Gruppo di Studio per la Patologia Mammaria

LINFONODO SENTINELLA POSITIVO: EVOLUZIONE NELL'APPROCCIO TERAPEUTICO

III Zoom Journal Club 2013

Bologna, 21/02/2014

Alba Fiorentino

Sacro Cuore Hospital, Negrar-Verona

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Negrar (Verona)

Linfonodo sentinella positivo:

evoluzione nell'approccio terapeutico

La linfoadenectomia può essere omessa?

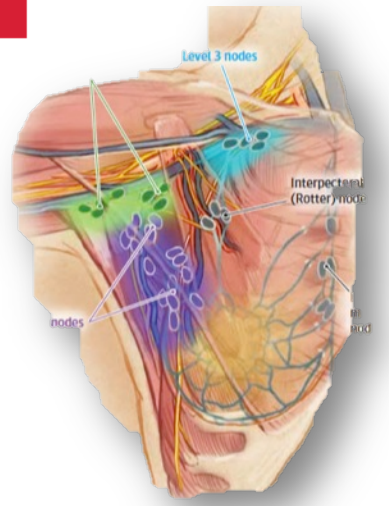
Background

Introduction

Clinical Review & Education

Review

Axillary Node Interventions in Breast Cancer
A Systematic Review



The risk of local regional recurrence:

1. Absolute number of **lymph nodes with metastases**,
2. The **size** of the metastatic disease in the node (axillary tumor burden),
3. **Larger tumor** size,
4. **Higher tumor** grade,
5. **Young**er age at diagnosis,
6. **Lymphovascular invasion**.

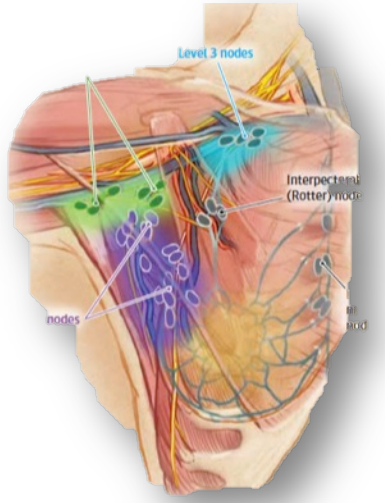
JAMA. 2013;310(13):1385-1394. doi:10.1001/jama.2013.277804

Introduction

REVIEW ARTICLE

Breast Cancer (2013) 20:41–46

The changing role of axillary lymph node dissection for breast cancer



The *historical roles of ALND* in breast cancer include

(a) the **assessment of nodal status**,

(b) the **prevention of axillary recurrence**, and

(c) the possibility of **survival benefit from the removal of positive axillary nodes**

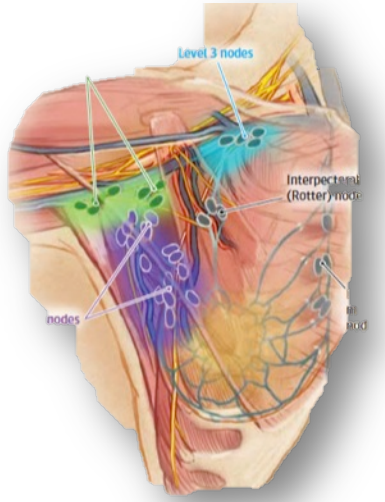
- Several randomized clinical trials have demonstrated that **ALND does not reduce the incidence of systemic recurrence or improve survival.**
- Several randomized studies confirmed that **SLN biopsy achieves the same survival and regional control as ALND in SLN-negative patients** with invasive breast cancer (Axillary recurrence in less than 1 % of patients).

Introduction

REVIEW ARTICLE

Breast Cancer (2013) 20:41–46

The changing role of axillary lymph node dissection for breast cancer



It has been shown that **SLN is the only positive lymph node in 38–67 %** of patients when ALND followed.

This finding not only provides strong support for the SLN concept, but also **suggests that unnecessary ALND** can be avoided in such patients, because removal of negative lymph nodes does not provide any significant benefit as mentioned above.

Linfonodo sentinella positivo:

evoluzione nell'approccio terapeutico

La linfoadenectomia può essere omessa?

Micrometastasi

Macrometastasi

Micrometastases: background

It has been shown that **85–90 % of patients with SLN micrometastases do not have disease in other non-SLNs**

Breast Cancer (2013) 20:41–46

Axillary dissection versus no axillary dissection in patients with sentinel-node micrometastases (IBCSG 23–01): a phase 3 randomised controlled trial

Viviana Galimberti, Bernard F Cole, Stefano Zurrida, Giuseppe Viale, Alberto Luini, Paolo Veronesi, Paola Baratella, Camelia Chifu, Manuela Sargenti, Mattia Intra, Oreste Gentilini, Mauro G Mastropasqua, Giovanni Mazzarol, Samuele Massarut, Jean-Rémi Garbay, Janez Zgajnar, Hanne Galatius, Angelo Recalcati, David Littlejohn, Monika Bamert, Marco Colleoni, Karen N Price, Meredith M Regan, Aron Goldhirsch, Alan S Coates, Richard D Gelber, Umberto Veronesi, for the International Breast Cancer Study Group Trial 23–01 investigators

