

con il Patrocinio dell'Associazione Italiana di Oncologia Medica



Progetto **CANOA**
CARCINOMA
MAMMARIO:

QUALI NOVITÀ PERIL2014?

“Saper leggere” uno studio clinico per migliorare la pratica clinica

Coordinatori scientifici:
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Giovanni L. Pappagallo



PROGRAMMA

Ospedaletto di Pescantina (VR) 21-22 marzo 2014
Park Hotel Villa Quaranta

Progetto Canoa Carcinoma Mammario

Gruppo C

QUESITO GRADE:

Nelle pazienti con recidiva loco-regionale da carcinoma mammario, la chemioterapia dopo escissione chirurgica aumenta la sopravvivenza?

STUDIO CALOR

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Background

- Between 10% and 35% of women with operable breast cancer will experience an isolated locoregional recurrence (ILRR) following their primary treatment
- ILRR predicts a poor prognosis (DFS 5 years 50%)



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Background

- Few trials of adjuvant drug therapy have been completed (SAKK 23/82 → tamoxifene improved DFS for ER+ post-mastectomy ILRR)
- No prospective randomized trial of adjuvant chemotherapy for ILRR has been published in the past 30 years
- The utility of chemotherapy for women who experience an ILRR after primary treatment remains an open question



NSABP

*National Surgical Adjuvant
Breast and Bowel Project*



IBCSG

International Breast Cancer Study Group

BIG

BREASTINTERNATIONALGROUP

Chemotherapy Prolongs Survival for Isolated Local or Regional Recurrence of Breast Cancer: The CALOR Trial

Chemotherapy as Adjuvant for LOcally Recurrent Breast Cancer.
IBCSG 27-02, NSABP B-37, BIG 1-02 (BOOG, GEICAM, IBCSG)

S. Aebi, S. Gelber, I. Láng, S.J. Anderson, A. Robidoux, M. Martín, J.W.R. Nortier, E.P. Mamounas, C.E. Geyer, Jr., R. Maibach, R.D. Gelber, N. Wolmark, I. Wapnir, for the **CALOR** Trial Investigators

Eligibility criteria

- **First proven ipsilateral local and/or regional recurrence**
 - Breast
 - Chest wall
 - Mastectomy scar and/or skin
 - Axillary or internal mammary lymph nodes

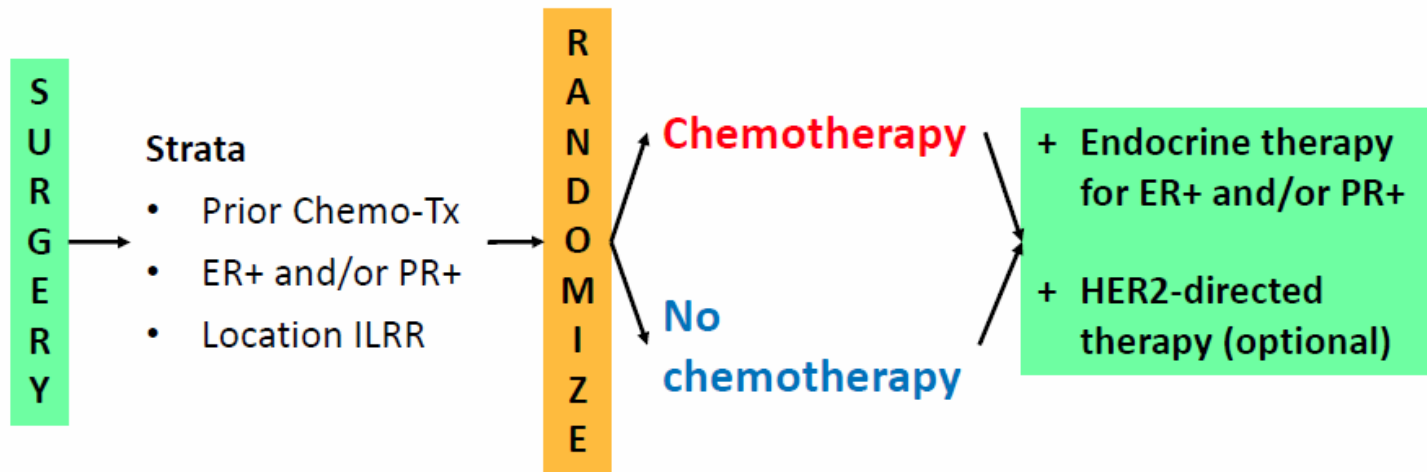
- **Complete gross excision of recurrence**
negative or microscopically involved margins

