Venerdì 26 maggio 2017

Che cosa c'è di nuovo in chirurgia?

Presentazione e discussione **A. Paduos**

08.30 Presentazione

Aggiornamenti in chirurgia dell'ascella

08.35 • *Quando la dissezione ascellare?*
M.G. Lazzaretti

08.50 • *Il valore dell'esame estemporaneo sul linfonodo sentinella*
I. Castellano

09.05 Aggiornamenti in chirurgia della mammella

• *Screening e mastectomia: sono cambiate le indicazioni?*
M. Bortolini

09.20 Discussione

SERVIZIO SANITARIO REGIONALE
EMILIA-ROMAGNA
Azienda Unità Sanitaria Locale di Modena

Ospedale Ramazzini – Carpi
Unità Operativa Chirurgia Generale
(Unità semplice di Chirurgia Senologica)

AGGIORNAMENTI IN CHIRURGIA DELL'ASCELLA:

QUANDO LA DISSEZIONE ASCELLARE?

Maria Grazia Lazzaretti

VALUTAZIONE ASCELLA

- **PROGNOSI**
- **RACCOMANDAZIONI PER LA TERAPIA ADIUVANTE**

…NONOSTANTE MECCANISMI MOLECOLARI…

…SE CI SONO METASTASI…

SOPRAVVIVENZA SOVRAPPONIBILE, MA:

- ✓ **RISCHIO DI ULTERIORI METASTASI**
- ✓ **POSSIBILITA' DI SVILUPPARE RECIDIVE ASCELLARI SINTOMATICHE**
- ✓ **RISCHIO DI SOTTOUTILIZZO DI TERAPIE ADIUVANTI PER MANCANZA DI CORRETTA STADIAZIONE**

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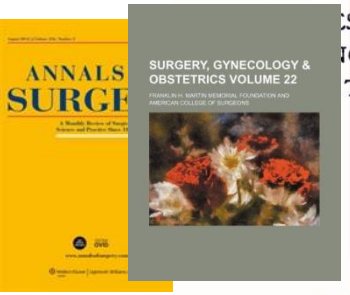
TEORIA VIRCHOW/HALSTED



THE ACCURACY OF CLINICAL NODAL STAGING AND OF LIMITED AXILLARY DISSECTION AS A DETERMINANT OF HISTOLOGIC NODAL STATUS IN CARCINOMA OF THE BREAST

Fisher B et Al; Surg Gynecol Obstet 1981

BREAST CANCER: RISK OF AXILLARY RECURRENCE IN NODE-NEGATIVE PATIENTS FOLLOWING PARTIAL DISSECTION OF THE AXILLA

Graversen HP et Al; Eur J Surg Oncol 1988

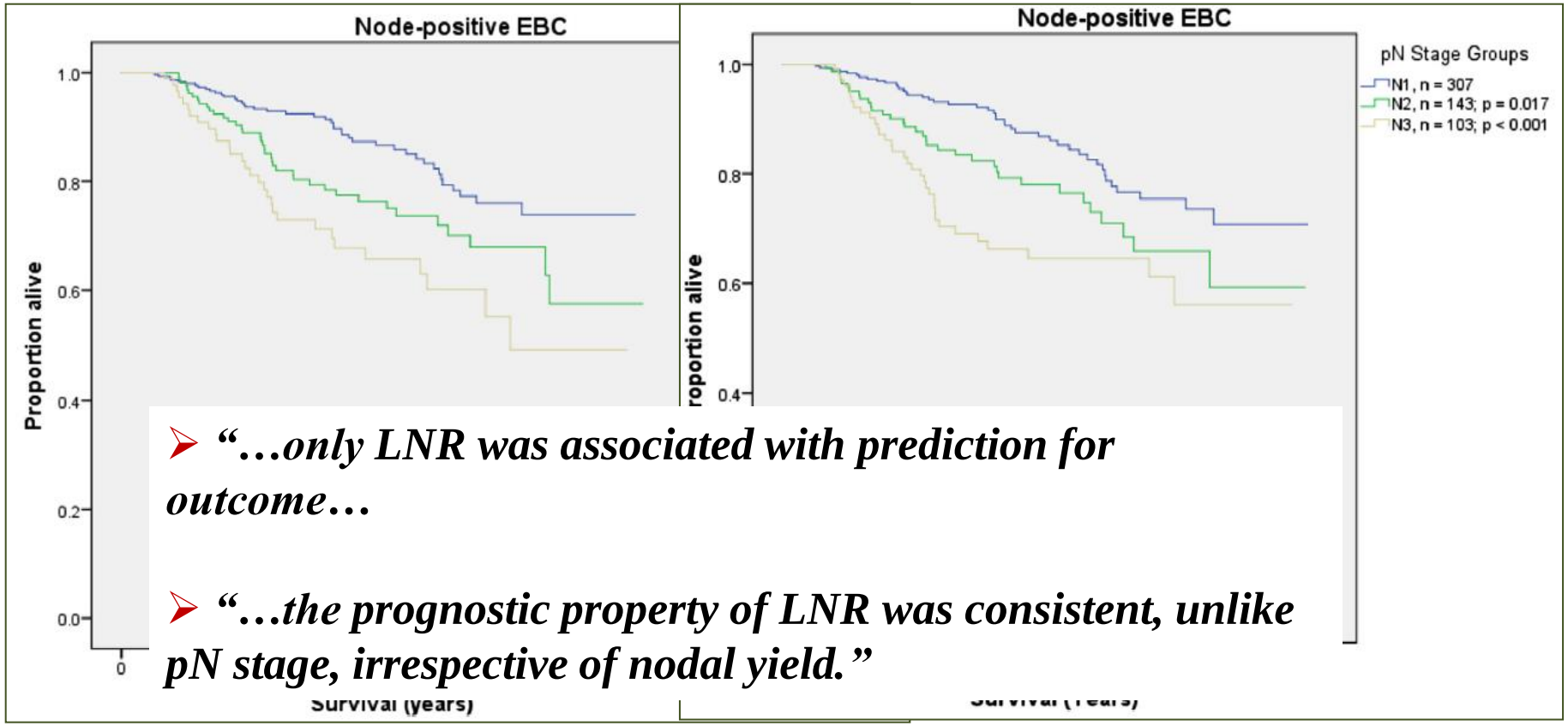
DOES THE NUMBER OF LYMPH NODES EXAMINED IN PATIENTS WITH LYMPH NODE-NEGATIVE BREAST CARCINOMA HAVE PROGNOSTIC SIGNIFICANCE?

Salama JK et Al; Cancer 2005

Eusoma Mandatory Quality Indicators for Breast Centre Certification

4	Proportion of patients with invasive cancer and axillary clearance performed with at least 10 lymph nodes examined	M	85%	98%

LYMPH NODE RATIO IN SENTINEL LYMPH NODE BIOPSY ERA: ARE WE LOSING PROGNOSTIC INFORMATION?



