

Loco-Regional Recurrence in Breast Cancer

Progetto CANOA 2019



23 marzo 2019
Ospedaletto di Pescantina (VR)

Progetto CANOA

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Definition

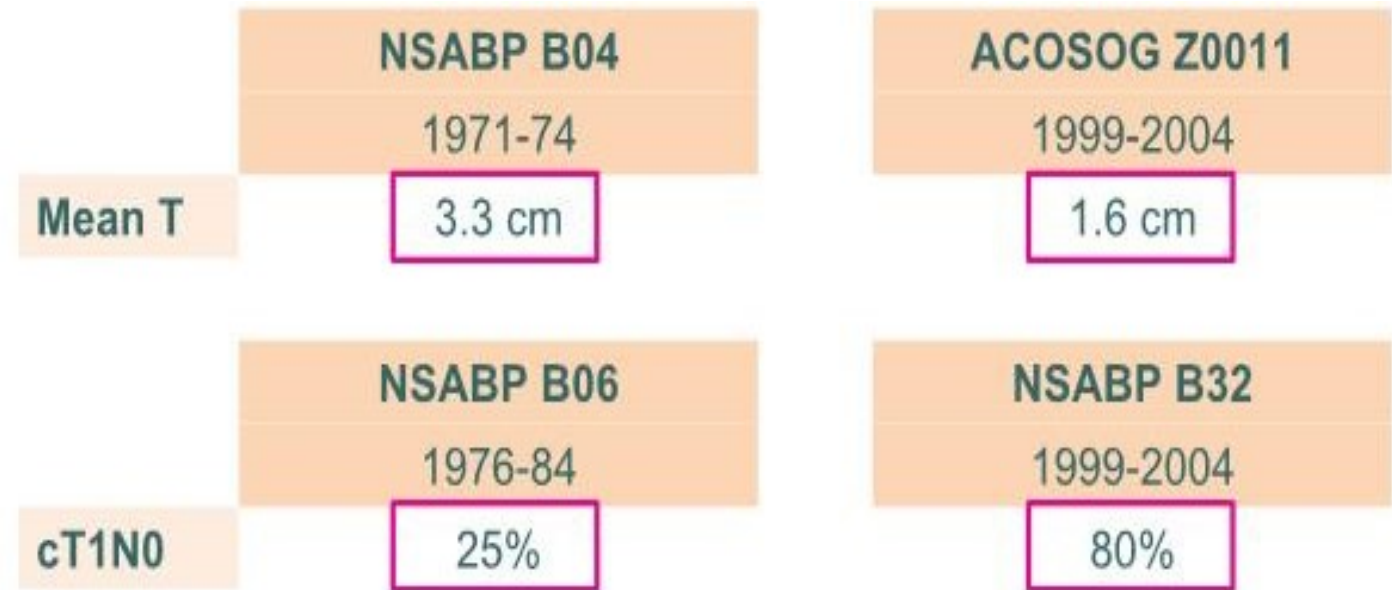
LR Recurrence

- ✓ Local: IBTR, chest wall
- ✓ Regional: Lymphnodes

Incidence of LRR

- ✓ @10yrs after MRM : 5 - 10 %
- ✓ @10yrs after BCT : 10 - 15 % (higher rate without RT)
- ✓ @ 9yrs after BCT: <3% as updated 2016, with incorporation of “RT-BOOST” trials: (Poortmans P., BCC 2019)

BC presentation over time



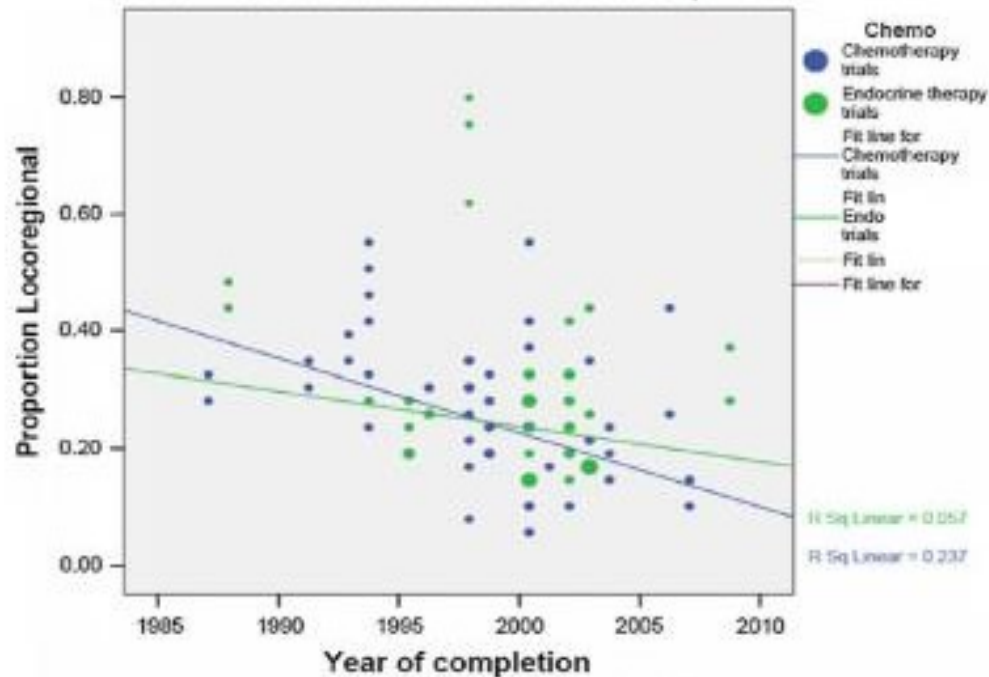
Fisher B, Cancer 1977;39:2827
Fisher B, N Engl J Med 1989;320:822

Giuliano A, JAMA 2011;305:569
Krag D, Lancet Oncol 2007;8:881

Proportion of LLR over time

n = 86,598

LRR ↓ 30% to 15% of all recurrences p < .001



Cases weighted by #patients

LRR & OS

The four-to-one ratio

LRR impacts on survival

4 : 1

$\frac{3}{4}$ LR occurred during first <5 yrs

$\frac{1}{2}$ mortality events occur >5 yrs

LR & Survival

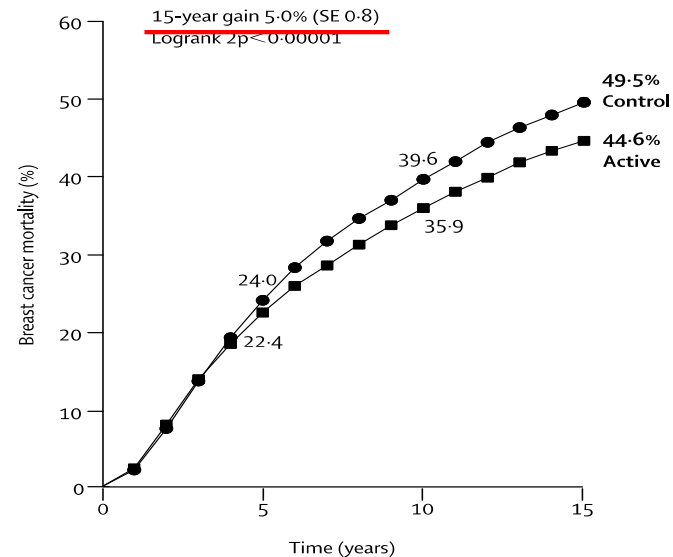
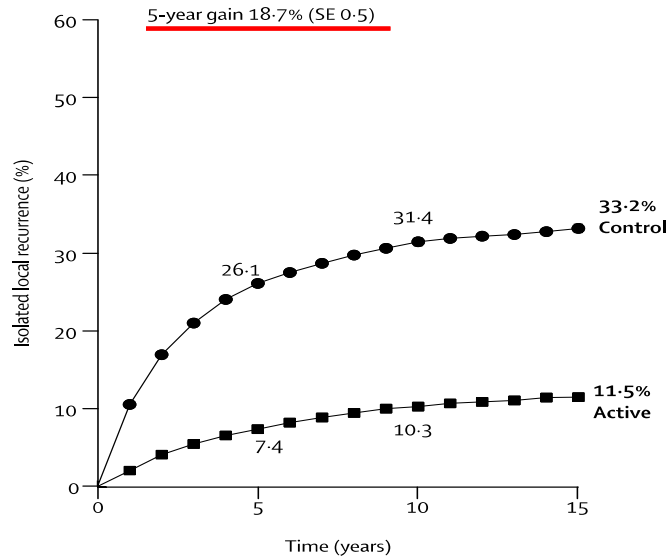
LR and BCM for treatment comparisons

