Current management of the axilla in early breast cancer

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Breast and Surgical Endocrine Unit

University of Cape Town / Groote Schuur Hospital

Outline

1. *Where did it all start and why do we do axillary surgery?*

2. *Clinically node negative disease*
   - Which SLNB positive patients can also avoid axillary dissection?
   - Are there alternatives to Axillary dissection?
   - *What to do in patients who received neoadjuvant chemotherapy?*

3. *Clinically node positive disease*
   - *Do all node positive patients need an ALND?*

4. *Future of axillary surgery*

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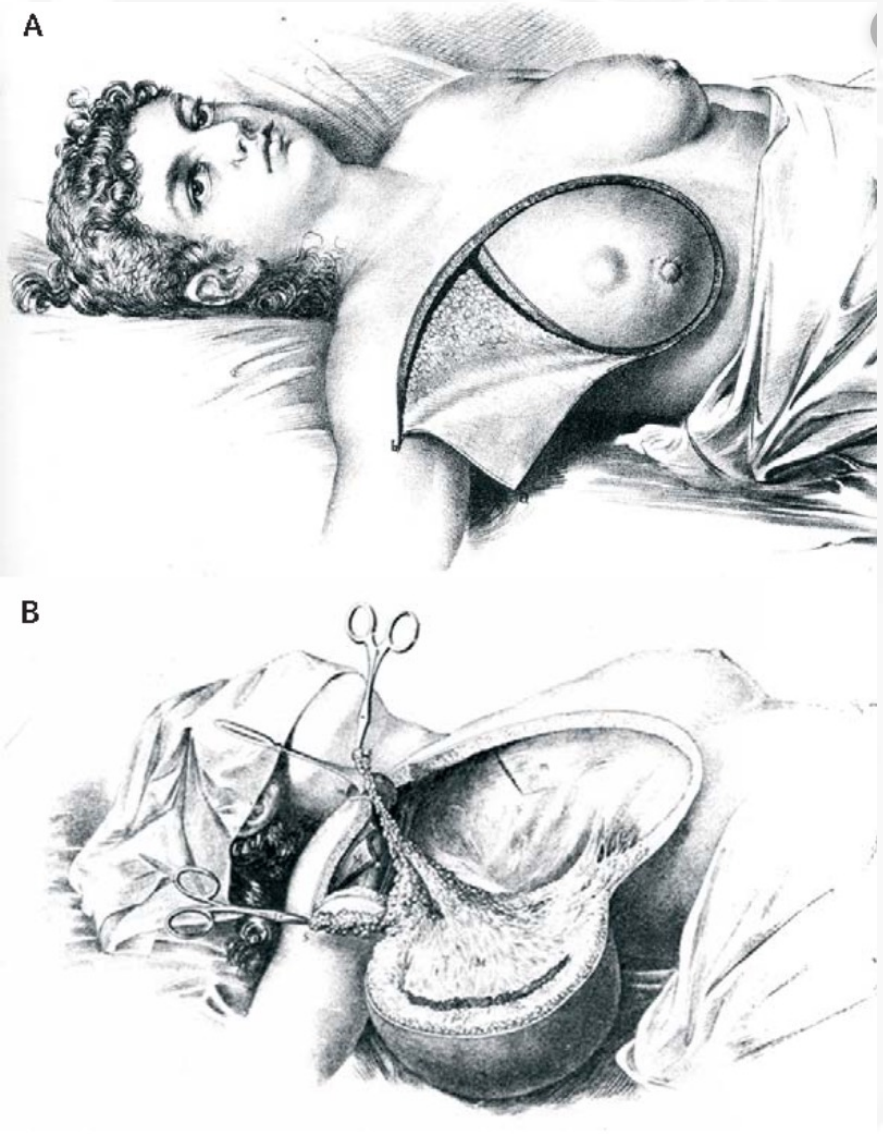
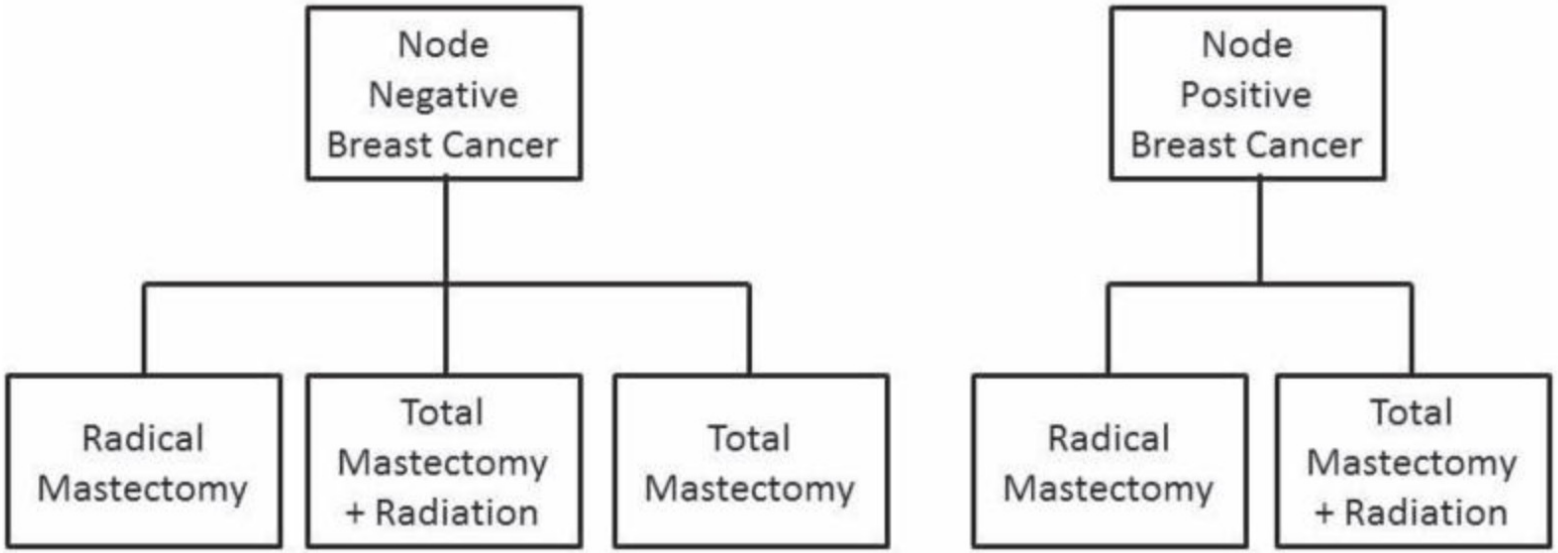
Background