- ***"…only LNR was associated with prediction for outcome…***
- ***"…the prognostic property of LNR was consistent, unlike pN stage, irrespective of nodal yield."***

Quintyne KI et Al; Clin Breast Cancer 2016

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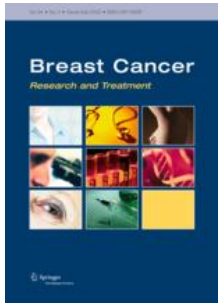
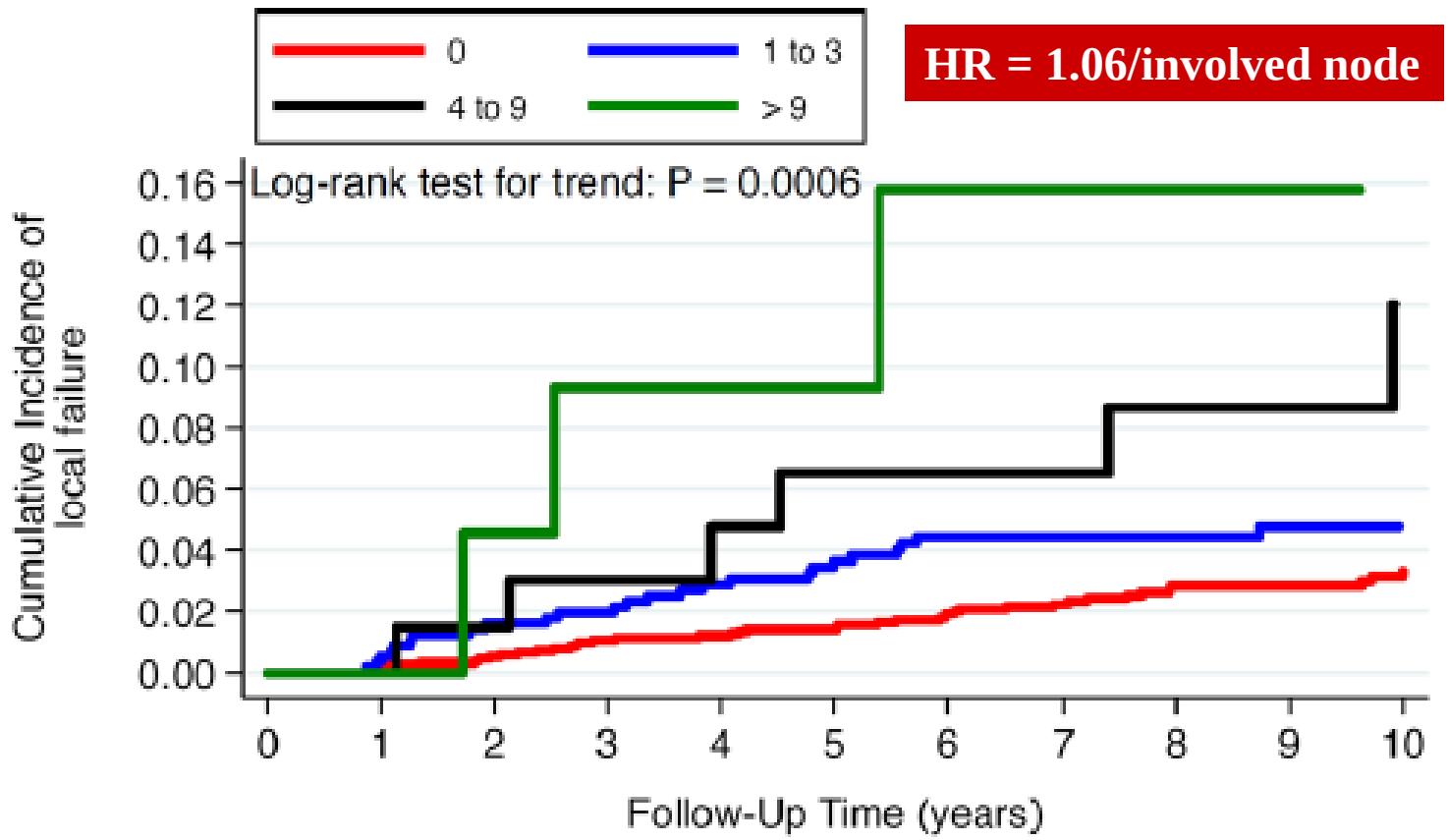


BREAST CANCER SUBTYPE, AGE AND LYMPH NODE STATUS AS PREDICTORS OF LOCAL RECURRENCE FOLLOWING BREAST-CONSERVING THERAPY

Multi-institutional cohort 2233 pts



HR = 1.06/involved node

Braunstein LZ et Al; Breast Cancer Res Treat 2017

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CHIRURGIA DELL'ASCELLA = STADIAZIONE

RECIDIVE ASCELLARI < ATTESO

BIOPSIA DEL LINFONODO SENTINELLA

STANDARD NELLA STADIAZIONE DELL'ASCELLA

…MA…:

- **NON SERVE PER ALCUNE PAZIENTI**
- **SE POSITIVO, NON SEMPRE NECESSARIA UNA D.A.**
- **SE FNAC+ PRE-INTERVENTO: SEMPRE D.A.?**

