THE SURGEON'S ROLE: THE AXILLA

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UQ MEDICINE
AUSTRALIA'S GLOBAL MEDICAL SCHOOL

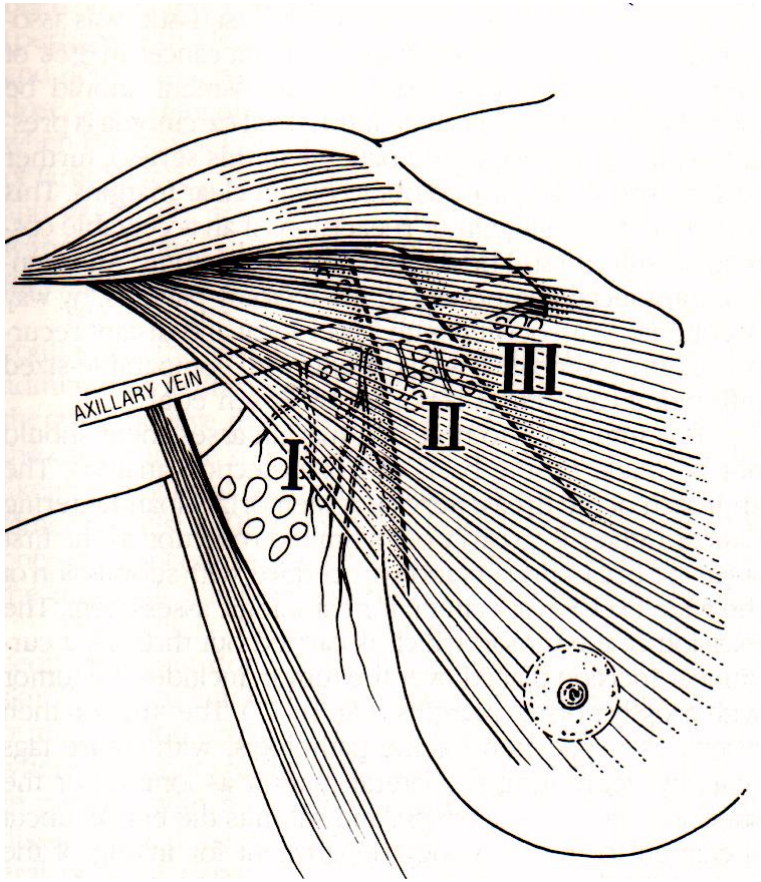
What are the concerns with treatment to the axilla

- Not necessary for the majority of primary breast cancer
  - All node negative
  - Some node positive
- Morbidity of treatment
  - More surgery, drains, seroma
  - Neuralgia and parasthesia
  - Shoulder mobility
  - LYMPHOEDEMA

Surgery to the axilla
…not as straightforward as described

- Sampling techniques
  - Sentinel node biopsy
  - Anything less than a dissection/clearance

- Level I dissection
- Level II dissection
- Level III dissection (clearance)