Lancet Oncol 2013; 14: 297–305

Micrometastases: Background

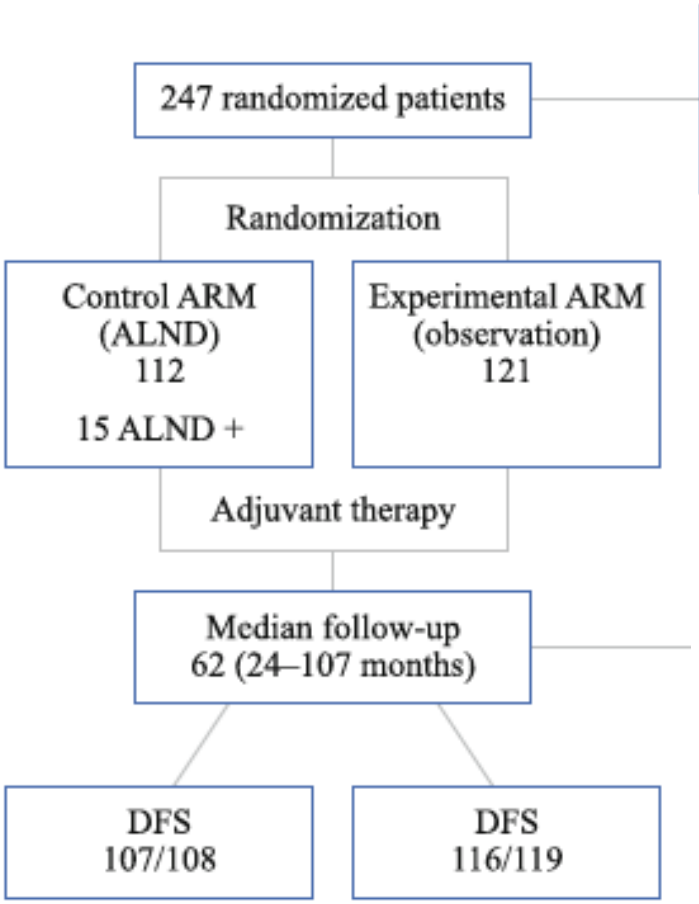


FIG. 1 Flow chart of study enrollment

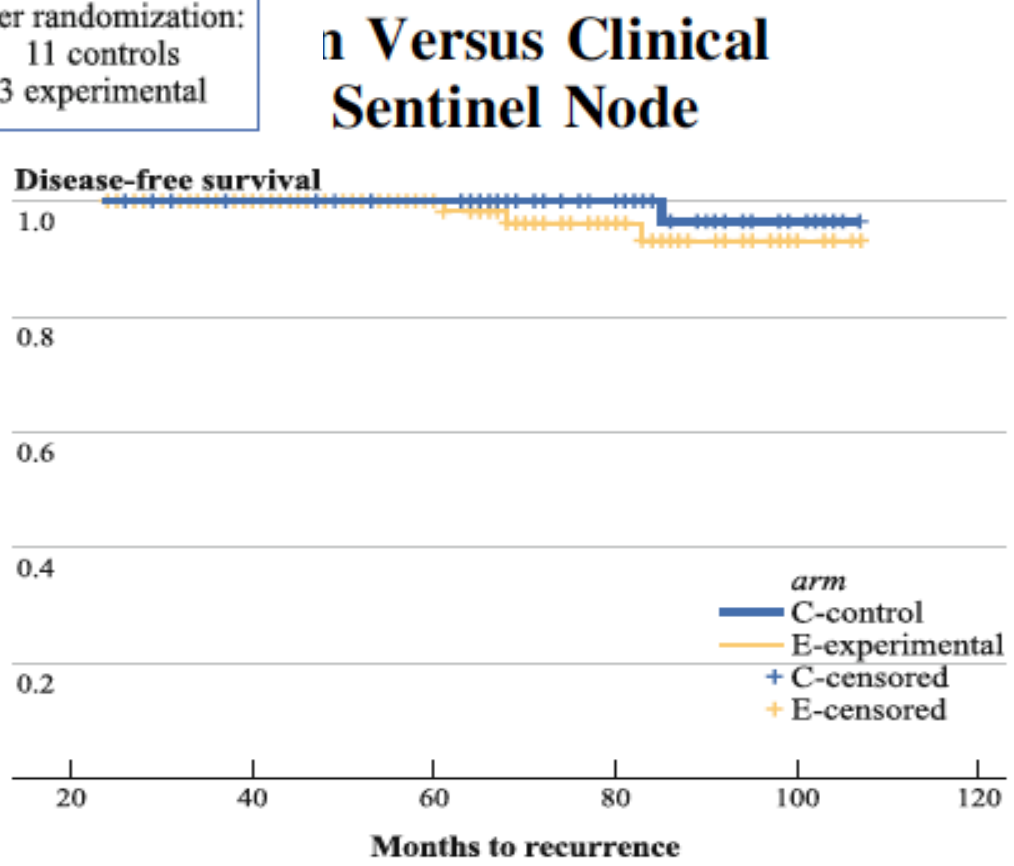


FIG. 2 Disease-free survival in control (*C*) and experimental (*E*) arms

Micrometastases: results

Axillary dissection versus no axillary dissection in patients with sentinel-node micrometastases (IBCSG 23–01): a phase 3 randomised controlled trial