CHIRURGIA DELL'ASCELLA & COMPLICANZE

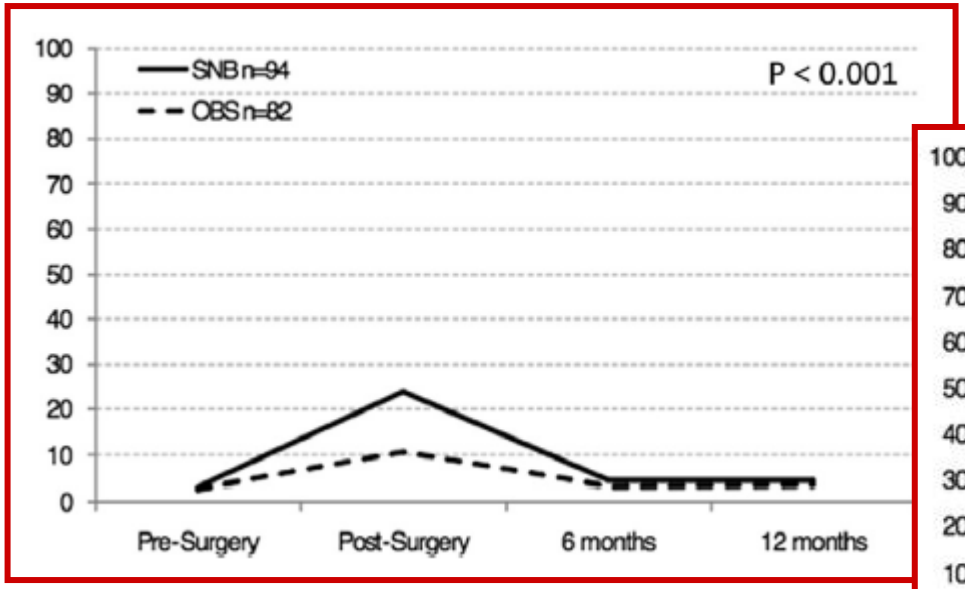
Metis, Settembre 2015

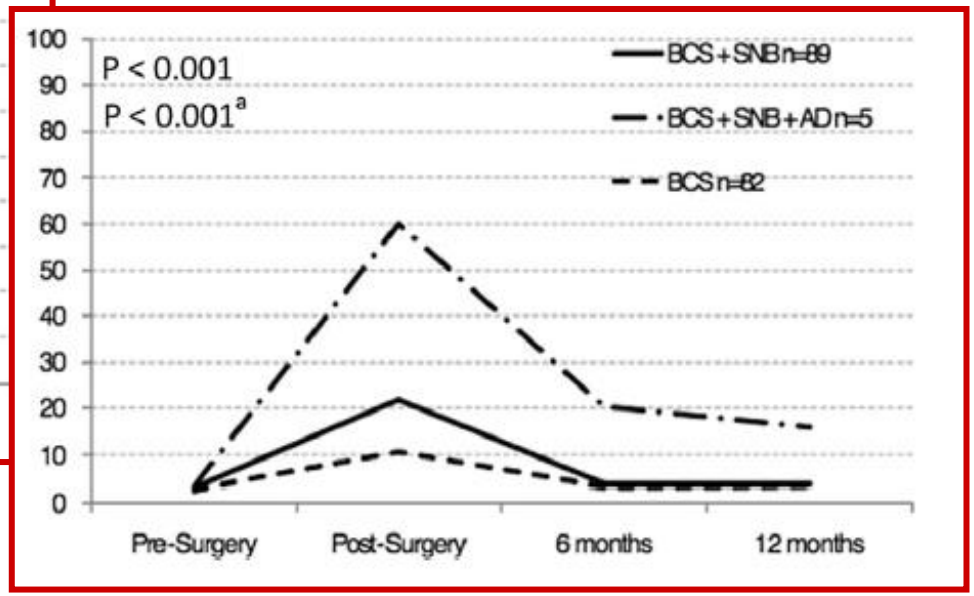
"Quando U. Veronesi iniziò, a distanza di quasi 20 anni, la sua nuova ricerca conservativa riguardante i linfonodi, l'edema nelle pubblicazioni riapparve alla grande, come esito talmente brutale da consigliare di lasciare i linfonodi in sede sacrificandone solo alcuni per studiarne lo stadio. Questo comportava comunque l'interruzione della catena.

Come per la conservazione della ghiandola, i senologi sono tornati ad essere appagati: il LS, dicono, evita il linfedema. E' vero! Non si vedono più i linfedemi di un tempo: braccia grosse, indurite, pesanti, arrossate, ciondolanti. Ma l'interruzione sussiste!"

BREAST CANCER SUBTYPE, AGE AND LYMPH NODE STATUS AS PREDICTORS OF LOCAL RECURRENCE FOLLOWING BREAST-CONSERVING THERAPY

First 176 pts recruited
Quick D.A.S.H.
(Disability Arm, Shoulder and Hand Questionnaire)
94 SNB arm vs 82 observation arm





Gentilini O. et Al; EJSO 2016

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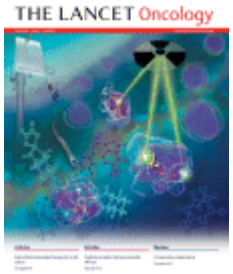

KYOTO BREAST CANCER CONSENSUS CONFERENCE 1 DE-ESCALATION OF AXILLARY SURGERY IN EARLY BREAST CANCER

35 MULTIDISCIPLINARY PANEL MEMBERS

TREND TO DE-ESCALATION

1. **advent of sentinel node biopsy**
2. **improvements in adjuvant therapies**
3. **down-staging of disease with neo-adjuvant approaches**
4. **predictive biomarkers superseding nodal status as prime determinants of eligibility for adjuvant systemic therapy**

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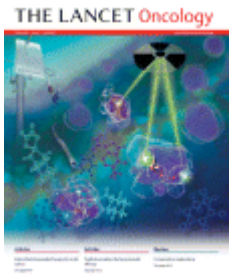
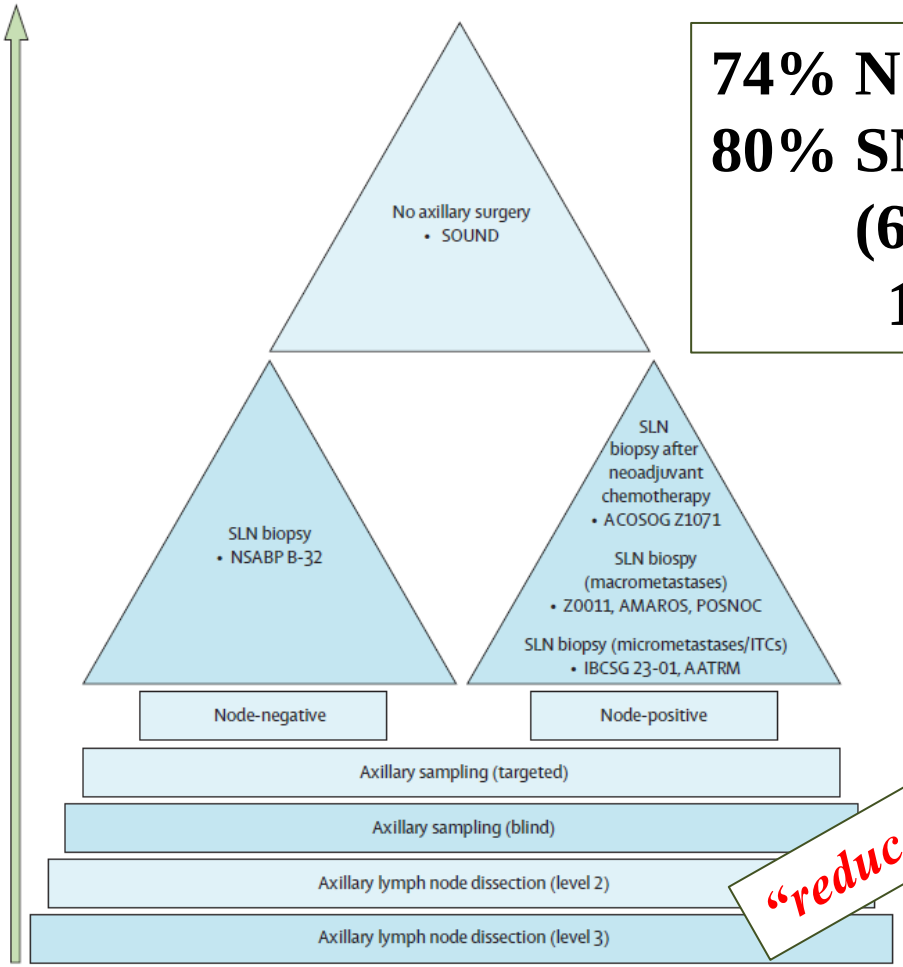
Jatoi I et Al; Lancet Oncol 2016



