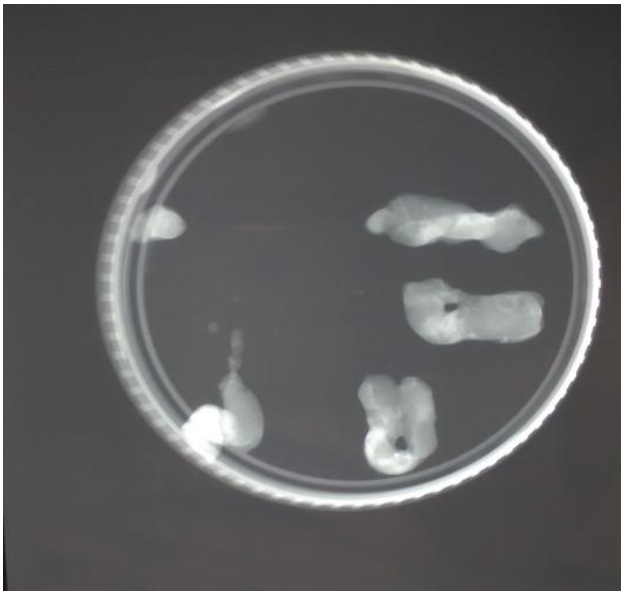
✓ **TRATTAMENTO ORMONALE** con LH-RH agonista più Tamoxifene per 5 aa

✓ Follow-up sempre negativo

# LUGLIO 2014 SOSPENSIONE DELLA OT, MA...

Giugno 2015 (dopo soli 11 mesi) **MAMMOGRAFIA DI CONTROLLO**: "...a destra, in supero-esterna, si segnala sfumato cluster di microcalcificazioni, del diametro massimo di 0.5 cm, di aspetto granulare, dubbie. Si richiede completamento delle indagini con prelievo microistologico con tecnica VABB stx a dx"

Luglio 2015 **MAMMOTOME SU MICROCALCIFICAZIONI MAMMELLA DX**  
E.I.: Frustoli mammari con rari focolai di ca intraduttale G1 con cancerizzazione lobulare, associati a microcalcificazioni; categoria diagnostica: B5; ER 90%, PgR 5%, Ki-67 3%, Her-2 neg



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**Agosto 2015 intervento chirurgico di QUADRANTECTOMIA SUPERO-ESTERNA DESTRA E BIOPSIA LINFONODO SENTINELLA**

**DESCRIZIONE MACROSCOPICA:** Porzione di parenchima mammario che misura cm 9x6x4; è presente porzione di cute che misura cm 5x1,5; in sede parenchimale si identifica area rettangolare di circa cm 0,5 circondata da tessuto biancastro fibroso; il restante parenchima appare di aspetto variegato con aree giallastre alternate ad aree biancastre; 2 linfonodi sentinella + 1 linfonodo satellite

**DIAGNOSI:** Esiti riparativi postbiopistici associati ad attivazione di istiociti multinucleati del tipo "da corpo estraneo"; parenchima circostante esente da localizzazioni neoplastiche; margini chirurgici indenni; 3 linfonodi asportati negativi sede di iperplasia linfoide reattiva

