Loco-regional Recurrence in Breast Cancer

Roma, 27 ottobre 2018

Alberto Zambelli
Oncologia Medica
Ospedale Papa Giovanni XXIII
Bergamo

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)

Buchanan CL, et al. J Am Coll Surg 2006

LRR & OS
The four-to-one ratio

LRR impacts on survival

4 : 1

¾ LR occurred during first <5 yrs

½ mortality events occur >5 yrs

EBCTCG Lancet 2005

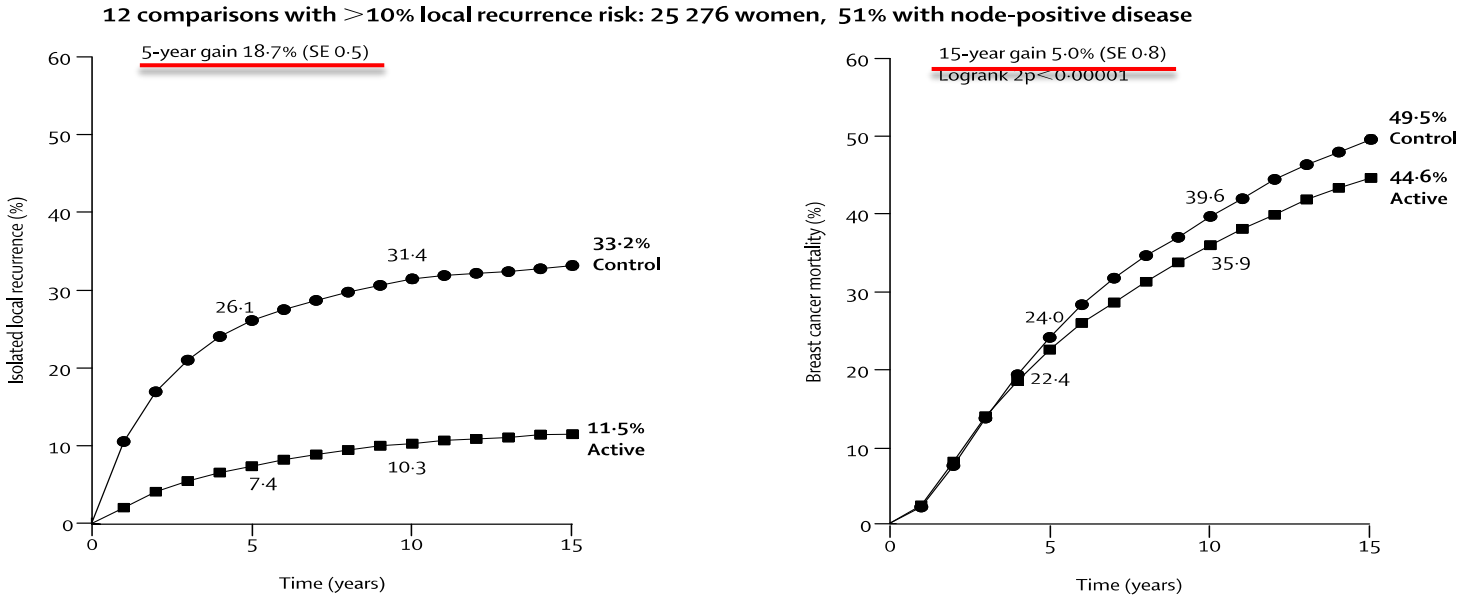
LR & Survival

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)**



EBCTCG Lancet 2005

NACT and LR after BCT

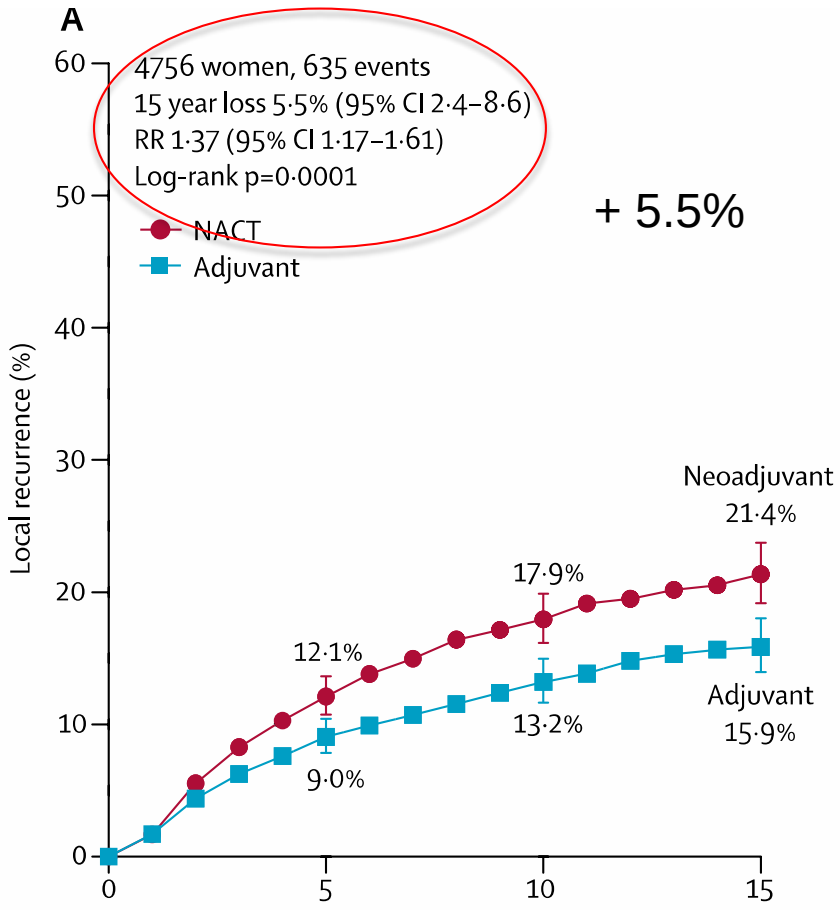
- Now RT is usually incorporeted in adj plan and LR is reduced.
- However the increasing use of NACT derived

