

**RADIOTERAPIA IN ALTERNATIVA  
ALLA CHIRURGIA IN PRESENZA  
DI LINFONODO SENTINELLA  
POSITIVO**

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REIMS**

**4<sup>e</sup> INCONTRO ITALO-FRANCESE SUL CARCINOMA MAMMARIO**

**ASSISI 23-24 NOVEMBRE 2013**

**\* L'invasione linfonodale (pN+) resta a tutt'oggi il primo fattore di rischio di ricaduta locoregionale e a distanza**

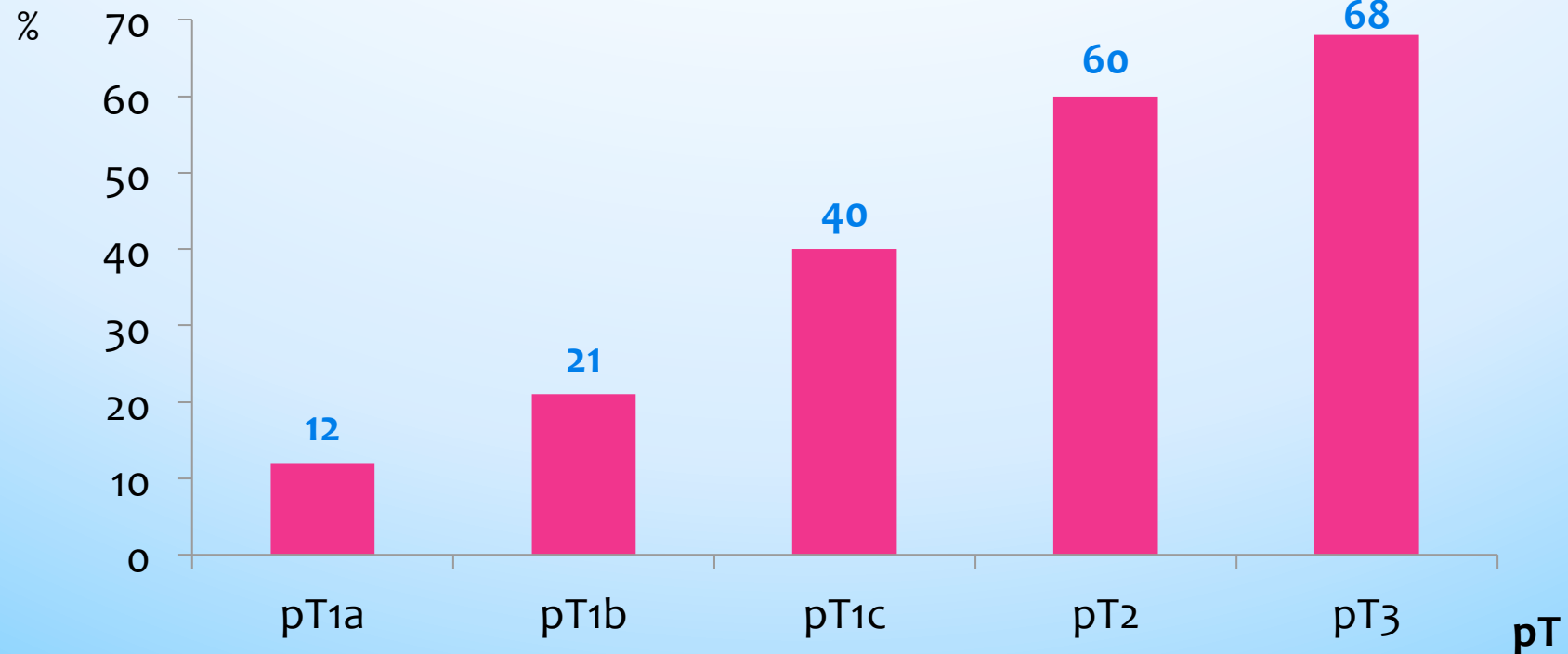
**\* Diversi fattori influenzano il rischio d'invasione linfonodale ascellare:**

- Il diametro tumorale
- Il grading SBR
- La presenza di emboli
- La topografia
- La multicentricità
- Anche in caso di assenza di linfonodi palpabili, un'invasione (pN+) è presente nel 30-40% dei casi

# AXILLARY NODAL INVOLVEMENT (ANI) ACCORDING TO pT

FRENCH SURVEY RESULTS (1024 PTS)