# TERAPIA ADIUVANTE

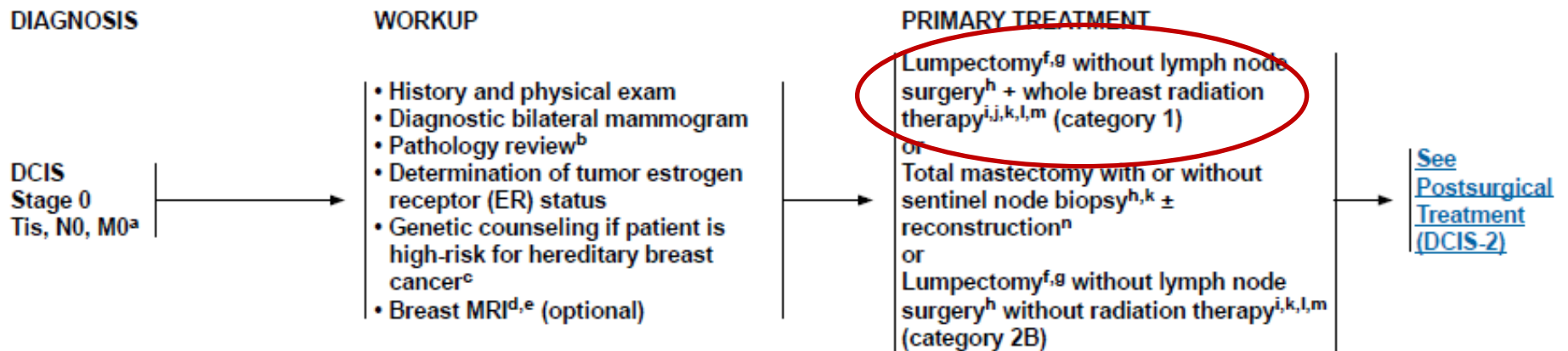
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Trattasi di un DCIS G1 con caratteristiche biologiche di malattia "a basso rischio" (Ø 0.5 cm, ER+++ , ki-67 3%, margini chirurgici >1 cm) insorto dopo un anno dalla sospensione della OT

QUALE TERAPIA ORMONALE?

RADIOTERAPIA ADIUVANTE??

# RADIOTERAPIA E DCIS



<sup>m</sup>Whole-breast radiation therapy following lumpectomy reduces recurrence rates in DCIS by about 50%. Approximately half of the recurrences are invasive and half are DCIS. A number of factors determine local recurrence risk: palpable mass, larger size, higher grade, close or involved margins, and age <50 years. If the patient and physician view the individual risk as "low," some patients may be treated by excision alone. Data evaluating the three local treatments show no differences in patient survival.