LR : + 5.5 %

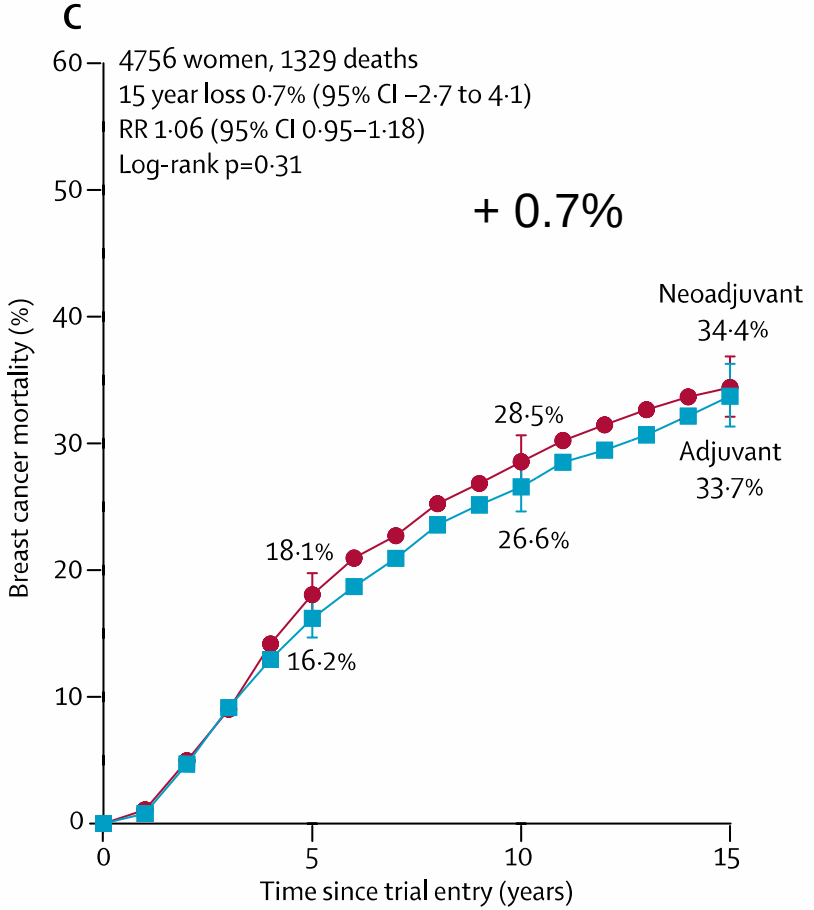
- Tumor downsized by NACT might have higher LR after BCT

EBCTCG Lancet 2018

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%)

EBCTCG 2018

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 managment after initial SN bx
  - Repaet 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
- Isolatd axillary recurrence is uncommon
  - <0.6% after neg SN bx
  - 1.1% after pos SN bx, WBRT
- Axillary LRR after SN bx may be due to false neg rate and be prognostically different than LRR after ALND

Pepels M Breast Canc Res Treat 2011
Giuliano A JAMA 2017

Axillary Recurrence after Neg SB bx

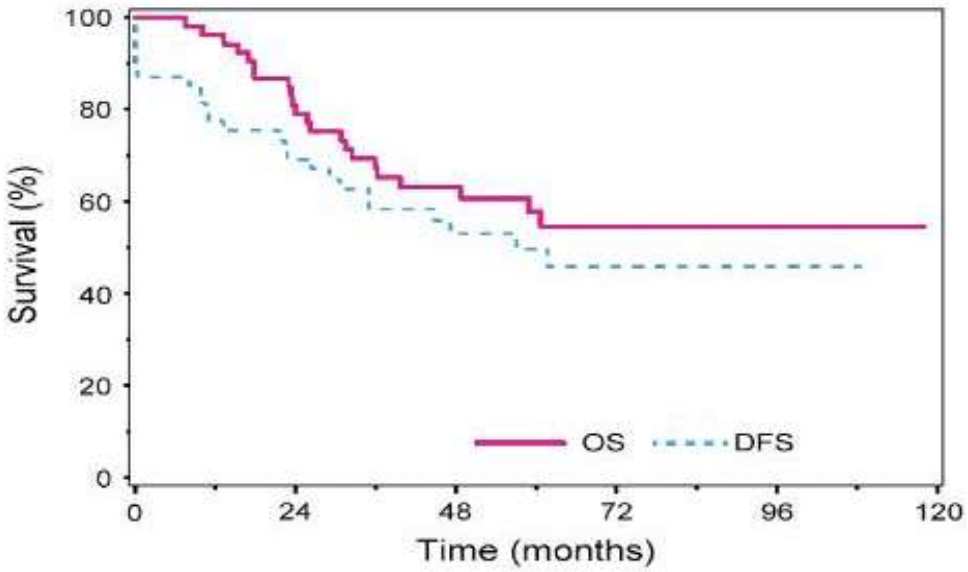
- Dutch Cancer Registry
- 16 centers, neg SN bx 2002-2004

- 54 Axillary Recurrences
  - Median TTR: 30 mo (3-79)
  - Salvage ALND: 45 (83%)
  - Median N+: 3 (1-24); >3+ 42%