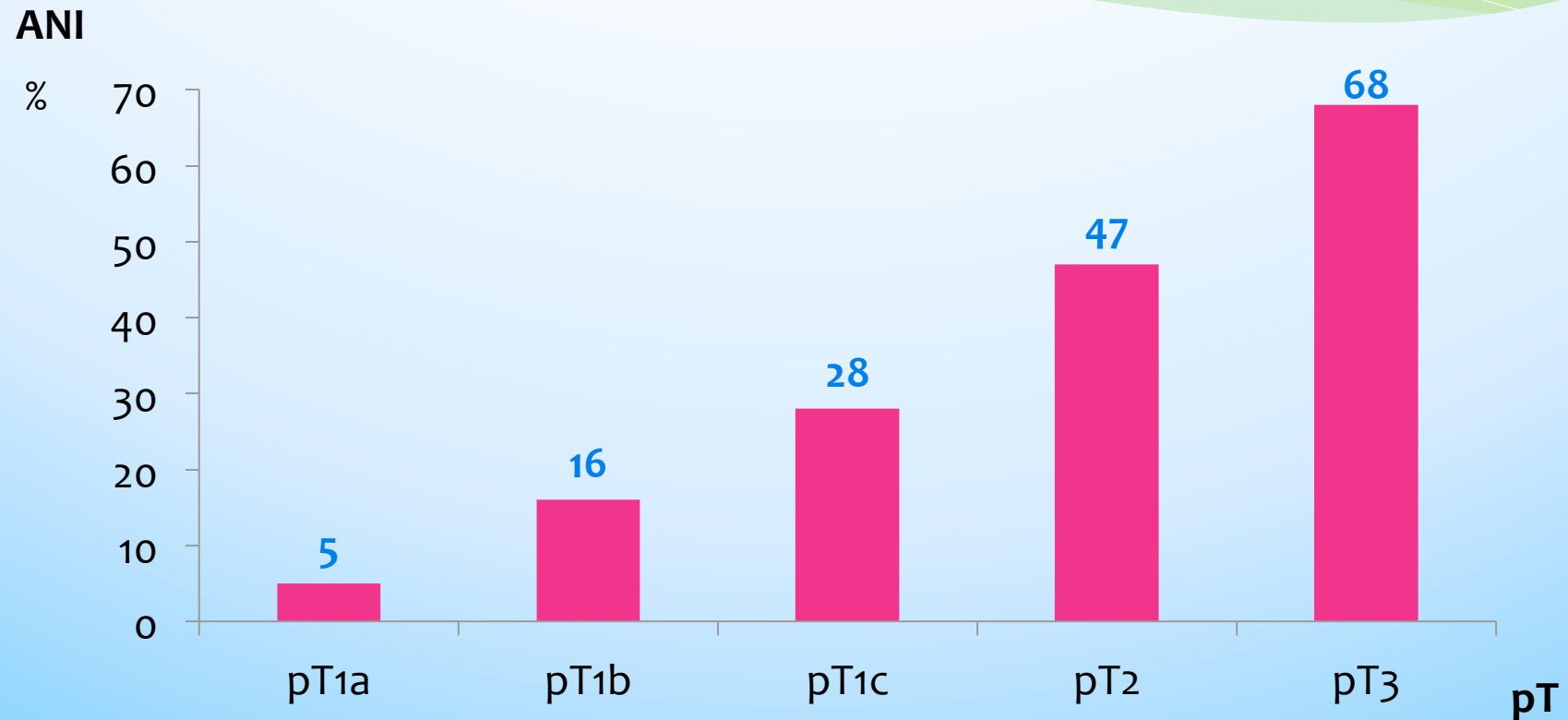
2001-2002  
ANI



Réf: CUTULI BRCT 2006, 95: 55-64

# AXILLARY NODAL INVOLVEMENT (ANI) ACCORDING TO pT

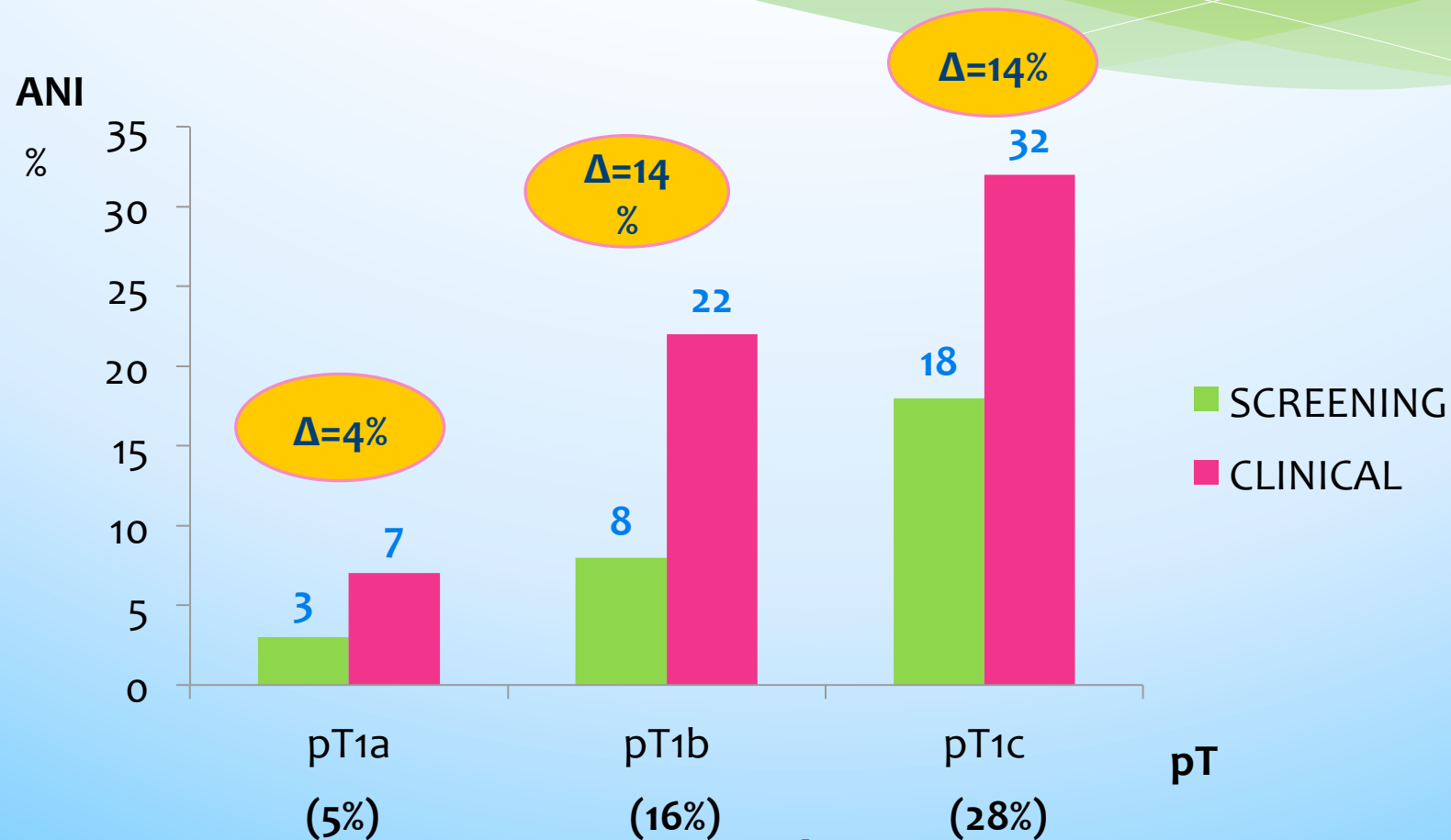
VAN NUYS GROUP RESULTS (1891 PTS)



Réf: SILVERSTEIN WORLD J S 2001, 25: 767-772

# AXILLARY NODAL INVOLVEMENT (ANI) INFLUENCE OF SCREENING

VAN NUYS GROUP RESULTS (1891 PTS)



# **VALORE « CURATIVO » DELLA DISSEZIONE ASCELLARE (DA): MOLTO DISCUSO IN LETTERATURA+++**

- **E stabilito che una DA con  $\geq 10$  linfonodi prelevati permette un controllo ascellare nel 97-98% dei casi**
- **Alcuni studi concludono a un impatto della qualità della DA sulla sopravvivenza...**
- **La prognosi delle recidive ascellari è sfavorevole**

**THE IMPACT OF PROPHYLACTIC AXILLARY NODE  
DISSECTION ON BREAST CANCER SURVIVAL  
A BAYESIAN META-ANALYSIS**

*ORR RK Ann Surg Oncol 1999, 6: 109-106*

**Evaluation of 6 trials:**



*survival by 5.4% with AD*

# PROGNOSI DELLE RECIDIVE ASCELLARI (I)

**STUDIO DI BOSTON**

*GRILLIS IG, IJROBP 2003, 56: 658-70*

**Analisi di 1293 pazienti trattate con CC+RT (STADIO I-II)**

- ➔ **21 REC. ASCELL. (1.6%)**
- ➔ **SOPRAVVIVENZA A 10 ANNI : 44%**



# PROGNOSI DELLE RECIDIVE ASCELLARI (II)

## STUDIO DI STRASBURGO

*QUETIN P, Presse Med 2001, 30: 996-1000*

Analisi di 1119 pazienti trattate con CC+RT (STADIO I-II)

➔ 16 REC. ASCELL. (1.4%)

➔ 60 % DI DECESSI

**\* DA una quindicina d'anni, il linfonodo sentinella (LS) ha progressivamente rimpiazzato la DA, diminuendo considerevolmente le complicanze:  
(dolori /limitazione funzionale del MS / linfedema)**

**\* Dopo i risultati del trial NSABP B-32 e dello studio dell'IEO è stata confermata l'efficacia della tecnica, evitando così la DA per le pazienti con LS-**

**\* Si pone ora il problema per i LS+: quale alternativa??**

 **chirurgia?**

 **radioterapia?**

 **sorveglianza?**

# PROBLEMATICHE DEL LS+: CASO DEI pNoi+

➤ **Rischio di malattia ascellare residua:**

**STUDIO DI C. VAN DEURZEN** *JNCI 2008, 100: 1574-80*

Analisi di 29 articoli (2002-2007) con 836 pazienti pNoi+

\* rischio di N+ residuo: 12.3% (9.5%-15.7%)

**STUDIO MULTICENTRICO FRANCESE HOUVENAEGHEL G**

*JCO 2006, 24: 1814-22*

Analisi di 700 casi con micrometastasi (388: HE/312: IC)

\* Residuo N+: 13.4%

# FATTORI PREDITTIVI DI MALATTIA RESIDUA

- T2 vs T1
- ca. Duttale vs lobulare
- SBR<sub>3</sub> vs SBR<sub>1-2</sub>
- Presenza di emboli vascolari
- Ratio LS+/LS prelevati
- Recettori ormonali negativi