- **No evidence of supraclavicular lymph nodes**

- **No evidence of distant metastases**

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Trial design



- ◆ **Chemotherapy chosen by investigators**
Recommendation: ≥ 2 drugs, 3 to 6 months of therapy

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ILRR Radiation Therapy

- Recommended for all patients
- **Mandatory for patients with microscopically involved margins**
- ≥ 40 Gy



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Endpoints

- 1° ENDPOINT: **Disease-free survival**
- 2° ENDPOINT: **Overall survival**
 - Site of first recurrence
 - Incidence of second malignancy
 - Cause of death without relapse of breast cancer

Statistical Considerations

- **Original simple size for HR=0.74**
977 patients, 347 DFS events (DFS 50%→60%)
- **Amendment 3, 2008:**
Revised simple size for HR=0.60
265 patients, 124 events (DFS 50%→66%)
- **August 22, 2003 → January 31, 2010**
Closure of the trial with 162 patients
No interim analysis
Median follow up 4.9 years

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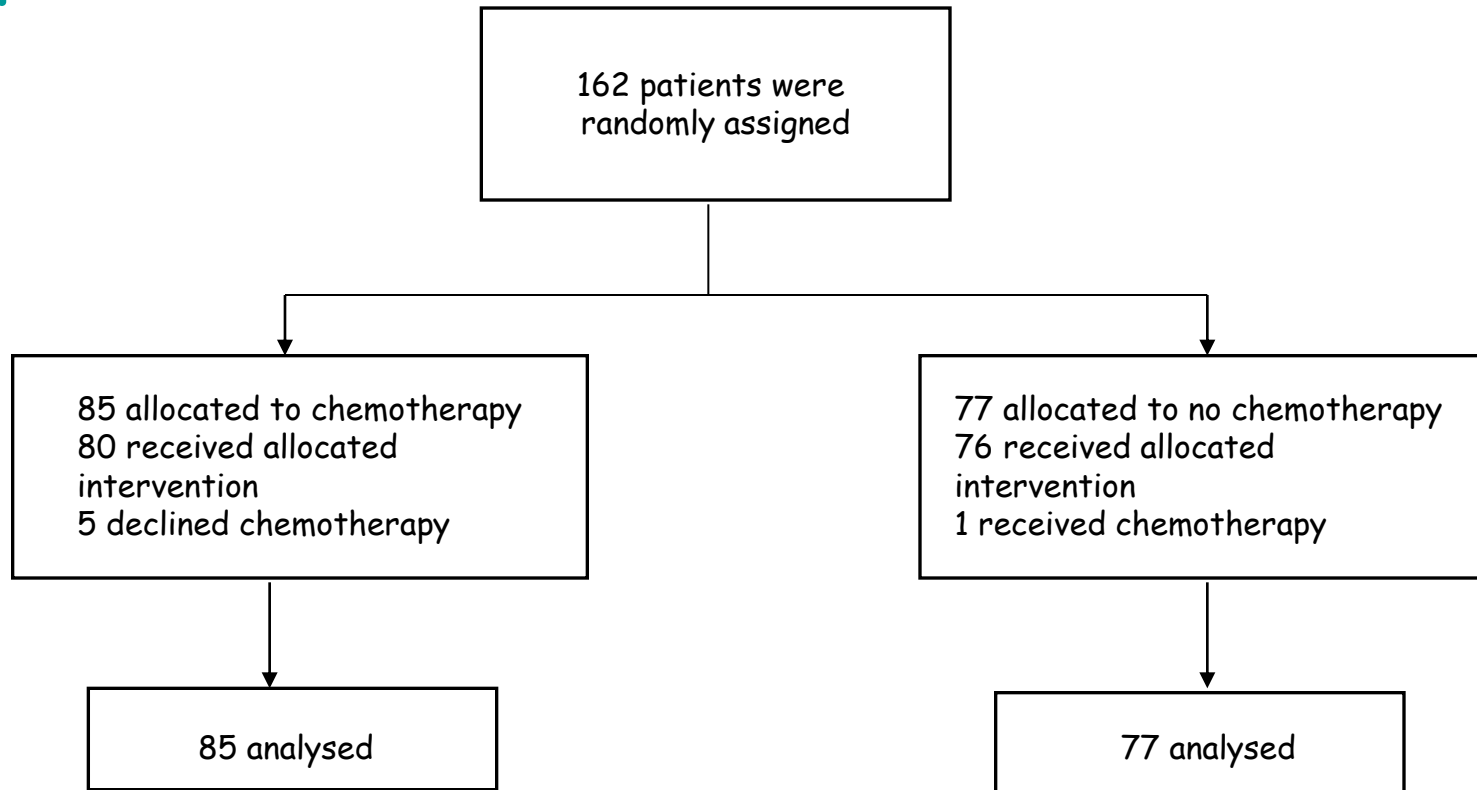
Calor International Collaboration

