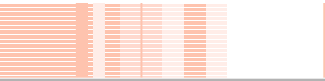


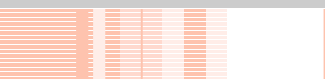


Omissione della dissezione ascellare
in pazienti
con linfonodo sentinella con micro o
macro metastasi

Torino, 10 maggio 2016



Nel formulare la raccomandazione si è tenuto conto delle seguenti linee guida e raccomandazioni internazionali e nazionali e dei seguenti trials clinici randomizzati:

- NCCN Clinical practice Guidelines in Oncology – Breast – Versione 1.2016
 - American Society of Clinical Oncology Clinical Practice Guideline Update – Maggio 2014
 - NICE guideline CG80 6-year surveillance 2015 – Early and locally advanced breast cancer (2013)
 - AIOM Linee guida neoplasie della mammella - Edizione 2015
 - Primary breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up – 2015
 - St Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer – 2015
 - Consensus sull'irradiazione delle stazioni linfonodali mammarie - Gruppo di lavoro AIRO per la patologia mammaria – 2015
 - Esmo 2015, Annals of Oncology, settembre 2015
 - Axillary dissection versus no axillary dissection in patients with sentinel-node micrometastases (IBCSG 23-01): a phase 3 randomised controlled trial. Galimberti V et al. International Breast Cancer Study Group Trial 23-01 Investigators. Lancet Oncol. 2013 Apr;14(4):297-305.
 - Impact of immediate versus delayed axillary node dissection on surgical outcomes in breast cancer patients with positive sentinel nodes: results from American College of Surgeons Oncology Group Trials Z0010 and Z0011. Giuliano AE et al. American College of Surgeons Oncology Group Trials Z0010 and Z0011. J Clin Oncol. 2008 Jul 20;26(21):3530-5
 - Amaros Trial, Lancet Oncology 2014 nov; 15(12): 1303-1310.
- 

Raccomandazione del Gruppo di Studio

La **dissezione ascellare** (con asportazione di almeno 10 linfonodi) per la valutazione patologica accurata dell'ascella è indicata:

- in presenza di linfonodi ascellari clinicamente sospetti per metastasi
- nel caso di mancato reperimento del linfonodo sentinella
- nei tumori T4 e nel carcinoma infiammatorio

L'omissione della dissezione ascellare in caso di linfonodo sentinella metastatico prevede due scenari

SENTINELLA CON MICROMETASTASI

Raccomandazione del Gruppo di Studio

- 1) La dissezione ascellare può essere omessa.
- 2) Deve essere valutata l'opportunità della dissezione ascellare nelle pazienti in cui la conoscenza delle caratteristiche istologiche degli altri linfonodi potrebbe modificare la terapia adiuvante programmata.
- 3) Deve essere valutata l'opportunità della dissezione ascellare nelle pazienti sottoposte a mastectomia (che non sono incluse nello studio Z0011 e rappresentano solo il 9% delle pazienti incluse nello studio IBCSG – 23- 01).
- 4) E' auspicabile ricerca e inclusione in trials clinici randomizzati per le pazienti sottoposte a mastectomia

Sentinella con MACROMETASTASI

Raccomandazione del Gruppo di Studio

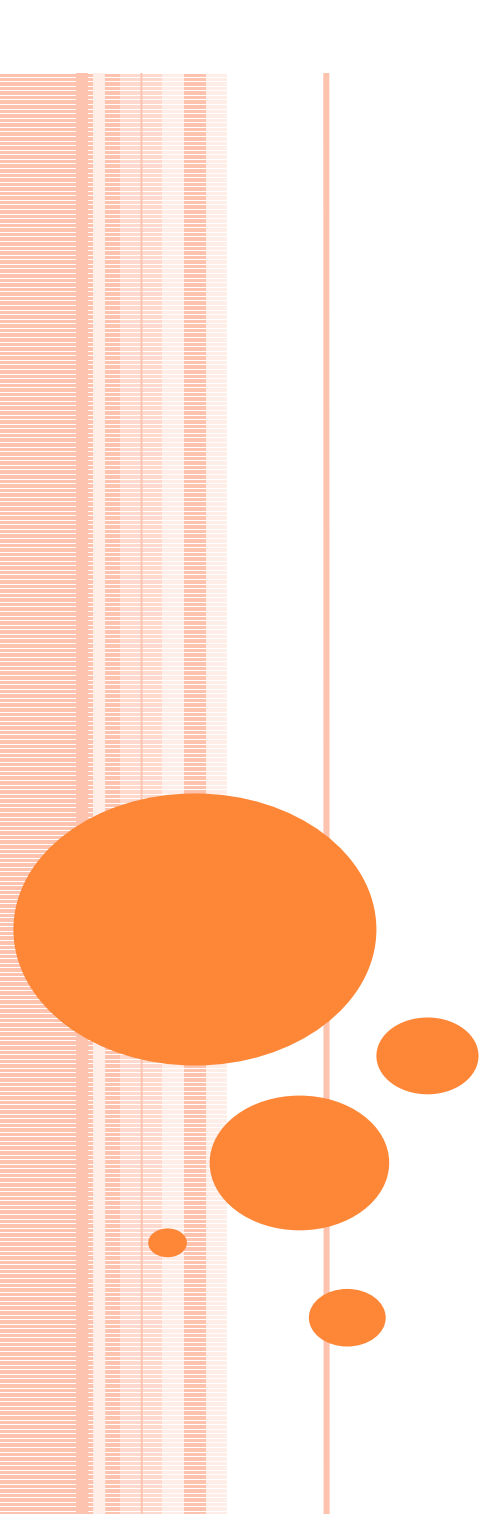
- 1) L'omissione della dissezione ascellare in caso di linfonodo sentinella con macrometastasi può essere presa in considerazione soltanto se sono soddisfatti tutti i seguenti criteri (studio Z0011):
 - Ascella negativa alla valutazione clinica, all'ecografia e all'eventuale FNA nei casi dubbi
 - T1 o T2
 - 1 o 2 linfonodi sentinella con macrometastasi.
 - Chirurgia conservativa
 - Radioterapia convenzionale su tutto il volume mammario
 - Non chemioterapia preoperatoria
- 2) L'eventuale omissione della dissezione ascellare in questa popolazione deve essere sempre preceduta da un colloquio con ogni paziente per un'attenta valutazione del rapporto rischio/beneficio.
- 3) Considerare questa opzione con cautela in caso di metastasi con diffusione extracapsulare
- 4) La dissezione ascellare **non** può essere omessa, al di fuori di trials clinici, nelle pazienti sottoposte a mastectomia
- 5) Per le pazienti candidate a mastectomia per le quali sia prevista la radioterapia, il trattamento radiante sull'ascella può sostituire la dissezione ascellare (St Gallen 2015, NCCN 2016, AIRO 2015).