KYOTO BREAST CANCER CONSENSUS CONFERENCE 1
DE-ESCALATION OF AXILLARY SURGERY IN EARLY BREAST CANCER

35 MULTIDISCIPLINARY PANEL MEMBERS



74% No ALND in low volume +SNs
80% SNB after NACT
(60% >2 nodes removed
17% placed a marker)

"reduced morbidity and enhanced quality of life"

Jatoi I et Al; Lancet Oncol 2016

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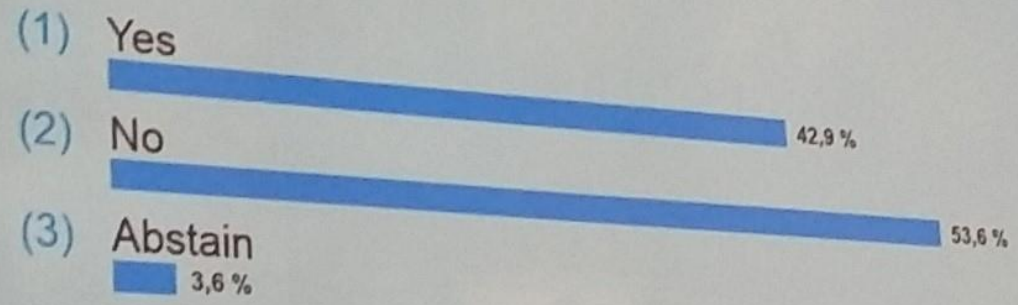
st.gallenoncology conferences

Surgery of the Axilla following Neo-Adjuvant Chemotherapy

20. In a patient who is clinically node-positive at diagnosis and who downstages after chemotherapy: Is SN biopsy appropriate with 1-2 LN detected?



15th St.Gallen International Breast Cancer Conference 2017 Consensus

BIG Breast International Group

IBCSG International Breast Cancer Study Group

Cochrane Library
Cochrane Database of Systematic Reviews

COCHRANE LYBRARY

Axillary treatment for operable primary breast c
(Review)

26 RCTs

No Ax surgery vs ALND	10 trials	3849	oderate quality evidence
Ax sampling vs ALND	6 tri	59 pts	Low quality evidence
SLNB vs ALN	ls	9426 pts	Moderate quality evidence
R	4 trials	2585 pts	High quality

"ALND of the clinically and radiologically uninvolved axilla is no longer acceptable practice in people with breast cancer."

LES RGERY vs ALND: < OS (HR=1.08)
> LR (HR 1.53)

Low quality evidence suggests increased risk of lymphoedema with ALND

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Bromham N et Al; Cochrane Collaboration 2017

Cochrane Library
Cochrane Database of Systematic Reviews

COCHRANE LYBRARY

Axillary treatment for operable primary breast cancer (Review)

Comparison 5 Less surgery versus ALND, Outcome 4 Local recurrence

Study or subgroup	Less surgery n/N	More surgery n/N	Hazard Ratio CI	Weight
1 axillary sampling vs ALND				
Cape Town (1)	8/232			
Cape Town (2)	9/173			
Cardiff	31/99			
Edinburgh 1	15/234			
Subtotal (95% CI)	**738**			
Heterogeneity: Chi² = 2.01, df = 3 (P = 0.57); I² =0.0%				
Test for overall effect: Z = 1.67 (P = 0.095)				
2 SLNB vs ALND				
Milan (3)	4/259			
Subtotal (95% CI)	**259**			
Heterogeneity: not applicable				
Test for overall effect: Z = 0.08 (P = 0.93)				
3 radiotherapy vs ALND				
Manchester	41/1113			
NSABP B-04 (4)	42/2025			
NSABP B-04 (5)	18/3896			
SE Scotland (6)	21/2204			
SE Scotland (7)	17/878			
WSSA Glasgow (8)	13/483			
WSSA Glasgow	1/41			
Subtotal (95% CI)	**10640**	**11616**		**76.5 %**
Heterogeneity: Chi² = 4.34, df = 6 (P = 0.63); I² =0.0%				
Test for overall effect: Z = 2.07 (P = 0.038)				
Total (95% CI)				**100.0 %**
Heterogeneity: Chi² = 12.34, df = 11 (P = 0.34); I² =11%				
Test for overall effect: Z = 1.05 (P = 0.30)				
Test for subgroup differences: Chi² = 5.99, df = 2 (P = 0.05), I² =67%				

0.01 0.1 1 10 100
Favours less surgery Favours more surgery

Comparison 5 Less surgery versus

Study or subgroup	Less surgery n/N	More su
1 no axillary surgery vs ALND		
Milan 2	9/110	
NSABP B-04	107/365	10
Subtotal (95% CI)	**475**	
Heterogeneity: Chi² = 1.66, df = 1 (P = 0.20); I² =40%		
Test for overall effect: Z = 0.59 (P = 0.55)		
2 axillary sampling vs ALND		
E'dburgh Sample/Clear	53/203	5
Subtotal (95% CI)	**203**	
Heterogeneity: not applicable		
Test for overall effect: Z = 0.27 (P = 0.79)		
3 radiotherapy vs ALND		
NSABP B-04 (1)	127/294	12
NSABP B-04 (2)	111/365	10
Subtotal (95% CI)	**659**	
Heterogeneity: Chi² = 0.00, df = 1 (P = 0.95); I² =0.0%		
Test for overall effect: Z = 0.96 (P = 0.34)		
Total (95% CI)		
Heterogeneity: Chi² = 1.69, df = 4 (P = 0.79); I² =0.0%		
Test for overall effect: Z = 1.15 (P = 0.25)		
Test for subgroup differences: Chi² = 0.02, df = 2 (P = 0.99), I² =		

Comparison 5 Less surgery versus ALND, Outcome 7 Lymphoedema. Increase in arm volume at 12 months postop.