	Participants
BIG	89
IBCSG	57
Individual Centers (Hungary, South Africa, Peru)	39
SAKK (Switzerland)	16
ANZ BCTG (Australia)	2
GEICAM (Spain)	20
BOOG (The Netherlands)	12
NSABP	73
Total participation	162

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Trial profile



All 162 randomly assigned patients are included in the intention to treat analyses

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Baseline Characteristics

	Chemotherapy N=85	No chemotherapy N=77
Primary surgery		
Mastectomy	33 (39%)	31 (40%)
Breast conserving surgery	52 (61%)	46 (60%)
Prior chemotherapy	49 (58%)	52 (68%)
Time from primary to surgery to ILRR surgery (years, range)	5.0 (2.9-9.5)	6.2 (2.9-11.3)
Menopausal status at ILRR		
Premenopausal	20 (24%)	14 (18%)
Postmenopausal	65 (76%)	63 (82%)
Age at ILRR (range, years)	56 (48-61)	56 (50-64)

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Baseline Characteristics

	Chemotherapy N=85	No chemotherapy N=77
Location of ILRR		
Breast	47 (55%)	42 (55%)
Mastectomy scar/chest wall	28 (33%)	25 (32%)
Regional Lymph nodes	10 (12%)	10 (13%)
ER status of the ILRR		
Positive	56 (66%)	48 (62%)
PgR status of the ILRR		
Positive	44 (52%)	35 (45%)
ER status of the Primary tumor		
Positive	49 (58%)	47 (61%)

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Therapies for ILRR

	Chemotherapy N=85	No chemotherapy N=77
Radiation therapy	31 (36%)	29 (38%)
HER2-directed therapies	6 (7%)	4 (5%)
Hormonal therapies for ER+ ILRR	91%	92%
LHRH agonist or oophorectomy	4 (7%)	10 (19%)
Fulvestrant	0	1 (2%)
Tamoxifen	15 (26%)	15 (29%)
Aromatase Inhibitors	47 (81%)	41 (79%)
None	5 (9%)	2 (4%)