	Breast cancer mortality (%)			
	5-year risk (active vs control)	5-year absolute reduction (SE)	15-year risk (active vs control)	15-year absolute reduction (SE)
(a) <10% (mean 1%)	18.8 vs 19.5	0.6 (0.6)	41.3 vs 42.3	1.0 (0.9)
(b) 10–20% (mean 17%)	21.8 vs 23.3	1.5 (0.6)	44.0 vs 48.5	4.5 (0.8)
(c) >20% (mean 26%)	24.9 vs 26.7	1.8 (1.3)	47.4 vs 53.4	6.0 (1.6)
Subtotal (b+c) (mean 19%)	22.4 vs 24.0	1.6 (0.6)	44.6 vs 49.5	5.0 (0.8)

Weighted regression line through zero, relating mortality reduction to recurrence reduction: 5.2%, SE 0.8, absolute reduction in 15-year breast cancer mortality for 20% absolute reduction in 5-year local recurrence risk.

Table 2: Breast cancer mortality risks by time since randomisation and by category of absolute reduction in 5-year local recurrence risk (from figure 4)

12 comparisons with >10% local recurrence risk: 25 276 women, 51% with node-positive disease



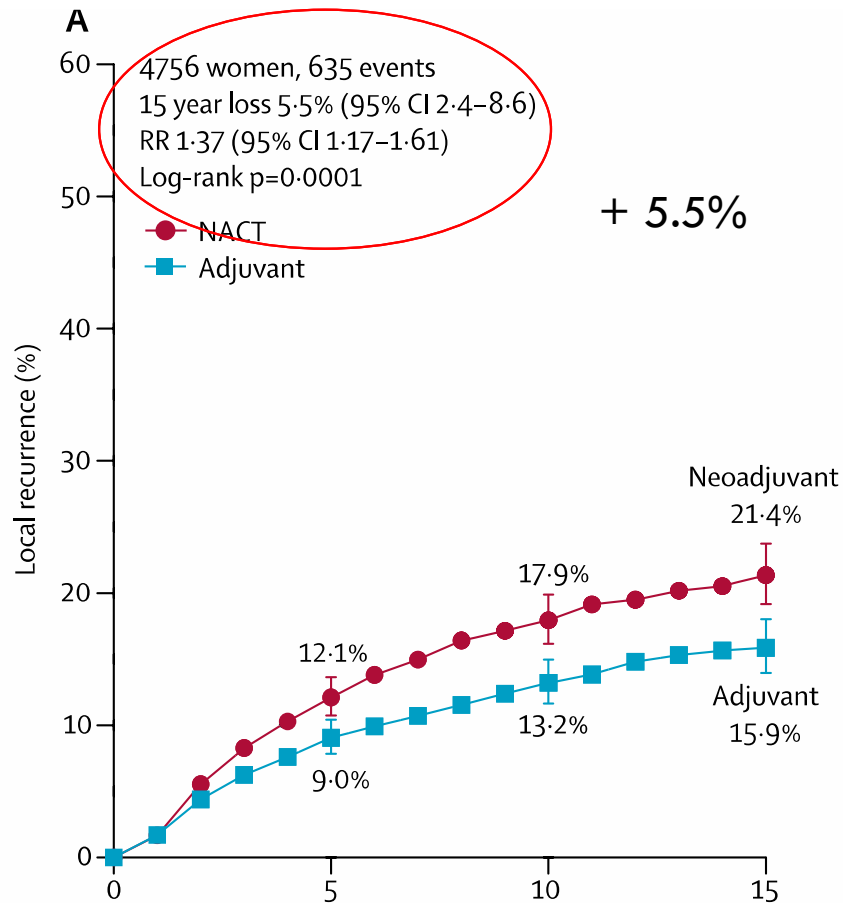
NACT and LR after BCT

- ✓ Now RT is usually incorporated in adj plan and LR is reduced.
- ✓ However the increasing use of NACT derived

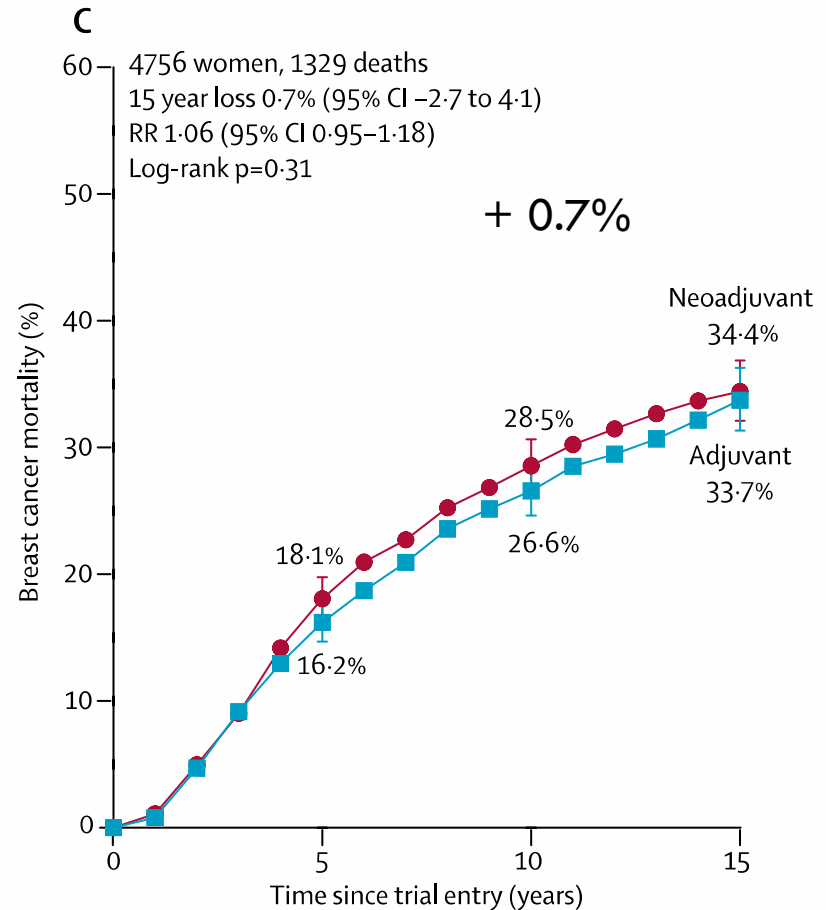
LR : + 5.5 %

- ✓ Tumor downsized by NACT might have higher LR after BCT

Outcomes for NACT vs Adj CT



Local recurrence crude rates (events per woman-years) and log-rank analyses



Breast cancer mortality crude rates (events per woman-years) and log-rank analyses