La Rt riduce il rischio di recidiva locale di  
circa il **50%**

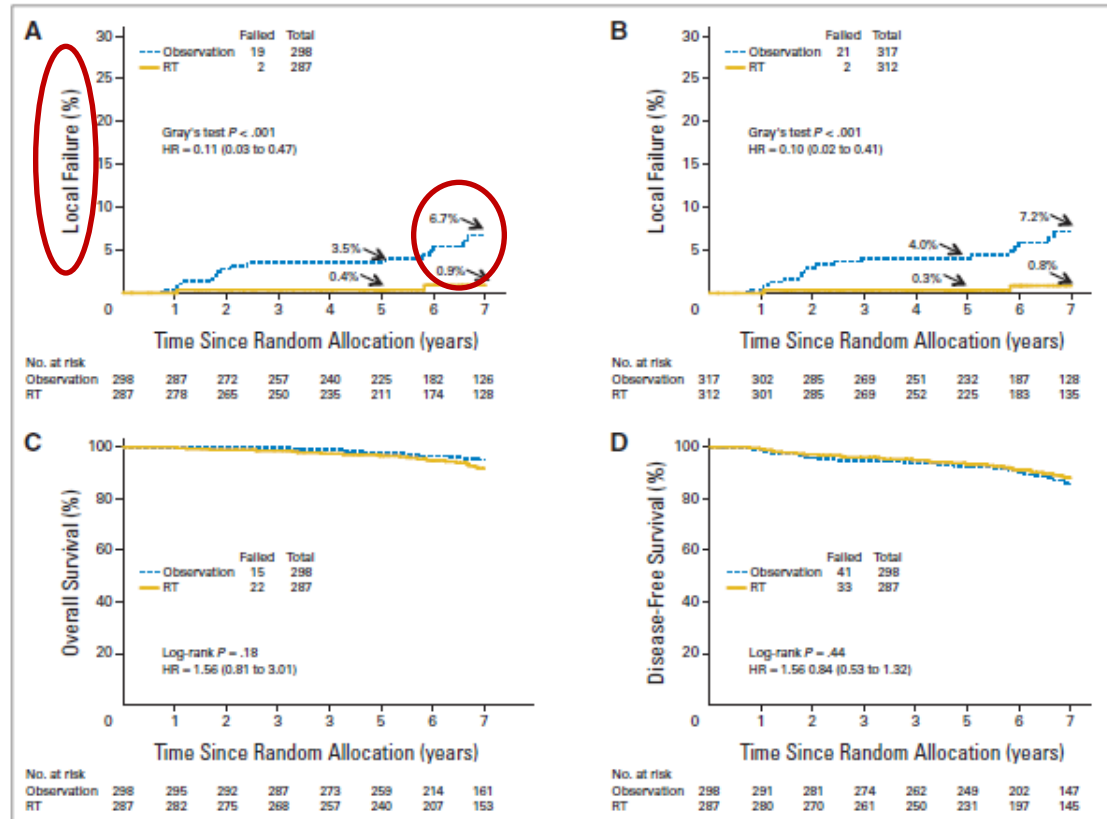
# RADIOTERAPIA E DCIS LOW-GRADE

J Clin Oncol. 2015 Mar 1;33(7):709-15. doi: 10.1200/JCO.2014.57.9029. Epub 2015 Jan 20.

## RTOG 9804: a prospective randomized trial for good-risk ductal carcinoma in situ comparing radiotherapy with observation.

McCormick B<sup>1</sup>, Winter K<sup>2</sup>, Hudis C<sup>2</sup>, Kuerer HM<sup>2</sup>, Rakovitch E<sup>2</sup>, Smith BL<sup>2</sup>, Sneige N<sup>2</sup>, Moughan J<sup>2</sup>, Shah A<sup>2</sup>, Germain I<sup>2</sup>, Hartford AC<sup>2</sup>, Rashtian A<sup>2</sup>, Walker EM<sup>2</sup>, Yuen A<sup>2</sup>, Strom EA<sup>2</sup>, Wilcox JL<sup>2</sup>, Vallow LA<sup>2</sup>, Small W Jr<sup>2</sup>, Pu AT<sup>2</sup>, Kerlin K<sup>2</sup>, White J<sup>2</sup>.

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	
	R
	a
	n
	d
	o
	m
	i
	z
	e
	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



Follow-up mediano 7,17 years

Local failure → 0,9% RT arm

Local failure → 6,7% no RT arm

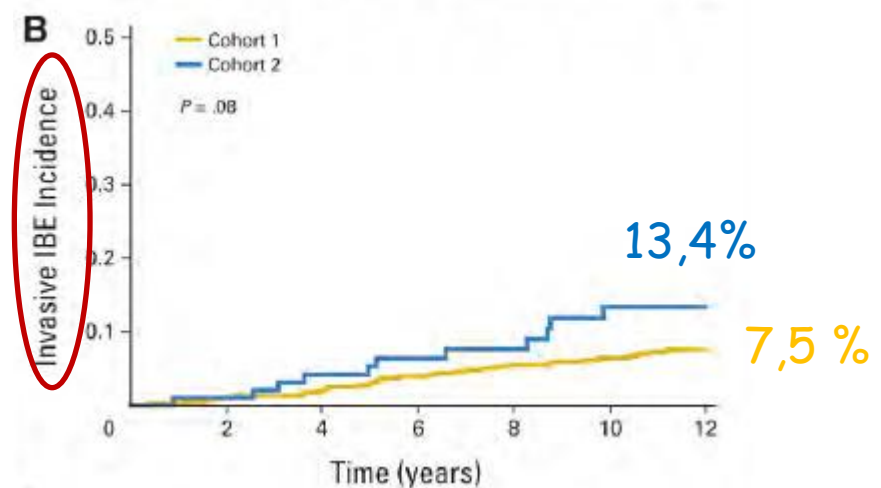
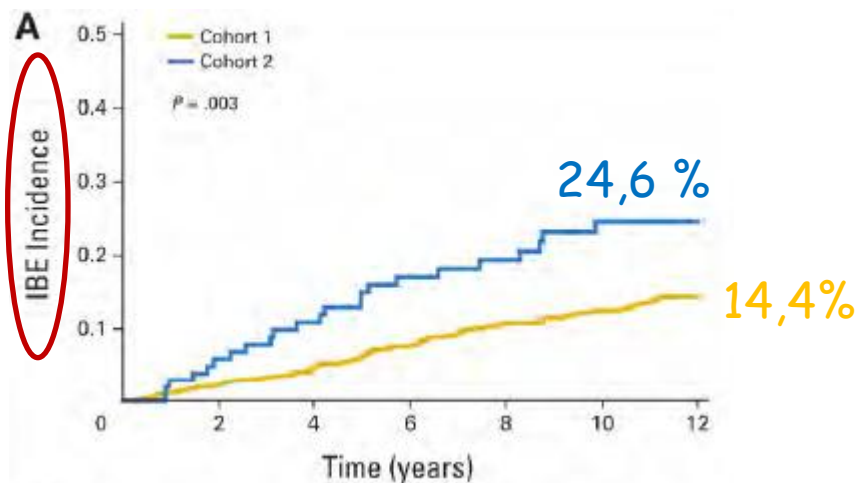
**p < 0,001**