Study or subgroup	Less surgery n/N	More surgery n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
1 no axillary surgery vs ALND					
Addenbrookes (1)	6/53	12/45		4.2 %	0.35 [0.12, 1.03]
Guy's (2)	0/91	6/104		2.2 %	0.08 [0.00, 1.49]
Institut Bergonie (3)	3/258	41/274		14.4 %	0.07 [0.02, 0.22]
NSABP B-04 (4)	48/312	177/577		38.5 %	0.41 [0.29, 0.59]
Subtotal (95% CI)	**714**	**1000**		**59.4 %**	**0.31 [0.23, 0.43]**
Total events: 57 (Less surgery), 236 (More surgery)					
Heterogeneity: Chi² = 9.68, df = 3 (P = 0.02); I² =69%					
Test for overall effect: Z = 7.29 (P < 0.00001)					
2 axillary sampling vs ALND					
Cardiff (5)	11/45	20/40		5.9 %	0.32 [0.13, 0.81]
Subtotal (95% CI)	**45**	**40**		**5.9 %**	**0.32 [0.13, 0.81]**
Total events: 11 (Less surgery), 20 (More surgery)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.40 (P = 0.016)					
3 SLNB vs ALND					
GIVOM Sentinella (6)	15/336	30/341		10.4 %	0.48 [0.26, 0.92]
Milan (7)	0/100	12/100		4.6 %	0.04 [0.00, 0.60]
SNAC (8)	29/544	47/544		16.3 %	0.60 [0.37, 0.96]
Subtotal (95% CI)	**980**	**985**		**31.3 %**	**0.48 [0.33, 0.69]**
Total events: 44 (Less surgery), 89 (More surgery)					
Heterogeneity: Chi² = 4.06, df = 2 (P = 0.13); I² =51%					
Test for overall effect: Z = 3.92 (P = 0.000090)					
4 radiotherapy vs ALND					
SE Scotland	5/100	10/100		3.5 %	0.47 [0.16, 1.44]
Subtotal (95% CI)	**100**	**100**		**3.5 %**	**0.47 [0.16, 1.44]**
Total events: 5 (Less surgery), 10 (More surgery)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.32 (P = 0.19)					
Total (95% CI)	**1839**	**2125**		**100.0 %**	**0.37 [0.29, 0.46]**
Total events: 117 (Less surgery), 355 (More surgery)					
Heterogeneity: Chi² = 16.78, df = 8 (P = 0.03); I² =52%					
Test for overall effect: Z = 8.64 (P < 0.00001)					
Test for subgroup differences: Chi² = 3.25, df = 3 (P = 0.36), I² =8%					

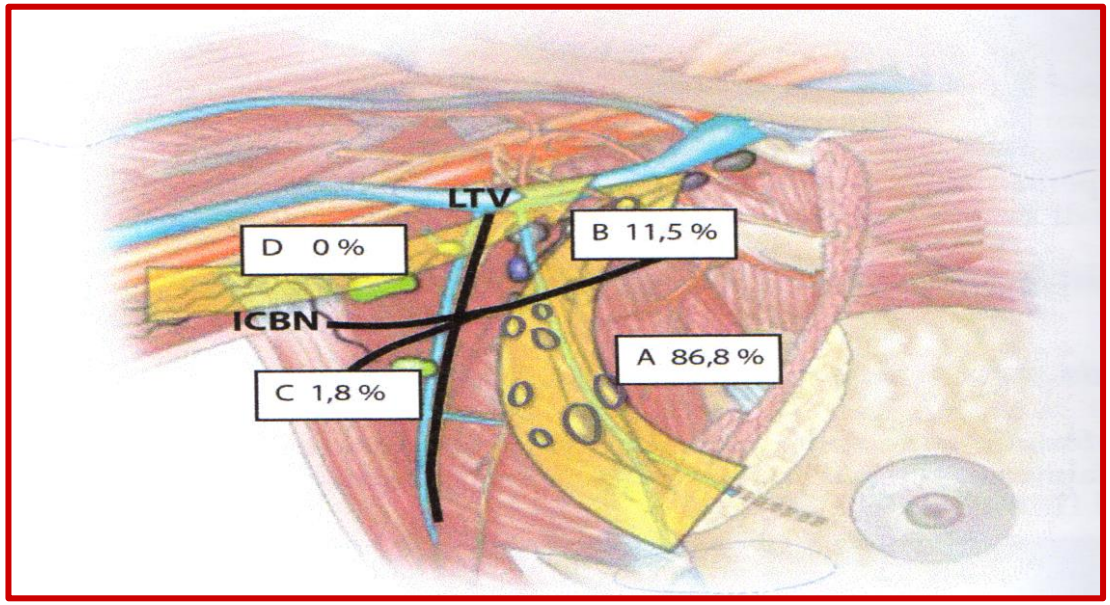
p < 0.00001

0.001 0.01 0.1 1 10 100 1000
Favours less surgery Favours more surgery

…SE DISSEZIONE ASCELLARE…

POSSIBILITA' DI RIDURRE GLI EFFETTI NEGATIVI A LIVELLO DI QUELLI DA RADIOTERAPIA?

Axillary Reverse Mapping



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AXILLARY REVERSE MAPPING

IS AXILLARY REVERSE MAPPING FEASIBLE IN BREAST CANCER PATIENTS?

Noguchi M et Al; EJSO 2015

IS THERE A ROLE FOR AXILLARY REVER MAPPING IN THE CURRENT MANAGEMENT OF BREAS ER TREATMENT?

s EJTh et Al; EJSO 2016

SYSTEMATIC REVIEW LARY REVERSE MAPPING IN

"…preservation of these nodes with proven axillary node metastasis warrants further research as de of lymphatic and lymphovenous anastomosis."

"…ARM is co cated for patients with clinically positive breast cancer."

"…this literature review does not show enough evidence to mandate the introduction of ARM into current cancer guidelines."

"PRACTICE CHANGING?"

AXILLARY REVERSE MAPPING IN N0 PATIENTS REQUIRING SENTINEL NODE BIOPSY – A SYSTEMATIC REVIEW OF THE LITERATURE AND NECESSITY OF A RANDOMIZED STUDY

Parks RM et Al; The Breast 2017

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DISSEZIONE ASCELLARE

INDICAZIONI RESIDUE:

1. **CLINICAMENTE N+ (palpazione, US, FNAC?)**
2. **CARCINOMA INFIAMMATORIO**
3. **MALATTIA RESIDUA ASCELLARE DOPO CTNA**
4. **LINFONODO SENTINELLA NON IDENTIFICATO**
5. ***MASTECTOMIA CON MACROMETASTASI NEL SENTINELLA***
6. ***PAZIENTI PER LE QUALI SONO NECESSARIE ULTERIORI INFORMAZIONI SUL NUMERO DI LINFONODI METASTATICI***

D.A. & ASCELLA cN+

TUMOUR BURDEN

PREDICTING THE EXTENT OF NODAL DISEASE IN EARLY-STAGE BREAST CANCER

	US (one to two suspicious lymph nodes) ($N = 149$)	SLND ($N = 518$)	p value
Mean number of positive lymph nodes	3.6	2.2	<0.001
Number of positive lymph nodes			
1	44 (30)	290 (56)	<0.001
2	38 (26)	127 (25)	
3	20 (13)	43 (8)	
≥4	47 (32)	58 (11)	
Largest lymph node metastasis (mm)	13.4	5.3	<0.0001

"…having metastases identified by US was the strongest predictor of having more than three positive lymph nodes (OR = 4.01)."

"…lobular histology was also predictive of having more than three positive lymph nodes (OR = 1.77)."