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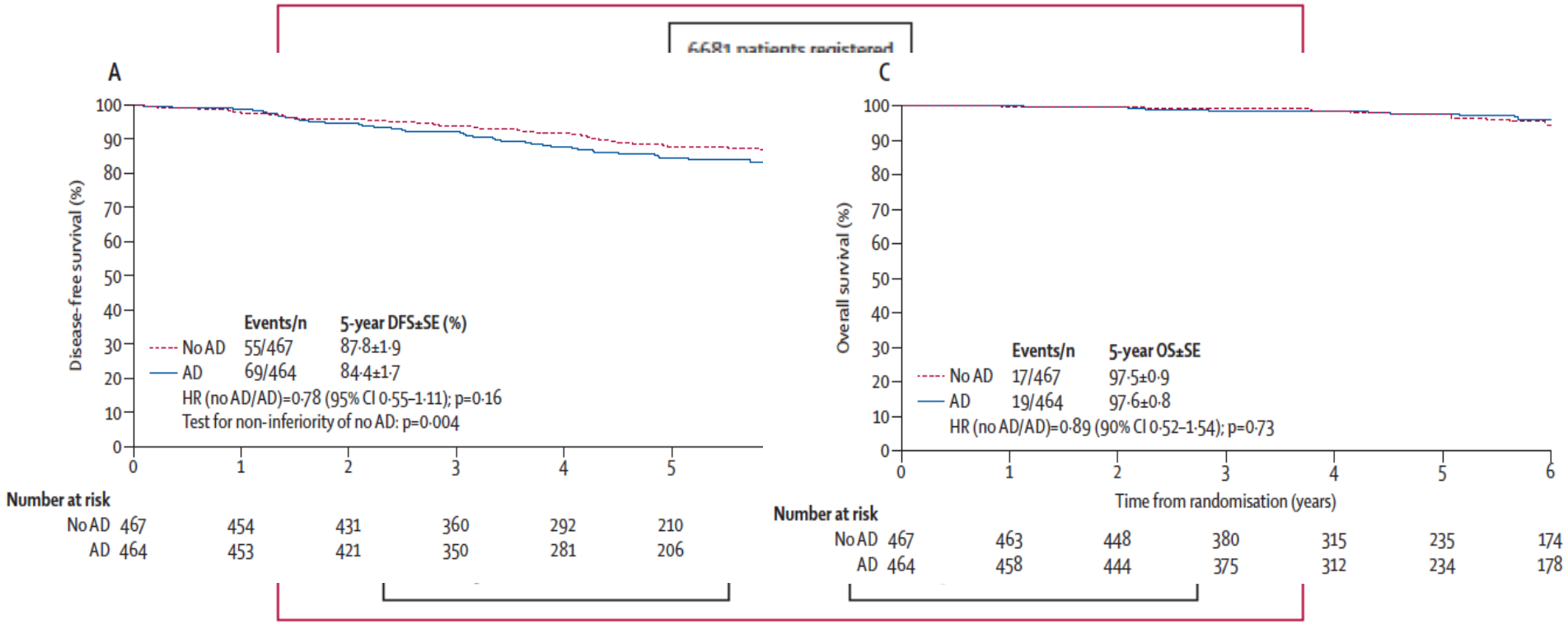

Micrometastases: results

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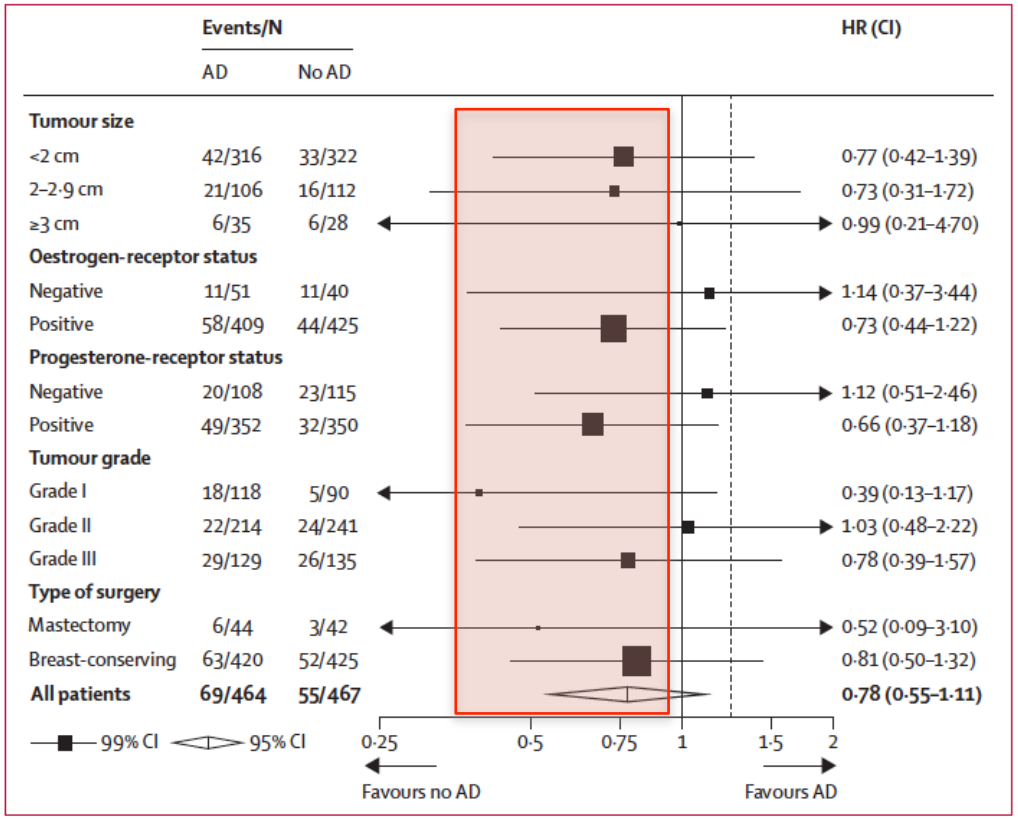