A
B

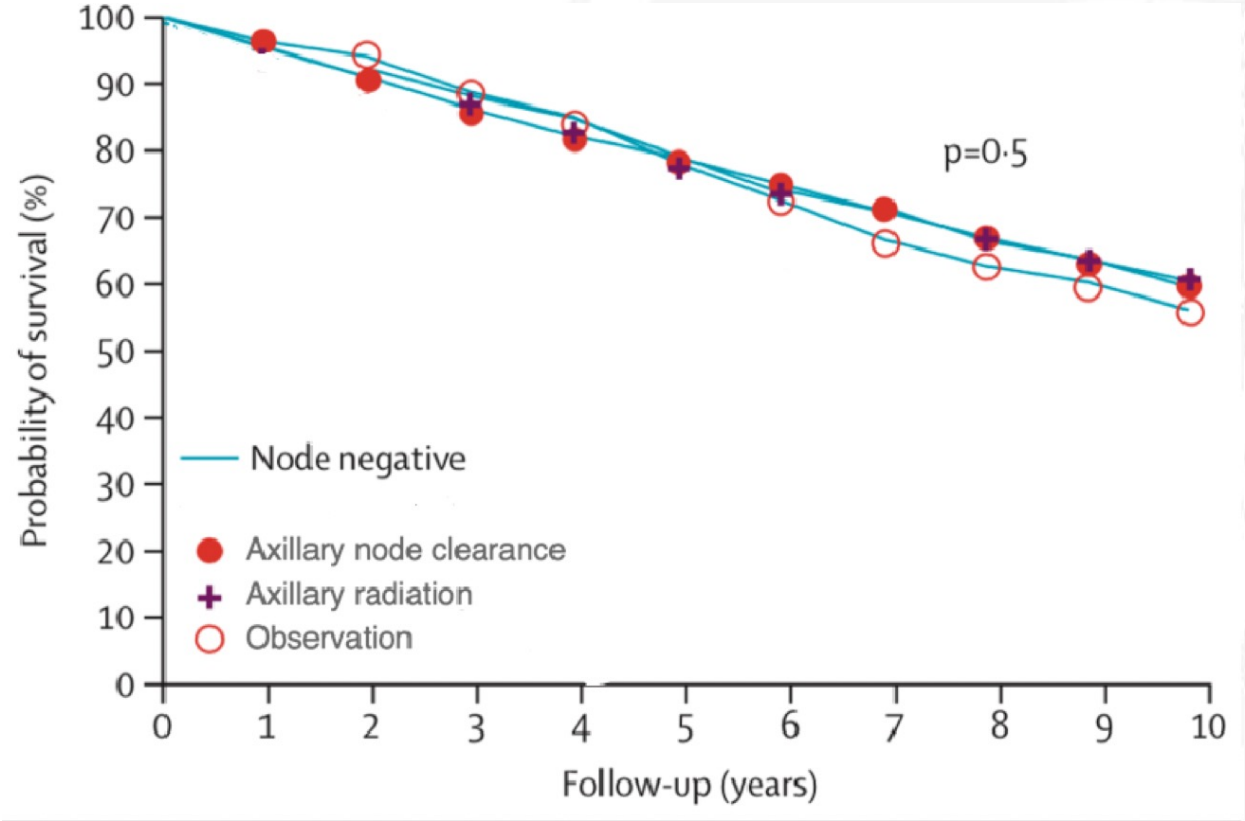
NSABP B-04



1971 – 1974, 1079 patients

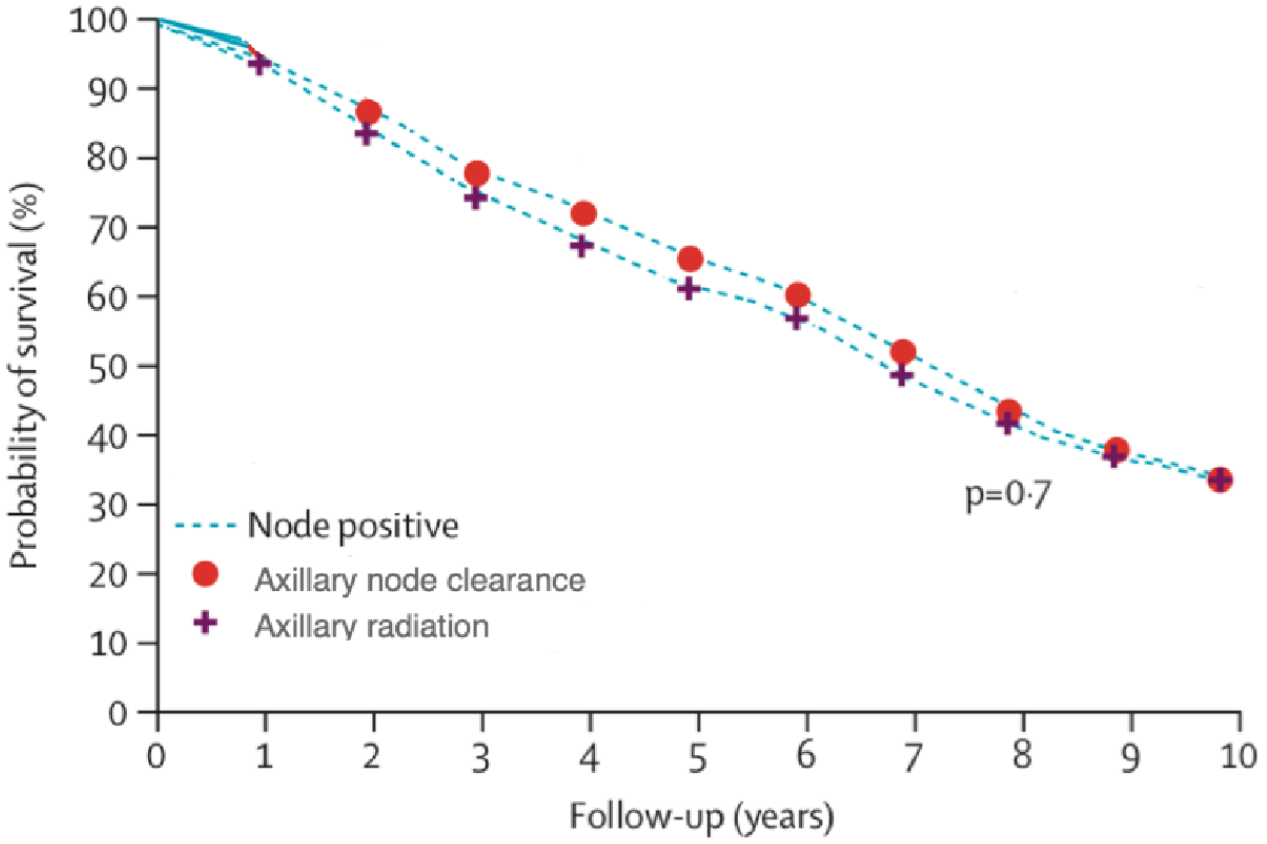
Fisher et al NEJM 347: 567-75; 2002.

NSABP B-04



Fisher et al NEJM 347: 567-75; 2002.