# RADIOTERAPIA E DCIS LOW-GRADE

## 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. Baeltner, James N. Ingle, Edith A. Perez, Abram Recht, Joseph A. Sparano, and Nancy E. Davidson



Cohort 1:  
Low or intermediate grade  
Tumor size  $\leq 2,5$  cm

# QUALE FRAZIONAMENTO?

Systematic review

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

Cecilia Nilsson<sup>a</sup>, Antonis Valachis<sup>b,\*</sup>

<sup>a</sup>Center for Clinical Research, Västmanlands County Hospital, Västerås; and <sup>b</sup>Centre for Clinical Research Sörmland, Uppsala University, Eskilstuna, Sweden

Radiotherapy and Oncology 14 (2015) 50–55

Conclusion: Hypofractionated radiotherapy seems to be a safe option in patients with DCIS after breast-conserving surgery while the addition of boost reduces the risk for local recurrence in the presence of positive margins. However, the level of evidence for these observations ranges between very low and low and the results of the ongoing randomized trials are necessary to confirm the results with higher level of evidence.

# TERAPIA ORMONALE



National  
Comprehensive  
Cancer  
Network®

## NCCN Guidelines Version 1.2016 Ductal Carcinoma in Situ (DCIS)

[NCCN Guidelines Index](#)  
[Breast Cancer Table of Contents](#)  
[Discussion](#)

### DCIS POSTSURGICAL TREATMENT

### SURVEILLANCE/FOLLOW-UP

Risk reduction therapy for ipsilateral breast following breast-conserving surgery:

- Consider endocrine therapy for 5 years for:
  - ▶ Patients treated with breast-conserving therapy (lumpectomy) and radiation therapy<sup>P</sup> (category 1), especially for those with ER-positive DCIS.
  - ▶ The benefit of endocrine therapy for ER-negative DCIS is uncertain
  - ▶ Patients treated with excision alone<sup>P</sup>
- Endocrine therapy:
  - ▶ Tamoxifen<sup>P</sup> for premenopausal patients
  - ▶ Tamoxifen<sup>P</sup> or aromatase inhibitor for postmenopausal patients with some advantage for aromatase inhibitor therapy in patients <60 years old or with concerns for thromboembolism

Risk reduction therapy for contralateral breast:

- Counseling regarding risk reduction  
[See NCCN Guidelines for Breast Cancer Risk Reduction](#)

- Interval history and physical exam every 6–12 mo for 5 y, then annually
- Mammogram every 12 mo (and 6–12 mo postradiation therapy if breast conserved [category 2B])
- If treated with endocrine therapy, monitor per [NCCN Guidelines for Breast Cancer Risk Reduction](#)

# TERAPIA ORMONALE

Primary results, NRG Oncology/NSABP B-35: A clinical trial of anastrozole (A) versus tamoxifen (tam) in postmenopausal patients with DCIS undergoing lumpectomy plus radiotherapy.