10 RCT; 2 RCT no surg (+13%), 8 RCT with surg (+3%)

The challenge of LRR treatment

- ✓ LRR is increasingly uncommon, so evidence to guide practice is limited. Most data from pts treated with MRM/ALND and RT
- ✓ Changing treatment landscape has raised new questions:
 - Axillary management after initial SN bx
 - Repeat lumpectomy
- ✓ We are in a real “data-free” zone

Management of LRR

1. Nodes

- ✓ Management of N recurrence after SN bx
- ✓ Management of the axilla after IBTR or chest wall recurrence

2. Breast

- ✓ Repeat lumpectomy without RT

3. Systemic Rx

- ✓ SAKK trial
- ✓ CALOR trial

Nodes



Management of N rec after SN bx

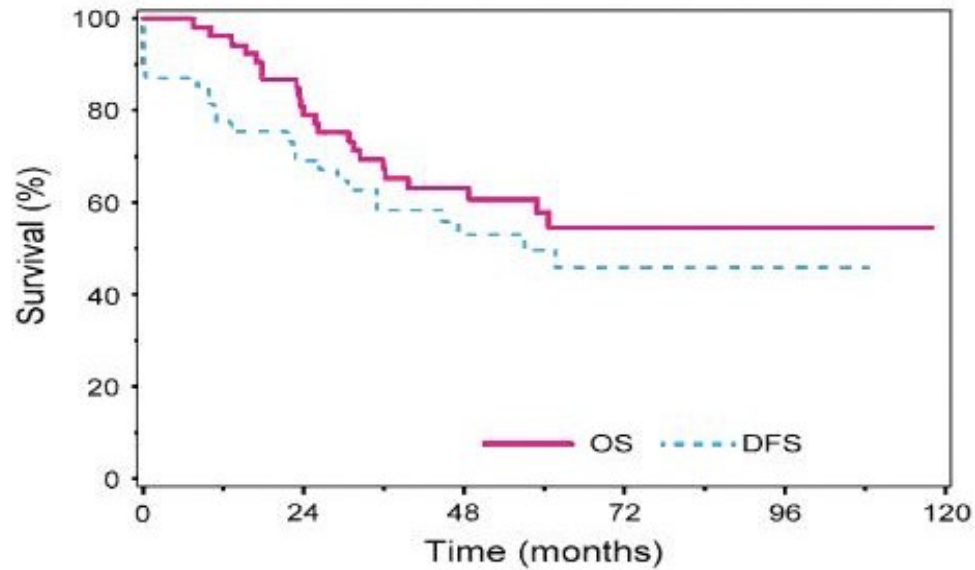
- ✓ Mets work up essential prior to any local therapy for LRR
 - ✓ 50% LRR accompanied by distant mets
- ✓ Isolated axillary recurrence is uncommon
 - ✓ <0.6% after neg SN bx
 - ✓ 1.1% after pos SN bx, WBRT (Z011)
- ✓ Axillary LRR after SN bx may be due to false neg rate and be prognostically different than LRR after ALND

Axillary Recurrence after Neg SB bx

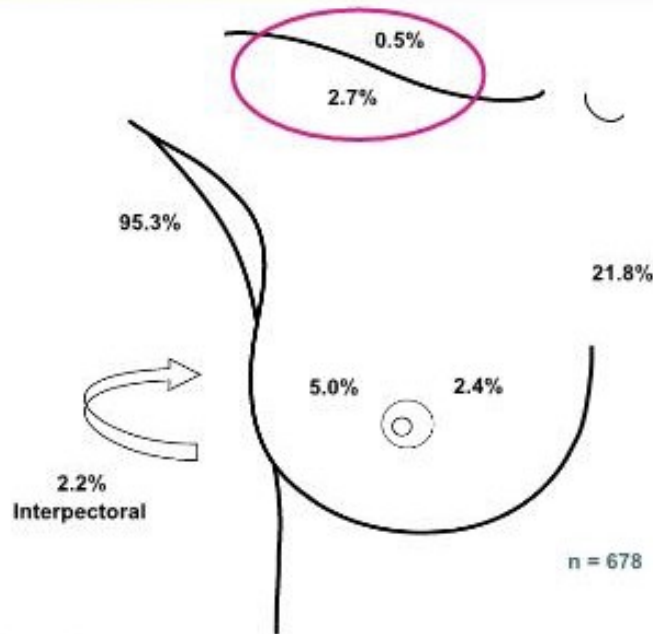
- ✓ Dutch Cancer Registry (>10K pts)
- ✓ 16 centers, neg SN bx 2002-2004
- ✓ 54 Axillary Recurrences
 - Median TTR: 30 mo (3-79)
 - Salvage ALND: 45 (83%)
 - Median N+: 3 (1-24); >3+ 42%

Dutch Experience

55%DFS 5yrs: quite respectable



Supraclavicular (SC) lymphatic drainage in the untreated breast



Management of SC Recurrence

(with no distant mets)

Danish Breast Cancer Group Trials 1977-2003
N 45.854

305 (1%) SC +/- other LRR (no dMets)

49% systemic Rx only

26% local + systemic

25% no systemic Rx

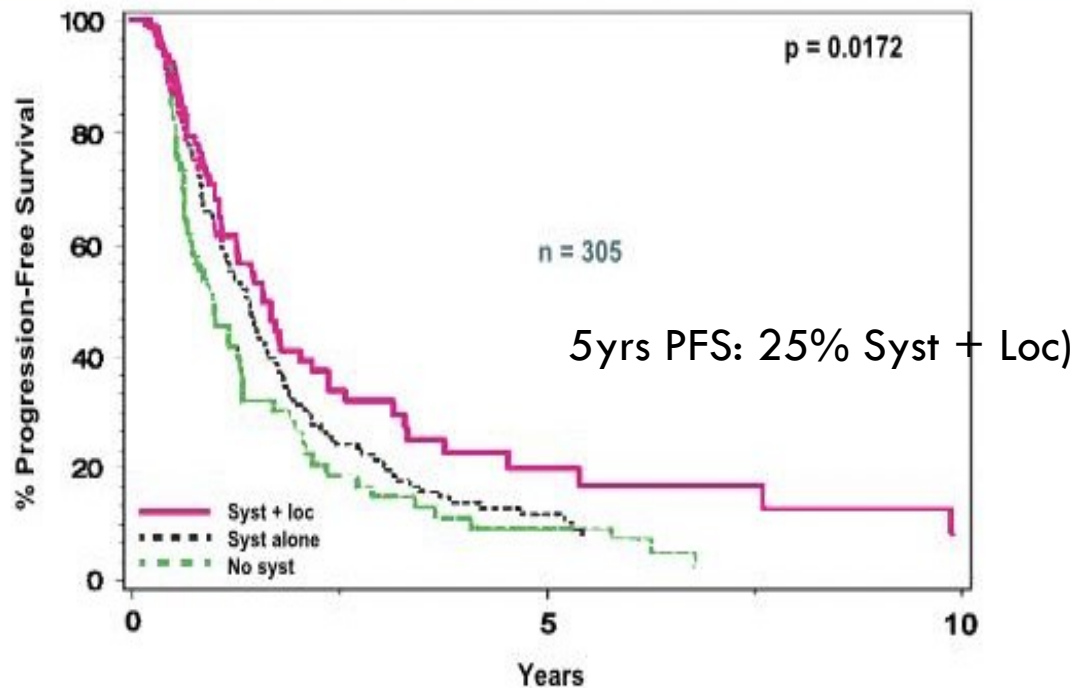
19% surgical excision

33% RT

10% surgery + RT

Management of SC Recurrence

(no distant mets)