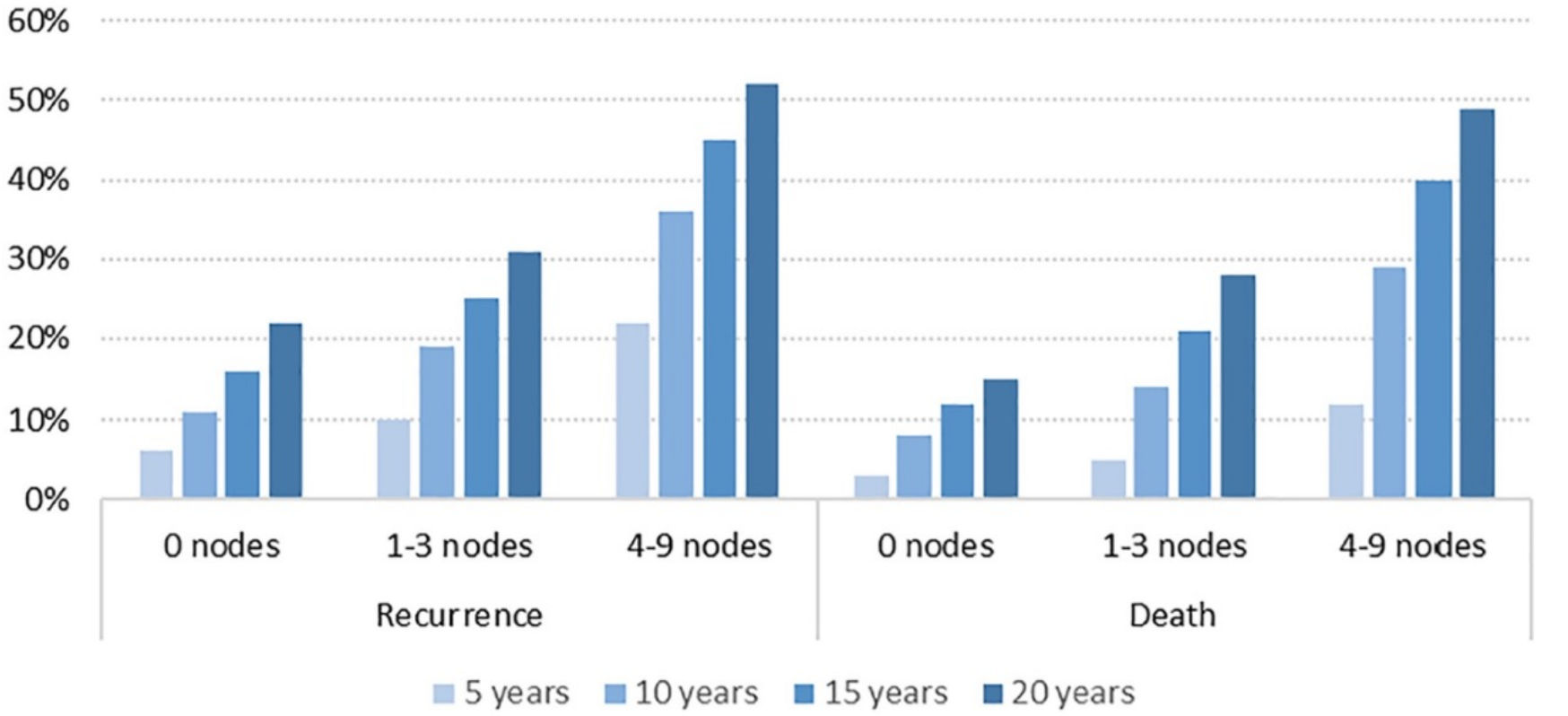
NSABP B-04



Fisher et al NEJM 347: 567-75; 2002.

No trials have shown a significant survival benefit from axillary surgery, both in node positive as well as node negative patients

Long term outcomes after estrogen receptor positive breast cancer



Why axillary surgery

DIAGNOSTIC

- Check if metastasis occurred
- Determine how many nodes are involved

TREATMENT

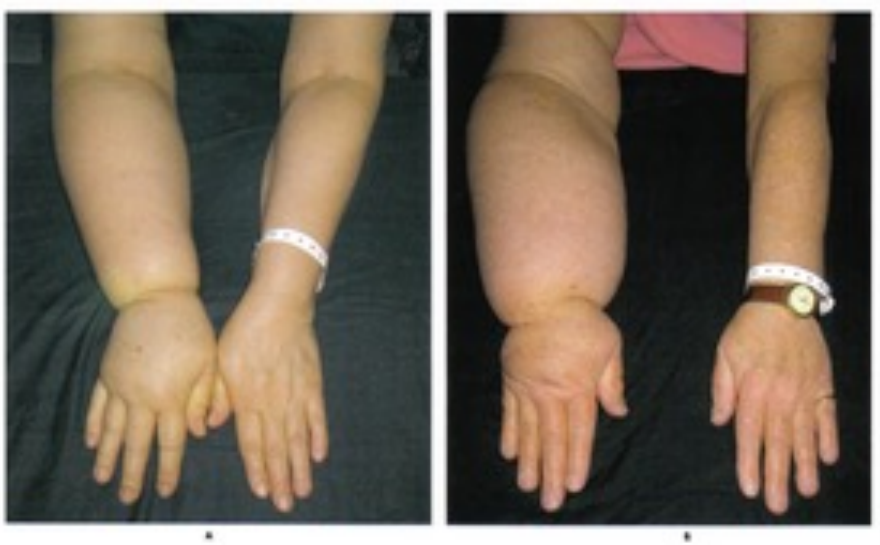
- Remove disease to aid local control (secondary benefit)

Guide local and systemic adjuvant treatment

Strong determent of prognosis

Overtreatment comes with surgical morbidity

- 6 months after surgical intervention, 73% of women continued to experience pain and limited range of motion of the involved extremity



Hack 1999
Journal of Clinical oncology

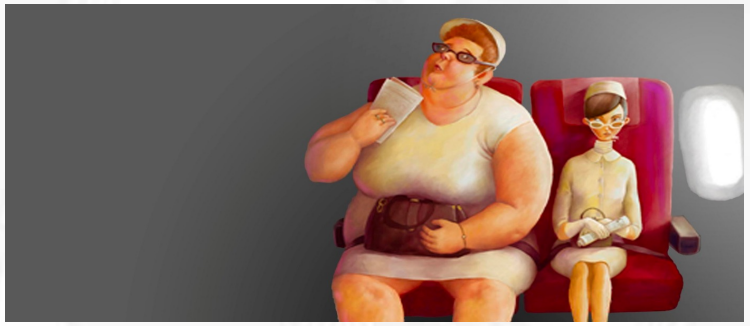
Current approach to the axilla

1. Clinically *Node-Negative* Disease (cN0)

Lymph nodes: How to find them

- **Clinical exam** – not reliable
- ***PET-CT scanning***
  - (97% specificity, low sensit… treat
  - If –ve not reliable
  - Expensive
- ***Ultrasound of th…***
  - Identifies 1 i… a's
  - Cheap
  - Simple
  - If negati… lances of pN2 drop to about 2%

DO ULTRASOUND!



Definition of clinically cN0 axilla

- Negative axilla both on clinical examination and radiology (Ultrasound) and **negative** cyto−/histopathology in case of a suspicious axillary lymph node

Sentinel lymph node biopsy standard of care in cN0 axilla

Lymphatic Mapping and Sentinel Lymph Node Biopsy in Early-Stage Breast Carcinoma

A Metaanalysis

Theodore Kim, M.D.[1]
Armando E. Giuliano, M.D.[2]
Gary H. Lyman, M.D., M.P.H.[3]

[1] Department of Medicine, Tufts-New England Medical Center, Boston, Massachusetts.

[2] Department of Surgery, John Wayne Cancer Institute, Santa Monica, California.

[3] James P. Wilmot Cancer Center, University of Rochester School of Medicine and Dentistry, Rochester, New York.

69 observational studies: SLNB validated by back-up ALND

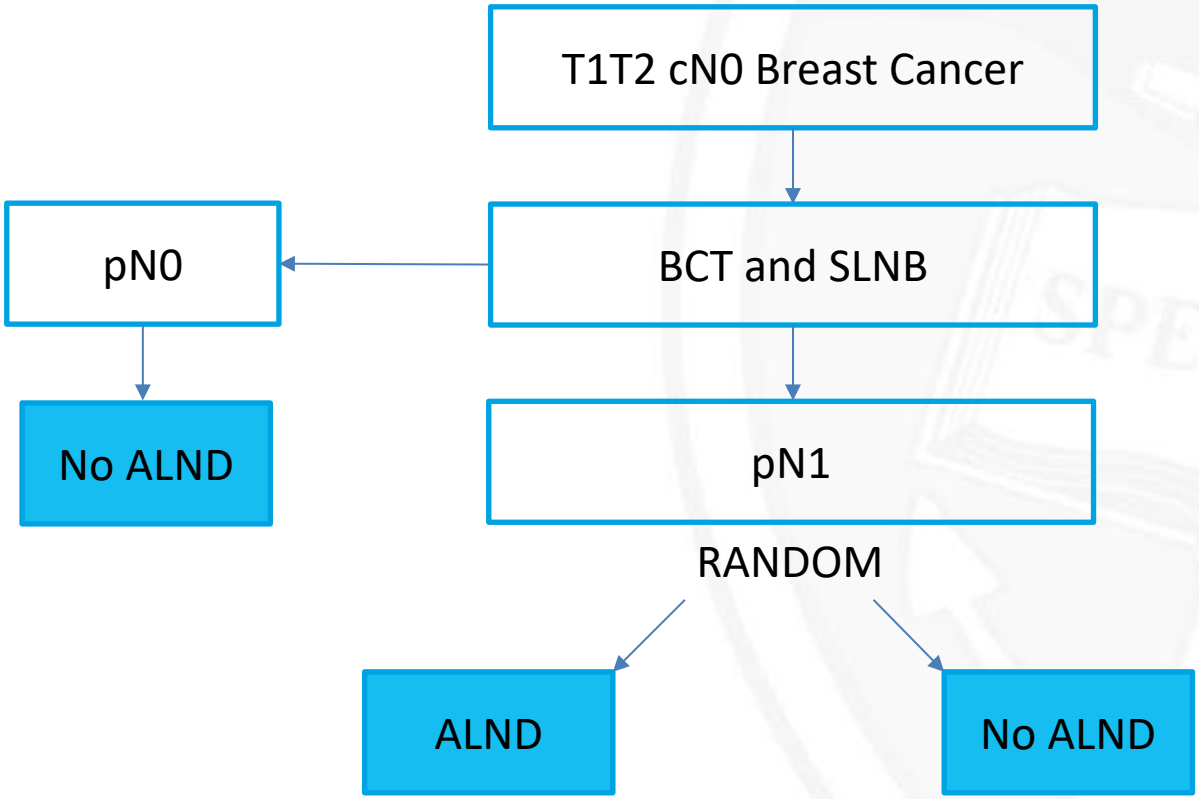
More than 8,000 patients the identification rate of SN was 96%, with a FN rate of 7.3%

Gold standard IR > 90%
False negative rate < 10%

Which cN0 patients with positive SLNB can avoid axillary dissection?