Bulte J, Breast Cancer Res Treat 2013

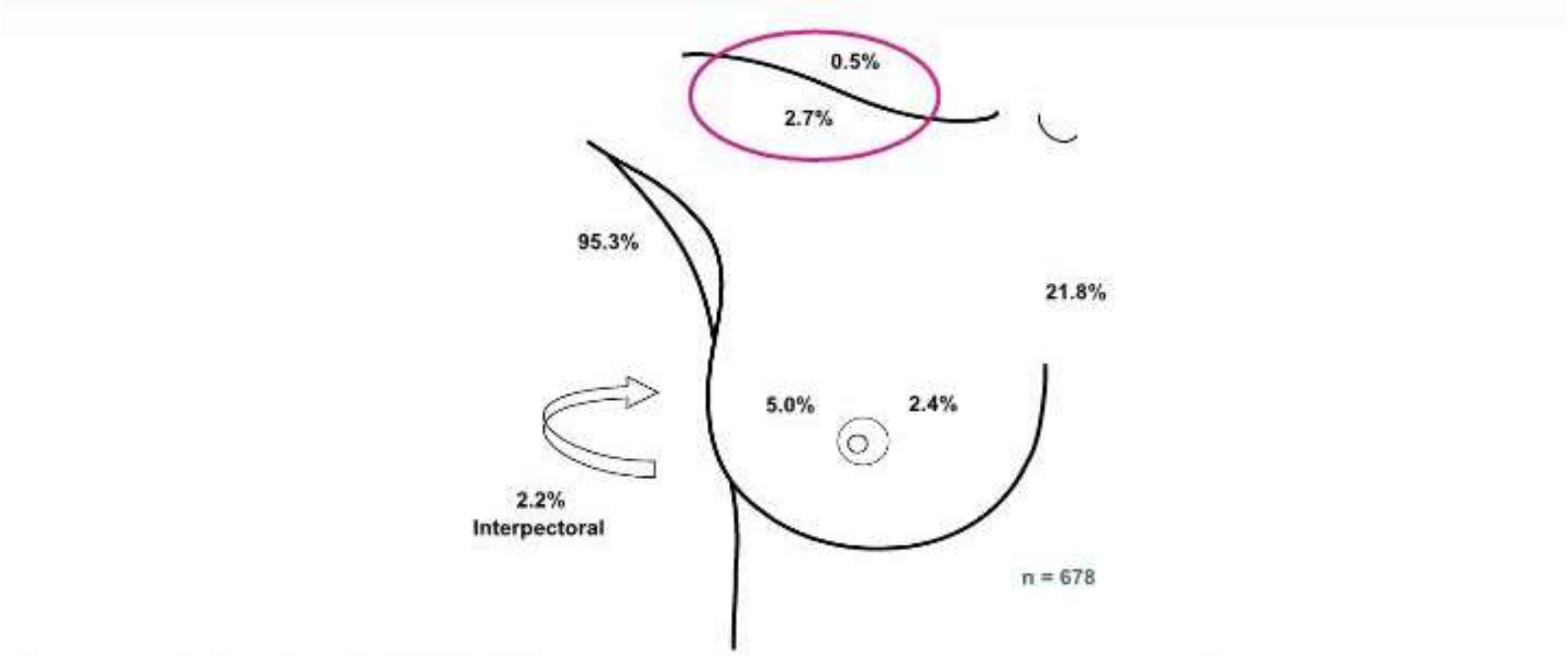
Dutch Experience

55% OS 5yrs



Bulte J, Breast Cancer Res Treat 2013

Supraclavicular (SC) lymphatic drainage in the untreated breast



Management of SC Recurrence

(with no distant mets)

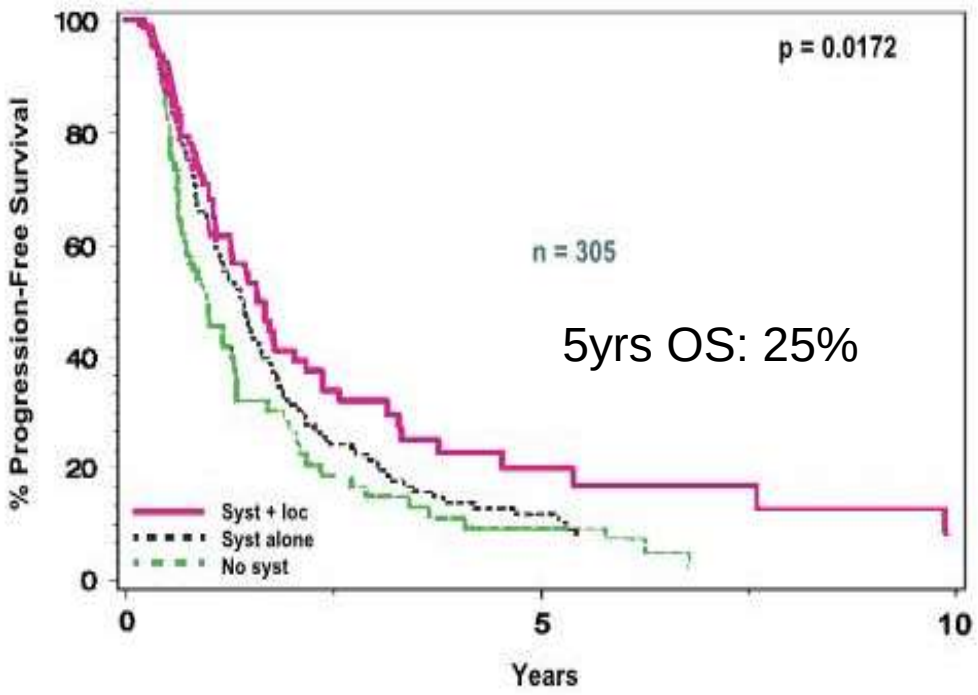
Danish Breast Cancer Group Trials 1977-2003
N 45.854

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

49% systemic Rx only	19% surgical excision
26% local + systemic	33% RT
25% no systemic Rx	10% surgery + RT

Pederesen A, Breast Can Res Treat 201

Management of SC Recurrence
(no distant mets)