Motivazioni ed eventuali commenti

L'omissione della dissezione in caso di micrometastasi nel linfonodo sentinella è un'opzione **accettata da tutte le linee guida consultate**, in considerazione del favorevole rapporto minor rischio di complicanze (linfedema, infezioni, sieroma, deficit sensoriali e motori)

L'omissione della dissezione ascellare in caso di **macrometastasi** e **chirurgia conservativa** seguita da radioterapia è un'opzione accettata da tutte le linee guida, con cautela nelle pazienti con linfonodi bulky o con estensione extracapsulare (ASCO 2014, ESMO 2015).

L'AIOM in questa popolazione precisa che la dissezione ascellare rimane ad oggi indicata nel caso di presenza di 1 o 2 linfonodi sentinella positivi all'istologia, a meno che non siano intervenute controindicazioni di carattere locale o sistemico oppure la paziente rifiuti la dissezione ascellare e che l'eventuale non effettuazione della dissezione ascellare nel sottogruppo di donne con caratteristiche analoghe a quelle del trial ACSOG Z0011 deve essere sempre preceduta da un colloquio con ogni paziente per una attenta valutazione del rapporto rischio/beneficio.



Per le donne sottoposte a mastectomia invece, le linee guida anglosassoni prevedono sempre la dissezione ascellare, sia per le micro sia per le macrometastasi nel linfonodo sentinella, sottolineando la mancanza di dati.

L'AIOM consente per le micrometastasi l'opzione di omettere la dissezione ascellare dopo discussione multidisciplinare del caso, pur sottolineando la scarsità dei dati disponibili. Le linee guida NCCN e la Consensus di S. Gallo prevedono la possibilità di omettere la dissezione ascellare anche in donne sottoposte a mastectomia purchè candidate a ricevere trattamento radioterapico.

Tutte le linee guida sottolineano la necessità di studi randomizzati nelle pazienti candidate a mastectomia



2) American Society of Clinical Oncology Clinical Practice Guideline Update – Maggio 2014

VOLUME 32 - NUMBER 13 - MAY 1 2014

JOURNAL OF CLINICAL ONCOLOGY

ASCO SPECIAL ARTICLE

Sentinel Lymph Node Biopsy for Patients With Early-Stage Breast Cancer: American Society of Clinical Oncology Clinical Practice Guideline Update

Gary H. Lyman, Sarah Temin, Stephen B. Edge, Lisa A. Newman, Rodrick B. Turner, Donald J. Wenzel, Al B. Benson III, Linda D. Boushman, Harold J. Burstein, Hiram Cody III, James Hayman, Cheryl L. Perkins, Donald A. Pridmore, and Arzoo E. Ghilano

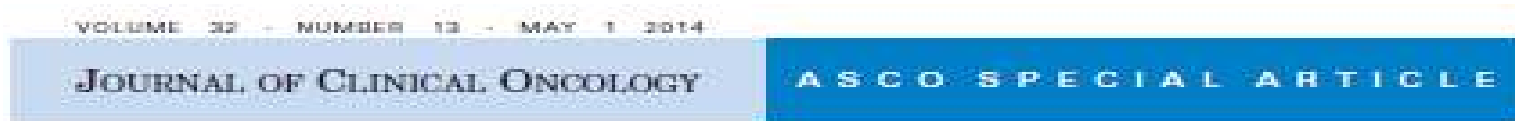
*Is ALND necessary for all patients with metastatic findings on SNB planning to undergo **BCS** with whole-breast radiotherapy?*

*Clinicians **should not recommend ALND** for women with early stage breast cancer and one or two SLN metastases who will undergo BCS with conventionally fractionated whole-breast radiotherapy”*

*Clinicians may also consider this recommendation with **caution in cases of** women with large or bulky metastatic axillary SLNs and/or those with gross extranodal extension of the tumor. These were exclusion criteria for Z0011”*



2) American Society of Clinical Oncology Clinical Practice Guideline Update – Maggio 2014



Sentinel Lymph Node Biopsy for Patients With Early-Stage Breast Cancer: American Society of Clinical Oncology Clinical Practice Guideline Update

Gary H. Lyman, Sarah Temin, Stephen B. Edge, Lisa A. Newman, Rodrick B. Turner, Donald E. Weaver, Al B. Benson III, Linda D. Boushman, Harold J. Burstein, Hiram Cody III, James Hayman, Cheryl L. Perkins, Donald A. Prideloff, and Aracando E. Giuliano