Micrometastases: Bias

Axillary dissection versus no axillary dissection in patients with sentinel-node micrometastases (IBCSG 23–01): a phase 3 randomised controlled trial

Lancet Oncol 2013; 14: 297–305

Statistical bias

Accrual started on April 1, 2001, and closed on Feb 28, 2010, after 934 patients had been randomised. The primary reasons for early closure were that the projected time to complete accrual was too long and the event rate was lower than expected.

Micrometastases: Bias

Axillary dissection versus no axillary dissection in patients with sentinel-node micrometastases (IBCSG 23–01): a phase 3 randomised controlled trial

Lancet Oncol 2013; 14: 297–305

Come gli autori superano il limite statistico?

requirement of micrometastic sentinel nodes. Although accrual was lower than projected, the protocol-specified criterion of non-inferiority of no axillary dissection compared with axillary dissection was fulfilled. In fact, disease-free survival was much better than anticipated overall: 5-year disease-free survival was well above the 70% assumed in the protocol. Most patients (92%) in our study had tumours smaller than 3 cm, received breast-conserving surgery (91%), and had adjuvant systemic therapy (96%), and thus our results are most directly applicable to these patient subpopulations.

Micrometastases: Bias

Axillary dissection versus no axillary dissection in patients with sentinel-node micrometastases (IBCSG 23–01): a phase 3 randomised controlled trial

Lancet Oncol 2013; 14: 297–305

Discrepanza di linfonodi positivi.

	Axillary dissection (n=464)	No axillary dissection (n=467)
Additional involved nodes		
No	405 (87%)	455 (97%)
Yes	59 (13%)	12 (3%)

Micrometastases: background

Axillary dissection versus no axillary dissection in patients with sentinel-node micrometastases (IBCSG 23–01): a phase 3 randomised controlled trial

Lancet Oncol 2013; 14: 297–305

Come gli autori superano la Discrepanza di linfonodi positivi.

	Axillary dissection (n=464)	No axillary dissection (n=467)
With radiotherapy	410/420 (98%)	413/425 (97%)
Intraoperative radiotherapy only	79/420 (19%)	80/425 (19%)
Postoperative radiotherapy only	293/420 (70%)	297/425 (70%)
Combination radiotherapy	36/420 (9%)	35/425 (8%)
Unspecified radiotherapy	2/420 (<1%)	1/425 (<1%)
Without radiotherapy	10/420 (2%)	12/425 (3%)

Micrometastases: Take home message

Axillary dissection versus no axillary dissection in patients with sentinel-node micrometastases (IBCSG 23–01): a phase 3 randomised controlled trial

Lancet Oncol 2013; 14: 297–305

- 10-15% of patients with SLN micrometastases have disease in other non-SLNs
- Low events
- Reduction of neurophaty, lymphoedema

2011 St Gallen Consensus Conference[29] has already moved in that direction recommending that micro-metastases in a single sentinel node should not be an indication for axillary dissection irrespective of the type of breast surgery given.

Linfonodo sentinella positivo:

evoluzione nell'approccio terapeutico

La linfoadenectomia può essere omessa?

Macrometastasi

Macrometastases: Background

Whereas **48–87 % of patients with macrometastases** in SLN have disease in other non-SLNs.

Breast Cancer (2013) 20:41–46

ORIGINAL CONTRIBUTION

Axillary Dissection vs No Axillary Dissection in Women With Invasive Breast Cancer and Sentinel Node Metastasis