ACOSOG Z0011 TRIAL

Prospective trial (2011) – 813 patients



All patients received tangential field irradiation without a third field

ACOSOG Z0011 TRIAL

Outcomes of Z11

(Median f/u: 6.3 years)

Recurrence Type	ALND (420)	SLNB only (436)
Locoregional (%)	2.8	4.1
Local	1.8	3.6
Axillary	0.5	0.9
DFS (%)	92.5	91.8
OS (%)	83.9	82.2

ACOSOG Z0011 TRIAL

Outcomes of Z11
10 year results

	SN Alone (%)	SN + Ax Dissection (%)	p
LRR	6.2	5.3	0.36
DFS	80.3	78.3	0.30
OS	83.6	86.3	0.40

ACOSOG Z0011 TRIAL

Conclusion from Z011

Low metastatic axillary burden – no benefit from completion ALND when combined with WBRT and systemic therapy

Because of these results we stopped doing intraoperative assessment of SNs for patient who did not receive NACT

The Breast 45 (2019) 89–96

Contents lists available at ScienceDirect

The Breast

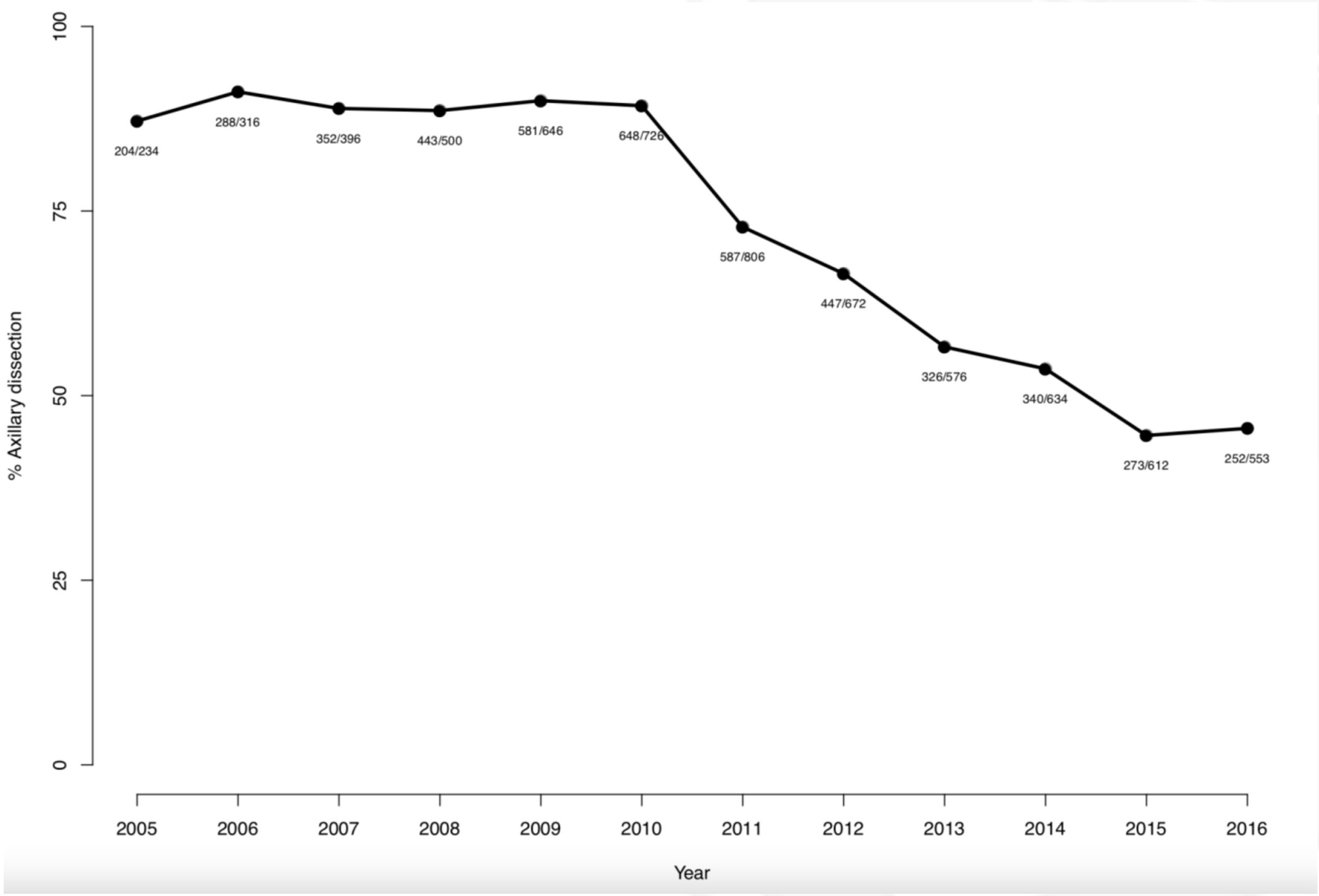
journal homepage: www.elsevier.com/brst

Original article

Trends in axillary lymph node dissection for early-stage breast cancer in Europe: Impact of evidence on practice

Carlos A. Garcia-Etienne [a, *], Robert E. Mansel [b], Mariano Tomatis [c], Joerg Heil [d], Laura Biganzoli [e, f], Alberta Ferrari [a], Lorenza Marotti [f], Adele Sgarella [a], Antonio Ponti [c], the EUSOMA Working Group[1]

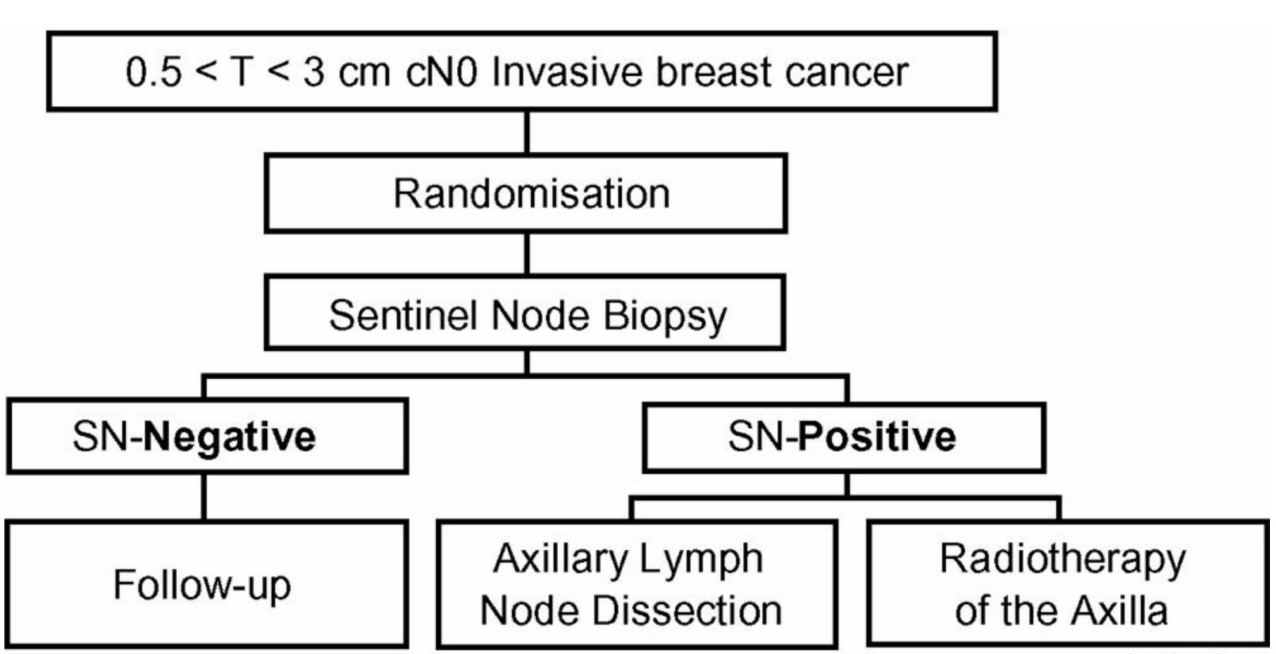
[a] *Breast Surgery, Fondazione IRCCS Policlinico San Matteo, Università degli Studi di Pavia, Italy*
[b] *School of Medicine, Cardiff University, United Kingdom*
[c] *AOU Città della Salute e della Scienza, CPO Piemonte and EUSOMA Data Centre, Turin, Italy*
[d] *University of Heidelberg, Germany*
[e] *Nuovo Ospedale di Prato, Italy*
[f] *EUSOMA, Florence, Italy*