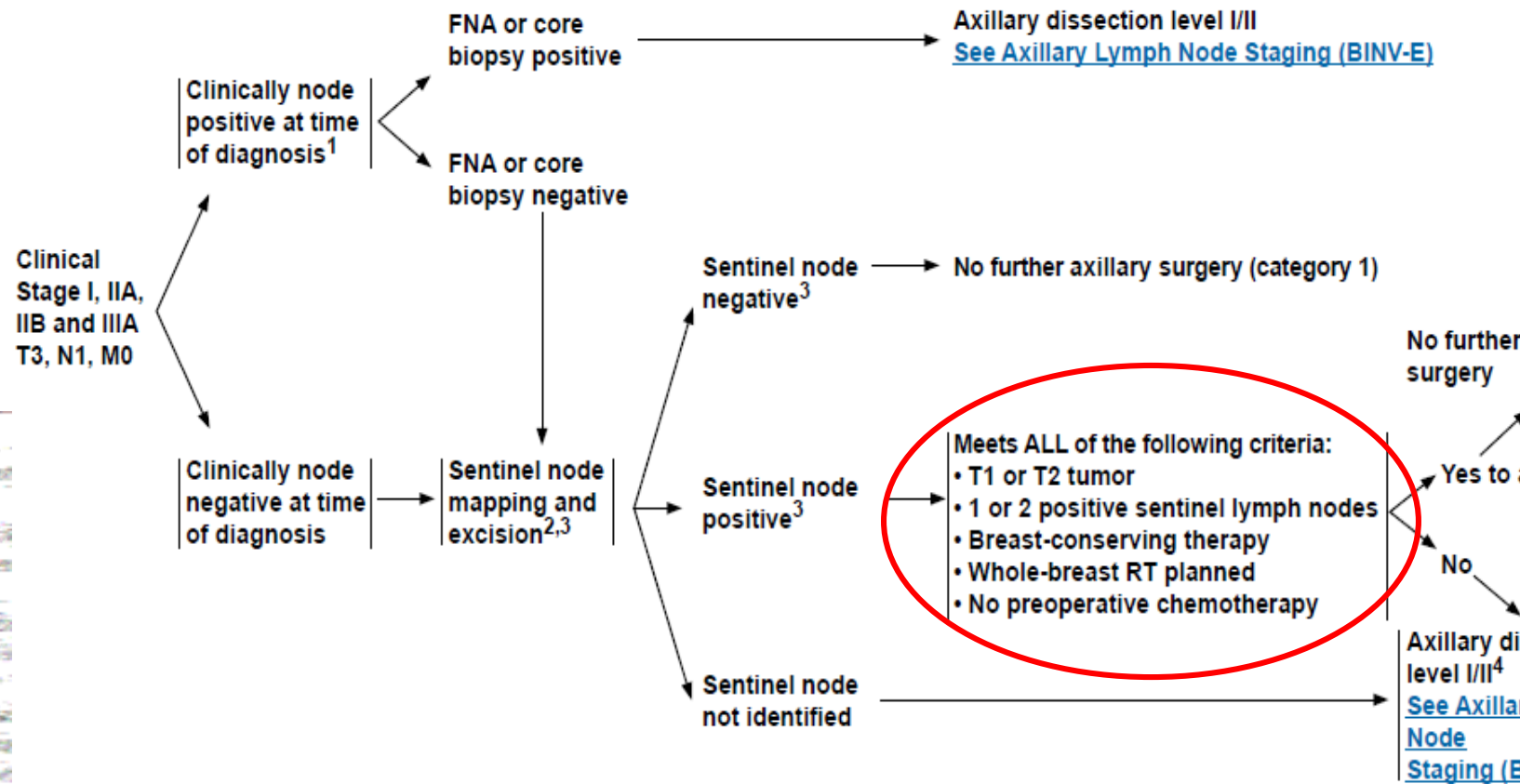
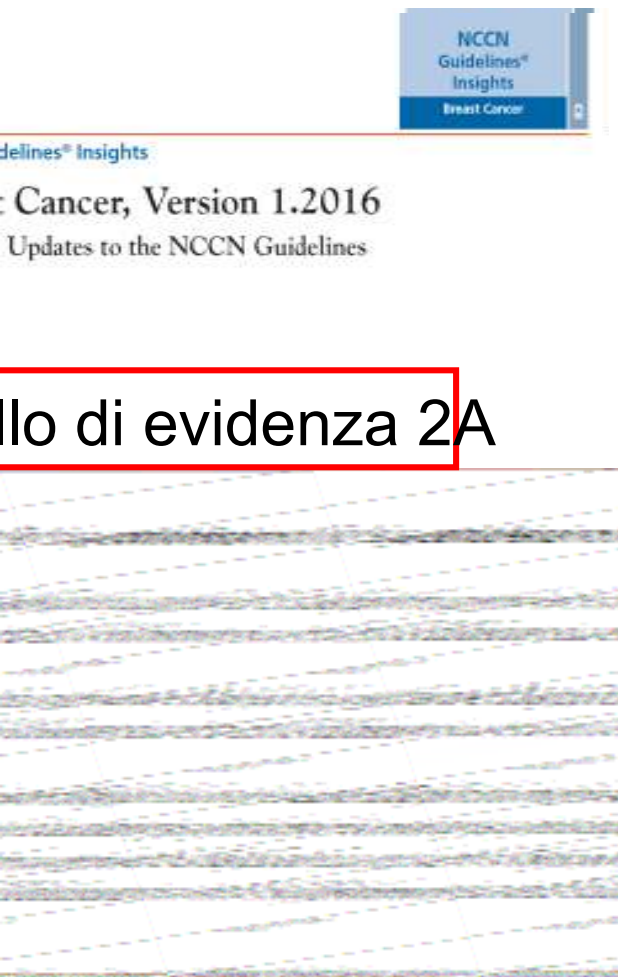
*ALND necessary for all patients with metastatic findings on SNB who are planning to undergo **mastectomy**?*