2015 ASCO Annual Meeting

## Abstract:

**Background:** The primary endpoint of NSABP B-35, a phase III trial comparing 1 mg/day anastrozole to 20 mg/day tamoxifen, each given for 5 years, was breast cancer-free interval (BCFI), defined as the time from randomization to any breast cancer (BC) event including local, regional, or distant recurrence or contralateral disease, invasive or DCIS. **Methods:** Postmenopausal women with ER-receptor or PgR-receptor positive (by IHC analysis) DCIS and no invasive BC who had undergone a lumpectomy with clear resection margins were randomly assigned to receive either 20 mg/day tam or 1 mg/day A (blinded) for 5 years. Stratification was by age (<60 v ≥60). **Results:** From 1/6/2003 to 6/15/2006, 3,104 pts were entered and randomized (1552 in groups tam and A each). As of 2/28/15, follow-up information was available on 3,083 pts for OS and on 3,077 pts for all other disease-free endpoints, with mean time of follow-up of 8.6 years. There were 198 BCFI events, 114 in the tam group and 84 in the A group (HR, 0.73; p=0.03). 10-year point estimates for BCFI were 89.2% for tam and 93.5% for A. A significant time-by-treatment interaction (p=0.02) indicated that the effect was not evident until later in the study. There was a significant interaction between treatment and age group (p=0.04); benefit of A is only in women <60 years old. As to secondary endpoints, there were 495 DFS events, 260 in the tam group and 235 in the A group (HR, 0.89; p=0.21). 10-year point estimates for DFS were 77.9% for tam and 82.7% for A. There were 186 deaths, 88 in the tam group and 98 in the A group (HR, 1.11; p=0.48). 10-year point estimates for OS were 92.1% for tam, 92.5% for A. There were 8 deaths due to breast cancer in the tam group and 5 in the A group. There were 63 cases of invasive breast cancer in the tam group and 39 in the A group (HR, 0.61; p=0.02). There was a non-significant trend for a reduction in breast second primary cancers with A (HR, 0.68; p=0.07). **Conclusions:** Anastrozole provided a significant improvement compared to tamoxifen for BCFI, which was seen later in the study, primarily in women <60 years. Support: CA12027, 37377, 69651, 69974; 180868, 180822, 189867 196067, 114732; AstraZeneca Pharmaceuticals LP. Clinical trial information: **NCT00053898**



# TERAPIA ADIUVANTE

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QUALE TERAPIA ORMONALE



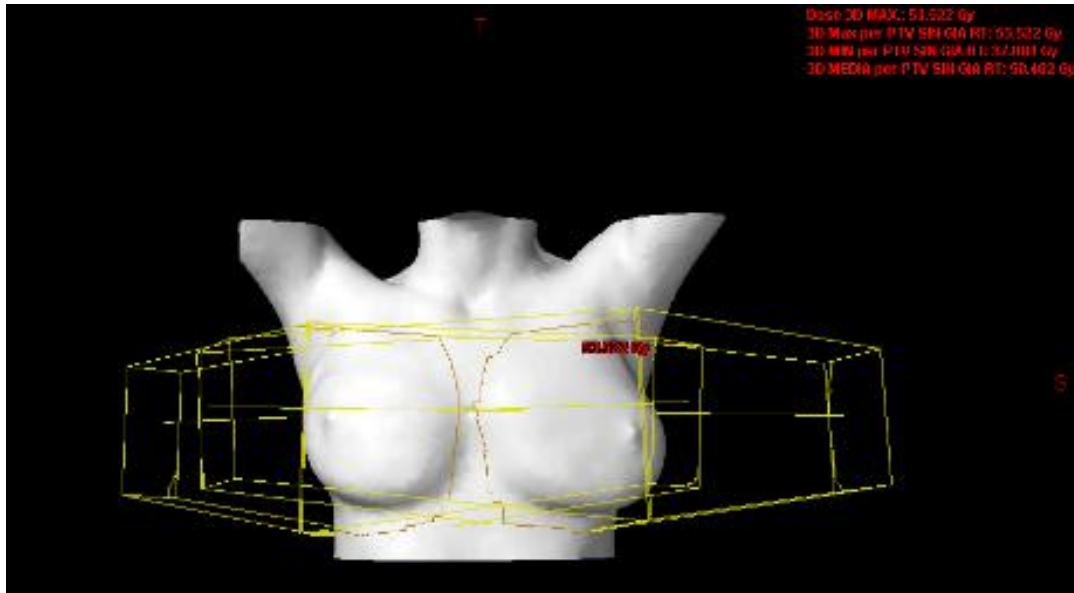
Inibitore aromatasi (Anastrozolo 1mg/die)