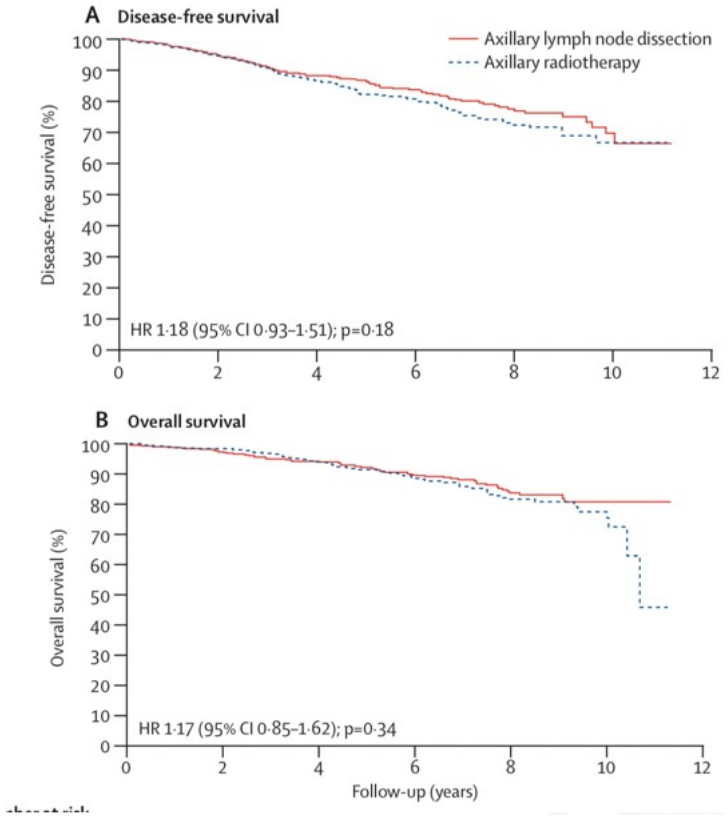

% Axillary dissection
0
25
50
75
100
204/234
288/316
352/396
443/500
581/646
648/726
587/806
447/672
326/576
340/634
273/612
252/553
2005
2006
2007
2008
2009
2010
2011
2012
2013
2014
2015
2016
Year

Is RT as good as ALND in cN0 patients with axillary metastasis?

AMAROS (EORTC) TRIAL

Prospective, randomized trial (2013) – 1 425 patients





10 Year results

	ALND	AXILLARY RT
AXILLARY RECURRENCE	0.93%	1.82%

No difference in DFS and OS

Lymphedema

- Double the rate of lymphedema after ALND vs Axillary RT

29% vs 14%

OTOASOR

Available online at www.sciencedirect.com

ScienceDirect

EJSO 43 (2017) 672–679

EJSO the Journal of Cancer Surgery

www.ejso.com

Eight-year follow up result of the OTOASOR trial: The Optimal Treatment Of the Axilla – Surgery Or Radiotherapy after positive sentinel lymph node biopsy in early-stage breast cancer: A randomized, single centre, phase III, non-inferiority trial

Á. Sávolt [a,*], G. Péley [b,†], C. Polgár [c], N. Udvarhelyi [d], G. Rubovszky [d], E. Kovács [e], B. Győrffy [f], M. Kásler [a], Z. Mátrai [a]

[a] *Department of Breast and Sarcoma Surgery, National Institute of Oncology, Budapest, Hungary*
[b] *Department of General Surgery, Norfolk and Norwich University Hospital, Norwich, UK*
[c] *Center of Radiotherapy, National Institute of Oncology, Budapest, Hungary*
[d] *Department of Pathology, National Institute of Oncology, Budapest, Hungary*
[e] *Department of Diagnostic Imaging, National Institute of Oncology, Budapest, Hungary*
[f] *MTA TTK Momentum Cancer Biomarker Res. Group, Hungarian Academy of Sciences, Budapest, Hungary*

Accepted 5 December 2016
Available online 16 January 2017

These 2 trials both show that in patients with a low burden of axillary disease, AxRT provides equal outcomes to ALND with less morbidity

What about patients undergoing mastectomy with a positive SN who do not need radiotherapy post operatively?

Can we omit RT and ALND of the positive axilla completely and just give adjuvant RT?

POSNAC

- POSNOC - POsitive Sentinel NOde: adjuvant therapy alone versus adjuvant therapy plus Clearance or axillary radiotherapy.
- A randomised controlled trial of axillary treatment in women with early stage breast cancer who have metastases in one or two sentinel nodes
- The study will compare adjuvant therapy alone with adjuvant therapy plus axillary treatment (axillary node clearance (ANC) or axillary radiotherapy (ART)).
- Primary Outcome
  - Axillary recurrence at 5 years

Difference between Z011 and POSNAC

	Z11	POSNAC
Size of metastasis	Micro or Macrometastasis	Macrometastasis
Extranodal invasion	No	Yes
Mastectomy	No	Yes
RT quality assurance	No	Yes
Mandatory pre-op ultrasound	No	Yes

POSNAC

- Results awaited

What if cN0 and patient planned for neoadjuvant chemotherapy?

Should the SLNB be done before chemotherapy starts or after chemotherapy?

SNB Before Neoadjuvant Therapy

Arguments in Favor

- Provides information on the status of the SNs without the confounding effects of neoadjuvant therapy
  - Guide further surgical management of the axilla
  - Selection of optimal local-regional XRT

SNB Before Neoadjuvant Therapy

Disadvantages

- Requires two surgical procedures
- Does not take advantage of the potential down-staging effects on lymph nodes

Current consensus

- Most experts agree that SLNB should preferably be done after neoadjuvant chemotherapy
- One procedure, prognostic value of a positive node after neoadjuvant chemotherapy

How accurate is SLNB after chemotherapy in cNo patients

RESEARCH ARTICLE

The Feasibility and Accuracy of Sentinel Lymph Node Biopsy in Initially Clinically Node-Negative Breast Cancer after Neoadjuvant Chemotherapy: A Systematic Review and Meta-Analysis