A Randomized Clinical Trial

JAMA. 2011;305(6):569-575

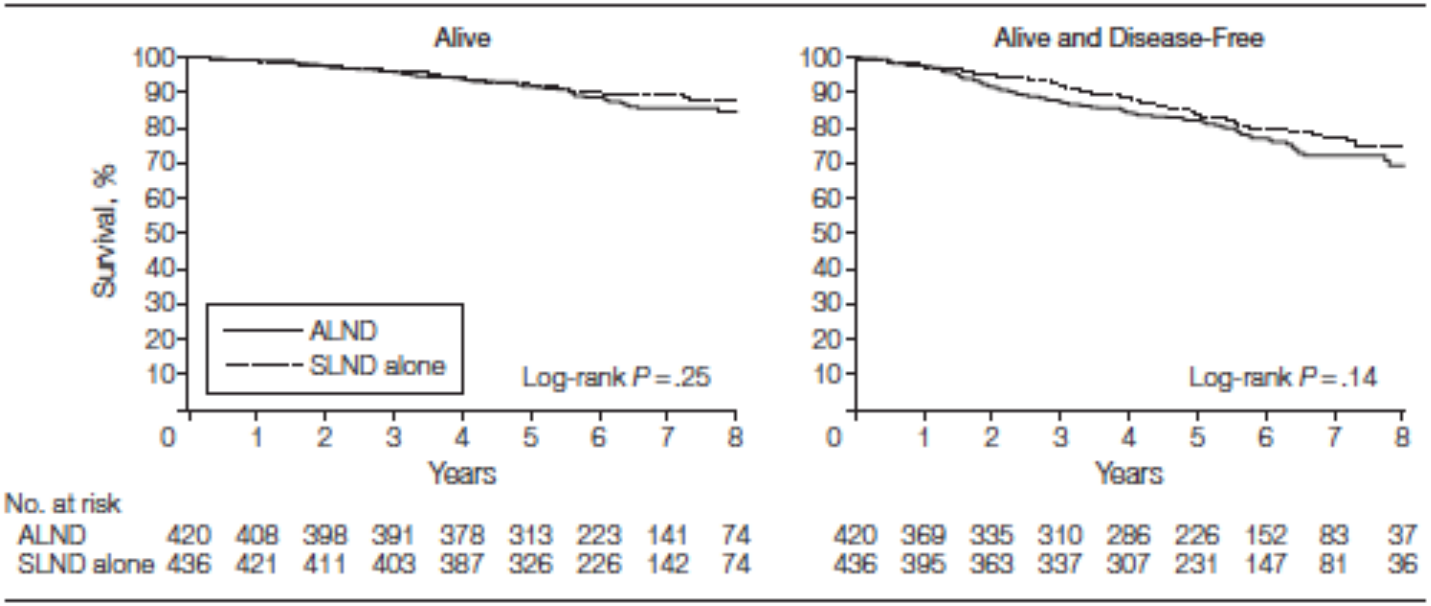
Macrometastases: Background

Axillary Dissection vs No Axillary Dissection in Women With Invasive Breast Cancer and Sentinel Node Metastasis

A Randomized Clinical Trial

ORIGINAL CONTRIBUTION

JAMA. 2011;305(6):569-575



ALND indicates axillary lymph node dissection; SLND, sentinel lymph node dissection.

Macrometastases: Bias

COMMENTARY

- The margin of noninferiority in the trial by Giuliano and colleagues is confusing.

Non inferiority:

survival rates not less than 75% of the obseverd axillary dissection group

↓

80% of 5-y OS in the axillary dissection

75% of 80 = 60% of 5-y OS

Noninferiority: in absolute value 80% vs 60%

Macrometastases: Bias

COMMENTARY

- The margin of noninferiority in the trial by Giuliano and colleagues is confusing.

Non inferiority:

Accrual 1900 patients, 500 events.

Noninferiority: 891 patients, 91 events.

Many patients had no positive nodes (7% vs 1.2%).

Large number of patients lost at FUP

Macrometastases: Take home message

- NO conclusive data
- NO background
- Evaluation of whom…..

A number of investigators have proposed **methods of predicting the risk** of involved non-SLNs after SLN biopsy.

"**The MSKCC nomogram**" has been developed at the Memorial Sloan-Kettering Cancer Center. However, this nomogram itself makes **no actual treatment recommendations,** because it can provide only risk estimates that will have to be judged on an individual basis .

Breast Cancer (2013) 20:41–46

Linfonodo sentinella positivo:

evoluzione nell'approccio terapeutico

La RT su N può essere un 'alternativa alla CH?

Linfonodo sentinella positivo:

La RT su N può essere un 'alternativa alla CH?

The Breast 22 (2013) S118–S128

Review

Is regional nodes radiotherapy an alternative to surgery?

Birgitte Vrou Offersen [a,*], Hanne Melgaard Nielsen [a], Marie Overgaard [b], Jens Overgaard [b]

There is only limited data on the optimal locoregional therapy of the clinical node-negative SN+ axilla. We will review the data on outcome after axillary dissection and/or regional RT in these patients. Since there are many reports on limited numbers of patients, we have chosen to limit the studies included in this review to those reporting data from studies of minimum 50 patients. Furthermore, we will discuss if regional RT can replace axillary dissection.

Linfonodo sentinella positivo:

La RT su N può essere un 'alternativa alla CH?

The Breast 22 (2013) S118–S128

Studies reporting on results from minimum 50 clinically node-negative (cN0) patients, where no sentinel node biopsy (SNB) was done, and where axillary lymph node dissection (ALND) and regional radiotherapy (RT) were not provided.