Take Home Msg

Management of Nodal Rec after SN Bx

Axilla

- ✓ ALND as a proper approach
- ✓ RT as indicated by findings of ALND and according to the initial therapy

Supraclavicular

- ✓ Isolated SC rec rare
- ✓ Combined local systemic rx

Breast (I) - axilla

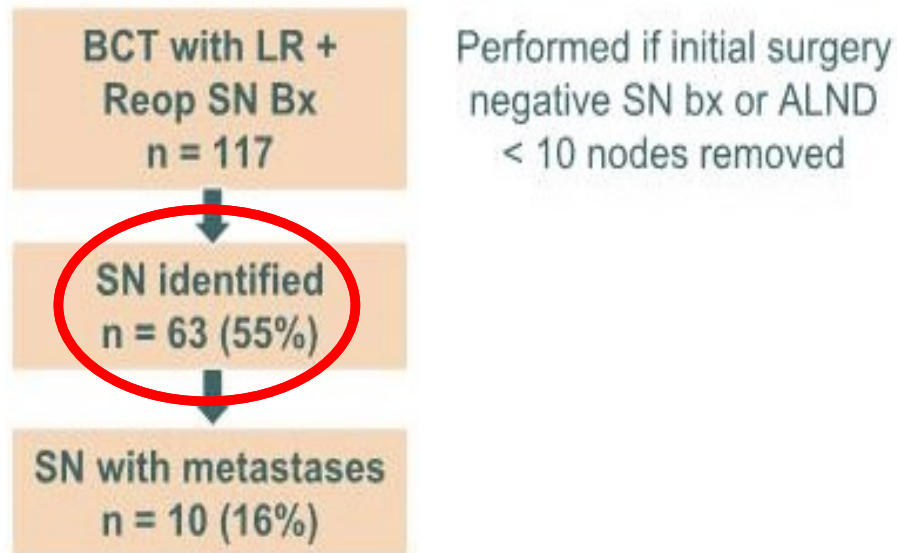


Re-operative SN Bx after LR

- ✓ Is it feasible and accurate ?
- ✓ Does it provide useful information ?

Reoperative SN Bx after BCT

MSKCC Experience



ALND not performed in all cases

Not available information about the false negative rate of SN Bx

Predictors of Success of Reoperative SN Bx

SN Bx and RT

Initial Axillary Procedure		SN ID Rate	
SN Bx		74%	
ALND		38%	p=0.0002
Initial RT		SN ID Rate	
Yes		50%	
No		72%	p=0.07

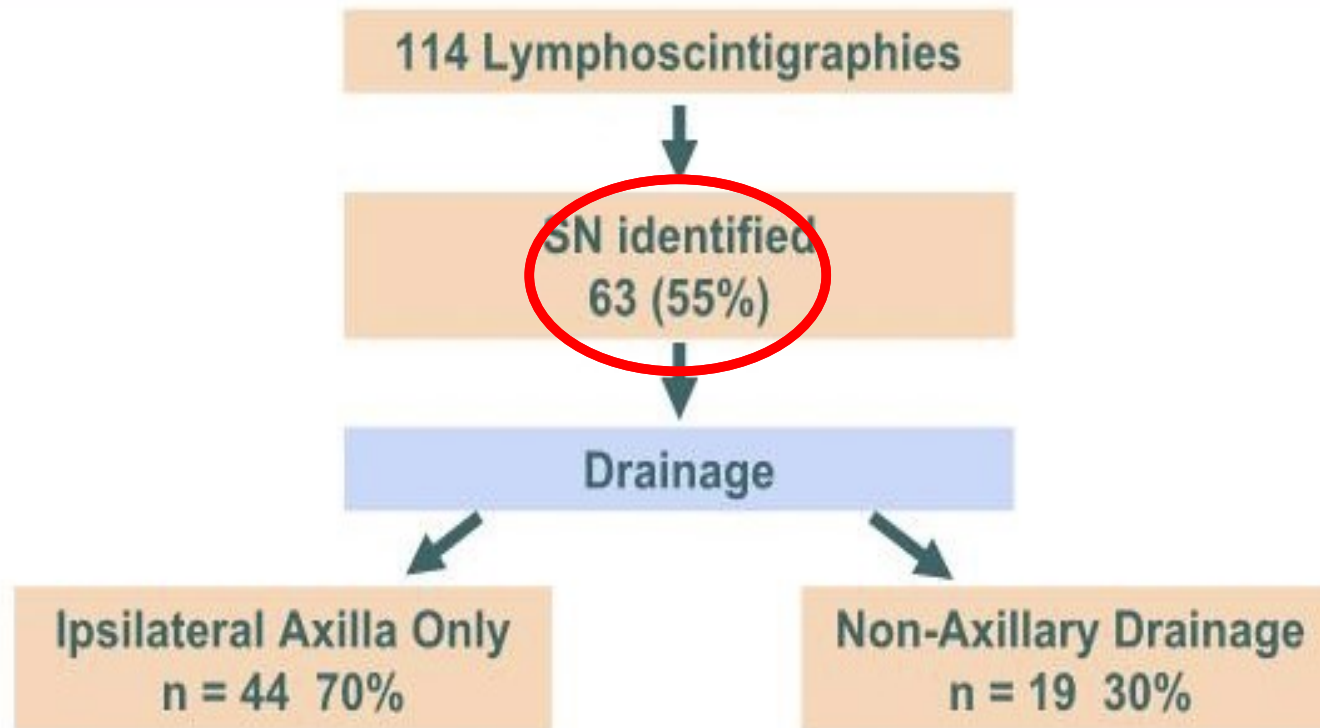
Success of Reoperative SN Bx

N of LNs first removed

SN ID Rate according to the N of Axillary Nodes Initially Removed

# Nodes Removed	SN ID Rate
0-2	80%
3-5	65%
6-8	53%
>9	38%

Location of Reoperative SNs



Extra axillary drainage in reop SN Bx

N 19

Internal Mammary

11/19

Controlateral

5/19

Reoperative SN Bx for LR of BC

Systematic Review

N = 692 pts (2002-2011)

Prior Axillary Surgery		Prior Breast Surgery	
SN Bx	n=301	BCT + RT n=574	83%
ALND	n=361	Mastectomy	n=62
None	n=30	Missing n=56	

52%

Reoperative SN Bx for LRBC

Systematic Review

Predictors of SN ID Rate

Axillary Surgery	SN ID Rate (95% CI)	p value
SN Bx	81% (76-85)	<0.001
ALND	52% (47-57)	

Breast Surgery	SN ID Rate (95% CI)	p value
Lumpectomy + RT	66% (61-70) N496	NS
Mastectomy	69% (53-81) N45	

Aberrant Drainage Pathway

Internal Mammary	46%
Controlateral Axilla	34%
Supra/infraclavicular	14%
Intramammary	2%
Interpectoral	2%