Chong Geng, Xiao Chen, Xiaohua Pan, Jiyu Li*

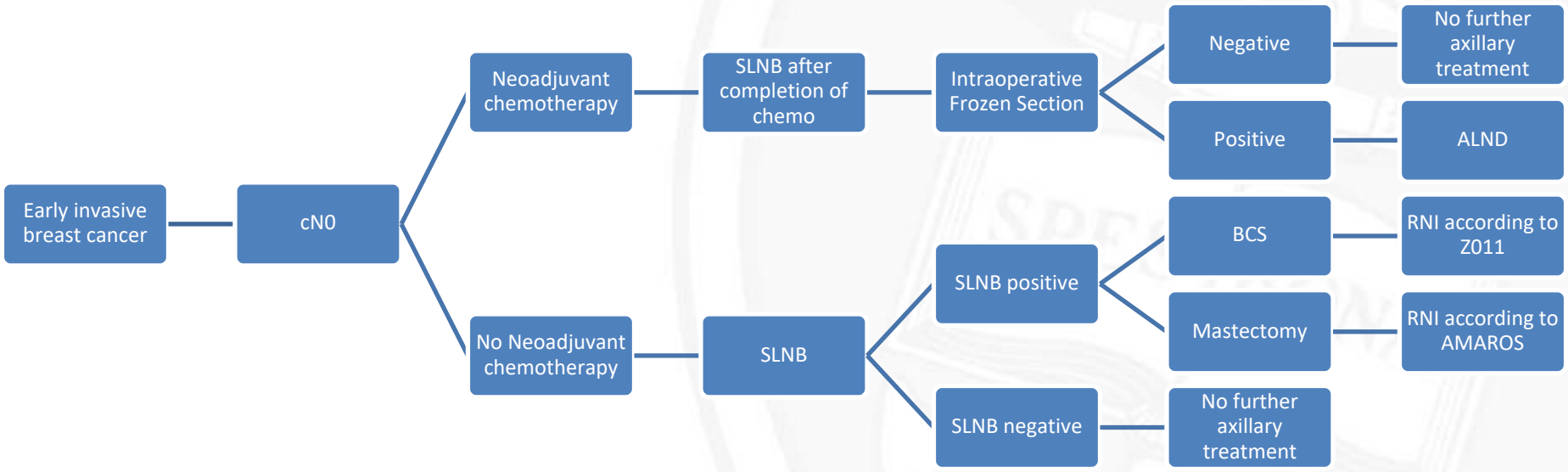
Department of Breast and Thyroid Surgery, Shandong Provincial Hospital Affiliated to Shandong University, Jinan, Shandong Province, China

A total of 1,456 patients from 16 studies
Pooled identification rate (IR) for SLNB was 96%
False negative rate (FNR) was 6%

Practical approach to SLNB in cN0 after neoadjuvant chemotherapy

- SLN biopsy after NAC
- Intraoperative Frozen Section of SLN – GSH protocol
- ALND for failed mapping
- ALND for any positive LN including micrometastatic disease

Management of cN0 patients at Groote Schuur Hospital Breast Unit



2. Clinically *Node-Positive* Disease (cN1)

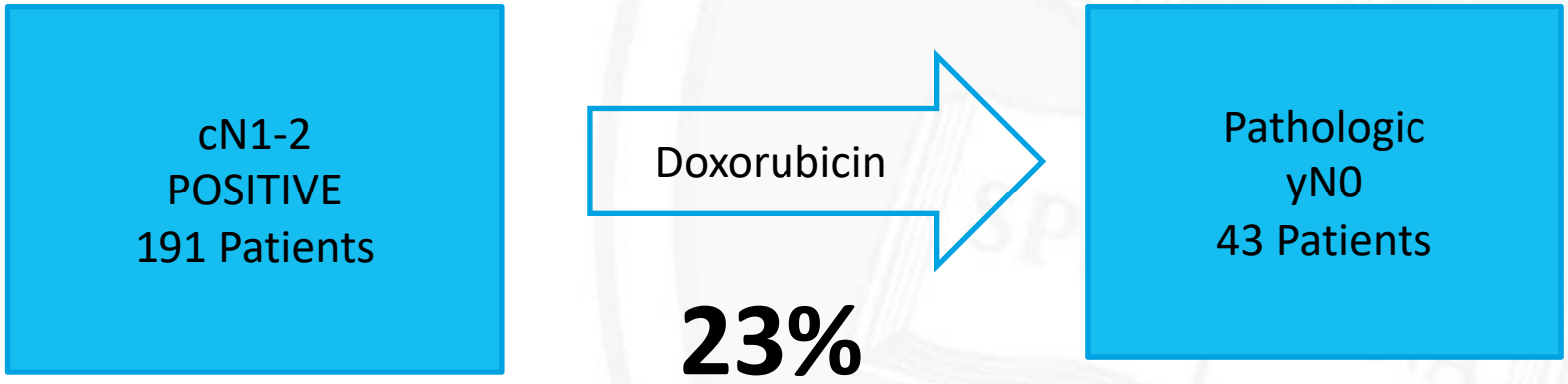
cN1

- Gold standard would be axillary lymph node dissection

But

- Neoadjuvant chemotherapy can convert a patient from node positive to node negative and spare an ALND with all the associated morbidity

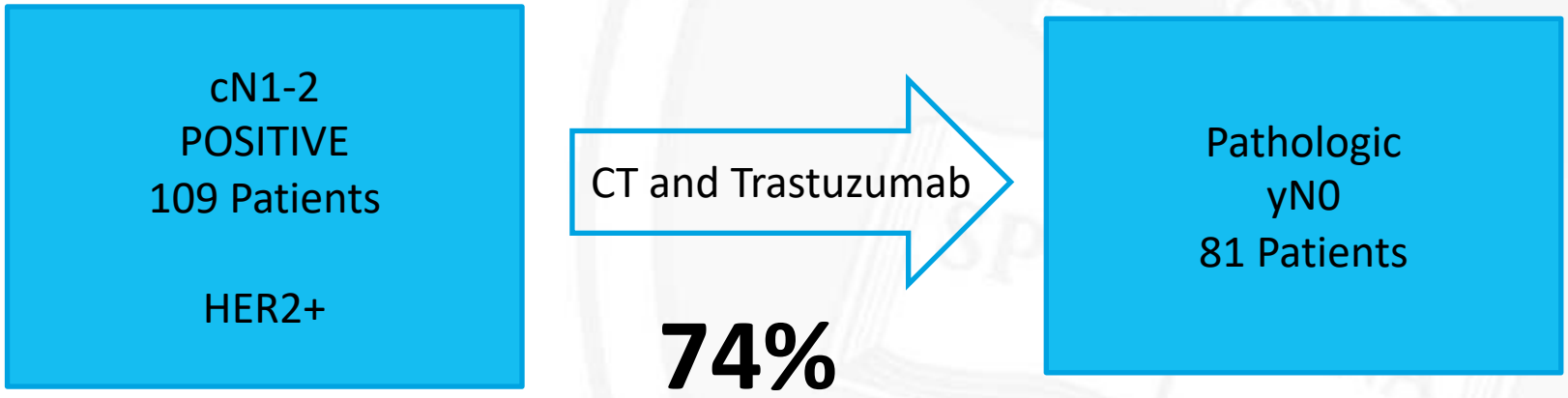
Conversion of Axillary metastasis: FNA positive to Pathologic negative



Median number of LNs removed 16

Kuerer H. Annals of surgery 1999

Conversion of Axillary metastasis: FNA positive to Pathologic negative



Median number of LNs removed 19

Dominici L. CANCER 2010

How accurate is SLN Biopsy after chemotherapy if cN1 convert cN0

- 2 largest Trials
  - ACOSOG Z1071
  - SENTINA

SLN Biopsy After Neoadjuvant Therapy cN1 convert cN0

	ACOSOG Z1071	SENTINA
N	649	592(cN+)*
Mapping	Dual tracer recommended (79%)	Technetium required
Pre-op biopsy?	Yes	Not required (biopsy =25%)
Nodal pCR	41%	52% ypN0 (?)
IR	92.7%	80.1%
FNR (Overall)	12.6%	14.2%
1 SLN	31.5%	24.3%
2 SLN	21.1%	18.5%
≥3SLN	9.1%	7.3%