Caudle AS et Al; Ann Surg Oncol 2014

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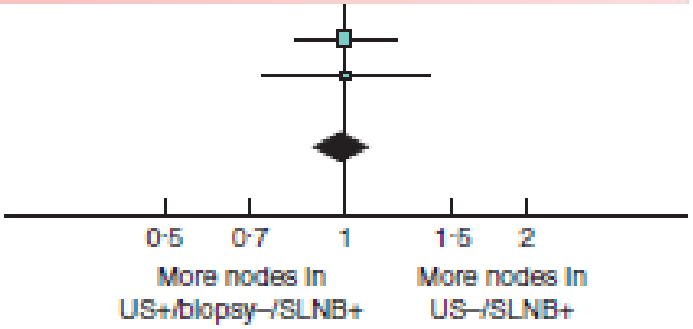
META-ANALYSIS OF ULTRASOUND-GUIDED BIOPSY OF SUSPICIOUS AXILLARY LYMPH NODES IN THE SELECTION OF PATIENTS WITH EXTENSIVE AXILLARY TUMOUR BURDEN IN BREAST CANCER

Reference	No. of patients with 1–3 nodes: US+/biopsy+	US+/biopsy–/SLNB+	Weight (%)	Risk ratio
Ciatto *et al.*[25]	69 of 206	71 of 109	27·6	0·66 (0·54, 0·82)
Damera *et al.*[19]	9 of 27	7 of 8	5·8	0·38 (0·21, 0·69)

Reference	No. of patients with 1–3 nodes: US+/biopsy+	US–/SLNB+	Weight (%)	Risk ratio
Damera *et al.*[19]	9 of 27	11 of 11	16·1	0·35 (0·21, 0·60)
Hinson *et al.*[27]	15 of 34	14 of 14	17·7	0·46 (0·31, 0·67)
Holwitt *et al.*[28]	65 of 74	12 of 30	17·0	2·20 (1·41, 3·43)
Lemos *et al.*[21]	5 of 6	2 of 3	12·0	1·25 (0·52, 3·00)

Reference	No. of patients with 1–3 nodes: US+/biopsy–/SLNB+	US–/SLNB+	Weight (%)	Risk ratio
Schlettecatte *et al.*[32]	7 of 7	24 of 24	30·4	1·00 (0·83, 1·21)
van Wely *et al.*[16]	13 of 19	256 of 376	10·9	1·00 (0·73, 1·37)
Total	42 of 49	311 of 432	100·0	0·99 (0·89, 1·10)

Heterogeneity: $\tau^2 = 0·00$; $\chi^2 = 1·10$, 5 d.f., $P = 0·95$; $I^2 = 0\%$
Test for overall effect: $Z = 0·20$, $P = 0·84$



" Patients with no suspicious nodes on ultrasound imaging and those with a negative ultrasound-guided biopsy could possibly be spared the sentinel lymph node procedure."

van Wely BJS et Al, BJS 2013

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SNB & TUMOUR LOAD

TOTAL TUMOUR LOAD ASSESSED BY ONE-STEP NUCLEIC ACID AMPLIFICATION ASSAY AS AN INTRAOPERATIVE PREDICTOR FOR NON-SENTINEL LYMPH NODE METASTASIS IN BREAST CANCER

	OR (95% CI) Univariate	*P* Univariate	OR (95% CI) Multivariate	*P* Multivariate
Age (years)	0.99 (0.94–1.05)	0.711		
Tumor size (mm)	1.08 (1.00–1.16)	0.047	1.06 (0.98–1.15)	0.168
Log TTL (copies/μL)	3.56 (1.57–8.09)	0.002	2.67 (1.06–6.70)	0.036
SLN macrometastases	4.64 (1.55–13.92)	0.006	2.63 (0.94–7.36)	0.066
Histologic type				
Invasive ductal carcinoma	1	0.974		
Invasive + ductal carcinoma in situ	0.97 (0.09–10.26)			
Invasive lobular carcinoma	0.58 (0.06–5.51)			
Invasive papillary carcinoma	–			
Histological tumor grade				
I	1	0.069		
II	0.15 (0.02–1.05)			
III	1.14 (0.18–7.28)			
Lymphovascular invasion (yes vs no)	1.60 (0.45–5.74)	0.471		
ER (positive vs negative)	2.33 (0.26–21.17)	0.451		
PR (positive vs negative)	6.28 (0.75–52.90)	0.091		
HER2 (positive vs negative)	0.71 (0.13–3.94)	0.699		
Multifocality (yes vs no)	2.78 (0.53–14.48)	0.226		

TTL only independent predictor of non SN metastases (OR = 2.67)

Nabais C et Al; The Breast 2016

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…& LA TERAPIA SISTEMICA PRIMARIA

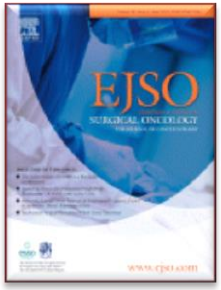
SENTINEL NODE BIOPSY PERFORMANCE AFTER NEOADJUVANT CHEMOTHERAPY IN LOCALLY ADVANCED BREAST CANCER: A SYSTEMATIC REVIEW AND META-ANALYSIS

Mocellin S et Al; Int J Cancer 2016

72 eligible studies
7451 pts
IR 89.6%
FNR 14.2%

…BUT…:

- **no survival benefit**
- **no therapeutic role of AD**
- ***role of minimal residual disease?***



SENTINEL NODE BIOPSY AFTER NEOADJUVANT TREATMENT IN BREAST CANCER: FIVE YEAR FOLLOW-UP OF PATIENTS WITH CLINICALLY NODE-NEGATIVE OR NODE-POSITIVE AXILLARY DISEASE BEFORE TREATMENT

- **FNR irrilevant**
- **AD has no effect on outcomes**

Galimberti V et Al; EJSO 2016

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AXILLARY NODAL MANAGEMENT FOLLOWING NEOADJUVANT CHEMOTHERAPY. A REVIEW

HOW TO AVOID AXILLARY LYMPH NODE DISSECTION?

1 **cN0, ER+, Her2neu- (suggested BCS)**

Initial surgery is the path most likely to avoid ALND

2 **cN0, TN or Her2neu+**

???