RADIOTERAPIA



Rt complementare su mammella residua

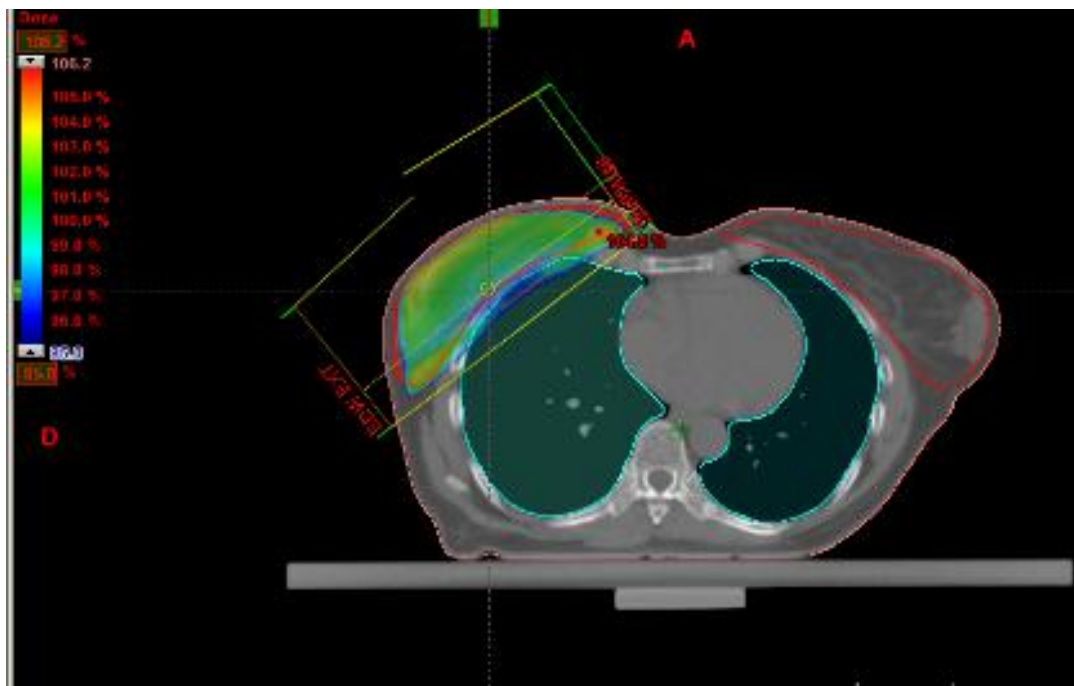
# PRESCRIZIONE



Tecnica 3D conformazionale

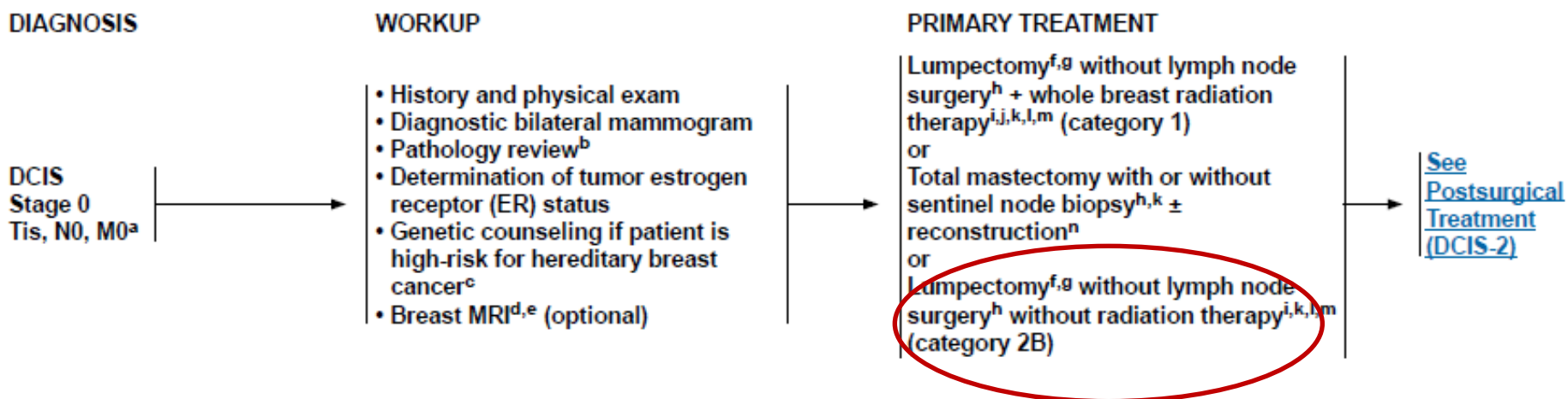
Campi tangenti di fotoni X da 6 MV

50 Gy su mammella dx residua  
con frazionamento  
convenzionale



Ricostruzione del trattamento  
precedente

# RADIOTERAPIA E DCIS LOW-GRADE: PROSPETTIVE FUTURE



Nel nostro caso si tratta di un **DCIS G1 con caratteristiche biologiche di malattia "a basso rischio"**, ma il fatto che la malattia sia insorto a distanza di un anno dalla sospensione