# RISCHIO DI RECIDIVA ASCELLARE

**STUDIO MULTICENTRICO OLANDESE**

*PEPELS MJ Ann Surg 2012, 255: 116-121*

**Recidive locoregionali senza trattamento ascellare (43%)**

**A 5 anni:**

857 pNo: 2.3%

795 pNoi+: 2%

1028 pN1mic: 5.6%

**Con RT o DA (57%): 0.9%**

# **DIFFICOLTA DI ANALISI (I) DEGLI STUDI CON LS+ (pN1mi)**

- **Variazioni importanti dell' incidenza di micrometastasi (3-25%)**

**(selezione dei pazienti? / metodologia di analisi? / divisione fra pN0i+ e pN1mi)**

- **Significato prognostico controverso fra pN0 et pN1mi/ pN0i+**

**(trattamenti locali e sistemici diversi ++)**

- **Molte serie con piccoli numeri di pazienti**

## DIFFICOLTA DI ANALISI (II) DEGLI STUDI CON LS+ (pN1mi)

➤ Risultati discordanti sulla prognosi:

**JOHN WAYNE CANCER INSTITUTE**

*HANSEN NM, JCO 2009, 27: 4679-88*

\* DFS and OS # for pNo / pNoi+ / pN1mi

**SWEDISH MEDICAL CENTER-SEATTLE**

*PUGLIESE MS, Ann Surg Oncol 2009, 16: 113-20*

\* DFS and OS # for pNo / pNoi+ / pN1mi

# MIRROR TRIAL: MICROMETASTASES OR ISOLATED TUMOR CELLS AND THE OUTCOME OF BREAST CANCER

DE BOER M NEJM 2009, 361: 653-663

3 cohorts:

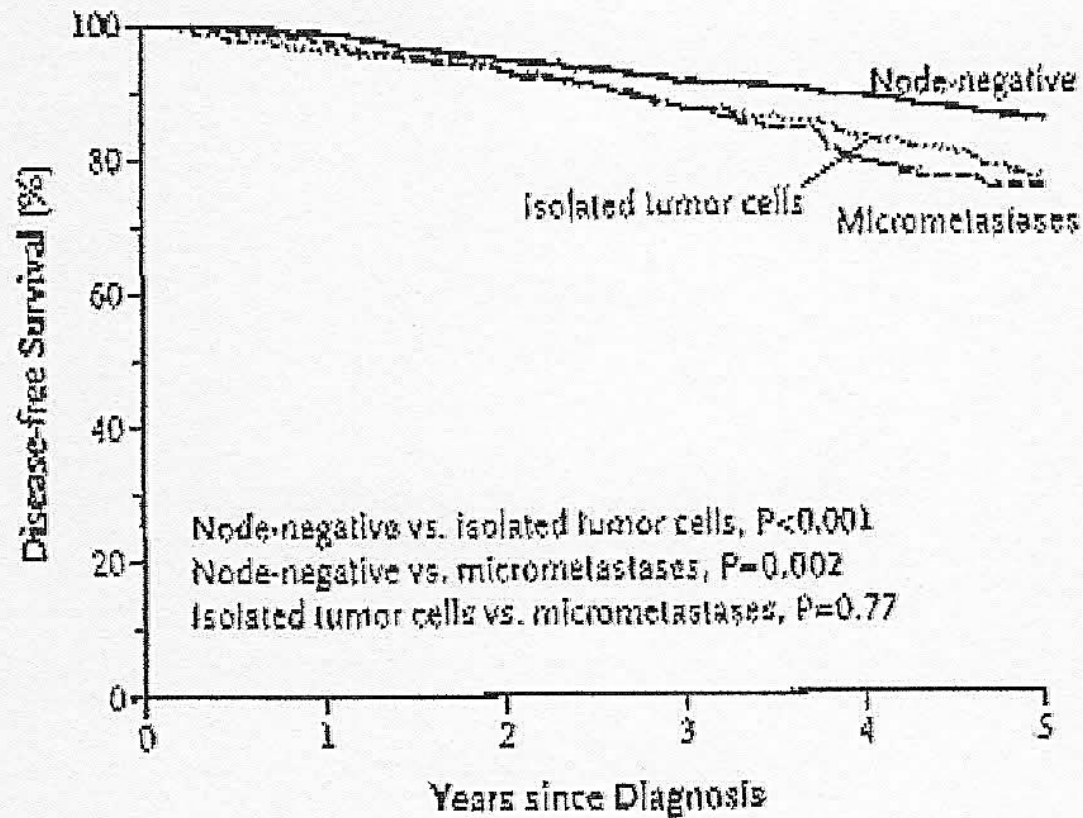
856 pts	pNo	<i>without systemic therapy</i>
856 pts	pNi+/pN1mic	<i>without systemic therapy</i>
995 pts	pNi+/pN1mic	<i>with systemic therapy</i>

Median fu: 5y

BCS  $\simeq$  70%    MASTECTOMY  $\simeq$  30%



# DISEASE-FREE SURVIVAL



No. at Risk						
Node-negative	856	838	800	761	722	628
Isolated tumor cells	513	493	453	367	282	199
Micrometastases	343	330	301	222	142	76

## MSKCC STUDY

*MILGROM S, Ann Surg Oncol 2012, 19: 3762-7*

SN+ after total mastectomy without axillary-specific treatment

533 patients treated between 1997 and 2009

\* 210 TM  
\* 325 BCS } SN+ without ALND

BCS: 90% RT

TM: 5% RT

FU: 58 months

4-y locoregional failures:

{ 2.9 (TM)  
2.4 (BCS)

## **ALLORA, COSA PROPORRE??**

➤ **Completing or not axillary treatment in pN1mi patients: a growing dilemma**

**... The recent literature suggest... an empirical but clear trend toward omitting ALND in pN1mi patients...**

***(SEER DATABASE / IEO EXPERIENCE)***

➤ **AXILLARY IRRADIATION in pN1mi patients: where to go from here?**

**... As the role of completion of ALND after SLNB is « de facto » fading, it is legitimate to question the real impact of axillary irradiation on treatment outcome in pN1mi patients ...**

***J BERNIER The Breast 2011, 20: 385-8***

# RAZIONALE (I)

- La radiotherapia ascellare (RT AXILL.) permette un buon controllo locale con limitati effetti secondari:

**NSABP B-04: (1971- 1974)**

MASTECTOMIA + R



DA



RT AXILL.

REC. AXILL= 4% (IDEM)

DFS e DSS= (IDEM)