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Therapies for ILRR

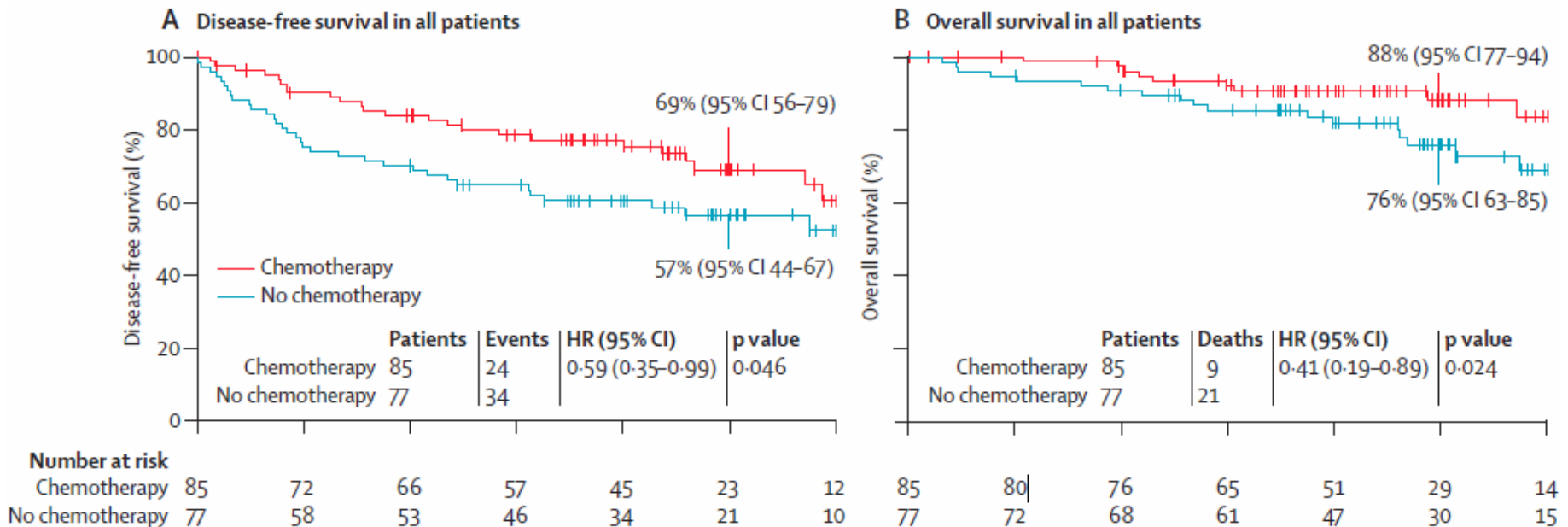
	Chemotherapy (n=85)	No chemotherapy (n=77)
No chemotherapy	5 (7%)	76 (99%)
Chemotherapy	80 (94%)	1 (1%)
Monochemotherapy	25 (29%)	0
Docetaxel or Paclitaxel	16 (19%)	0
Capecitabine	9 (11%)	0
Polychemotherapy	55 (65%)	0
CMF	2 (2%)	0
Gemcitabine + Navelbine	1 (1%)	0
Antracycline-based	38 (45%)	0
Taxane-based	13 (15%)	1 (1%)
Antracycline + taxane-based	1 (1%)	0

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Results: all patients

Kaplan-Meier curve of disease free survival and overall survival according to assigned treatment group



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Sites of first failure after ILRR

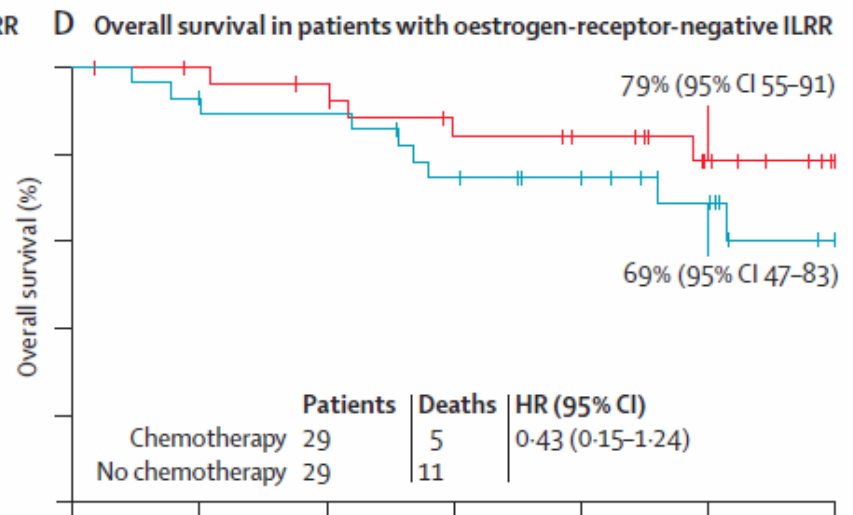
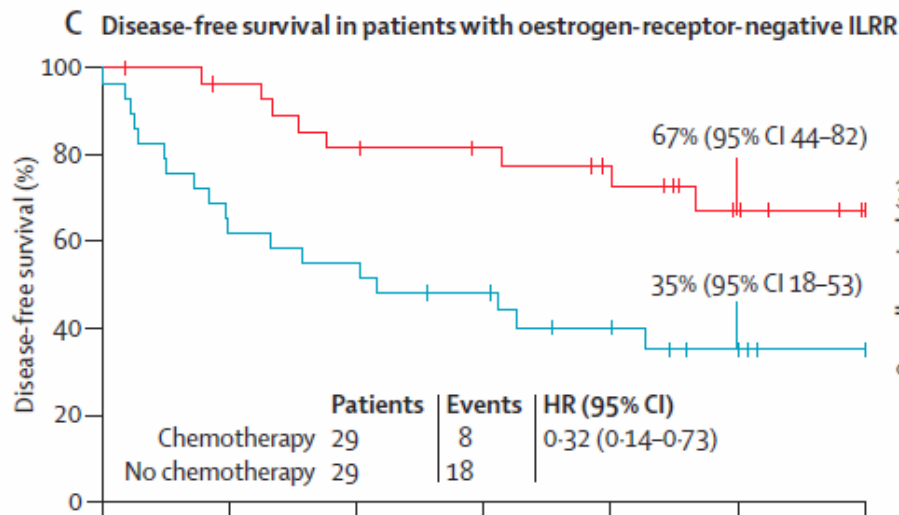
	Chemotherapy (N=85)	No Chemotherapy (N=77)
Failures	24	34
Local/regional	6	9
Distant	15	22
Soft tissue	0	2
Bone	8	5
Viscera	7	15
Contralateral breast	1	1
2° non-breast malignancy	1	0
Deaths without failure	1	2