*Clinicians **may** offer ALND for women with early-stage breast cancer with nodal metastases found on SNB who will undergo mastectomy.*

Type: evidence based;
benefits outweigh
harms. Evidence
quality: low. Strength of
recommendation: weak



1) NCCN Clinical practice Guidelines in Oncology – Breast – Versione 1.2016



SLNs are assessed for the
toxylin and eosin (H&E) staining
ificance of a lymph node that is
by cytokeratin IHC is not clear.
data on which treatment
E staining, the panel does not
define node involvement and
ns should be made based solely
n is further supported by a
010) for patients with H&E
tion by cytokeratin IHC was not
edian of 6.3
ning is equivocal, reliance on the
e. Multiple attempts have been
involved SLNs who have a low
hat complete axillary dissection
. None of the early studies
with positive SLN biopsies but
les.¹³³⁻¹³⁹ Nonetheless, a
mpared SLN resection alone with
or equal to 18 years of age with
Ns, and undergoing

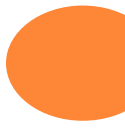
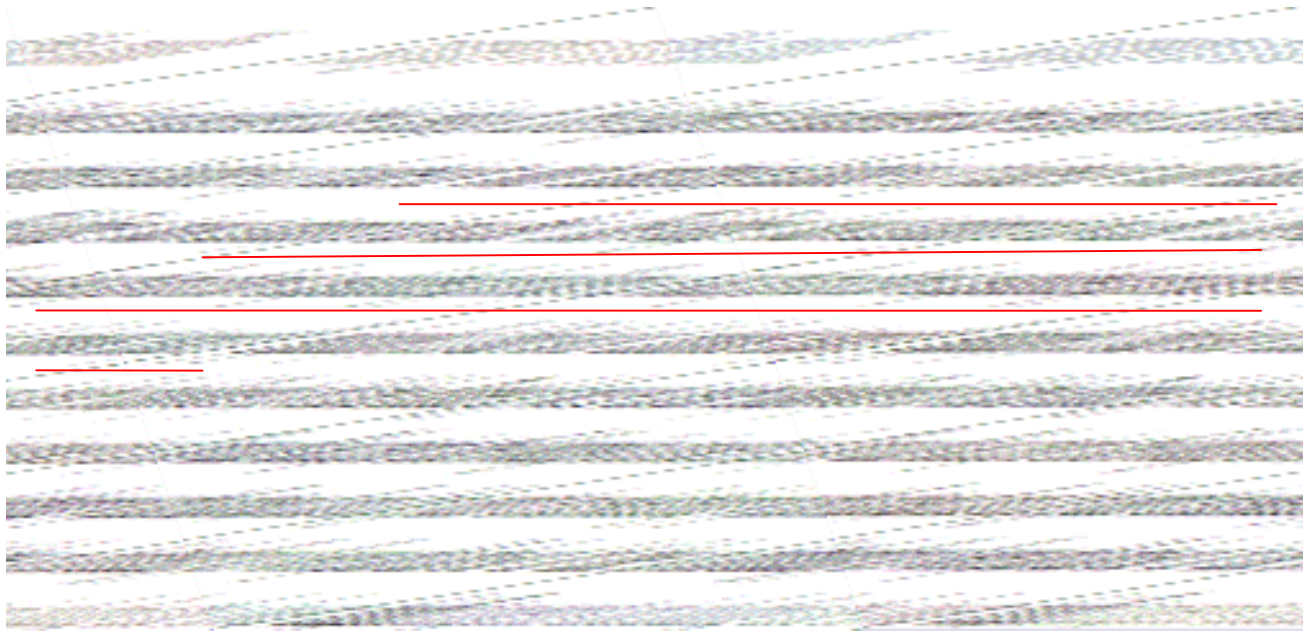
to 2 positive SLNs, did not receive neoadjuvant therapy, and is tre
with lumpectomy and whole breast radiation, the panel recommen

The panel recommends level I or II axillary dissection 1) when patients
have clinically positive nodes at the time of diagnosis that is confirmed
by FNA or core biopsy; or 2) when sentinel nodes are not identified. For
patients with clinically negative axillae who are undergoing mastectomy
and for whom radiation therapy is planned, the panel notes that axillary
radiation may replace axillary dissection level I/II for regional control of
disease.

gross disease in level II nodes, lymph node dissection should incl
tissue inferior to the axillary vein from the latissimus dorsi muscle
laterally to the medial border of the pectoralis minor muscle (level

Furthermore, according to the panel, without definitive data
demonstrating superior survival with ALN dissection or SLN rese
these procedures may be considered optional in patients who hav

5) St Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2015



3)NICE guideline CG80 6-year surveillance 2015 –

NICE National Institute for
Health and Care Excellence

SLNB versus ALND

In 3 reports from 2 RCTs (IBCSG 23-01²⁵ and ACSOG Z0011^{26,27}) identified by topic expert feedback and 1 systematic review and meta-analysis,²⁸ identified by search SLNB was non-inferior to ALND in people with micro-metastasis (defined in 1 trial as ≤ 2 mm) or 1–2 lymph nodes positive for metastasis. SLNB was non-inferior across outcomes such as 5-year disease-free survival, overall survival at 6.3 years' follow-up, local or regional recurrence. SLNB avoided adverse effects associated with ALND including sensory and motor neuropathy and

SLNB versus ALND

New evidence was identified that may change current recommendations.



ALND remains standard management for macro-metastasis in the lymph nodes. Evidence at 3-year surveillance suggested that SLNB may be effective in selected patients with micro-metastases. Further evidence suggests that SLNB alone may be suitable if small metastases affecting 1 or 2 sentinel nodes are detected. This may have an impact on the guideline, which currently recommends ALND as the preferred option for micro- and macro-metastases.