*Réf: FISHER B, 2002 NEJM 347: 567-575*

## ESPERIENZA DELL'ISTITUTO CURIE

658 pazienti  $T_1T_2 \leq 3\text{cm}$  No trattate dal 1982 al 1987

Randomizzazione

A 15 anni tassi di rec. Axill

DA

RT AXILL

DA 1%

RT 3%

MA SOPRAVVIVENZA IDENTICA: 75%

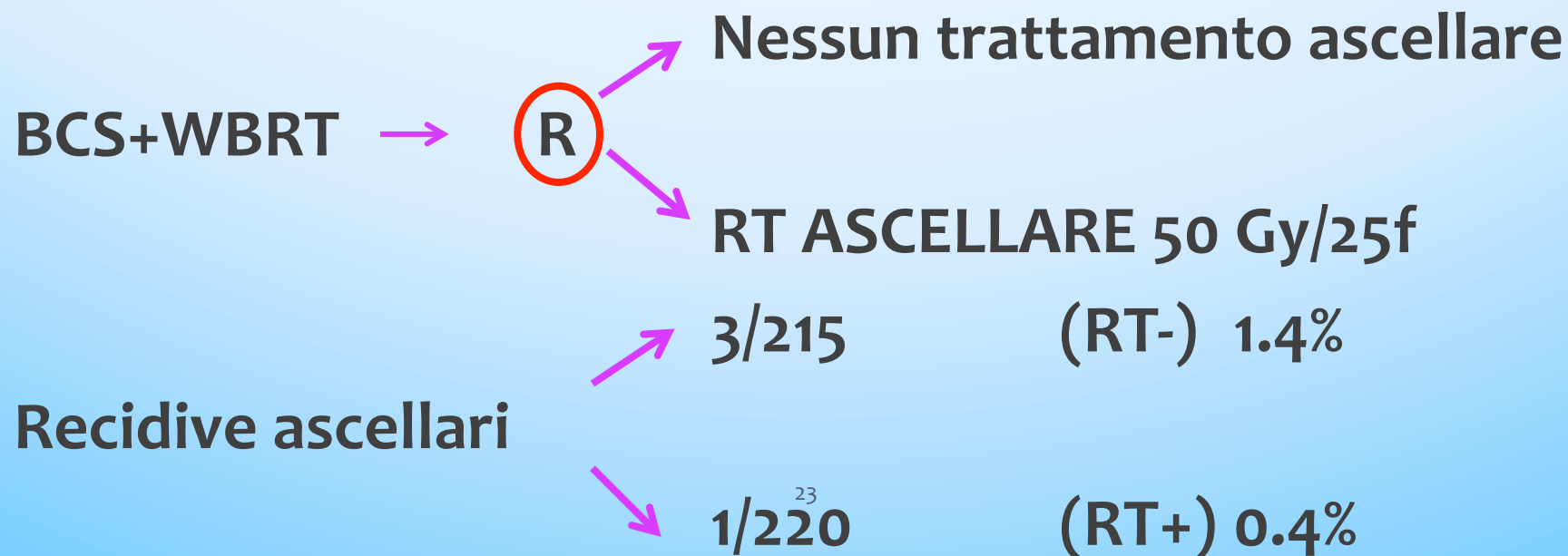
Réf: LOUIS-SYLVESTRE JCO 2004, 22: 97-101

# RADIOTERAPIA O DISSEZIONE ASCELLARE? TRATTAMENTI EQUIVALENTI?

## STUDIO DELL IEO

*VERONESI U Ann Oncol 2005, 16: 383-388*

Analisi di 435 pazienti T1No di > 45 anni (1995-1998)



## **EORTC AMAROS TRIAL**

**RADIOTHERAPY OR SURGERY OF THE AXILLA AFTER A  
POSITIVE SENTINEL NODE IN BREAST CANCER  
PATIENTS...**

***E RUTGERS ON BEHALF EORTC BREAST CANCER GROUP***

***ASCO 2013***



# Hypothesis

Axillary radiotherapy provides local control and survival comparable to ALND with fewer side effects in women with a positive axillary SN

*E RUTGERS ON BEHALF EORTC BREAST CANCER GROUP ASCO 2013*

# Eligibility Criteria

## Inclusion

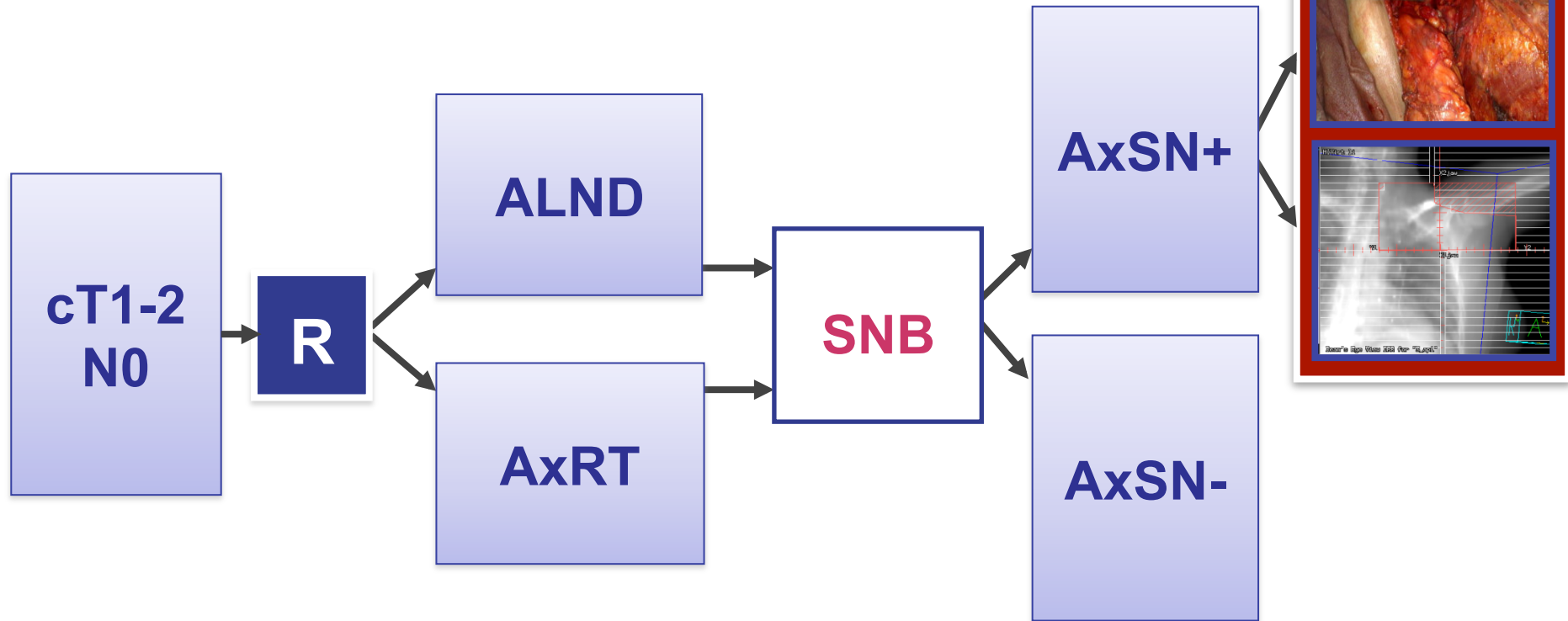
- Invasive breast cancer 0.5-5 cm
- Clinically N0
- BCT or mastectomy
- Any age
- Informed consent

## Exclusion

- Multicentric disease
- Neoadjuvant systemic treatment
- Previous axillary treatment
- Prior malignancy

*COURTESY OF E RUTGERS*

# Trial design



Stratification: institution  
Adjuvant systemic therapy by choice

*COURTESY OF E RUTGERS*

# Objectives

**Primary:** To demonstrate non-inferiority in axillary recurrence rate

**Secondary:**

1. To compare overall survival (OS) and disease-free survival (DFS)
2. To compare lymphedema, shoulder function and Quality of Life (QoL)