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Results: ER negative ILRR

Kaplan-Meier curve of disease free survival and overall survival according to assigned treatment group



Number at risk

Chemotherapy 29 26 22 20 17 10 6

No chemotherapy 29 18 16 13 9 5 2

29 27 25 20 18 12 6

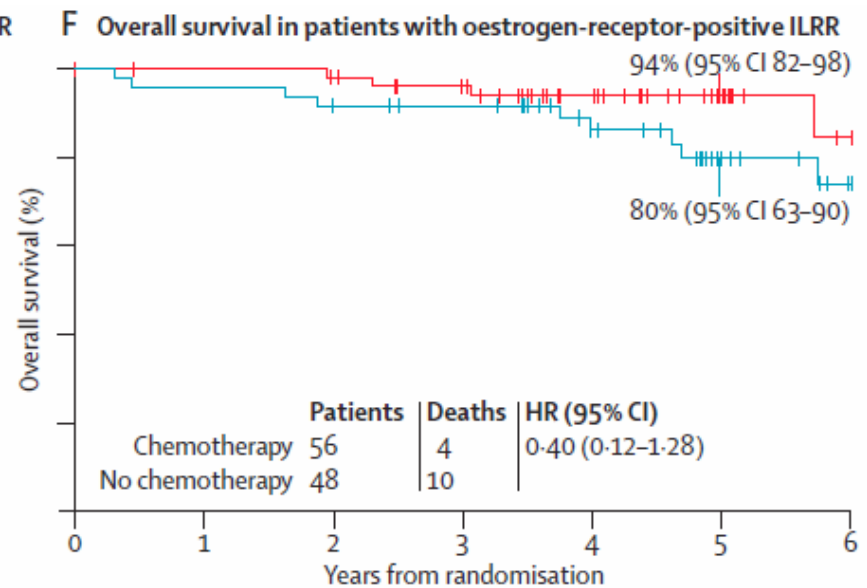
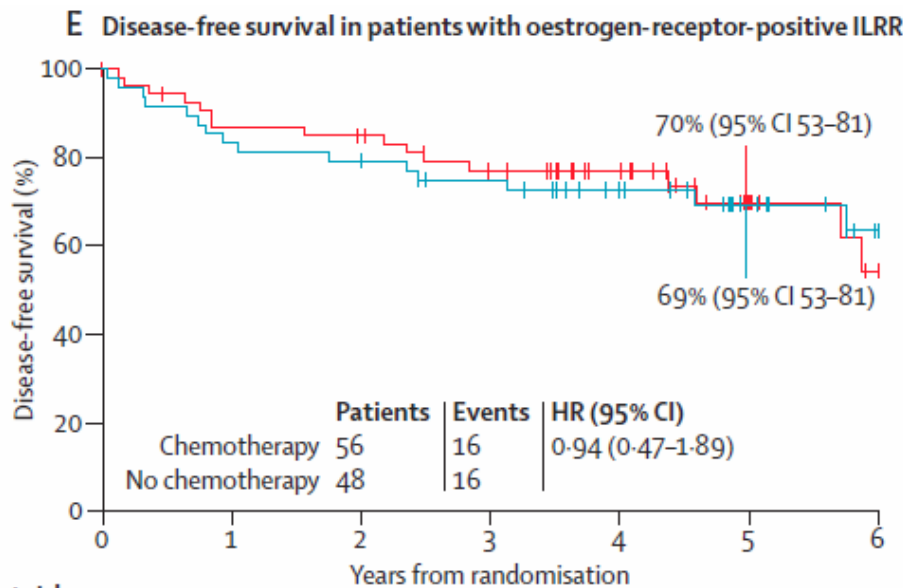
29 26 25 20 17 12 5