AIOM Linee guida neoplasie della mammella Edizione 2015

Metastasi nel linfonodo sentinella (> 2 mm)

La dissezione ascellare rimane ad oggi indicata nel caso di presenza di 1 o 2 linfonodi sentinella positivi all'istologia, a meno che non siano intervenute controindicazioni di carattere locale o sistemico oppure la paziente rifiuti la dissezione ascellare.

Eventuale non effettuazione della dissezione ascellare nel sottogruppo di donne con caratteristiche analoghe a quelle del trial ACSOG Z0011 deve essere sempre preceduta da un colloquio con ogni paziente per una attenta valutazione del rapporto rischio/beneficio.

Donne candidate alla mastectomia con biopsia del LS positiva dovrebbero procedere a ruotamento ascellare



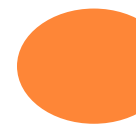
AIOM

2015

Linee guida

NEOPLASIE DELLA MAMMELLA

Edizione 2015
Aggiornata al 16 settembre 2015



AIOM Linee guida neoplasie della mammella Edizione 2015

Micrometastasi nel linfonodo sentinella

In presenza di micrometastasi nel linfonodo sentinella è possibile considerare l'omissione della dissezione ascellare dopo discussione multidisciplinare e valutazione con la paziente dei rischi e dei benefici.

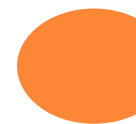
La discussione multidisciplinare deve valutare una eventuale dissezione ascellare in caso di:

1. Pazienti ad alto rischio laddove la conoscenza delle caratteristiche istologiche degli altri linfonodi dovesse modificare la terapia adiuvante programmata

2. Pazienti sottoposte a mastectomia totale.



Edizione 2015
Aggiornata al 16 settembre 2015



Primary breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

ankus¹, S. Kyriakides², S. Ohno³, F. Penault-Llorca^{4,5}, P. Poortmans⁶, E. Rutgers⁷,
ckrisson⁸ & F. Cardoso⁹, on behalf of the ESMO Guidelines Committee*

ent of Oncology and Radiotherapy, Medical University of Gdansk, Gdansk, Poland; ²Europa Donna Cyprus, Nicosia, Cyprus; ³Breast Oncology Center, Cancer
ospital, Tokyo, Japan; ⁴Department of Pathology, Centre Jean Perrin, Clermont-Ferrand; ⁵EA 4677 Université d'Auvergne, Clermont-Ferrand, France; ⁶Radboud
Medical Center, Nijmegen, The Netherlands; ⁷Department of Surgery, Netherlands Cancer Institute, Amsterdam, The Netherlands; ⁸Department of Diagnostic
Lund University, Malmö, Sweden; ⁹Breast Unit, Champalimaud Clinical Center, Lisbon, Portugal

The optimal management of micrometastatic spread and isolated tumour cells is the subject of ongoing research. Based on the results of the IBCSG 23-01 trial, further axillary treatment does not seem to be required when a sentinel node (SN) has micrometastasis (0.2–2 mm) [59]. The presence of macrometastatic spread in the SN traditionally mandated conventional axillary lymph node clearance. Recent results of a randomised, controlled trial (6.3 years of median follow-up) for patients with clinical T1–T2 cN0 invasive breast cancer and one to two sentinel lymph nodes containing metastases [treated with breast-conservation surgery (BCS) and tangential adjuvant RT], reported non-inferior rates of overall survival (OS), disease-free survival (DFS) and locoregional recurrence-free survival [60].

Another option in patients with cN0 and sentinel lymph node metastases (irrespective of the risk factors) is axillary irradiation, as demonstrated by the AMAROS study [51]. Therefore, all patients with micrometastatic spread or isolated tumour cells (<0.2 mm) in the SN and patients with limited involvement of the sentinel lymph node, undergoing tangential breast irradiation and adjuvant systemic treatment, may not need to have any further axillary procedure [II, B]. However, these results need to be confirmed and cannot be extended to patients with different characteristics than those of the trial's patient population.

No Axillary Dissections vs No Axillary Dissections vs
sive Breast Cancer With Invasive Breast Cancer With Inva
Metastatic Sentinel Node Metastatic Sentinel Node
Trial A Randomized Clinical Trial A Randomized Clinical Trial