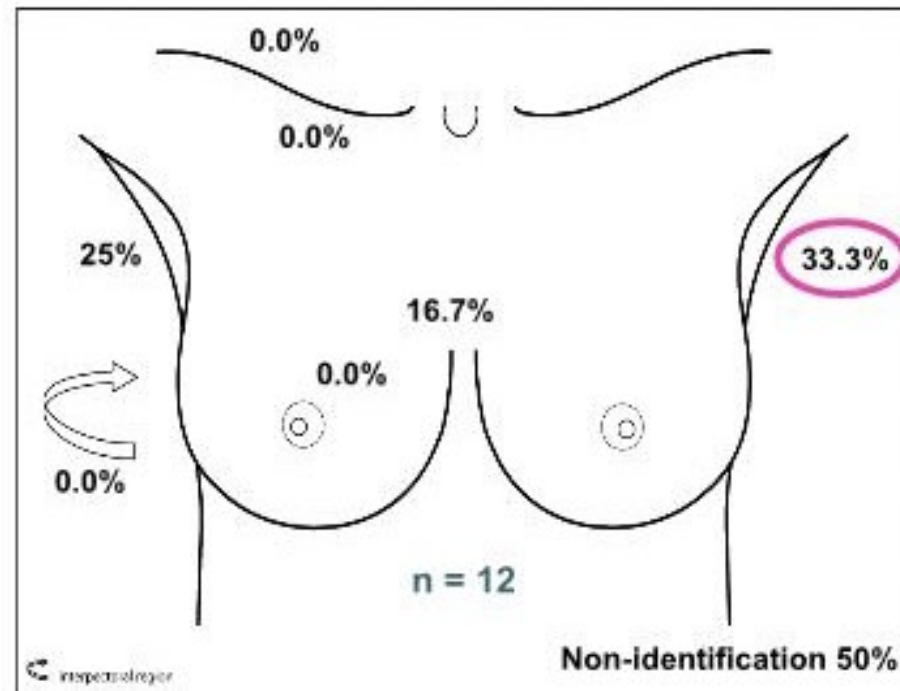
19/69 SN metastases in aberrant drainage pathways

Aberrant Drainage Pathway

Predictors of aberrant drainage

Denominator	Prior SN Bx	Prior ALND	
Succ Mapped	26%	74%	p<0.001
All Pts	14%	33%	p<0.001

Lymphatic Drainage after BCT with ALND



What do Contralateral Axillary mets mean?



AJCC TNM classifies contralateral nodal disease as Stage IV in both untreated primary tumors and with local recurrence/new primary and a previously treated axilla

Take home Msg

Management breast – axilla

- ✓ An SN can be identified in the majority of pts who had initial SN Bx (83%) and half of those with ALND (52%)
- ✓ Likelihood of SN identification is related to the N of Nodes removed, irrespective of breast surgical procedure
- ✓ False neg rate not well defined (specially after MRM)
- ✓ Aberrant drainage is common-this has implication for mapping technique and for cure

Breast (II)

Management of IBTR after BCT

is lumpectomy alone appropriate ?

Repeat Lumpectomy Alone for IBTR

Median FU 6-244 mo

Author	# Patients	Second LR
Ishitobi	65	25%
Kurtz	52	23%
Dalberg	14	13%
Salvadori	57	19%
Alpert	30	7%
Chen	179	15%
Gentilini	161	29%

High rates of additional LR
NOT the standard of care

Systemic Rx



Systemic Rx after LRR

Outcomes after LRR is variable

NASBP 06 ('76-'84) : no diff OS Lump vs Mast. @ 20yrs FU
Despite the higher rate of IBTR/LRR in Lump alone (14.3%).

5 recent NSABP trials ('84-'94): cumulative IBTR and the effect on
the risk of distant disease and death in N+ receiving Lump+RT+adj Rx

N 2669 pts (out of 10.100) @ FU 13.3yrs : LRR 424 (15.9%)
IBTR: 9.7% and otherLRR: 6.2%.

Is there any diff b/w IBTR vs. oLRR in term of survival ?

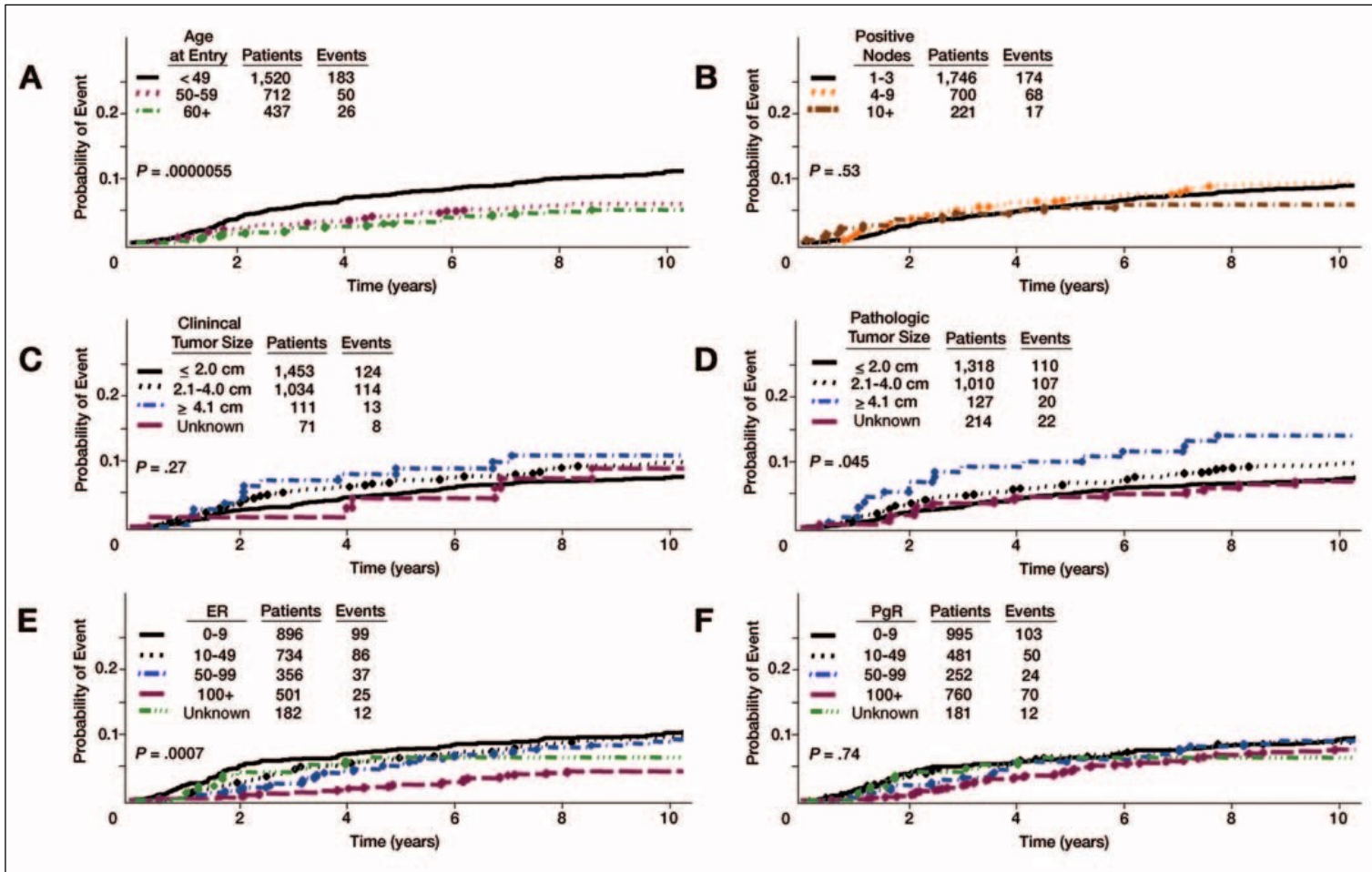
10-yr incidence of IBTR (N+)

Lumpectomy pts across NSABP trials (B15,16,18,22,25)