Study	Type	N	Year	Patients	HR status	FU median	pT1	Age	Results
Kent study [9]	-R	291 pts All BCS	1984–1994	94% of pts ≥50 yr had ≥2 yr tam	Not reported	5 yr	NR	90% >50 yr	22% actuarial 10-yr risk of lymphatic relapse 17% 10-yr risk of symptomatic lymphatic relapse.
Milan study [7]	-R	401 pts cT1-2 96% BCS	1986–1994	34% had tam	65% PgR+ 75% ER+	5.2 yr	91%	85% >50 yr 59% ≥60 yr	6.7% had reg recurrence at median 2.6 yr. Closely related to T1a (2.0%). T1b (1.7%), T1c (10.5%), T2 (18.4%) and grade III
Milan study [6]	-R	671 pts 172 +ALND 499 pts −ALND All BSC	1987–1992	All had ≥2 yr tam	No ALND: 0.8% ER-/PgR+ 92% ER+	15 yr	59% (no cALND)	All ≥70 yr	Crude cumulative 15 yr incidence of axillary rec in no ALND pts 5.8% overall, and 3.7% for pT1 pts No axillary recurrences in +ALND pts
Boston study [8]	-R	92 pts, clinical stage I/II All BCS	1988–1993	58% had tam 5 yr	All pts ER+	4.2 yr	83% Median T 12 mm	Median 69 yr	0 reg rec
Boston prospective trial [10]	-R	74 pts, clinical stage 1–2 Single arm multicenter trial. All BCS followed by "high tangential" RT, no reg RT	1998–2003	92% had 5 yr tam	All pts ER+	4.3 yr	89% Median T 12 mm	Median 75 yr All ≥55 yr	0 reg rec
IBCSG Trial 10-93 [11]	+R	473 pts with indication for tam irrespective of N status Randomisation to ±ALND Mastectomy 45% BCS+RT 33% BCS-RT 23%	1993–2002	96% had tam ≤5 yr	80% ER+	6.6 yr	56%	Median 74 yr All ≥60 yr	2% had axillary/reg rec as first event (1% vs 3% in ALND vs no ALND group). Sign better arm movement and less pain at first post-operative assessment in favour of no ALND, thereafter no difference between ±ALND 50% had cALND: 71% pN0, 20% pN1, 8% pN2
Milan trial [12,13]	+R	219 pts cT1 All quadrantectomy Randomisation to ±ALND RT to breast only Target enrolment was all eligible pts within 5 years	1996–2000	All tam for 5 yr, 85% completed tam	1% ER-/PgR+ 89% ER+ 91% Gr I + II	12.5 yr	94%	Median 70 yr All ≥65 yr	0 and 4 axillary rec in ALND and no ALND group. No differences in distant metastasis and breast cancer mortality. 50% had cALND: 77% pN0, 17% pN1, 6% pN2

Linfonodo sentinella positivo:

La RT su N può essere un 'alternativa alla CH?

Studies reporting on minimum 50 patients with clinically node-negative (cN0) and sentinel node-positive (SN+) breast cancer, where completion axillary lymph node dissection (cALND) was not performed and regional radiotherapy (RT) not given systematically.

Study	Type	*N*	Year	Patients	HR status	FU median	pT1	Age	Results
MD Anderson study [14]	-R	196 pts BCS 69%	1993–2005	58% RT 70% had chemotherapy	82% ER+ 70% PgR+	2.5 yr	72%	Median 56 yr	No axillary rec, 1 recurrence in fossa supraclavicularis
MIRROR study [15,20]	-R	2680 pts, nationwide T <1 cm of any grade or T 1–3 cm grade 1 or 2, pN0, pN0(i+), pN1(mic), no pN1(macro) BCS 71%, most had WBI No cALND was done in 34% of SN+ pts.	1997–2005	856 pts pN0 and no syst therapy 856 pts SN+ and no syst therapy 995 SN+ and syst therapy	91% HR+	5.1 yr	86%	Median 57 yr	pN0: 5 yr reg rec rate 2.3% (no axillary treatment) vs 1.6% (with axillary treatment), $P = NS$ pN0(i+): 5 yr reg rec rate 2.0% (no axillary treatment) vs 0.9% (with axillary treatment), $P = NS$ pN1(mic): 5 yr reg rec rate 5.6% (no axillary treatment) vs 1.0% (with axillary treatment), HR for reg rec: 4.39 (95% CI, 1.46–13.24)
MSKCC study [16]	-R	287 pts cN0, SN+ and no cALND (selection: older age, smaller T, fewer grade III) No reg RT	1997–2004	55% BCS	73% ER + 55% PgR +	1.9 yr	78%	Median 52 yr	Results compared with 1673 pts with SN+ and cALND from same period and institution. Axillary rec: ALND vs no ALND, 0.4% vs 2%, $P = 0.004$
National Cancer Data Base in the US [17]	-R	cN0 and SN+ 97,314 pts, 21% SNB only, Nationwide oncology outcomes registry	1998–2005	No cALND vs cALND: BCS 81% vs 50%, chemotherapy 61% vs 70%, postmastectomy RT 21% vs 33%, all findings significant	Not reported	5.3 yr for pts diagnosed 1998–2000	50% (range 1.5–3.0 cm)	Median 56 yr	Non-sign trend in pN1(macromet) group towards better outcome (axillary rec and OS) after cALND vs SN alone. No benefit from cALND in pN1(mic+) group
MSKCC study [18]	-R	326 pts all BCS and 93% had RT. 66 pts had tangential field RT in prone position, 20 pts had supraclavicular fields also	1997–2009	55% had chemotherapy 76% had endocrine therapy	≥80% ER+	4.6 yr	85%	Median 60 yr	3 pts developed regional recurrence
MSKCC study [19]	-R	535 pts, 325 BCS and 210 total mastectomy (TM) RT given to 94% of BCS vs 5% of TM pts. RT to TM included the chest wall and supraclavicular fossa	1997–2009	56 vs 68% had chemotherapy BCS vs TM, $P = 0.005$ 77% had endocrine therapy	88% (BCS) 83% (TM)	4.8 yr	85% (BCS) 69% (TM), $P < 0.001$	Median 59 yr (BCS), 55 yr (TM), $P = 0.001$	9 local recurrences (2.8%), 6 regional recurrences (1.8%), 17 distant failures, 49 deaths. No difference in loco-regional control between BCS and TM, but more distant failure among BCS pts
ACOSOG Z0011 trial [21]	+R	856 pts for analysis, cT1–T2, cN0 and 1–2 SNs with metastasis 89% had WBI Target enrolment 1900 pts.	1999–2004	96–97% had adjuvant systemic therapy	>83% HR+	6.3 yr	>67%	Median 54–56 yr	5 yr LRR free survival was 96.7% in SLND and 95.7% in cALND ($P = 0.28$) No difference in DFS or OS
IBCSG Trial 23-01 [22]	+R	931 pts cN0, T ≤5 cm SN biopsy with pN0(i+) or pN1(mic) 90% BCS 90–92% had RT	2001–2010	Endocrine therapy to 63–67% Chemotherapy 7–9%	89% ER+ 75% PgR+	4.8 yr	67%	Mean 54 yr	No difference in 5 yr DFS or OS 1% regional recurrence in the undissected axilla Late morbidity in ALND vs no ALND group: Lymphoedema 13% vs 4% Motor neuropathy 8% vs 3%