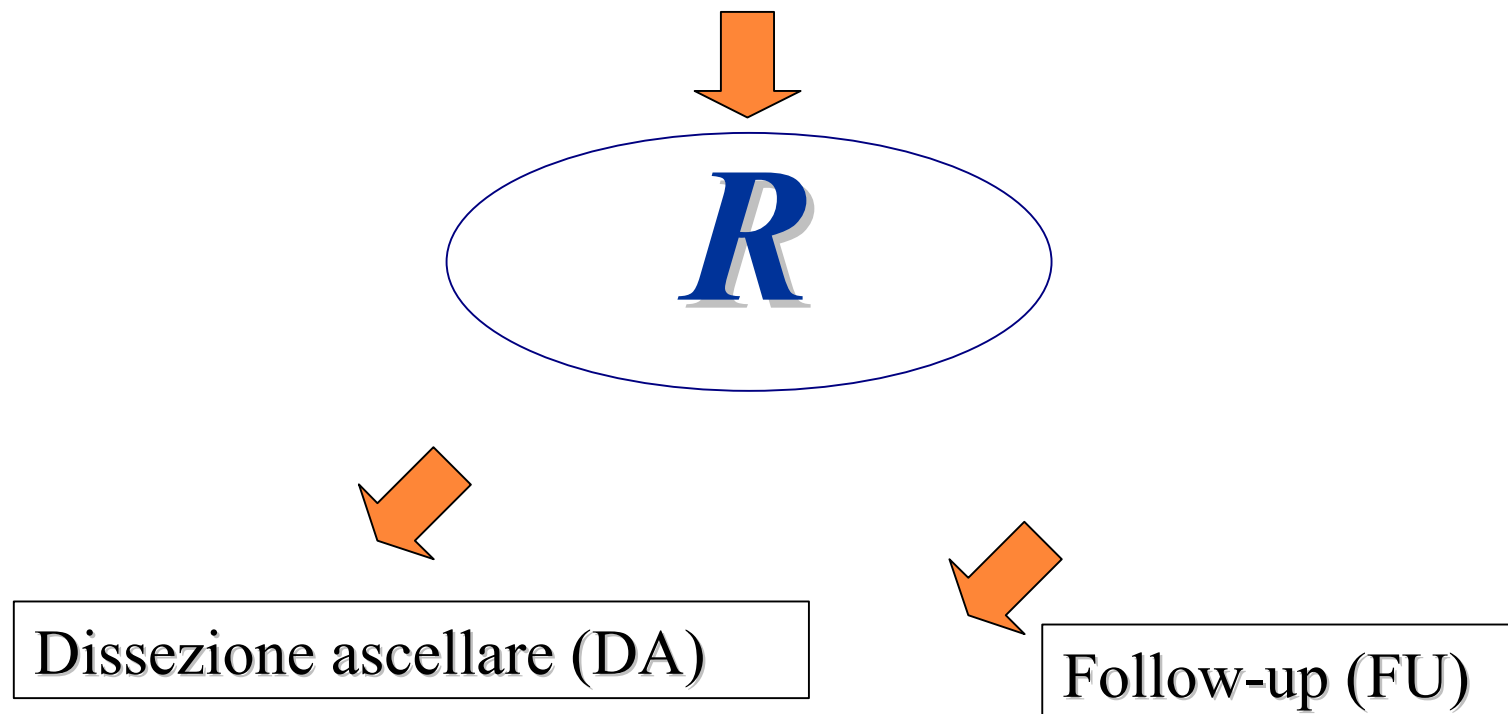
ACOSOG Z0011

Armando E. Giuliano, MD, accurately identify sentinel lymph nodes. Whether further nodal dissection improves breast cancer survival. **Objective:** To determine the effect of complete axillary lymph node dissection (ALND) versus sentinel lymph node dissection (SLND) on breast cancer survival in women with clinical T1-T2 breast cancer. **Design, Setting, and Patients:** A randomized trial conducted at 15 sites and enrolling patients with clinical T1-T2 breast cancer. **Interventions:** ALND or SLND. **Measurements and Main Results:** The trial closed early because the observed event rate was lower than expected. All patients underwent lumpectomy and tangential mastectomy. SLND metastases identified by SLND were associated with a 50% reduction in axillary treatment (cosmesis, morbidity, and cost) without affecting local control. Systemic therapy was the discretion of the treating physician. **Conclusion:** In women with clinical T1-T2 breast cancer, SLND was associated with a 50% reduction in axillary treatment without affecting local control. Systemic therapy was the discretion of the treating physician. **Limitations:** The trial closed early because the observed event rate was lower than expected. **Registration:** ClinicalTrials.gov, NCT00108183.



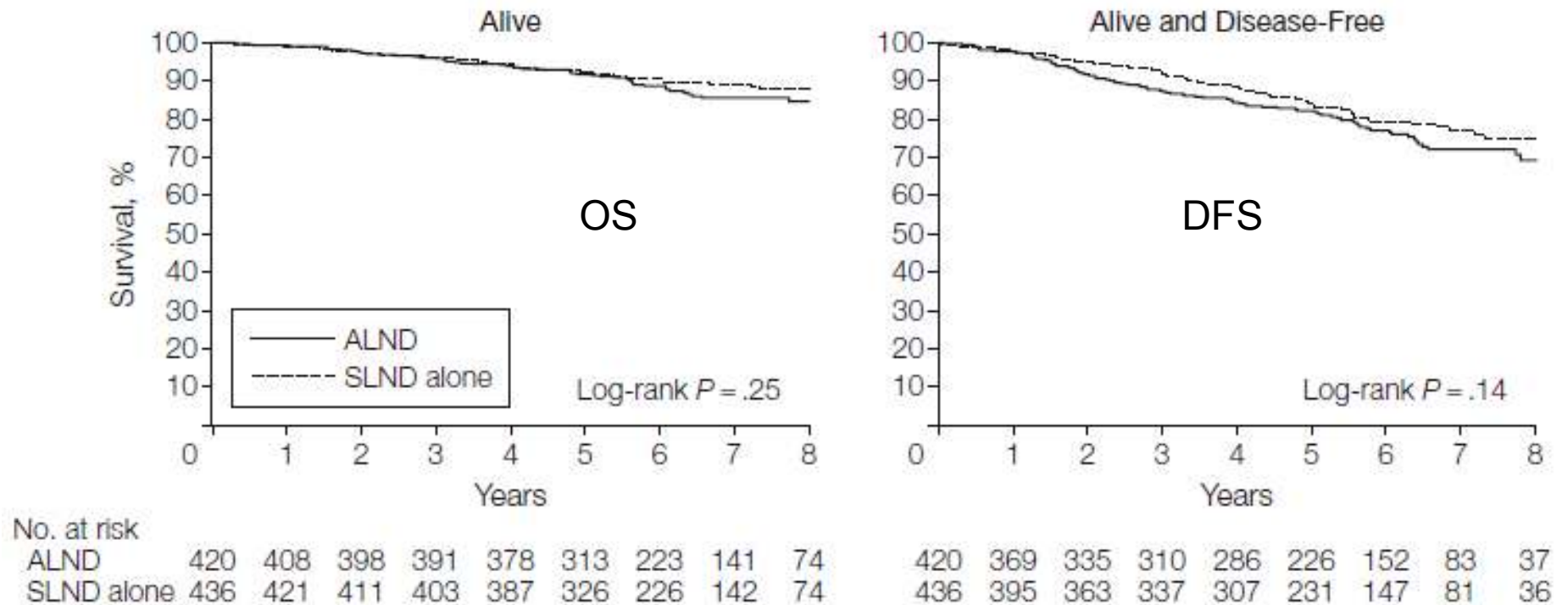
Trial Z0011: criteri di inclusione

- ✓ **Pazienti con tumore mammario < 5 cm, clinicamente N-**
- ✓ **Sottoposte a chirurgia mammaria conservativa con successiva RT complementare sulla mammella e terapia sistemica adiuvante**
- ✓ **Sottoposte a biopsia del linfonodo sentinella (LFNS) con mts in 1 o 2 LFNS**
- ✓ **NO chemioterapia o ormonoterapia neoadiuvante**