Young

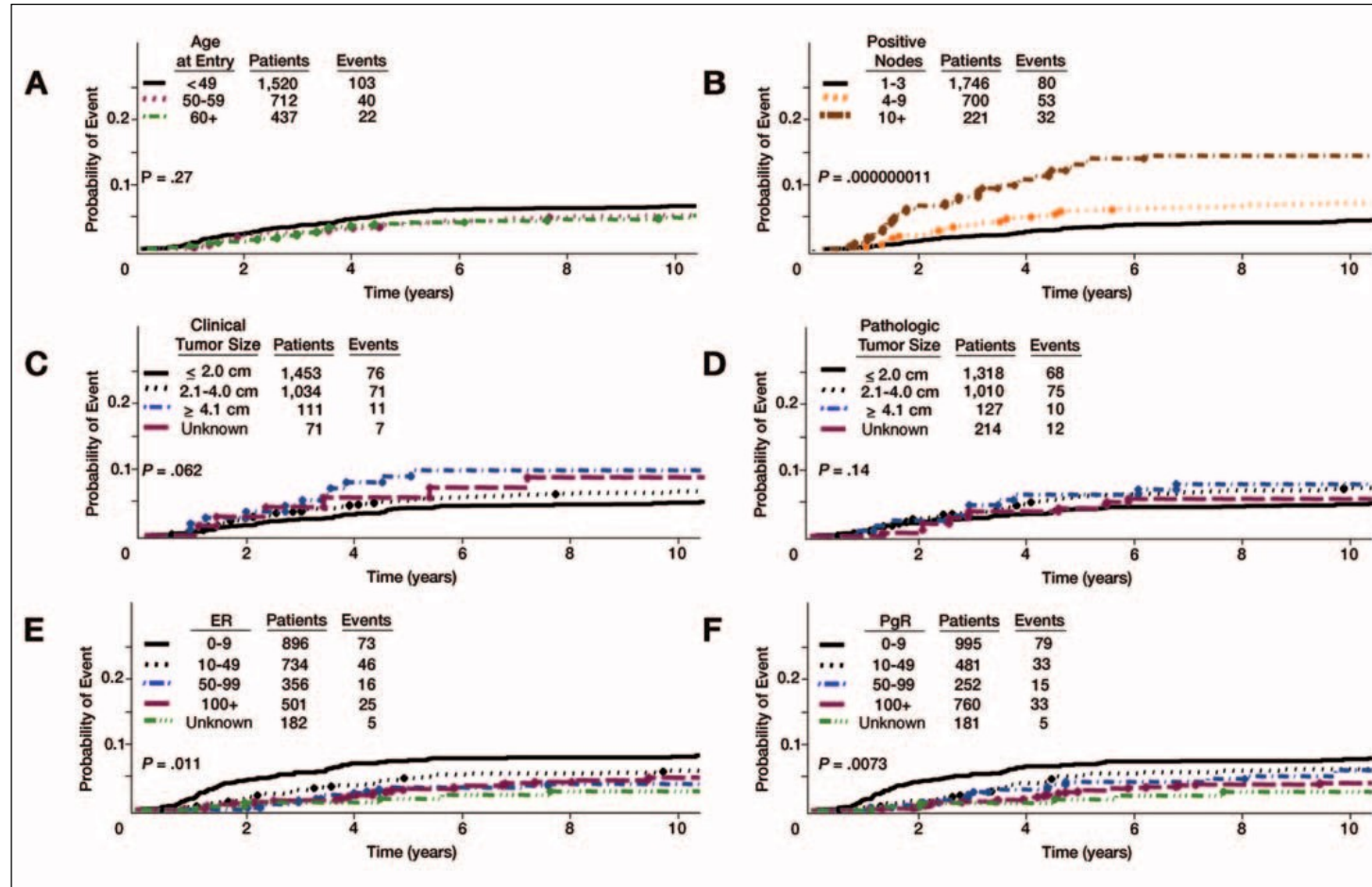
Large T

Poor ER



10-yr incidence of other LLR (N+)

Lumpectomy pts across NSABP trials (B15,16,18,22,25)



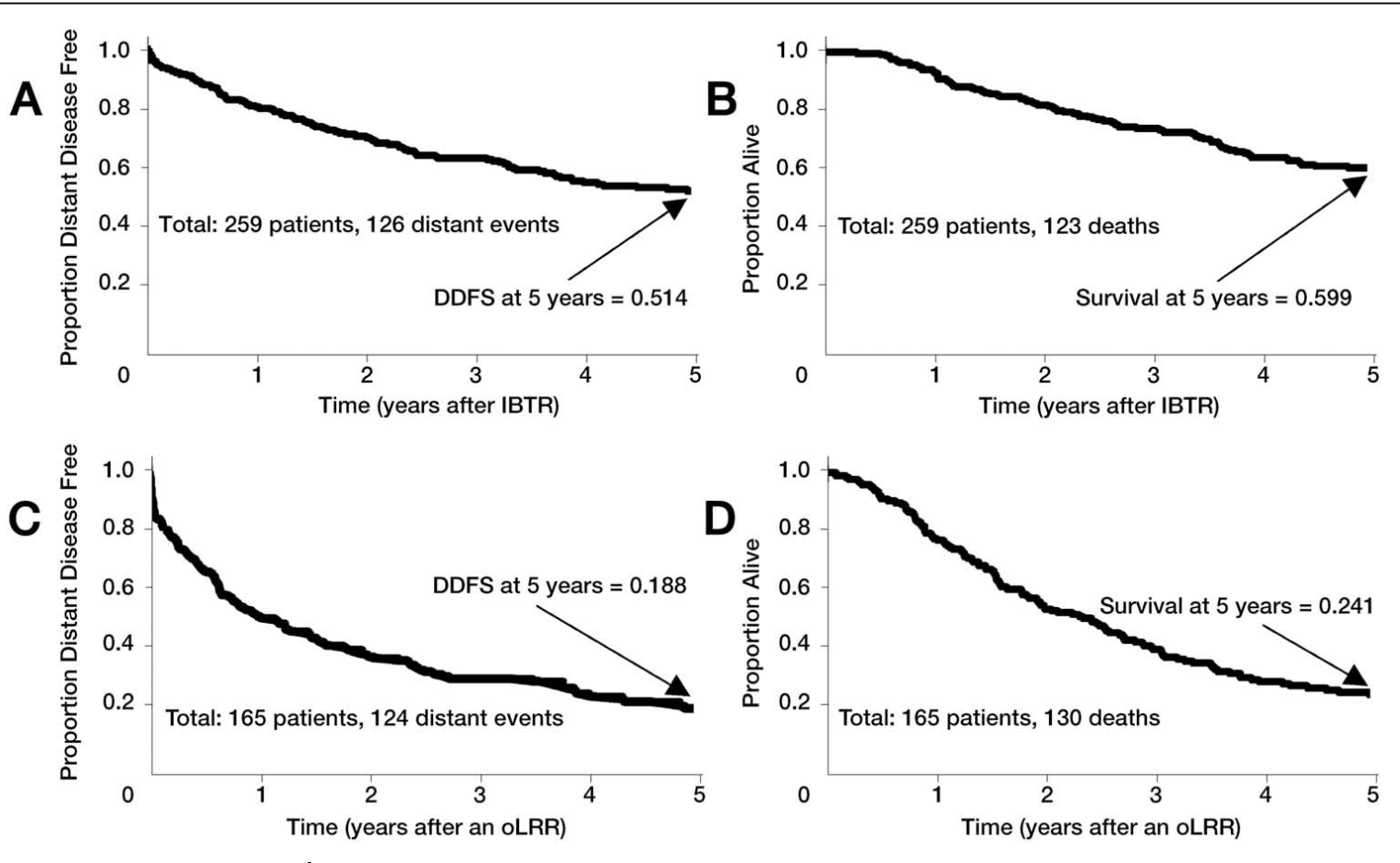
More N

Poor PgR

NSABP experience (5 trials)

Outcomes after incidence IBTR and oLRR

IBTR



oLRR

The mean/annual DDR 15% MR: 10% (45% & 28% in oLRR)

The time of LRR matters (<5yrs vs >5: second primary?)