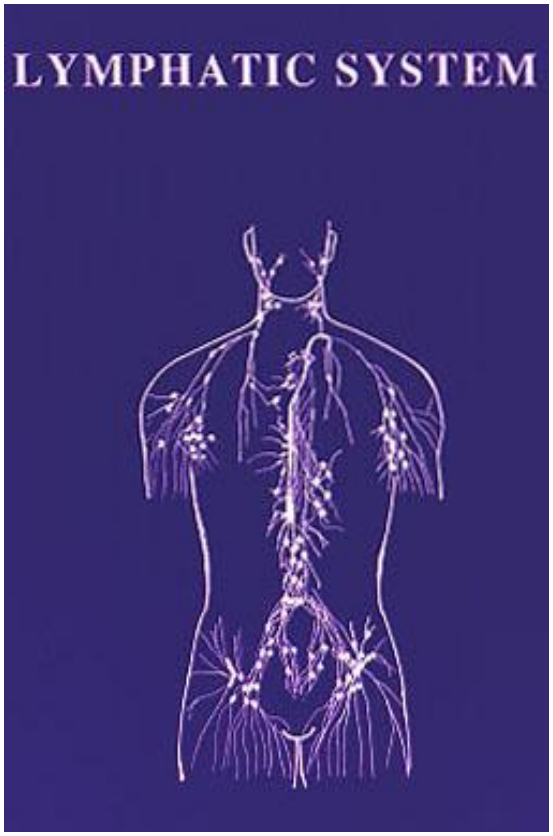
Effects of anticancer treatment

Improve
length of life &
cancer symptoms

Add
side-effects
inconvenience

Breast Cancer Scrabble

How do I explain the lymphatic system to patients?



Signs & Symptoms of Lymphoedema

Lymph volume exceeds transport capability

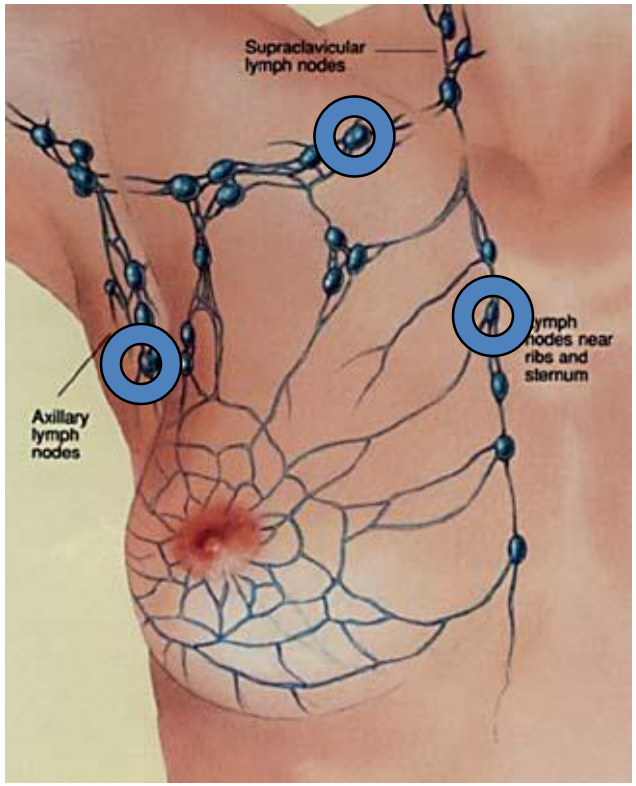
The fear of lymphoedema

- Numbness and paraesthesia
  - Common & not troublesome
- Damage to motor nerves
  - Rare
- Reduced shoulder mobility and stiffness
  - Temporary
- Chronic lymphoedema
  - 5-7% moderate to severe
  - 20% mild
  - 70-75% nil

Swelling can be controlled & managed effectively

Sentinel node biopsy

- Risk of lymphoedema is negligible



- It is an accurate predictor of nodal status
- Avoids axillary clearance for node negative disease (+node+)
- It is associated with less morbidity
- Equivalent local and distant control is achievable