Linfonodo sentinella positivo:

La RT su N può essere un 'alternativa alla CH?

The Breast 22 (2013) S118–S128

Studies reporting on minimum 50 patients with cN0, not always SNB, where patients were treated with either ALND or regional RT.

Study	Type	N	Year	Patients	HR status	FU median	pT1	Age	Results
Kamakura study [25]	-R	1517 pts T1–T2cN0, All BCS, all WBI A) 80 pts ALND B) 1134 pts tangential 2 field RT (no ALND) C) 303 pts 3-field RT (no ALND)	1983–2002	80% had chemotherapy. Postmenopausal pts with ER+ tumour also had tamoxifen.	A) 44/31% ER+/PgR+ B) 62/62% ER+/PgR+ C) 51/40% ER+/PgR+	A) 13.4 yr B) 4.6 yr C) 10.2 yr	38–47%	Median 43–48 yr	Group A) 1 pt (1.3%) had axillary recurrence (ax rec) Group B) 35 (3%) had ax rec, 10 yr cumulative ax rec rate: 1.3% vs 4.6% (ALND vs RT) 5 yr ax rec rates 2.5% vs 1.7% (2 field vs 3 field). $P = 0.18$ 5 yr regional rec rates 4.8% vs 2.4% (2 vs 3 fields) $P = 0.048$ (reg rec = supraclav rec+ax rec) No difference in OS among groups
Deventer study [28]	-R	180 pts T1/T2 cN0 no ALND but reg RT + tamoxifen 341 pts T1/T2 cN0 ALND (if pN+ the pt also had nodal RT)	1991–2000	In ALND pts: pN0:76.8% pN1:20.5% pN2:0.3%	HR unknown No ALND: 99% endocrine and 0.6% chemotherapy ALND: 22% endocrine and 10% chemotherapy	7.2 yr	68% (no ALND) 80% (ALND)	≥50 yr	Regional recurrence at 5 yr: 1.1% vs 1.5% in RT vs no-RT group. OS similar, but DFS better in RT group.
Institut Curie trial [26]	+R	658 pts, T <3 cm, cN0, <70 yr All BCS and WBI A) 326 pts. ALND B) 332 pts. No ALND but Ax RT given	1982–1987		77% ER + A) 19% received CMF, 14% endocrine therapy B) 9% received CMF, 8% endocrine therapy	15 yr	67%	Mean age group A/B: 52/50.6 yr	21% in ALND group were pN+ (57% 1LN+, 34% 2–3 LN+, 9%>3 LN+) At 15 yr isolated reg rec was 1% vs 3% in ALND vs RT group, $P = 0.04$ Distant metastasis and overall survival was no different
The EORTC 10981 AMAROS trial [27]	+R	647 pts SN+, cN0, 697 pts planned accrual R: pts SN with T 0.5–3 cm 1) ALND + WBI 2) WBI + reg RT Reg RT: 50 Gy/25 fr levels I + II + III and medial part of fossa supraclav	2001–2010	Premeno: 28% Postmeno: 61% Grades I, II, III 28, 43, 25%	Not reported		74%	Median 57 yr (24–87 yr)	Type of met/further nodal disease Macromet 63%/41% Micromet 25%/18% Single cell 12%/18%

Linfonodo sentinella positivo:

La RT su N può essere un 'alternativa alla CH?

The Breast 22 (2013) S118–S128

Is regional nodes radiotherapy an alternative to dissection?