Pederesen A, Breast Can Res Treat 201

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

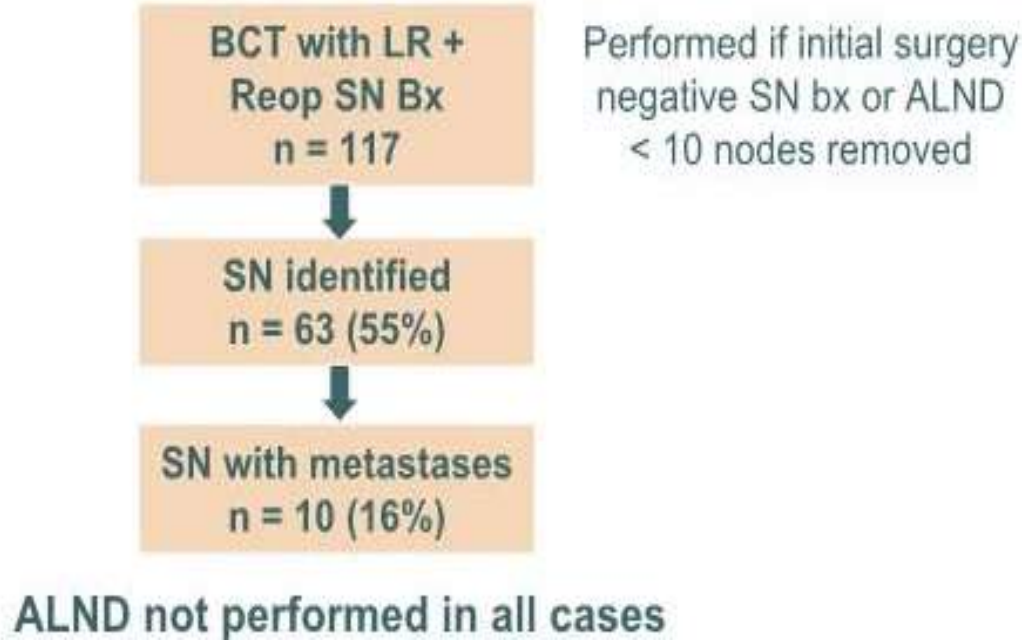
Breast (I) - axilla

Re-operative SN Bx after LR

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

Reoperative SN Bx after BCT

MSKCC Experience



Port E Ann Surg Oncol 200

Predictors of Success of Reoperative SN Bx

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

Port E Ann Surg Oncol 200

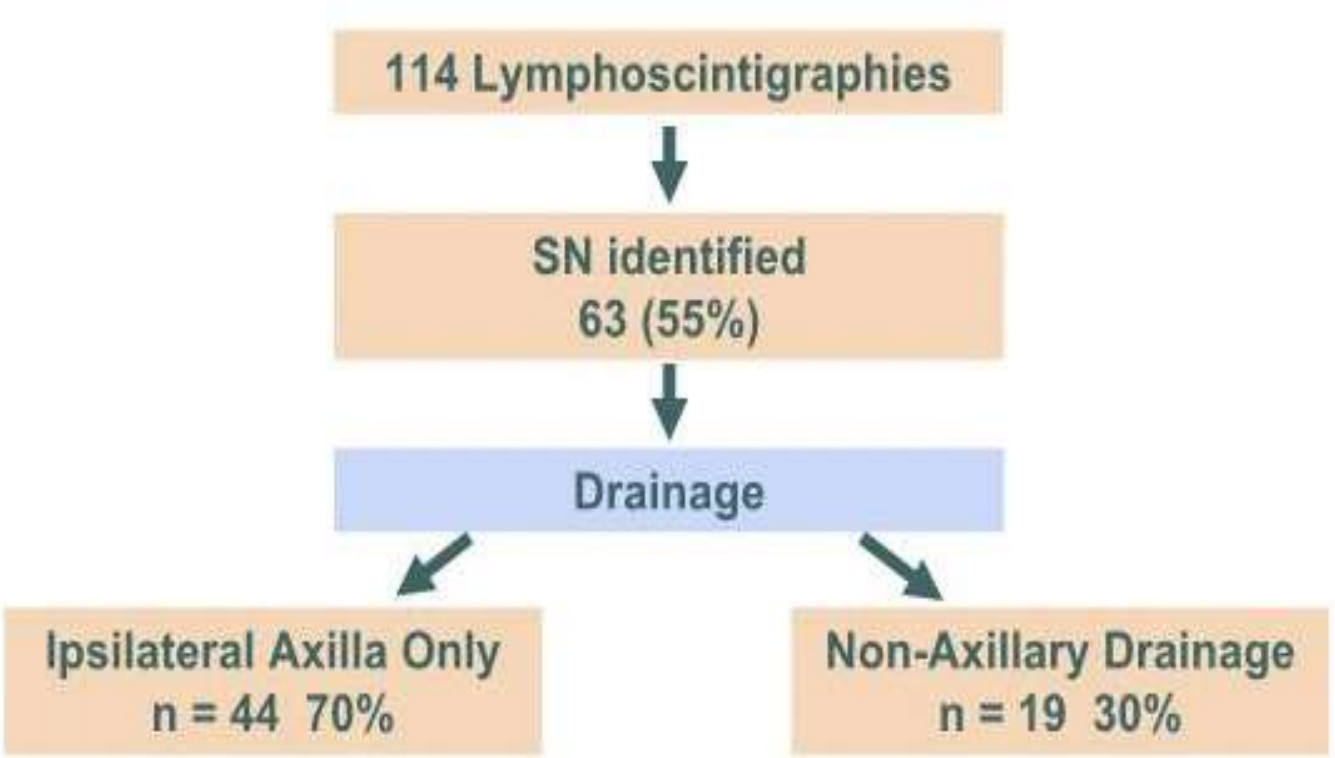
Success of Reoperative SN Bx

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%

Port E Ann Surg Oncol 200

Location of Reoperative SNs



Port E Ann Surg Oncol 2007

Extra axillary drainage in reop SN Bx

N 19	
Internal Mammary	11/19
Controlateral	5/19

Port E Ann Surg Oncol 200

Reoperative SN Bx for LRBC
Systematic Review

N = 692 pts (2002-2011)

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

Maaskant-Braat A Breast Can Res Treat 2013

Reoperative SN Bx for LRBC
Systematic Review

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	N 496 66% (61-70)	NS
Mastectomy	N 45 69% (53-81)	