# Endpoints and statistical design

Primary: 5-years axillary recurrence free rate

**Non inferiority hypothesis (design):**

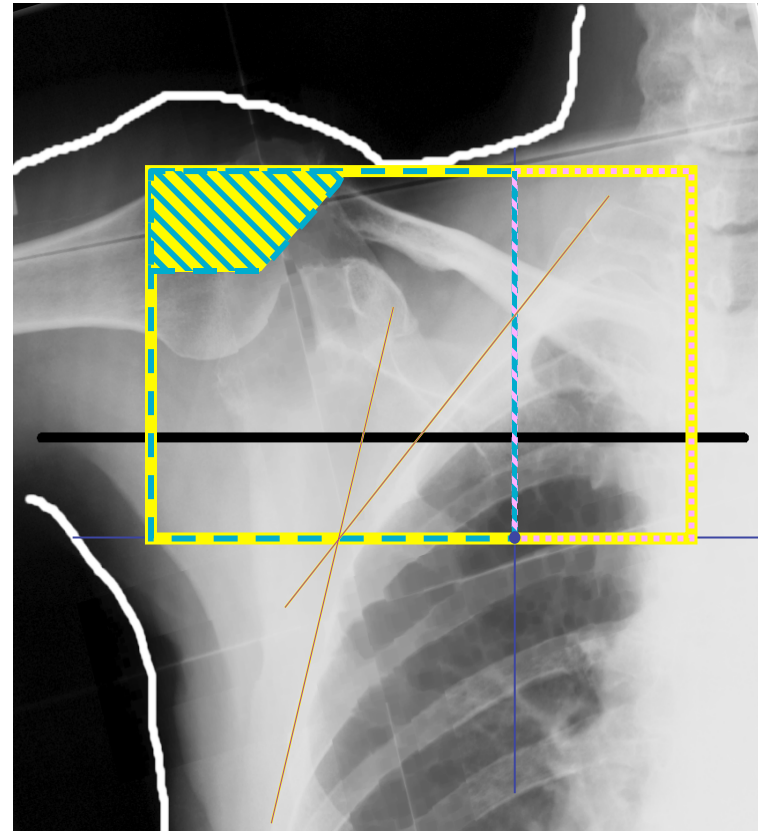
- assumption: ALND 98%; AxRT >96%
- one-sided log-rank; alpha = 0.05; power = 80%
- 52 events needed

Secondary:

- **Efficacy**: OS and DFS
- **Safety**: shoulder function, lymphedema, QoL

# AxRT

- **Timing:**  
Start < 12 weeks after SNB
- **Extent:**  
level I + II + III + medial SC
- **Dose & schedule:**  
25 x 2 Gy or equivalent
- **Quality control:**  
dummy run



*Hurkmans et al, Radiother Oncol 2003*

# ALND

- **Timing:**  
< 12 weeks after SNB
- **Extent:**  
Level I + II mandatory  
Level III optional
- **Additional AxRT:**  
 $\geq 4$  positive nodes

# Baseline clinical

	<b>ALND (744 pts)</b>	<b>AxRT (681 pts)</b>
<b>Median age (Q1-Q3)</b>	<b>56 (48 - 64)</b>	<b>55 (48 - 63)</b>
<b>Menopausal stage</b>		
pre-menopausal	<b>38.1 %</b>	<b>42.5 %</b>
post-menopausal	<b>57.7 %</b>	<b>54.5 %</b>
<b>Median tumor size (Q1-Q3)</b>	<b>17 mm (13 - 22)</b>	<b>18 mm (13 - 23)</b>
<b>Grade</b>		
1	<b>24.1 %</b>	<b>22.6 %</b>
2	<b>47.8 %</b>	<b>45.7 %</b>
3	<b>25.8 %</b>	<b>29.4 %</b>
<b>Pre-operative ultrasound axilla</b>	<b>59.2 %</b>	<b>61.5 %</b>



# Baseline treatment

	<b>ALND (744 pts)</b>	<b>AxRT (681 pts)</b>
<b>Breast surgery</b>		
BCS	<b>81.9 %</b>	<b>81.8 %</b>
Mastectomy	<b>17.1 %</b>	<b>17.8 %</b>
<b>Systemic treatment</b>		
chemotherapy	<b>60.9 %</b>	<b>61.3 %</b>
hormonal therapy	<b>78.6 %</b>	<b>77.1 %</b>
immunotherapy	<b>6.0 %</b>	<b>6.4 %</b>
no systemic treatment	<b>9.0 %</b>	<b>9.4 %</b>
<b>RT breast/chest wall</b>	<b>84.8 %</b>	<b>87.7 %</b>

# SN results

	ALND (744 pts)	AxRT (681 pts)
Median number of SN removed (Q1-Q3)	2 (1-3)	2 (1-3)
Size of metastases in SN		
macrometastases	59.4 %	61.5 %
micrometastases	28.9 %	28.6 %
ITC	11.7 %	9.8 %