The regional recurrence risk is fortunately historically low, and this has stimulated an interest into investigating less morbidity associated strategies towards the axilla. The studies listed in Tables 1–4 in this review all report low or very low regional recurrence risks, except in 2 studies which both reported risks higher than 1% per year [7,9].

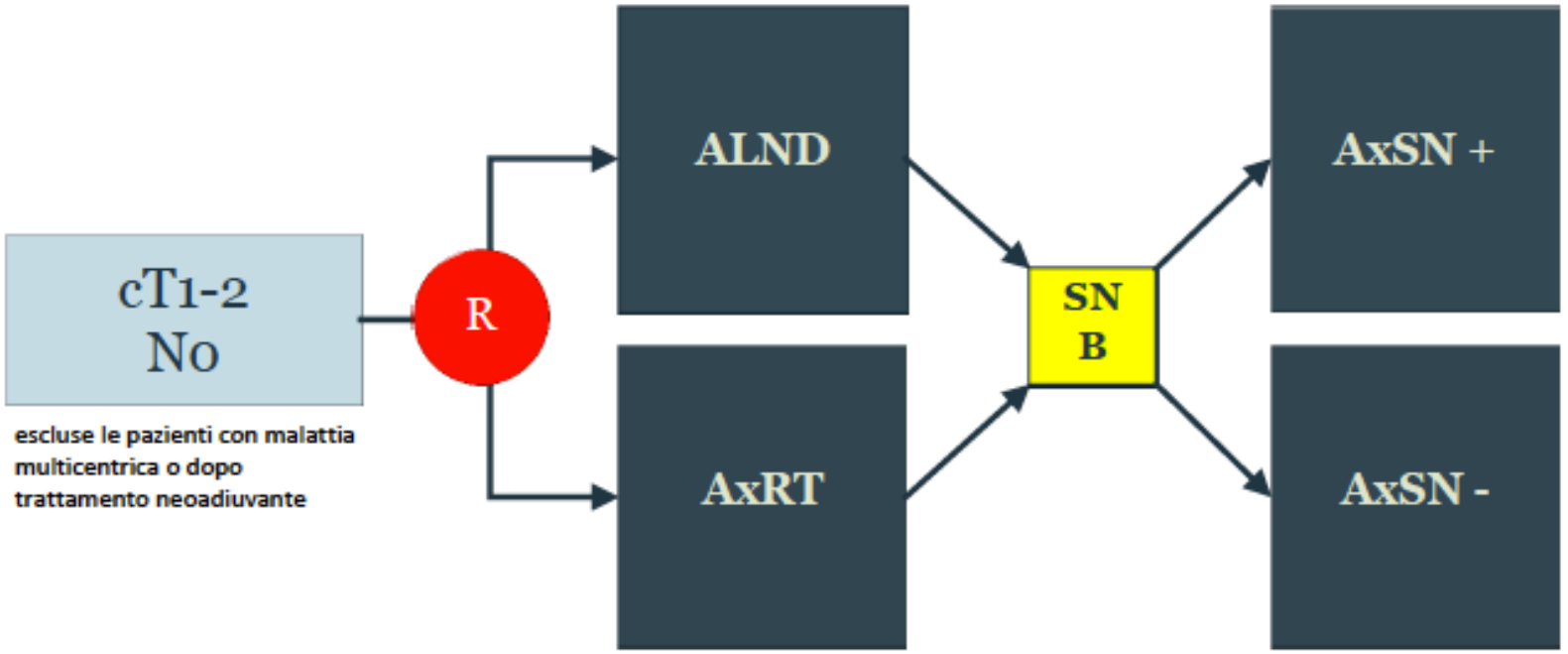
Unfortunately, there is a lack of information in all the studies included in Tables 1–4 in this review regarding the regional recurrence risk in relation to biological classification

Linfonodo sentinella positivo:

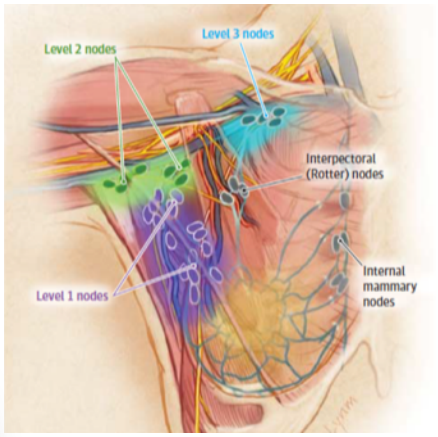
La RT su N può essere un 'alternativa alla CH?

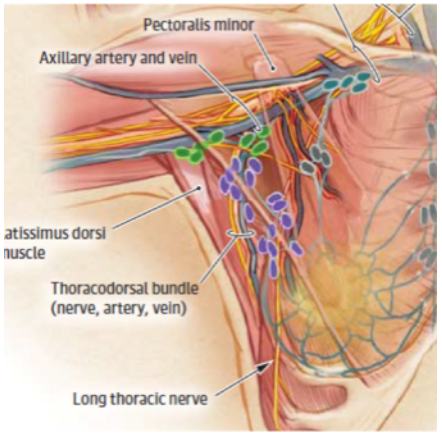
Presentazione ASCO 2013

EORTC-AMAROS Trial design



total. We need more data on biological characteristics to identify





Grazie per l'attenzione

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