Maaskant-Braat A Breast Can Res Treat 2013

Aberrant Drainage Pathway

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

Maaskant-Braat A Breast Can Res Treat 2013

Aberrant Drainage Pathway

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

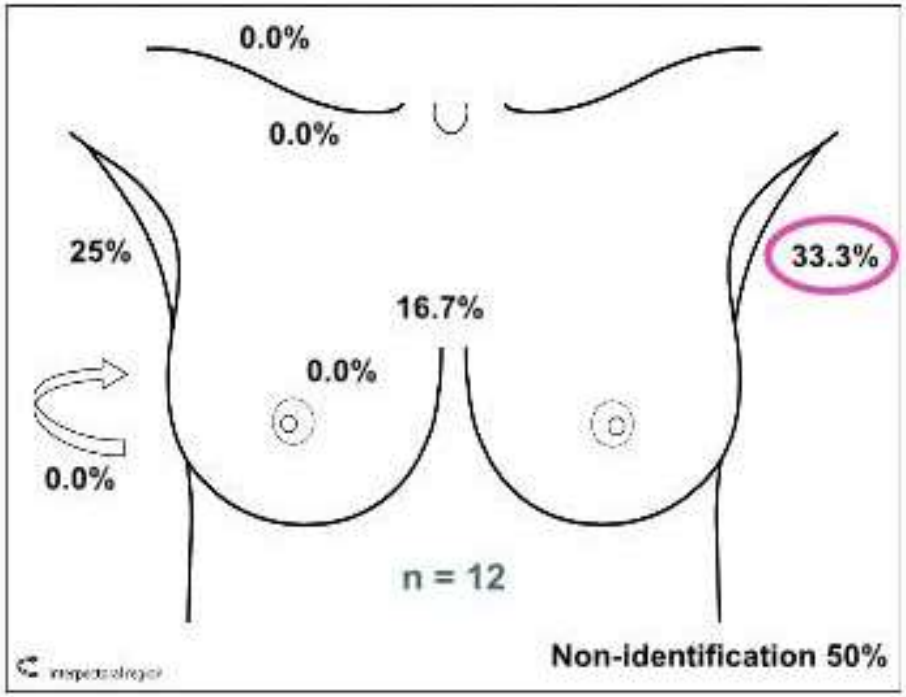
19/69 SN metastases in aberrant drainage pathways

Maaskant-Braat A Breast Can Res Treat 2013

What do Controlateral Axillary mets mean?

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

Lymphatic Drainage after BCT with ALND



Van der Ploeg I, Ann Surg Oncol 2010

Take home Msg

Managment breast – axilla

- An SN can be identified in the majority of pts who had initial SN Bx (81%) and in 50% of those with ALND
- 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 drainge common-this has implicatiob for mapping technique

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

Villa J J Surg Oncol 2014

Systemic Rx

Systemic Rx after LRR

Outcoms after LRR is variable

NASBP 06 : no diff OS Lump vs Mast. @ 20yrs FU
Notwithstanding highr rate of IBTR/LRR in Lump alone.

5 recent NSABP trials: cumulative IBRT and the effect on the risk
distant disease and death in NP+ve treated with Lump+RT+adj R

N 2669 pts> LRR 424 (15.9%)

Is there any diff b/w IBTR vs. oLRR ?

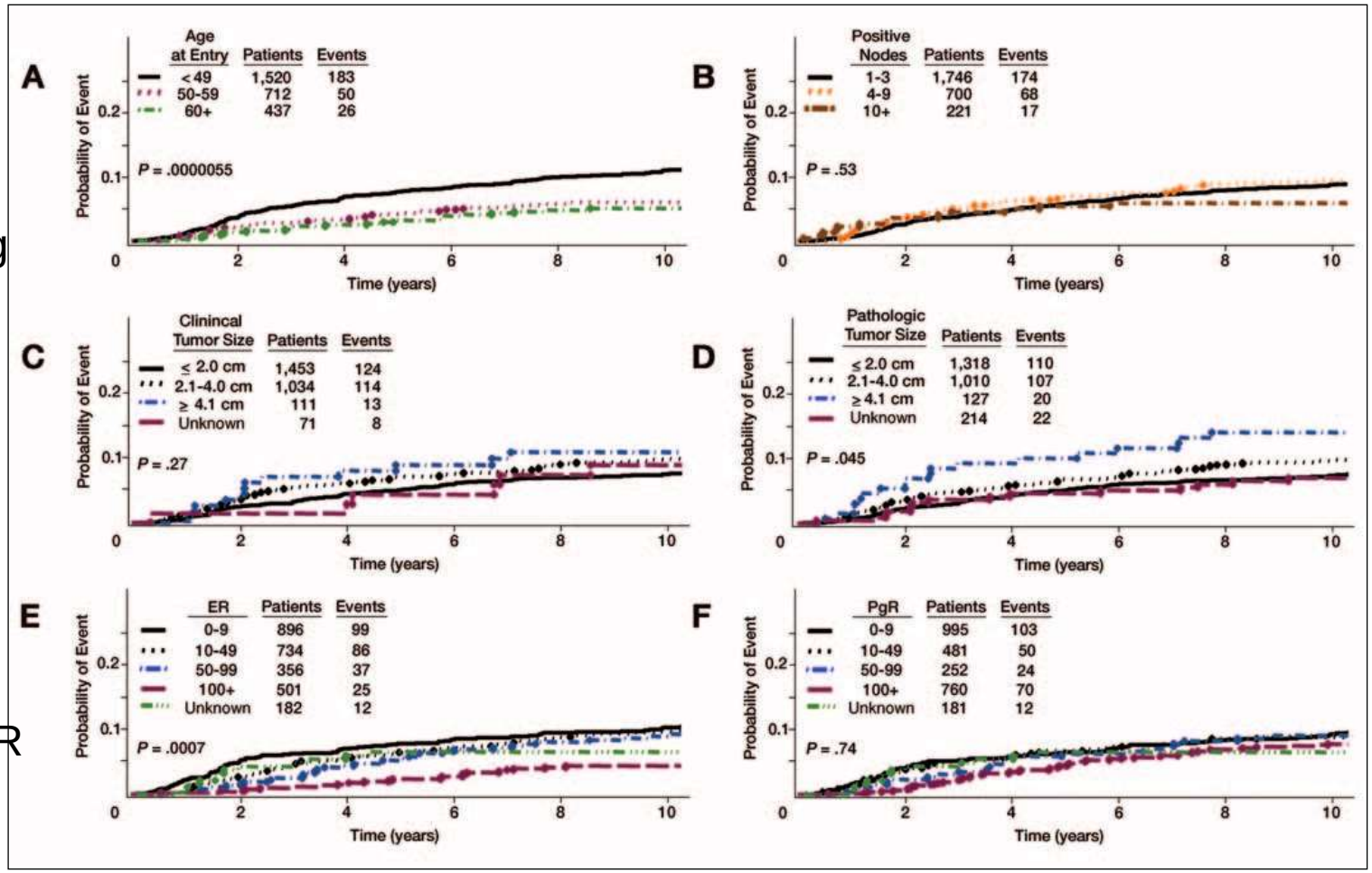
10-yr incidence of IBTR (NP)