Trial Z0011: risultati

Figure 2. Survival of the ALND Group Compared With SLND-Along Group



✓ Nel gruppo DA:

✓ 27.3% dei LFNS+ → mts addizionali nei linfonodi non sentinella

✓ 10% dei LFNS micromts → mts addizionali nei linfonodi non sentinella

✓ Il tasso di recidiva locale a 5 anni è stato: 1.6% nel gruppo solo LFNS
 3.1% nel gruppo DA (p=ns)

Trial Z0011: conclusioni degli autori

MA...

“Il trial Z0011 non include pazienti

- *sottoposte a mastectomia,*
- *sottoposte a chirurgia conservativa senza radioterapia,*
- *trattate con PBI,*
- *sottoposte a RT in posizione prona,*
- *sottoposte a trattamenti neoadiuvanti.*

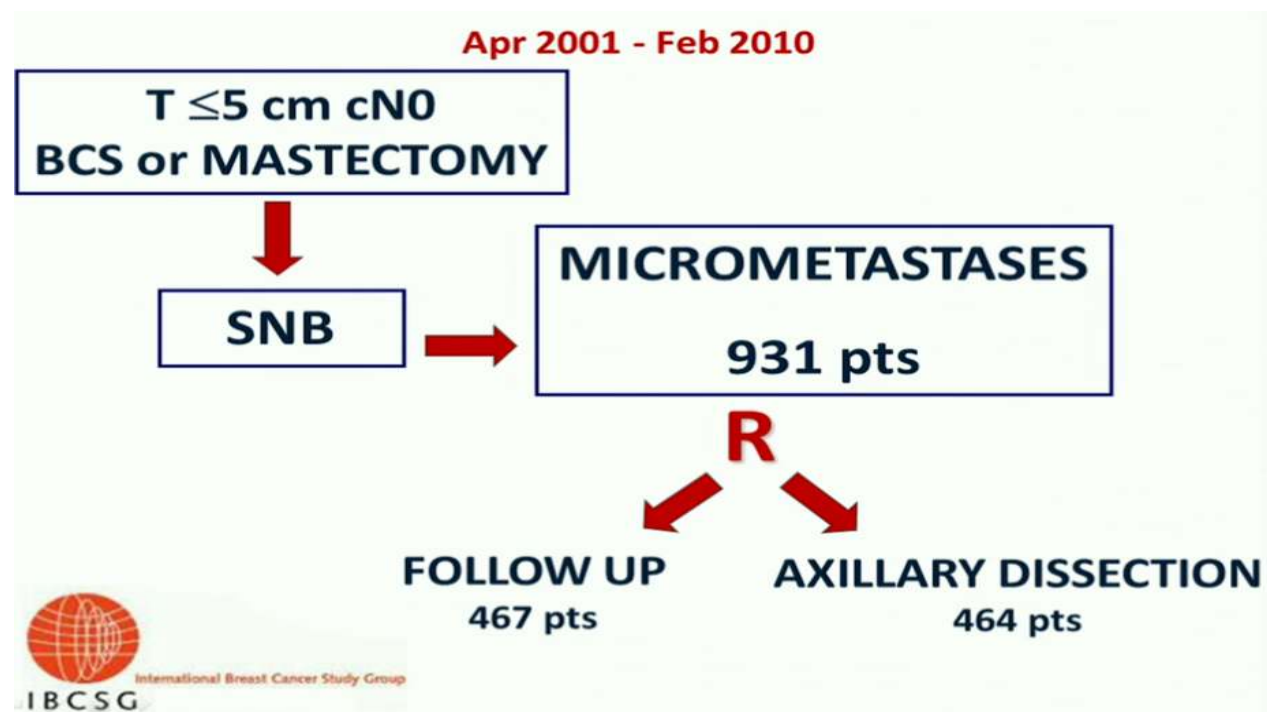
In queste pazienti la DA rimane lo standard di cura”



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

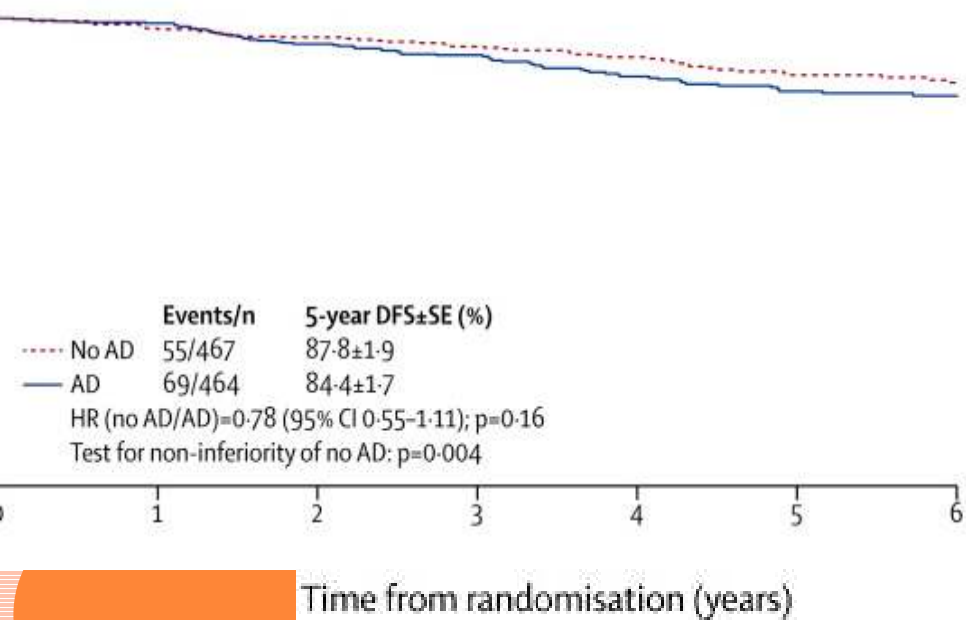
Galimberti V. et al, Lancet Oncol.