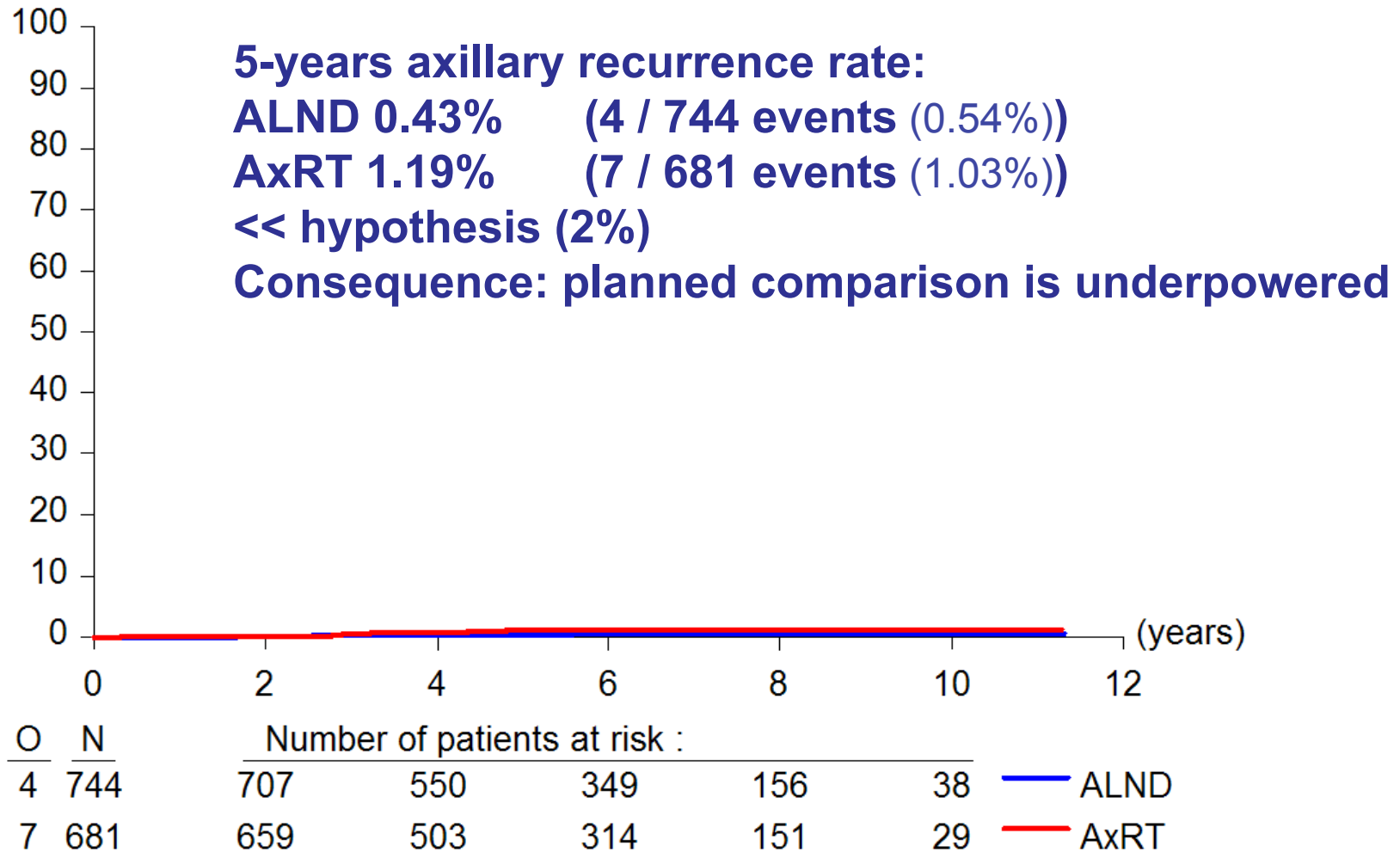
*Straver et al, Ann Surg Oncol 2010*

# ALND results

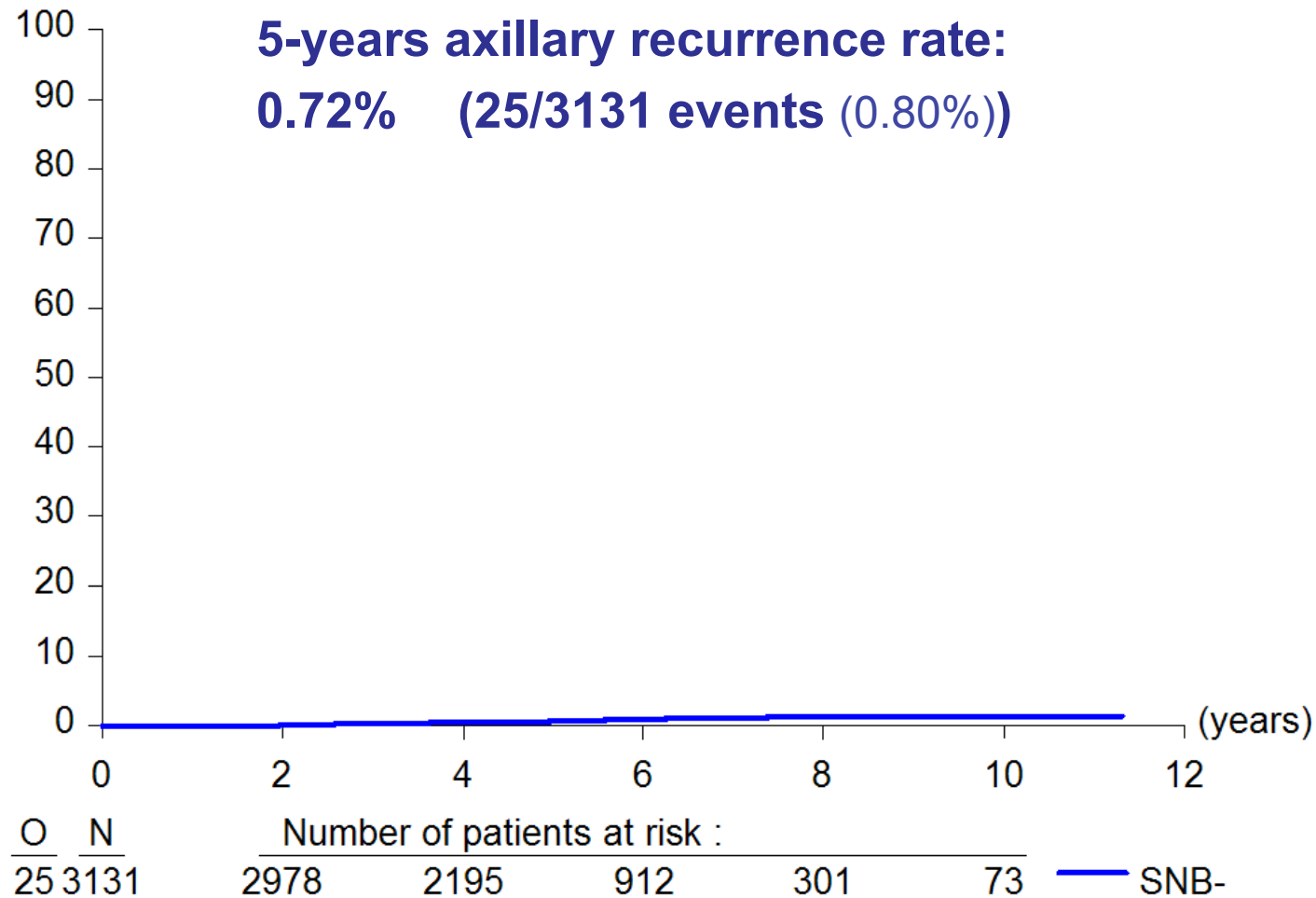
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	ALND (744 pts)
Median number of all nodes removed (Q1-Q3)	15 (12-20)
Number of additional positive nodes (besides SN)	
0	67.1 %
1-3	25.0 %
≥ 4	7.8 %