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

Young

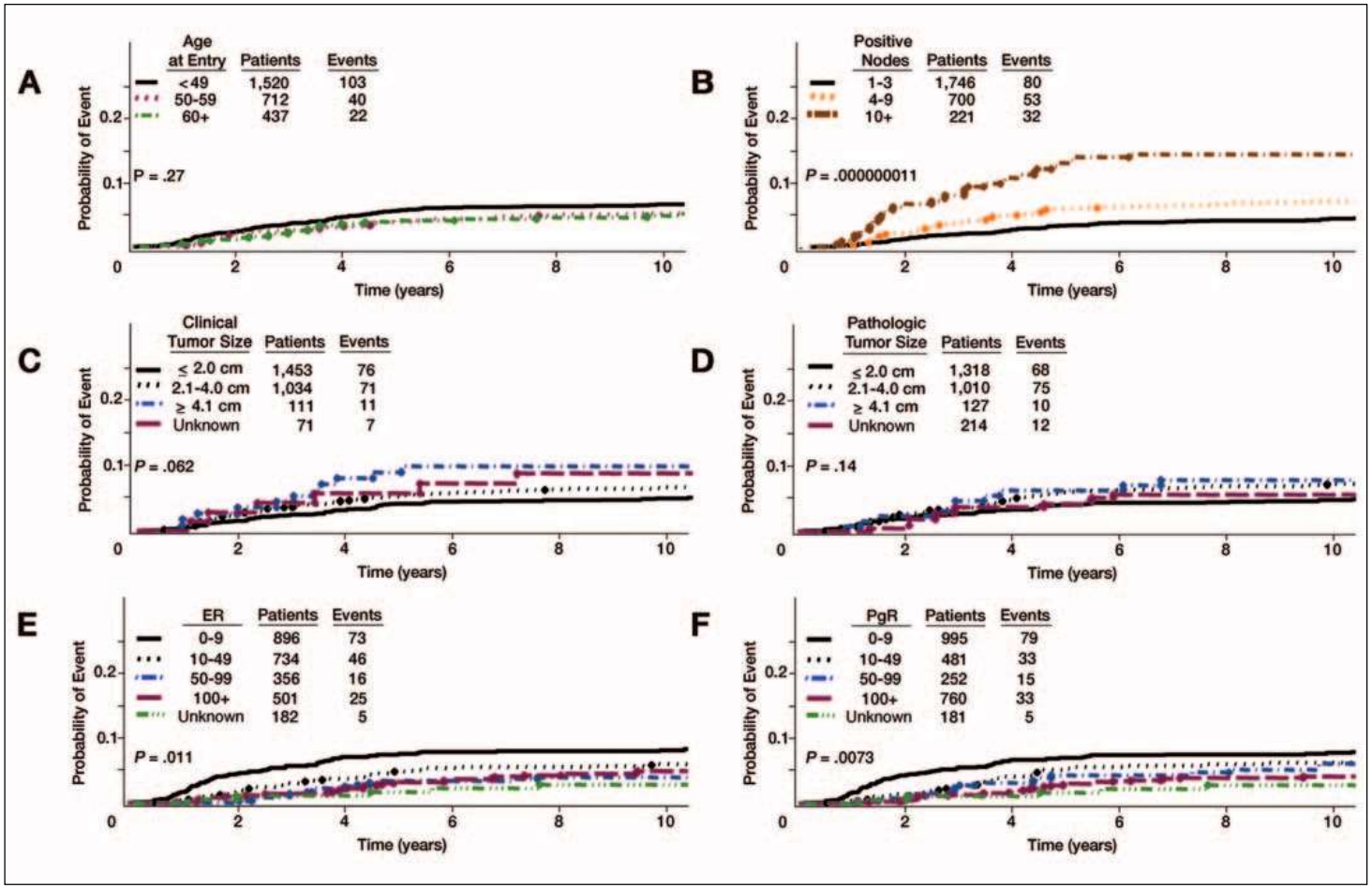
Poor ER

Large T



Wapnir JCO 2006

10-yrs incidence of other LLR (NP)
Lumpectomy pts across NSABP trials (B15,16,18,22,25)