LRR and systemic Rx



What data exist for systemic Rx following LRR

NOT MUCH

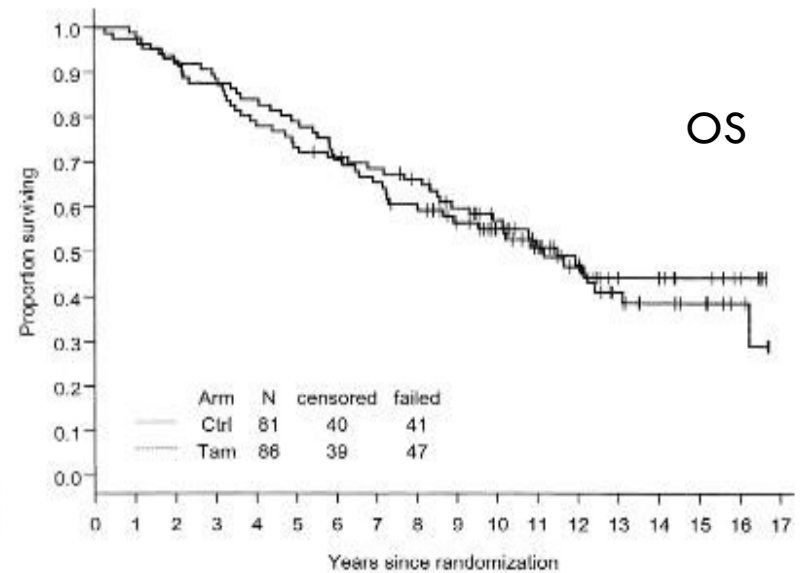
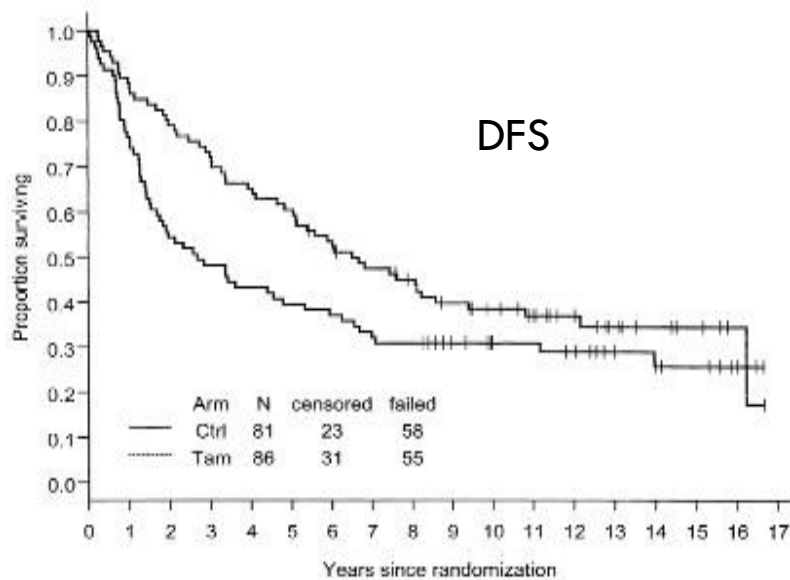
RCT in Rx of LRR

4 trials of adj systemic therapy have been reported

- ✓ Olsen (1971): Actinomycin D N: 32
- ✓ Fentoman (1993): Alpha IFN N: 32
- ✓ SAKK (1991): Tam N: 167
- ✓ Calor (2010): Chemotherapy N: 162

SAKK 23/82

N 167



@FU >10yrs: Tam improved DFS for ER+ post mastectomy

CALOR trial

Chemotherapy (CT) for Isolated Locoregional Recurrence (ILRR) of Breast Cancer in ER-Positive (ER+) and ER-Negative (ER-) Cohorts: Final Analysis of the CALOR Trial

International Breast Cancer Study Group, Breast International Group, NRG Oncology (NSABP Legacy)

Irene Wapnir, Karen N. Price, Stewart J. Anderson, Andre Robidoux, Miguel Martín, J. W. R. Nortier, Alexander H. G. Paterson, Mothaffar F. Rimawi, István Láng, José Manuel Baena Cañada, Beat J. K. Thürlimann, Eleftherios P. Mamounas, Charles E. Geyer Jr., Shari Gelber, Alan S. Coates, Richard D. Gelber, Priya Rastogi, Meredith M. Regan, Norman Wolmark, Stefan Aebi

Lancet Oncol 15:156-163, 2014; SABCs 2012, ASCO 2017 J Clin Oncol 2018

Phase 3 RCT

FU 9yrs long to capture the adj CT effect

Methods

- Patients had completely excised ILRR after unilateral breast cancer.
- Endpoints are disease-free survival (DFS), overall survival (OS) and breast cancer-free interval (BCFI).
- From August 2003 to January 2010, 162 patients were enrolled.
- Results at 8.8 years median follow-up are reported here according to ER status of the ILRR.

CALOR: Challenges

– INADEQUATE POWER

- Sample size (optimal 977) = 162

– PROTOCOL DEVIATIONS

- Polychemotherapy recommended – 31% monotherapy

– CHEMOTHERAPY BENEFIT UNCERTAIN

- ~65% hormone receptor-positive
- > 50% IBTR
- Average disease-free interval = 5-6 years
- 42% pts chemotherapy arm and 32% pts no chemotherapy arm had had no prior chemotherapy

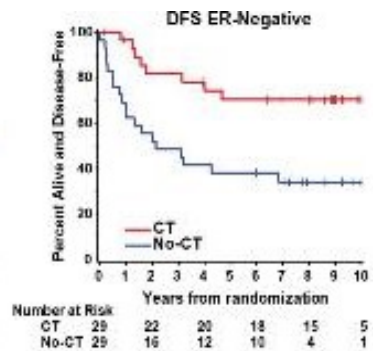
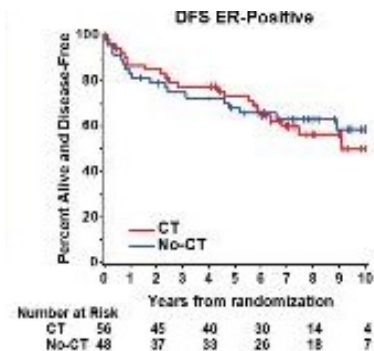
Baseline Characteristics

Characteristics		Chemotherapy (N=85)	No Chemotherapy (N=77)
Primary surgery – N (%)	Mastectomy	33 (39)	31 (40)
	Breast conserving	52 (61)	46 (60)
Time from primary to surgery for ILRR (years)	Median (range)	5.0 (0.3-31.6)	6.2 (0.4-22.0)
	N (%) ≥ 2 years	72 (85)	65 (84)
Menopausal status at ILRR – N (%)	Premenopausal	20 (24)	14 (18)
	Postmenopausal	65 (76)	63 (82)
Median age at ILRR – years (range)		56 (38-81)	56 (31-82)
ER of ILRR – N (%)	Negative	29 (34)	29 (38)
	Positive	56 (66)	48 (62)
ER of primary – N (%)	Negative	27 (32)	20 (26)
	Positive	49 (58)	47 (61)
	Unknown	9 (11)	10 (13)
Treatment for ILRR			
Radiation therapy		31 (36)	29 (38)
Endocrine therapy for ER positive ILRR		53 (92)	50 (98)
Chemotherapy	Monotherapy	25 (29%)	Variable chemo
	Polytherapy	55 (65%)	