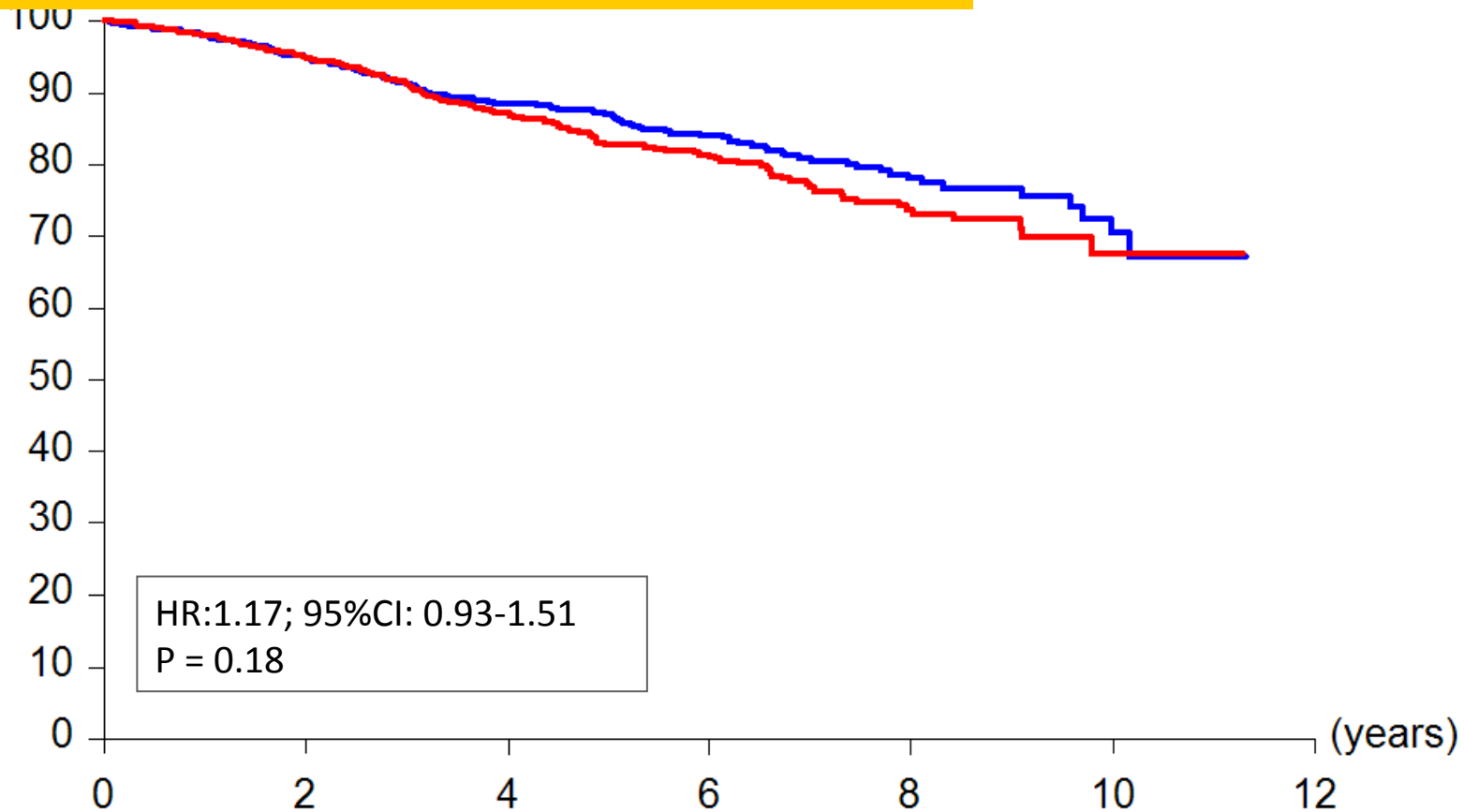
# Axillary recurrence rate



# Axillary recurrence rate SN-

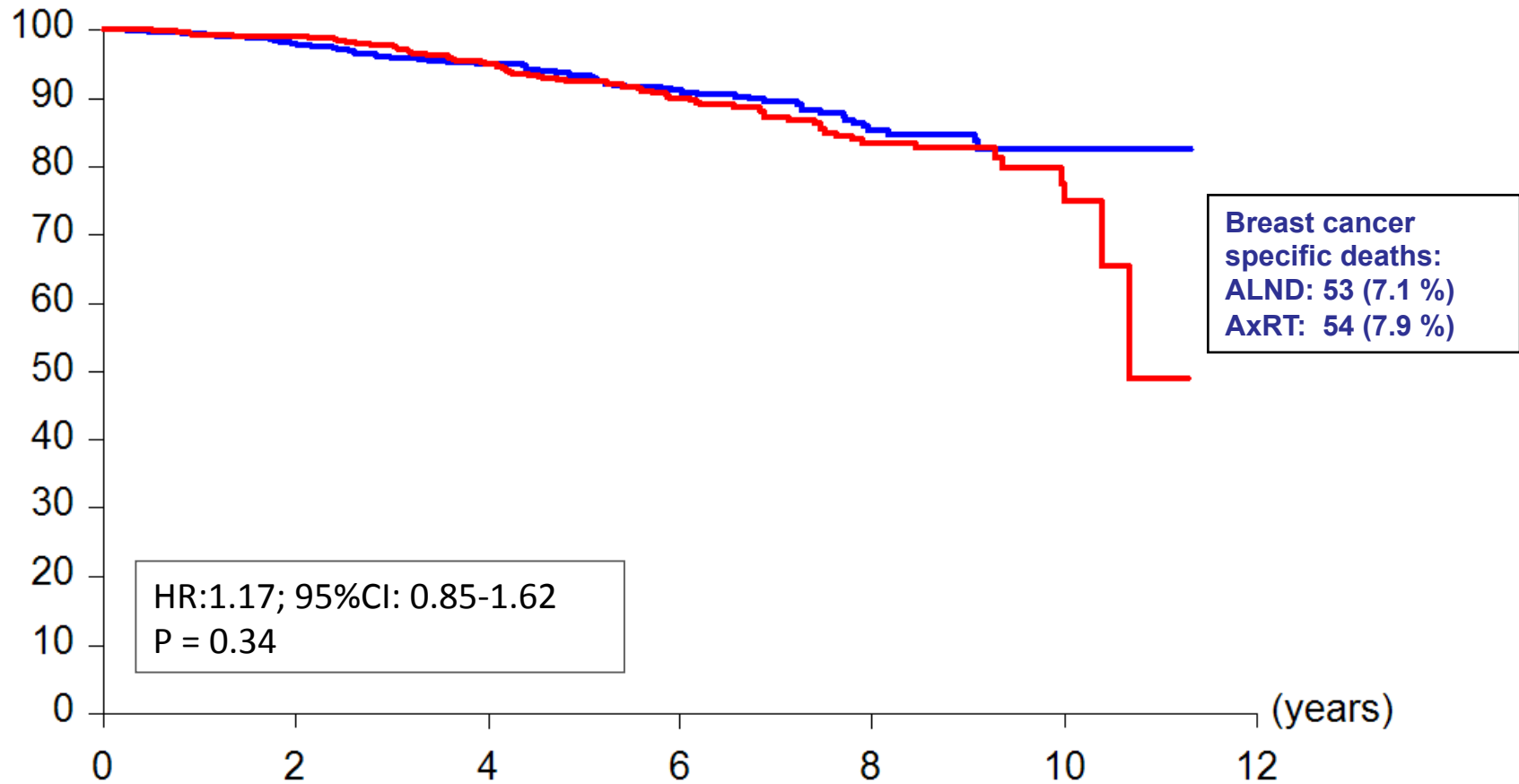


# Disease-free survival



O	N	Number of patients at risk :					
124	744	686	511	322	140	33	— ALND
134	681	633	468	284	131	24	— AxRT

# Overall survival



O	N	Number of patients at risk :					
71	744	708	552	352	157	38	— ALND
76	681	661	505	316	151	29	— AxRT

# RUOLO DEI CAMPI TANGENZIALI PER IL CONTROLLO DELL'ASCELLA:

Alcuni studi hanno confermato un basso tasso di recidive ascellari  
Dopo irradiazione con campi tangenziali:

**NSABP 06** (*FISHER B NEJM 1989, 320: 822-8*)

7.2% vs 4.5% p < 0.01  
(CC vs CC+RT)

**MANCHESTER** (*RIBEIRO G JCO 1990, 2: 27-34*)

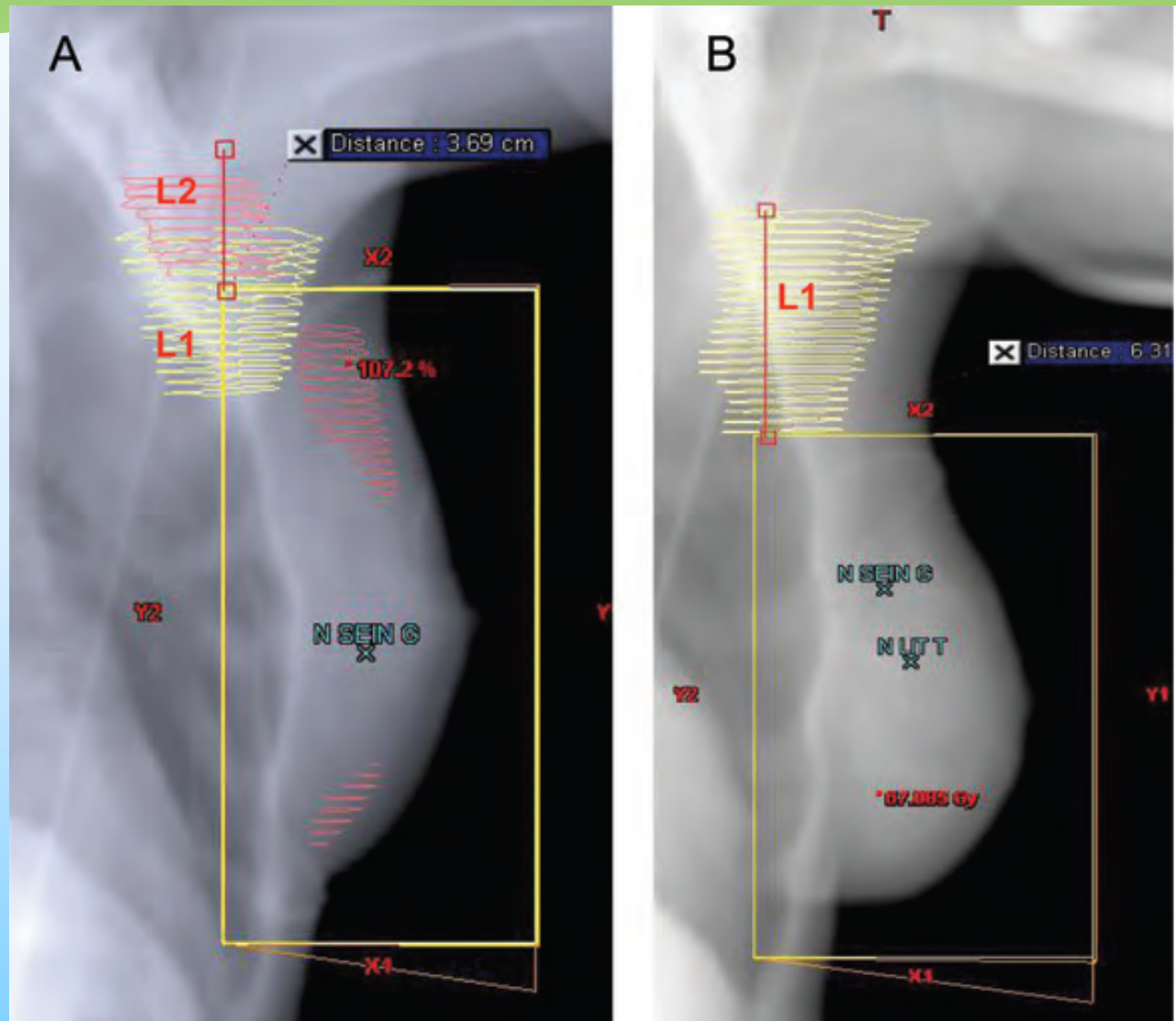
14% vs 4% p < 0.01  
(RT «PARZIALE » vs WBRT)