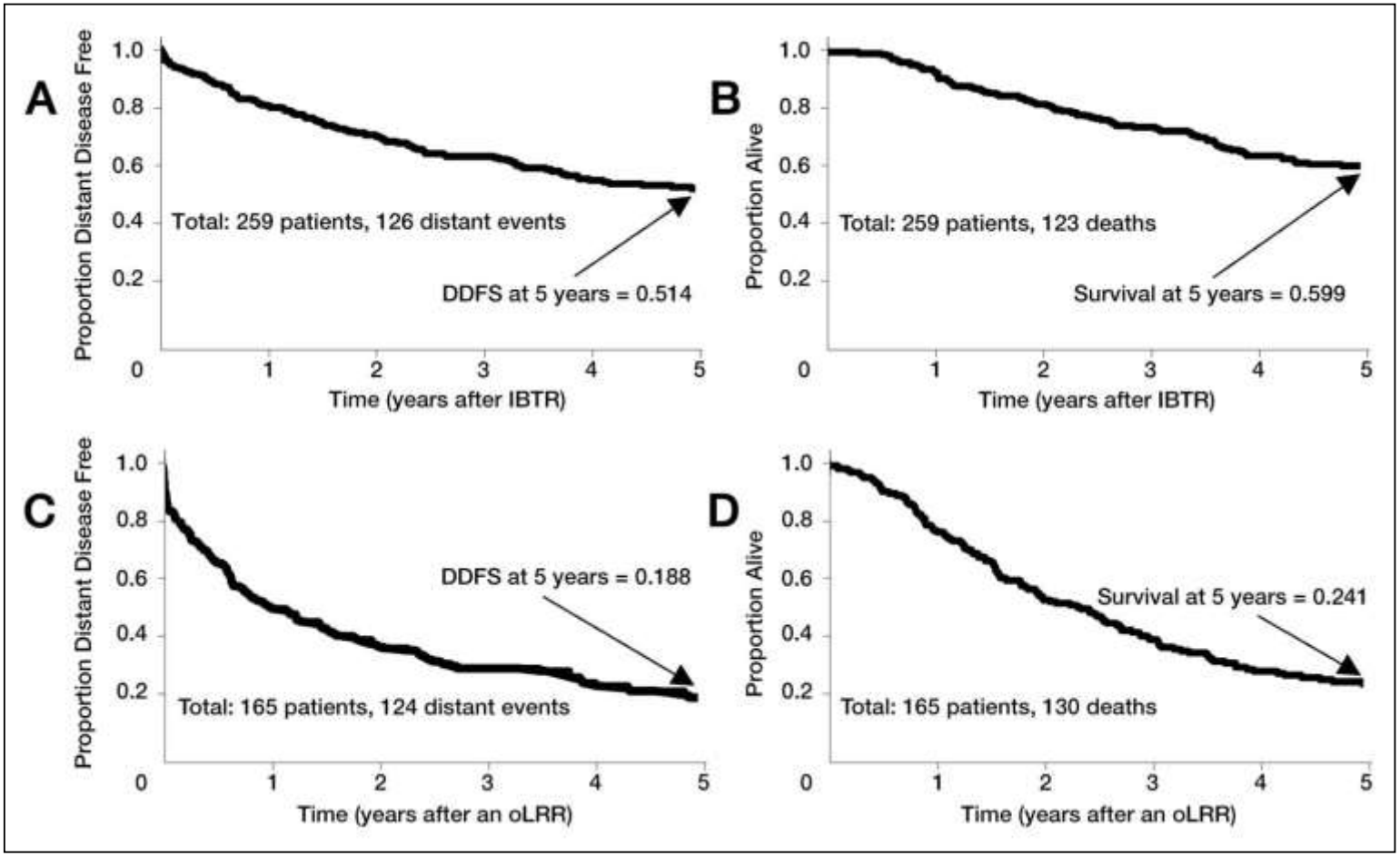
More N

Poor ER

Poor PgR

Wapnir JCO 2006

NSABP experience (5 trials)



Outcomes after incidence IBTR and oLRR

The time of LRR matters (<5yrs vs

Wapnir JCO 2006

Few direct evidences for LRR Rx

What data exist for systemic Rx following LRR

NOT MUCH

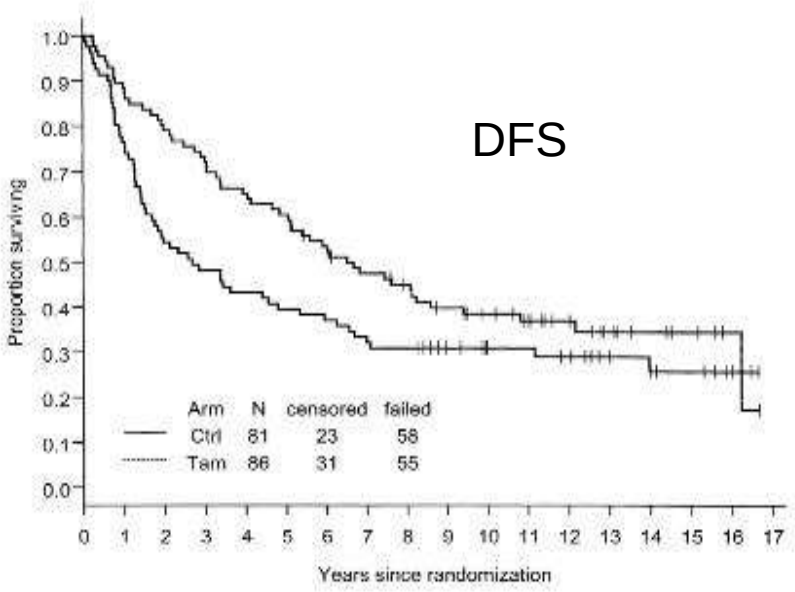
RCT in Rx of LRR

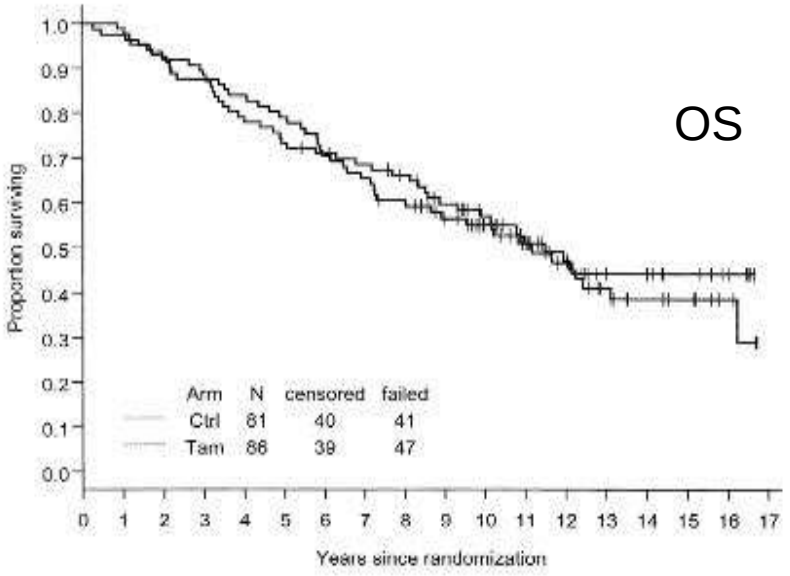
4 trials of adj systemic therapy have been reported

- Olsen (1971): Actinomycin D N: 32
- Fentoman (1993): Alpha IFN N:32
- SAKK (1991): Tam N: 178
- Calor (2010): Chemotherapy N: 162

SAKK 23/82

N 167





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

Waeber M, Ann Oncol 2003

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

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.