*1737 patients enrolled in 4 arm multicenter trial. 592 ARM C were cN+ to cN0

Meta-Analysis of SLNB for cN1 patients after neoadjuvant chemotherapy

13 articles: 1921 patients

Pooled IR: 90% Pooled FNR: 14%

	False negative rate
Single tracer	19% (11-27%)
Dual Tracer	11% (6 – 15%)
1 Node removed	20% (13 – 27%)
2 Nodes removed	12% (5 – 19%)
≥ 3 Nodes removed	4% (0 – 9%)

Tee SR. BJS 2018

Clipping the node for SLN after NAC

- Clipped node +/- SLN to reflect the status of the nodal basin in all-comers undergoing NAC

	N	Node +	pCR (%)	FNR (%)
Clipped node	191	120	37%	4.2% (95%CI 1.4-9.5)
SLN	118	74	37%	10.1% (95%CI 4.2-19.8)
SLN + clipped node	118	74	37%	1.4% (95%CI 0.03-7.3)

Also noted clipped node was not a SLN in ~ 20% pts

→ *"Targeted Axillary Dissection"*

Caudle AS. JCO 2016

Practical problems with Targeted Axillary Node Dissection

- Which node to clip? ⟶ The most abnormal node
- How many nodes to clip? ⟶ Clip only 1 node
- Logistical problems at time of removal
  - Need to localize node at the end of chemo with a wire (2nd procedure)
  - Difficulty in finding clipped node on ultrasound

To clip or not to clip

- Clipping node before NACT widely accepted as a standard of care
- Retrospective studies showing that the clipped node was not a sentinel lymph node (SLN) in approximately 20% of cases
- Majority of these reports, the sentinel lymph node biopsy (SLNB) procedure was not optimized for the post NACT setting
- Downsides to nodal clipping, including an increased number of procedures, additional costs, and, if the clipped node cannot be retrieved, which happens in up to 20% of cases
- Data from four multicenter prospective trials indicate that
  - SLNB procedure is optimized with dual tracer
  - retrieval of at least 3 SLNs
  - the false-negative rate of SLNB is < 10%, allowing for accurate staging without nodal clipping

ASO Author Reflections: Do We Need to Clip Metastatic Lymph Nodes at Diagnosis and Localize Them After Neoadjuvant Chemotherapy?

Giacomo Montagna, MD, MPH, and Monica Morrow, MD

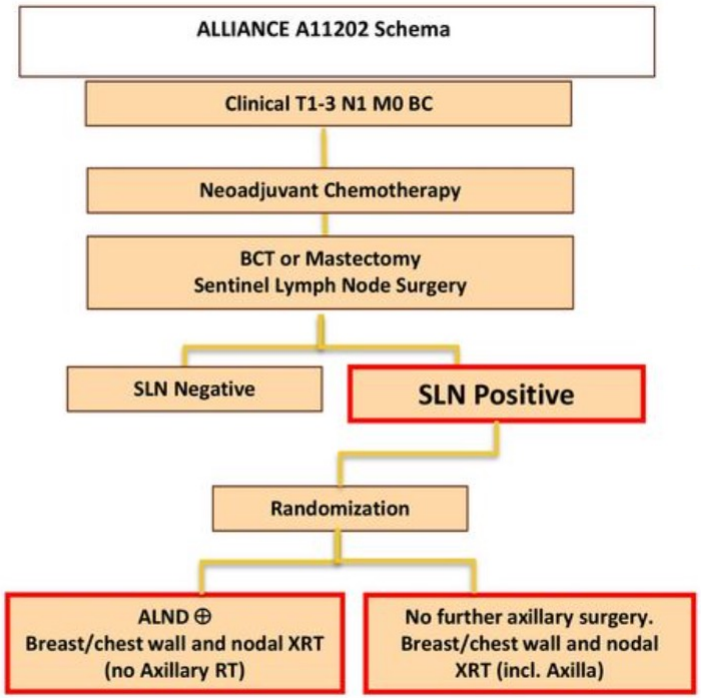
Breast Service, Department of Surgery, Memorial Sloan Kettering Cancer Center, New York, NY

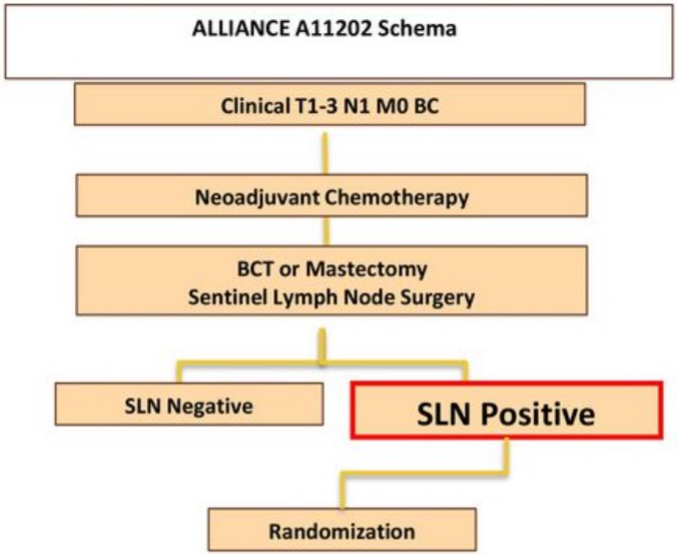
- 269 patients with biopsy-proven N+ disease
- 251 of 269 (93%) patients had 3 or more SLNs
- The median number of SLNs removed was 4
- The clipped node was an SLN in 88% (220/251) of cases.
- Of the 31 of 251 (12%) cases where the clipped node was not an SLN, 13 had a positive SLN mandating axillary lymph node dissection (ALND), and the clip was identified in the ALND specimen.
- In the remaining 18 (7%), where three or more negative SLNs were retrieved and an ALND was not performed, the clip was not retrieved.
- There have been no axillary failures in this group at a median follow-up of 55 months.

SLNB in cN1 patients that converts to cN0 after chemotherapy

- SLN biopsy after NAC with dual mapping agents
- If node not clipped, remove at least 3 SLN
- If node clipped, clipped node + SLNs (minimum 2 nodes, clipped node +1)
- Intraoperative frozen section of all nodes removed
- ALND for
  - failed mapping
  - fewer than 3 SLN (or failure to retrieve clipped node)
  - any positive LN including micrometastatic disease / ITCs *(unless on trial)*

Can RT replace ALND after NACT





Can axillary RT replace ALND ?

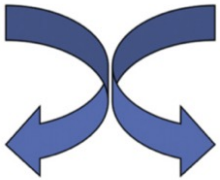
What about abandoning lymph node surgery completely in early node negative patients?

SOUND trial (Italian)