STUDIO CALOR



Results: ER positive ILRR

Kaplan-Meier curve of disease free survival and overall survival according to assigned treatment group



	Number at risk						
	0	1	2	3	4	5	6
Chemotherapy	56	47	44	37	28	13	6
No chemotherapy	48	40	37	33	25	16	8

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Results

Multivariable proportional hazards regression model of disease-free survival

	HR (95% CI)	P value
Oestrogen receptor status of ILRR (positive vs negative)	0.77 (0.43-1.37)	0.37
Location of ILRR		
Breast	Reference group	NA
Mastectomy scar or chest wall	0.84 (0.45-1.58)	0.59
Lymph nodes	1.18 (0.53-2.64)	0.69
Previous chemotherapy (yes vs no)	0.99 (0.57-1.73)	0.97
Interval from primary surgery (in years, continuous)	0.90 (0.85-0.96)	0.0021
Treatment (chemotherapy vs no chemotherapy)	0.49 (0.29-0.84)	0.0098

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Results

Of the 81 patients who received chemotherapy, 12 (15%) had serious adverse events.

The most common adverse events were:

- Neutropenia;
- Febrile neutropenia;
- Intestinal infection.

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Discussion: Strong points

1. Adjuvant chemotherapy reduces the risk of recurrence after primary breast cancer, it follows that **adjuvant chemotherapy should decrease the risk of recurrence in patients with resected ILRR**
2. **CALOR is the first randomised trial to provide evidence for the role of chemotherapy in this subset of patients ("the protocol design was straightforward and pragmatic")**
3. **Adjuvant chemotherapy in patients with ILRR of breast cancer improves outcomes (DFS and OS), particularly in ER negative ILRR**
4. **Personalised chemotherapy → enhanced the weight of the findings**
5. **Different characteristics in biology from primary tumor**
6. **Subsequent trials wanting to assign patients in this setting to no chemotherapy will be impossible**

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Discussion: Weak points

1. **Low accrual:** advances in local and systemic management and decision with non randomised trial or other setting
2. The ability to **draw conclusions from a study with such a reduction in sample size** is questionable
3. **Reporting of an overall result in the presence of a significant interaction is debatable** (test interaction between ER status and treatment effect suggests that treatment effect is heterogeneous)
4. **About HER2** status of the primary cancer and of the ILRR?
5. Whether **chemotherapy** has any benefit for **ER+ recurrence** is still unclear (**genomic signature**)

CALOR → linee guida AIOM 2013

- Trattamento loco-regionale con intento curativo va sempre preso in considerazione (chirurgia +/- RT)
 - Terapia sistemica:
 - ER/PgR+ → OT
 - HER2 + → trastuzumab
 - Allo stato attuale non esiste un consenso sull'opportunità o meno di eseguire una chemioterapia in caso di recidiva loco-regionale
 - Pertanto "...viene raccomandato l'inserimento all'interno di studi controllati...", ma "...sembra comunque ragionevole considerare un trattamento sistemico chemioterapico anche alla luce dei risultati dello studio CALOR..."
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Grazie per l'attenzione...