3 **cN+ or mastectomy pts**

NAC reduces the likelyhood of ALND

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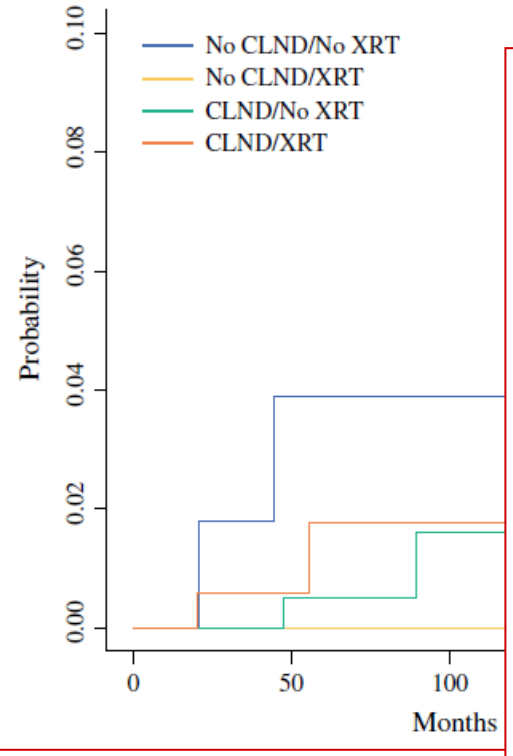
Pilewskie M et Al; Jama Oncol 2017

D.A…& MASTECTOMIA SN+

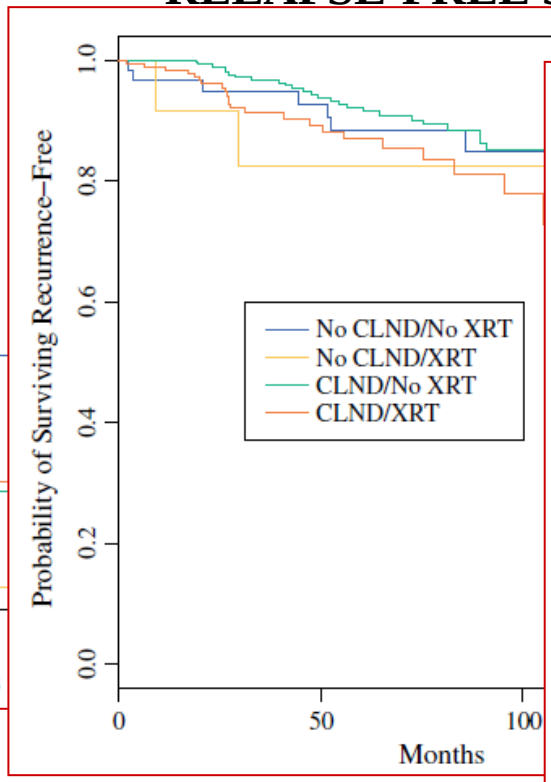
OUTCOMES OF SENTINEL LYMPH NODE-POSITIVE BREAST CANCER PATIENTS TREATED WITH MASTECTOMY WITHOUT AXILLARY THERAPY

525 SN+ pts

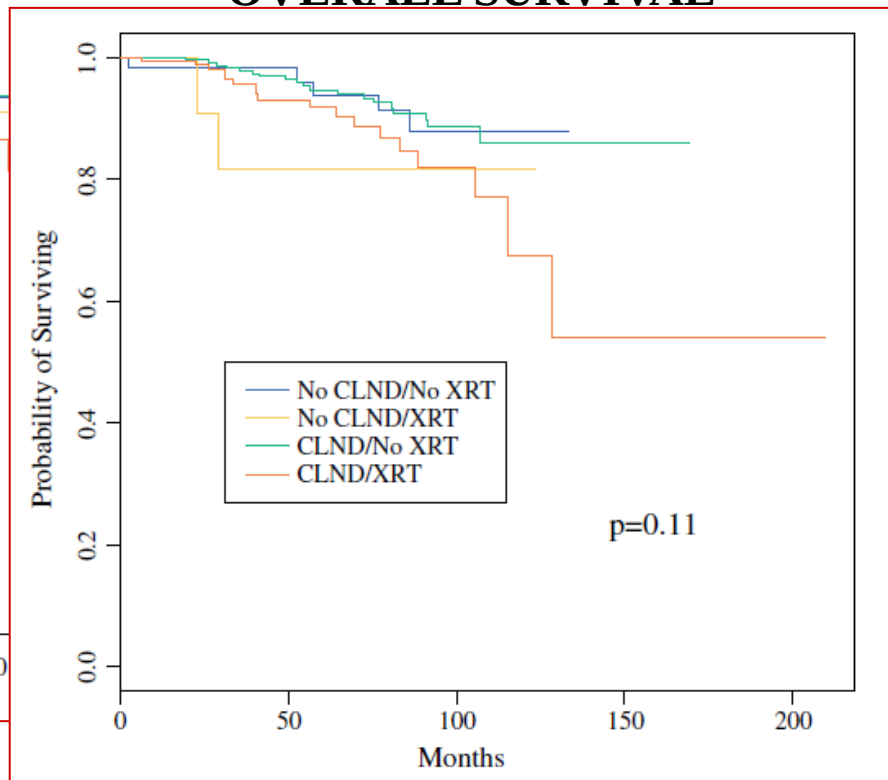
REGIONAL RECURRENCES



RELAPSE-FREE SURVIVAL



OVERALL SURVIVAL



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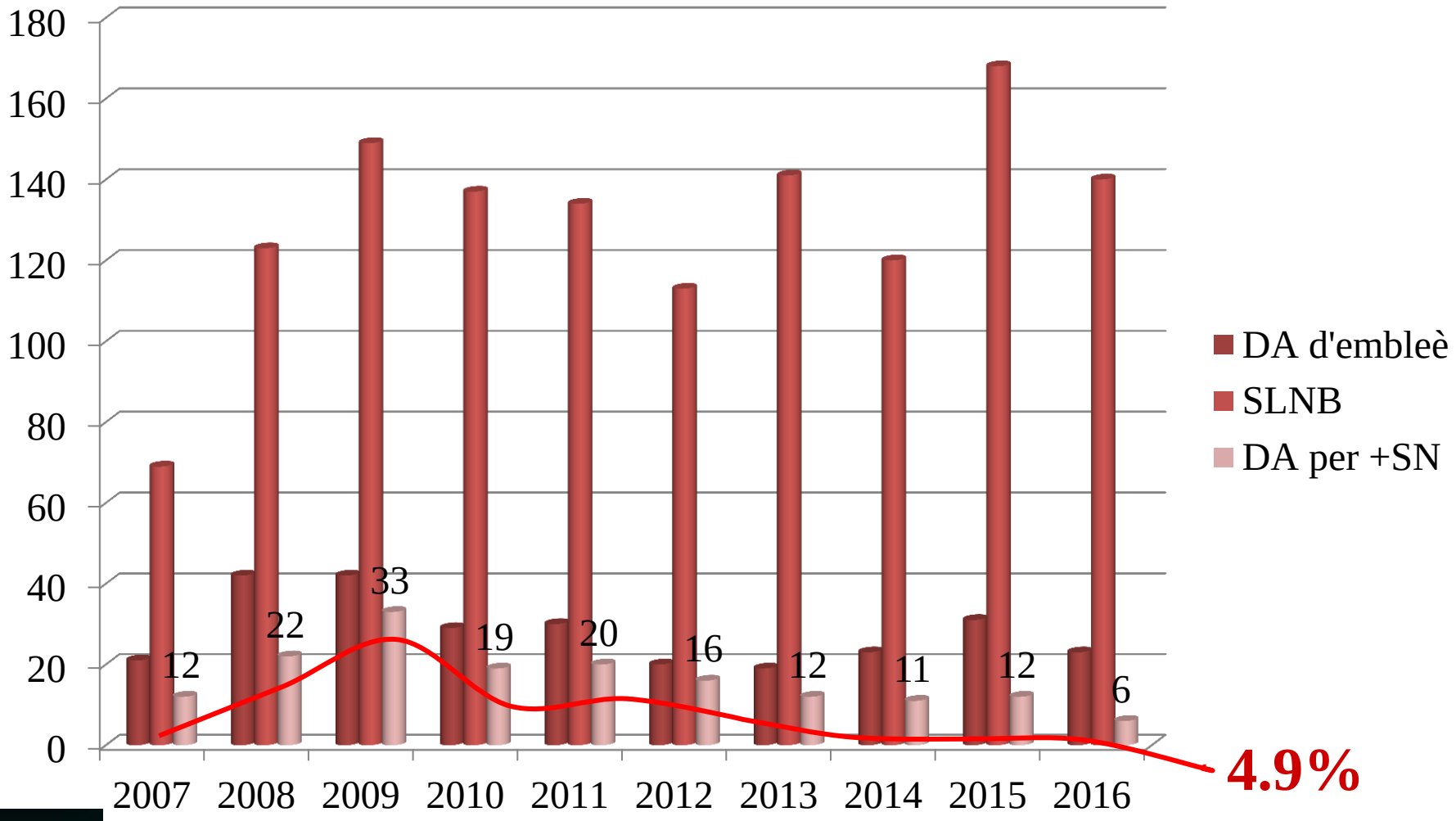
CASISTICA 2007 - 2016