Sentinel node vs **O**bservation after axillary **U**ltra-sou**ND**

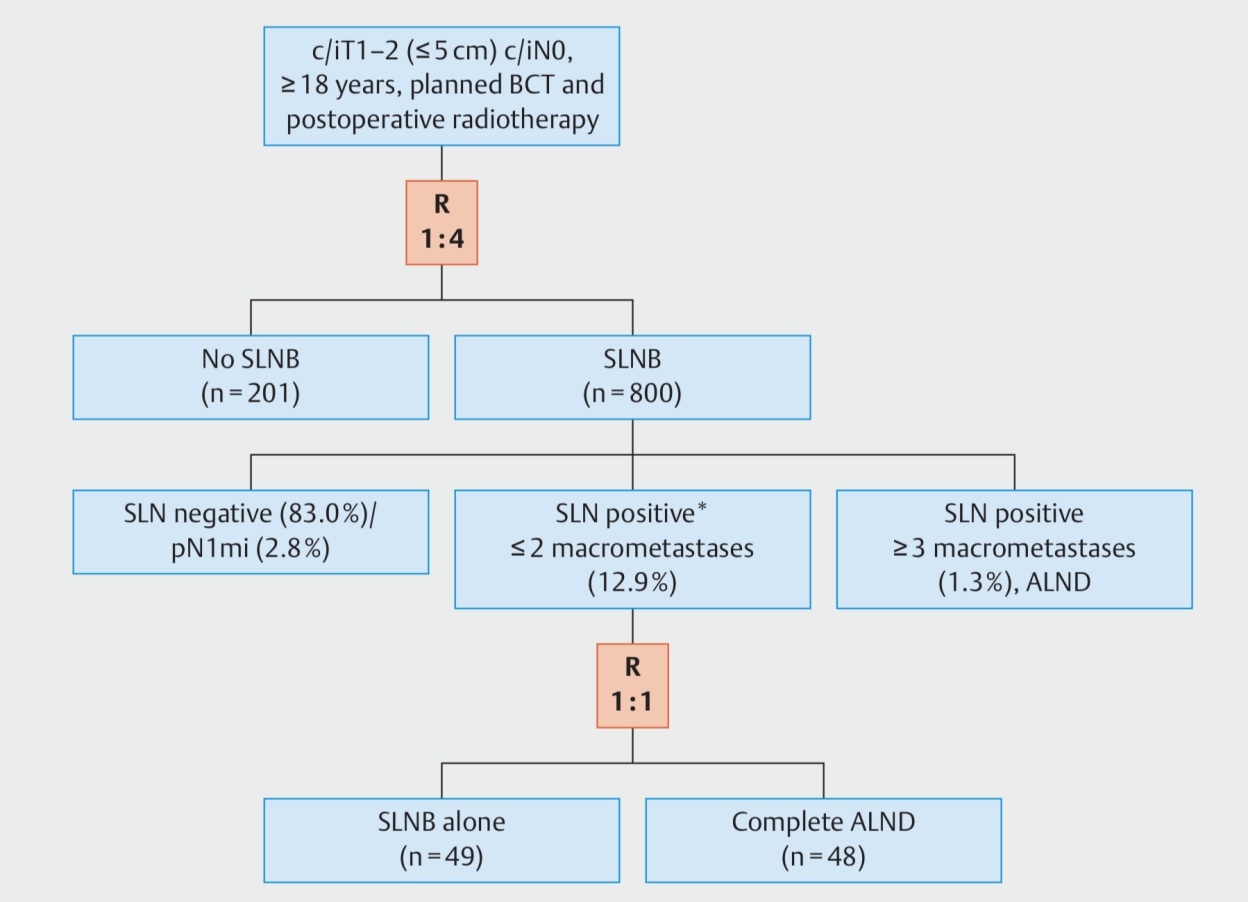
- Patients with breast cancer ≤2.0 cm
- Any age
- Candidates to Breast Conserving Surgery
- Negative preoperative axillary assessment (negative ultra-sound of the axilla or negative FNAC of a single doubtful axillary lymph node)

Randomization



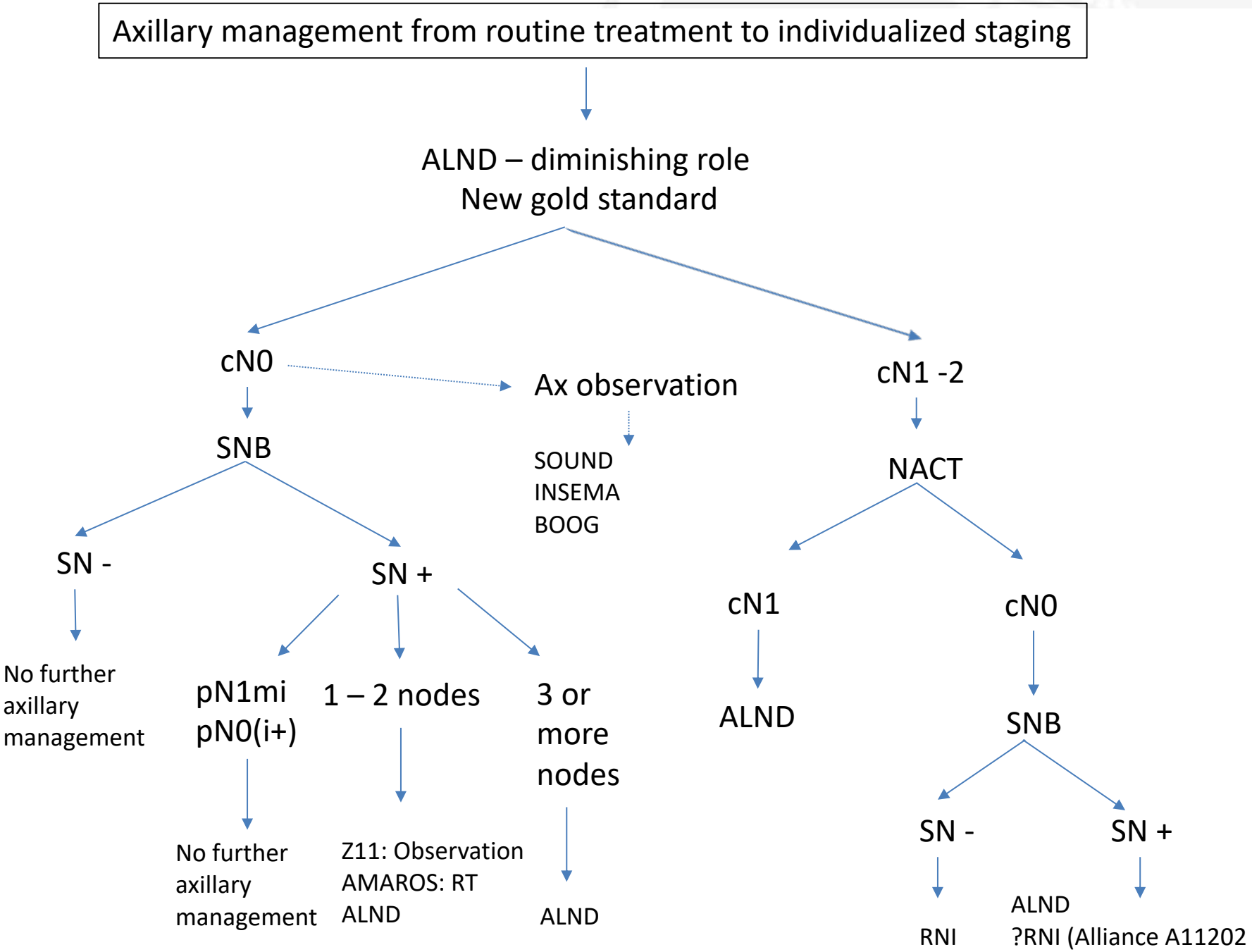
SNB policy No axillary surgery

INSEMA trial (German)



BOOG 2013-08 (Dutch)

- T1–2 invasive breast cancer
- BCT
- randomized to sentinel lymph node biopsy versus no sentinel lymph node biopsy


Axillary management from routine treatment to individualized staging
ALND – diminishing role
New gold standard
cN0
Ax observation
cN1 -2
SNB
SOUND
INSEMA
BOOG
NACT
SN -
SN +
cN1
cN0
No further axillary management
pN1mi
pN0(i+)
1 – 2 nodes
3 or more nodes
ALND
SNB
No further axillary management
Z11: Observation
AMAROS: RT
ALND
ALND
SN -
SN +
RNI
ALND
?RNI (Alliance A11202

Summary

- Axillary surgery add little in terms of survival in the treatment of breast cancer
- Main aim is diagnostic / prognostication
- If no survival benefit we need to decrease the amount of unnecessary ALNDs to avoid morbidity
- Do not overtreat patients with limited axillary disease (cN0), AxRT better than ALND
- Use chemotherapy to decrease the number of ALNDs in lymph node positive patients

Summary

- No intra-operative assessment needed in cN0 patients
- Perform SLNB as usual in cN0 patients after chemotherapy
- Alter SLNB technique if cN1 converted to cN0 with chemotherapy
- Perform frozen section if cN1 converted to cN0 with chemotherapy with ALND even if minimal residual disease

One final statement

- The axilla is not the ‘filter’ for distant mets
- The primary cancer tells you a lot more (if not all) about the biology of breast cancer
- Treatment (surgery) of the axilla has very little impact on survival
- So: It is biology, not anatomy that matters

In the world of surgical oncology

Biology is King
Selection is Queen
Technical maneuver is Prince

THANK YOU