della terapia ormonale potrebbe essere considerato come un fattore di maggiore aggressività??

# Feasibility of a prospective, randomised, open-label, international multicentre, phase III, non-inferiority trial to assess the safety of active surveillance for low risk ductal carcinoma in situ – The LORD study

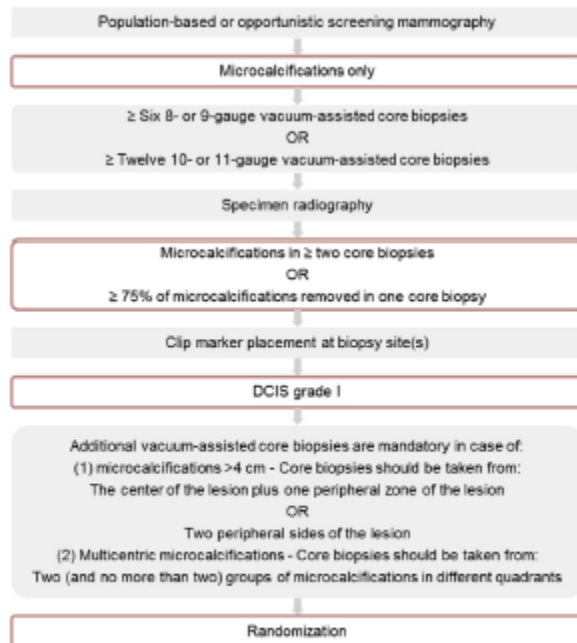


Fig. 1. Flow chart of diagnostic workup prior to randomisation.

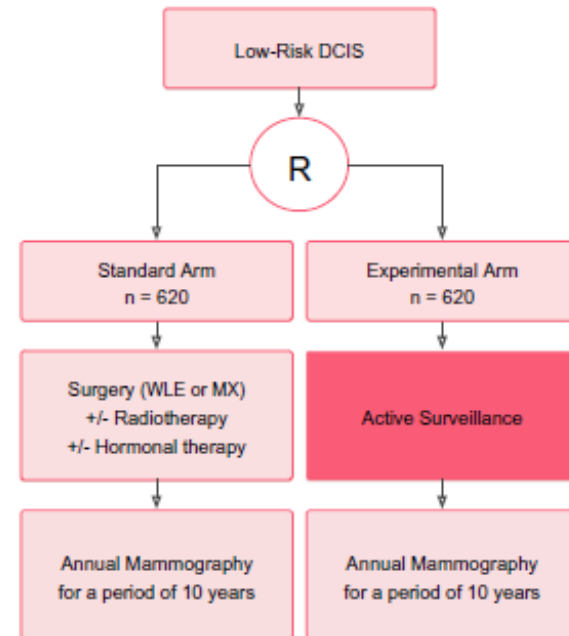


Fig. 2. Flow chart of study design. R = randomisation. WLE = wide local excision. MX = mastectomy.