Wapnir ASCO 2017

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

Wapnir ASCO 2017

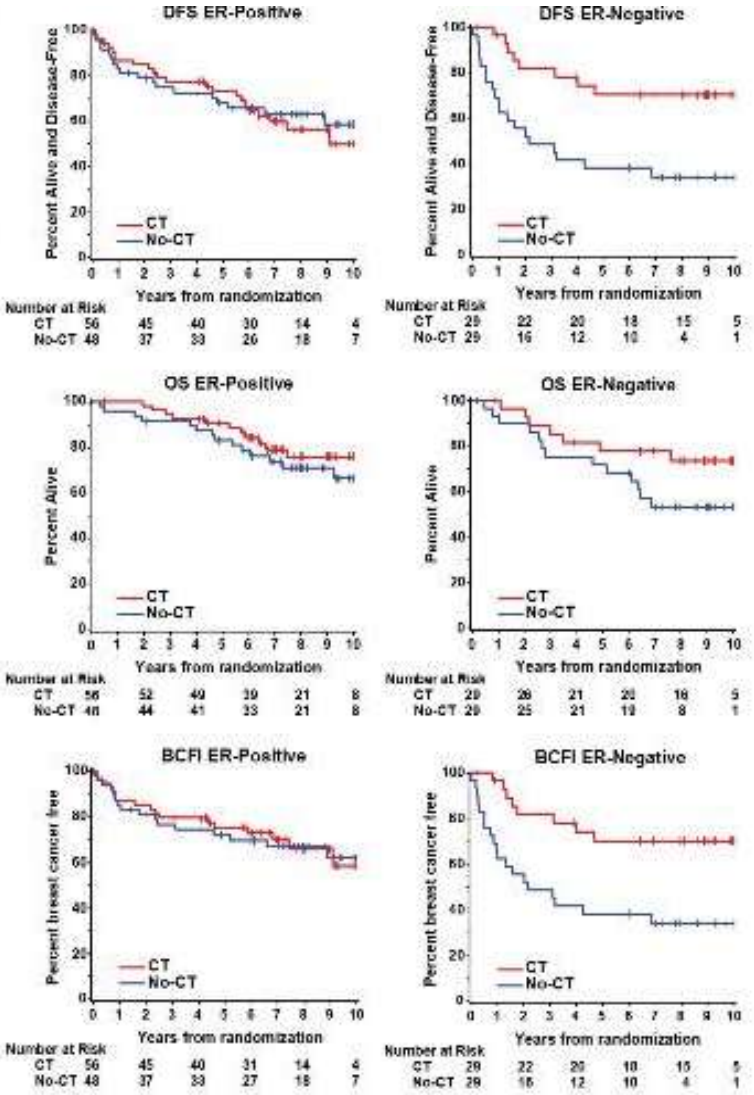
Baseline Characteristics

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%)	

Wapnir ASCO 201

Survival by ER expression

50% vs 59%



70% vs 34%

73% vs 53% NS

Wapnir ASCO 2017

Survival by ER expression

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

	ER-positive			ER-negative		
Endpoint	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			

Wapnir ASCO 2017

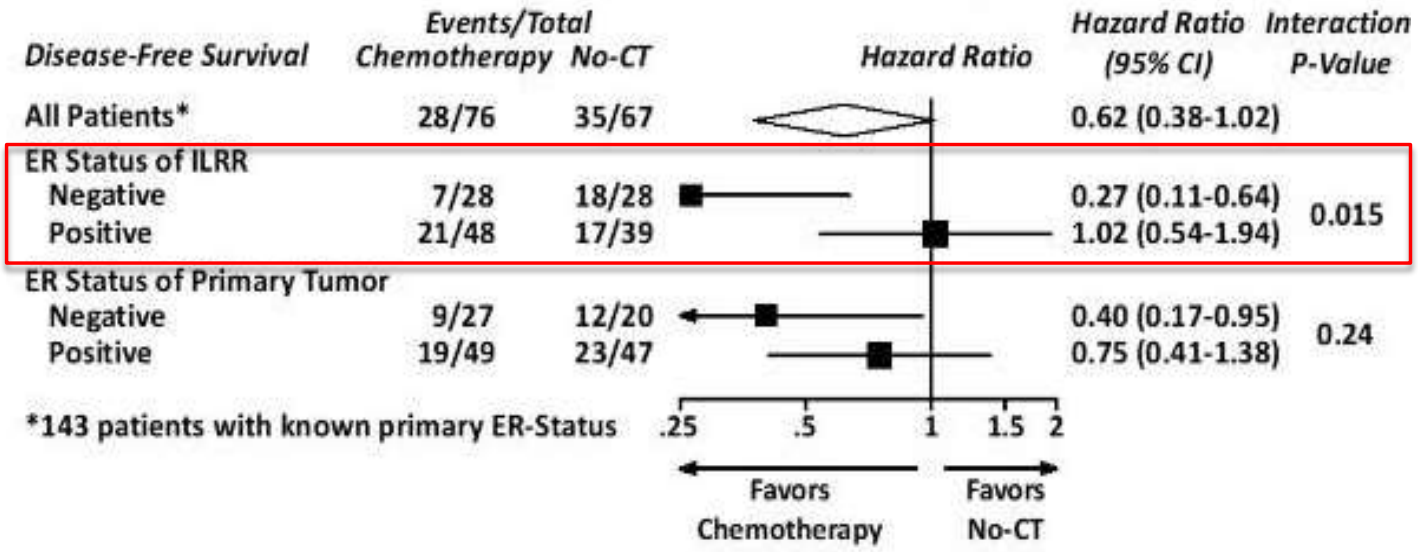
Multivariate Model of DFS

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)	

Wapnir ASCO 2017

CT effect by ER Status in primary or in IRLL

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



Wapnir ASCO 2017

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
- ✓ HER2 +ve rec: HER2 TT

  (<5% od pts in CALOR received antiHER2 adj Rx)
- ✓ TNBC rec: CT

- ✓ Duration ? (switch ?)
- ✓ Duration ?
- ✓ Which type of CT ?