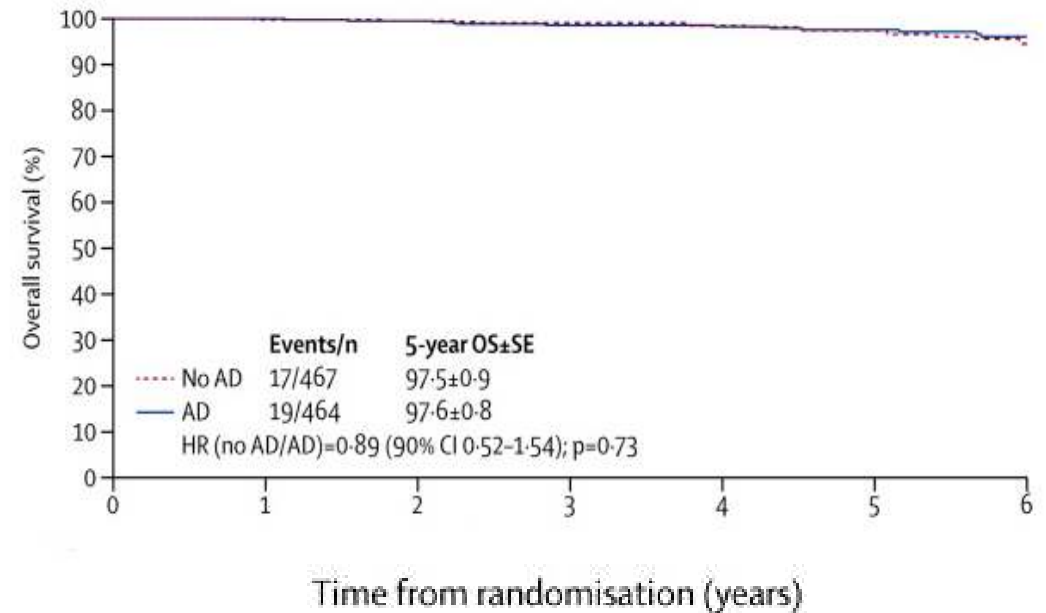
Only 9% of the patients received mastectomy

DISEASE-FREE SURVIVAL

Galimberti V. et al, Lancet Oncol. 2013



OVERALL SURVIVAL



Axillary dissection could be avoided in patients with early breast cancer and limited sentinel-lymph node involvement, thus eliminating complications of axillary surgery with no adverse effect on survival.

Disease free survival events	AD (n=464)	No AD (n=467)	Total (n=931)
Total	69 (15%)	55 (12%)	124 (13%)
Breast cancer events			
Local	10 (2%)	8 (2%)	18 (2%)
Regional	1 (<1%)	5 (1%)	6 (1%)
Distant	34 (7%)	25 (5%)	59 (6%)
Contralateral breast	3 (<1%)	9 (2%)	12 (1%)
Non breast cancer events			
Second (non breast) primary	20 (4%)	6 (1%)	26 (3%)
Death without prior cancer event	1 (<1%)	2 (<1%)	3 (<1%)
Deaths	19 (4%)	17 (4%)	36 (4%)

... non-sentinel axillary nodes were metastatic in 13% of the axillary dissection group

The discrepancy between the low rate of axillary recurrence in the group without axillary dissection and the high rate of axillary involvement in the axillary dissection group might be due to systemic treatment and whole breast irradiation, both of which can eliminate low volume axillary metastasis ...

Out-trial IEO:

No AD in 90 mastectomy pts with SN micrometastasis

All patients (N=90)	No	%.
First Event		
<i>Axillary LN mts</i>	1	1.1
<i>Regional LN mts</i>	1	1.1
<i>Contralateral BC</i>	1	1.1
<i>Liver mts</i>	2	2.2
<i>Liver + Bone mts</i>	1	1.1
<i>Brain mts</i>	1	1.1
<i>Other primary cancer</i>	1	1.1
<i>Death (unknown cause)</i>	1	1.1
TOTAL	9	10
Follow up (months)		
<i>Median (range)</i>	28 (5-115)	

Galimberti V., St Gallen 2013

The AMAROS trial compared axillary recurrence rate in 1425 sentinel node positive pts having breast-conserving surgery or mastectomy, randomized to receive ALND or radiotherapy to the axilla and supraclavicular nodes.

(Rutgers JCO 2013)

AXILLARY RECURRENCE RATES:

0.43% after ALND

1.19% after RT

*in spite of the findings that 32.8%
of pts having ALND had additional pos nodes*

DISEASE-FREE SURVIVAL: was not statistically different

LYMPHEDEMA: was significantly lower in RT group

In patients with positive SLN in whom it is clear that postmastectomy RT is indicated on the basis of the primary tumor characteristics, ALND can be avoided.