Studio on-going  
Iniziato arruolamento nel 2015

*L.E. Elshof et al / European Journal of Cancer 51 (2015) 1497–1510*



# RUOLO EMERGENTE DELL'ASSETTO GENETICO NEL DCIS

Breast Cancer Res Treat (2015) 152:389–398  
DOI 10.1007/s10549-015-3464-6



CLINICAL TRIAL

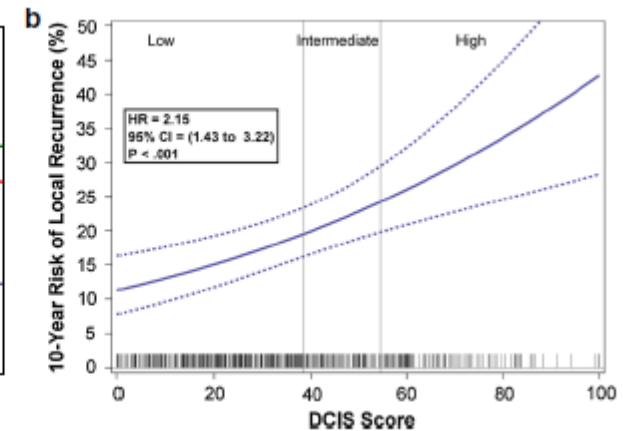
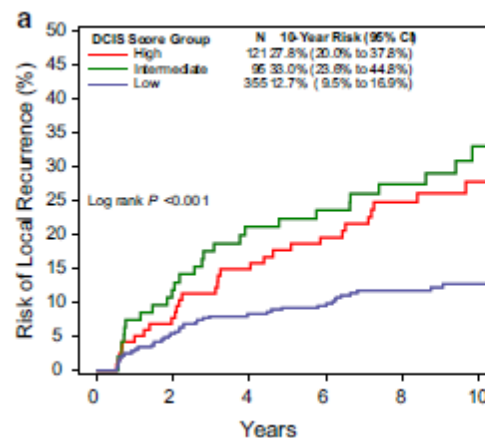
## A population-based validation study of the DCIS Score predicting recurrence risk in individuals treated by breast-conserving surgery alone

Eileen Rakovitch<sup>1,2,3</sup> · Sharon Nofech-Mozes<sup>3,4</sup> · Wedad Hanna<sup>3,4</sup> · Frederick L. Baehner<sup>5,6</sup> · Refik Saskin<sup>2</sup> · Steven M. Butler<sup>5</sup> · Alan Tuck<sup>7</sup> · Sandip Sengupta<sup>8</sup> · Leela Elavathil<sup>9</sup> · Prashant A. Jani<sup>10,11</sup> · Michel Bonin<sup>12</sup> · Martin C. Chang<sup>3,13</sup> · Susan J. Robertson<sup>14</sup> · Elzbieta Slodkowska<sup>4</sup> · Cindy Fong<sup>2</sup> · Joseph M. Anderson<sup>5</sup> · Farid Jamshidian<sup>5</sup> · Dave P. Miller<sup>5</sup> · Diana B. Cherbavaz<sup>5</sup> · Steven Shak<sup>5</sup> · Lawrence Paszat<sup>1,2,3</sup>

regardless of ER status (HR 2.15;  $P < 0.001$ ). DCIS Score provided independent information on LR risk beyond clinical and pathologic variables including size, age, grade, necrosis, multifocality, and subtype (adjusted HR 1.68;  $P = 0.02$ ). DCIS was associated with invasive LR (HR

**Table 2** Association of the DCIS Score and the development of local recurrence in patients treated by breast-conserving surgery alone with negative resection margins: univariable analysis

Endpoint	HR/50 U (95 % CI)*	P value*
Local recurrence in ER+ DCIS	2.26 (1.41, 3.59)	<0.001 <sup>§</sup>
In all patients regardless of ER status		
Local recurrence	2.15 (1.43, 3.22)	<0.001 <sup>§</sup>
Invasive local recurrence	1.78 (1.03, 3.05)	0.04
DCIS local recurrence	2.43 (1.31, 4.42)	0.005





**GRAZIE PER L'ATTENZIONE**