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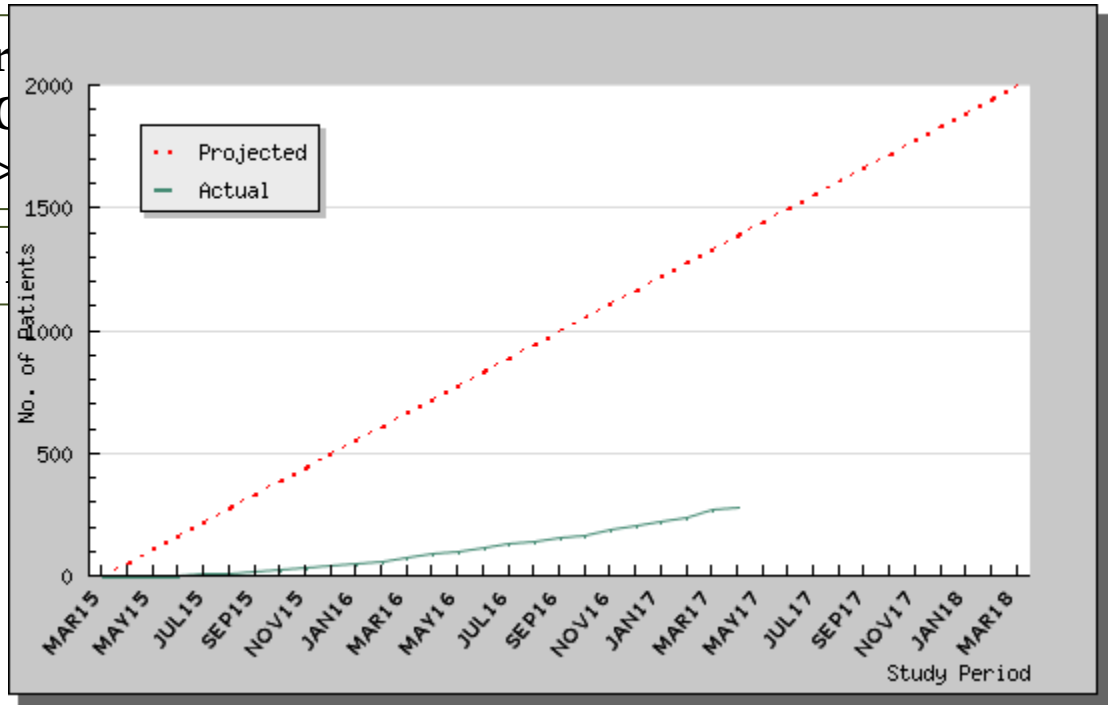
CASISTICA 2007 - 2016

PROTOCOLLI INTERNI

	2007	2015
INDICAZIONI	✓ cN0 (EOL, US, FNAC) ✓ T< 3cm ✓ unicentrico	✓ cN0 (EOL, US, FNAC) ✓ CTNA ✓ multicentrico ✓ recidiva dopo SNB
CONTROINDICAZIONI	✓ r ✓ C ✓ >	
SNB+	✓	



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CASISTICA 2007 - 2016

CASISTICA DISSEZIONE ASCELLARE
(264 pazienti operate dal 2010 al 2016)

	n°	n° medio linfonodi asportati (range)	n° medio linfonodi metastatici (range)	casi con => 3 linfonodi + (%)
US/FNAC+	108	22.9 (8-65)	8.7 (0-51)	84 (77.8)
SNB+	91	20.4 (9-41)	2.0 (0-19)	21 (23.1)
DA dopo NACT in cN+ negativizzati	35	22.2 (9-56)	1.5 (0-14)	5 (14.3)
controind. o volontà pazienti				0

ASCELLA POSITIVA ALLA PALPAZIONE	n° (%)	casi con => 3 linfonodi + (%)
US/FNAC+	51 (47.2)	43 (84.3)
SNB+	4 (4.4)	4 (100)

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CONSIDERAZIONI CONCLUSIVE

SNB REDUNDANT?

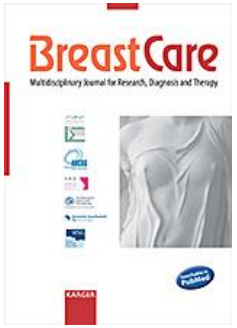
AXILLARY ULTRASOUND AND FINE-NEEDLE ASPIRATION CYTOLOGY IN THE PREOPERATIVE STAGING OF AXILLARY NODE METASTASES IN BREAST CANCER PATIENTS

Gipponi M et Al; The Breast 2016

PREOPERATIVE ULTRASOUND STAGING OF THE AXILLA MAKES PEROPERATIVE EXAMINATION OF THE SENTINEL NODE REDUNDANT IN BREAST CANCER: SAVING TISSUE, TIME AND

D.A. + Rt +…NACT

1. **T => 5 cm**
2. **> 3 linfonodi metastatici**
3. **importante EEC**
4. **linfonodi metastatici alla palpazione**



LYMPH NODE SURGERY – STEPWISE RETIREMENT FOR THE BREAST SURGEON?

"With decreasing use of ALND, opportunities for junior staff, fellows, and residents to practice this procedure will continue to decline. In parallel, the technical complexity of performing ALND will continue to increase in the more advanced, chemotherapy-resistant, or recurrent disease. Therefore, breast surgeons will not retire from lymph node surgery; instead, <u>they will be challanged by performing more difficult procedures with less experience</u>."

Landin J et Al; Breast Care 2016

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"…tailor more than to omit lymph node treatment…."

Poortmans 2016

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