MA: VECCHI STUDI, CON POCHI TRATTAMENTI SISTEMICI



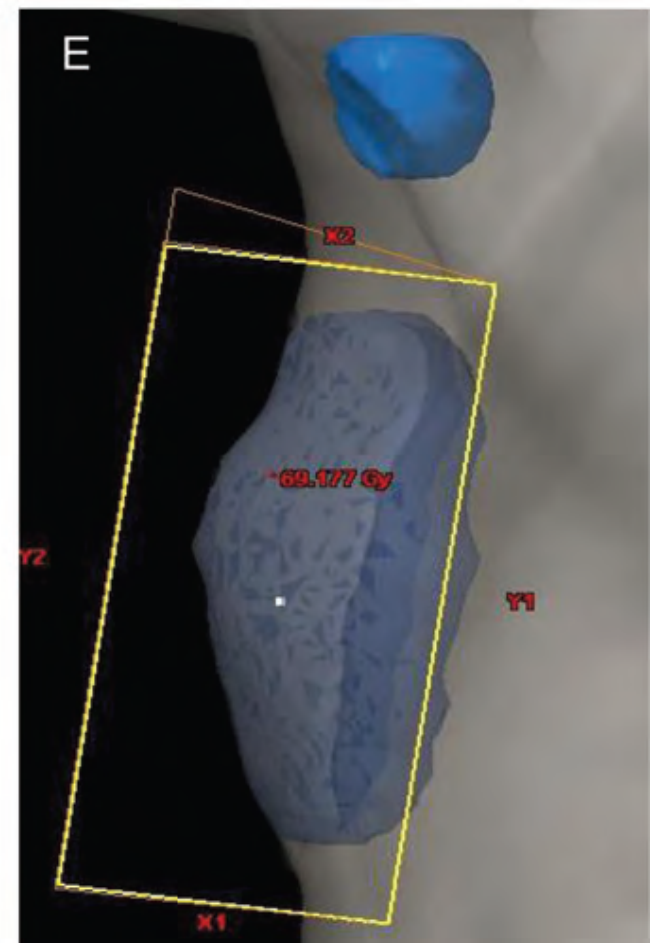
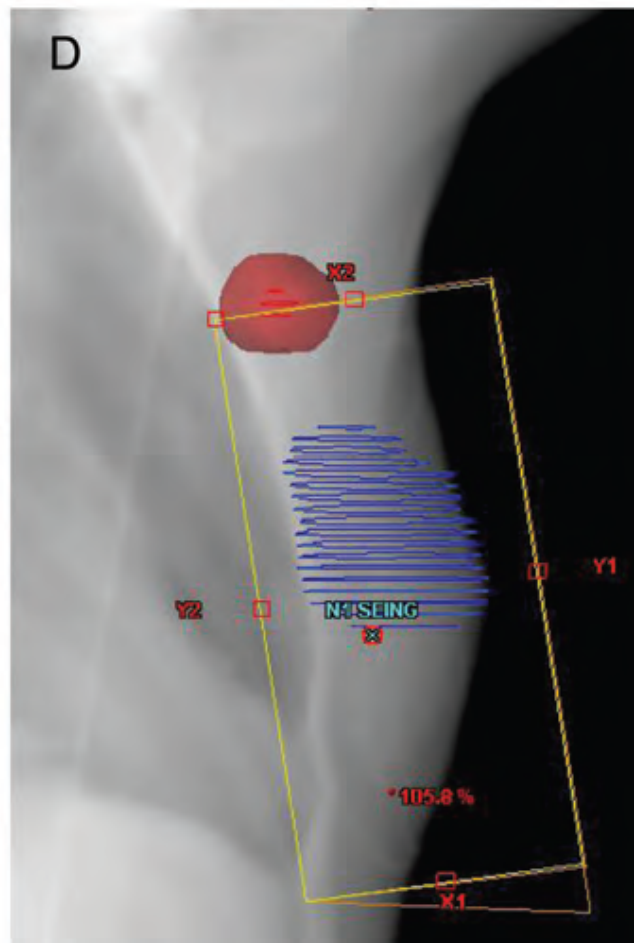
# STANDARD TANGENTIAL FIELDS AND DOSE DISTRIBUTION

*BELKACEMI Ann Oncol 2013, 24: 2023-28*



# STANDARD TANGENTIAL FIELDS AND DOSE DISTRIBUTION

*BELKACEMI Ann Oncol 2013, 24: 2023-28*



# LA TECNICA DEGLI « HIGH TANGENTS » permette una migliore COPERTURA DEL I °/II° LIVELLO ASCELLARE...

- REZNIK J                      *IJROBP* 2005, 61: 163-8
- OHASHI T                      *IJROBP* 2009, 73: 80-7
- ORECCHIA R                  *BR.J.RAD* 2005, 78: 51-4
- ARISTEI C                      *IJROBP* 2001, 51: 69-73

- Possibile nuova alternativa?
- Interesse delle clip?

# CONCLUSIONI:

## PROBLEMATICA MOLTO COMPLESSA +++

- Nessun trattamento per i pNoi+
- Per i pNmi:
  - RT ascellare: nuovo standard?
  - Sistematico? Selettivo?
- Per i pN1
  - ➔ DA?
  - ➔ RT?

NECESSITA DI NUOVI STUDI PIU PRECISI...

GRAZIE PER L'ATTENZIONE



**Table. — Guidelines for Management of Sentinel Lymph Node Findings**

<b>Biopsy Results</b>	<b>Guidelines</b>
Negative sentinel lymph node(s)	No further axillary surgery required. ALND may be omitted.
Positive lymph node at presentation (proven by FNA or core needle biopsy)	ALND should be performed.
Positive sentinel lymph node(s) 1 or 2 positive sentinel lymph nodes	ALND may be omitted if: <ul style="list-style-type: none"><li>• Primary tumor <math>\leq</math> 5 cm</li><li>• Clinically negative axilla</li><li>• Successful breast conservation</li><li>• Will receive whole-breast radiation therapy and likely systemic therapy</li></ul> ACOSOG Z0011 data do not apply to the following patients: <ul style="list-style-type: none"><li>• Those undergoing mastectomy</li><li>• Those receiving neoadjuvant chemotherapy</li><li>• Those receiving partial-breast radiation therapy or radiation therapy in the prone position</li></ul> For these patients, the standard of care is completion ALND.
3 or more positive sentinel lymph nodes	Completion ALND should be performed.

ALND = axillary lymph node dissection, FNA = fine-needle aspiration.