Survival by ER expression CT vs noCT

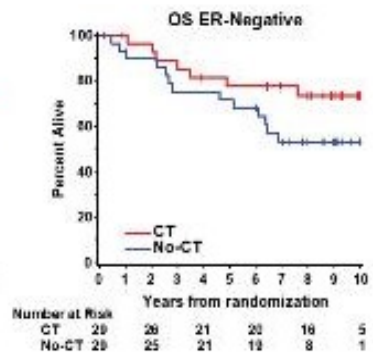
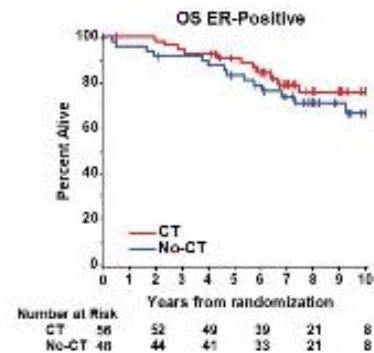
@10yrs FU

50% vs 59%



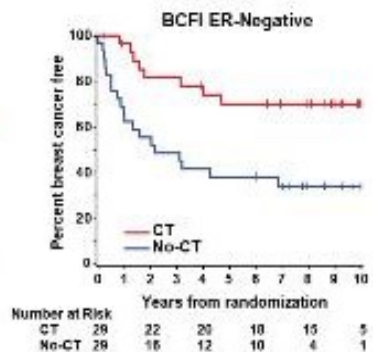
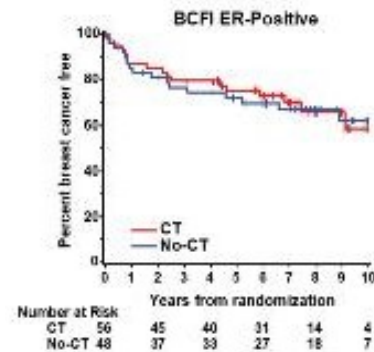
70% vs 34%

76% vs 66%



73% vs 53%

58% vs 62%



73% vs 53%

Survival by ER expression

Table 2. Ten-Year Outcome by ER Status of ILRR

Endpoint	ER-positive			ER-negative		
	CT	No-CT	HR (95% CI)	CT	No-CT	HR (95% CI)
10-yr DFS	50%	59%	1.07 (0.57-2.00)	70%	34%	0.29 (0.13-0.67)
	Interaction P-value = 0.013					
10-yr OS	76%	66%	0.70 (0.32-1.55)	73%	53%	0.48 (0.19-1.20)
	Interaction P-value = 0.53					
10-yr BFCI	58%	62%	0.94 (0.47-1.85)	70%	34%	0.29 (0.13-0.67)
	Interaction P-value = 0.034					

Multivariate Model of DFS

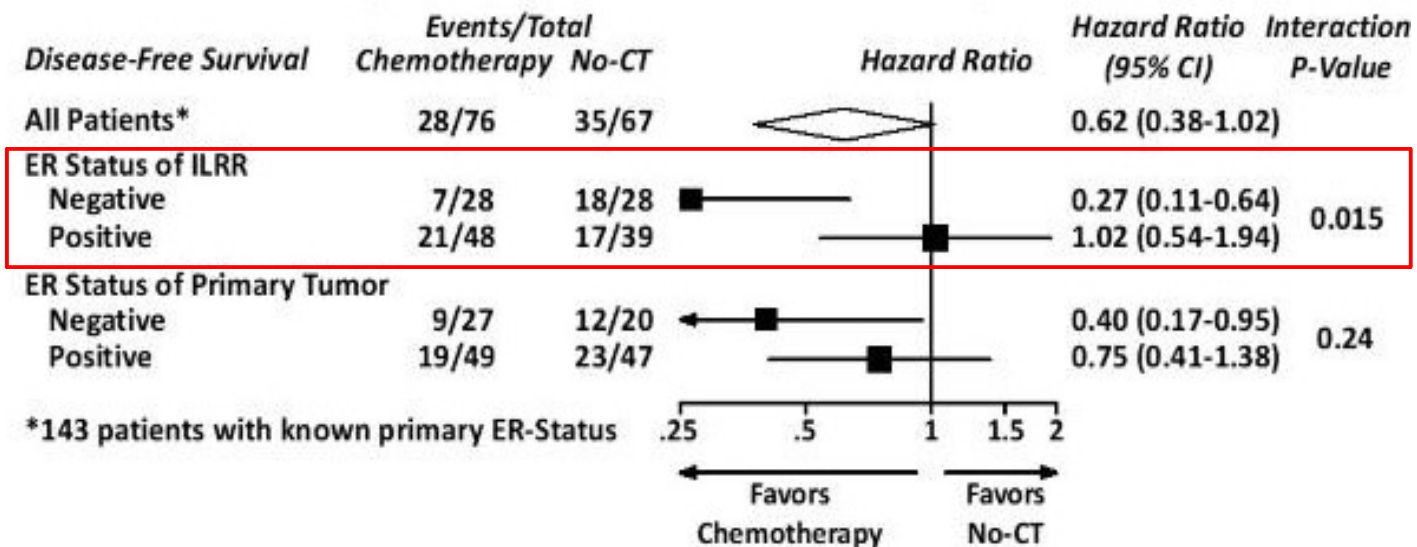
Predictors of adj CT benefit

Variable	Hazard Ratio (95% CI)	P-value
Location of ILRR		
Breast	(reference group)	
Mastectomy scar or chest wall	0.78 (0.43, 1.43)	0.43
Lymph nodes	1.01 (0.47, 2.16)	0.98
Prior chemotherapy (yes/no)	0.86 (0.52,1.43)	0.56
Interval from primary surgery (per year)	0.92 (0.87, 0.97)	0.0036
Interaction of Treatment by ER of ILRR		0.024
ER positive	0.87 (0.46, 1.64)	
ER negative	0.26 (0.11, 0.60)	

CT effect by ER Status in primary or in IRLR

ER in mets vs. primary T

Figure 2. Analysis of ER Status of ILRR and of Primary Among 143 Patients with Known Primary ER Status



Conclusion CALOR

- The final analysis of CALOR confirms that CT benefits patients with resected ER-negative ILRR.
- Long-term CALOR trial results do not support the use of CT for patients with ER-positive ILRR who received adjuvant endocrine therapy as part of their assigned treatment.
- The choice of adjuvant systemic therapy for ILRR should be informed by the biological characteristics of the ILRR rather than by those of the primary.
- In this pragmatic trial, participating oncologists were able to select effective chemotherapy regimens.

Recommendations/Open Questions

The main weakness: the small sample size:

1. A modest benefit of CT in pts with luminal LRR could not be excluded.
2. In particular for pts with LRR while in ET
3. Furthermore, the benefit in case of Luminal B (PgR neg) could not be evaluated

✓ ER +ve rec:

ET

✓ Duration ? (switch ?)

✓ HER2 +ve rec:

HER2 TT

✓ Duration ?

(<5% of pts in CALOR received antiHER2 adj Rx)

✓ TNBC rec:

CT

✓ Which type of CT ?