Extra-axillary Nodal Basins

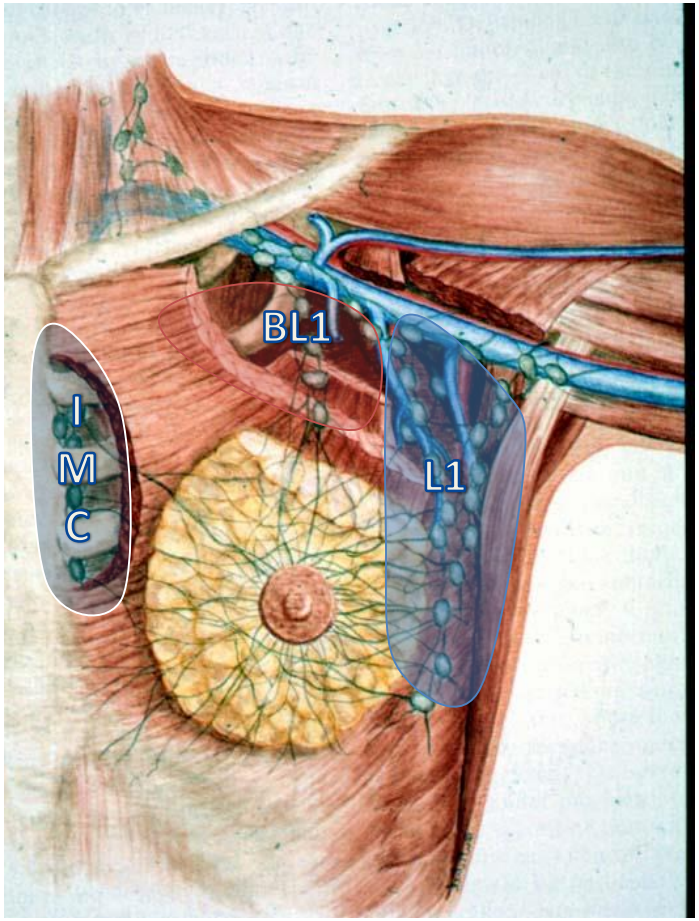
- Axilla Level 1 (L1)

  All nodes lateral to lateral border of pect. minor

- Axilla – beyond L1 (BL1)

  All nodes medial to lateral border of pect. Minor

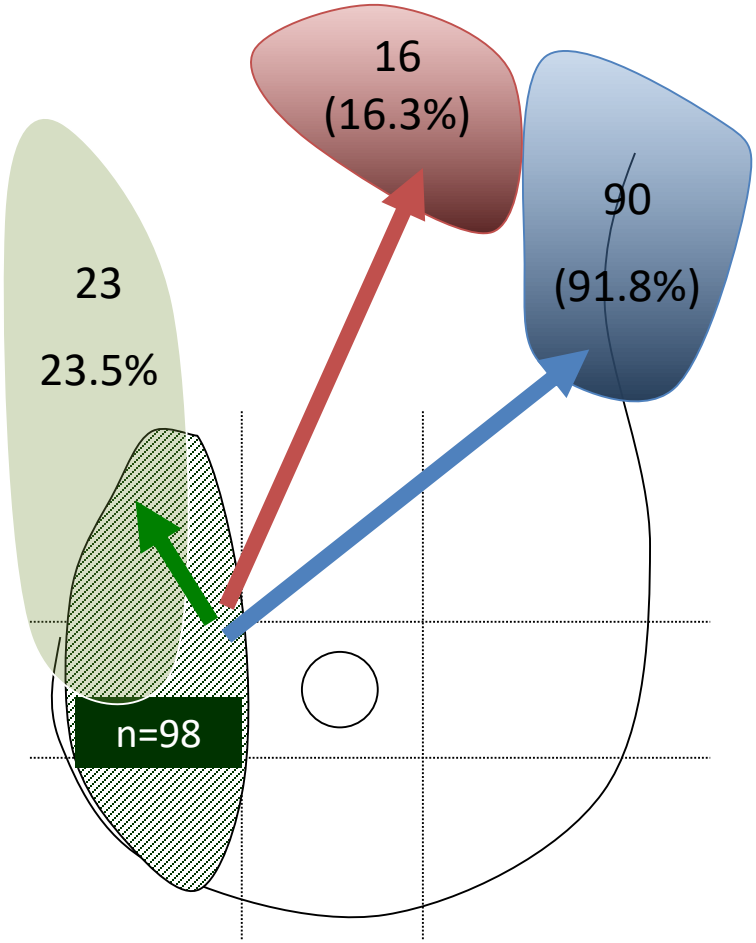
- Internal Mammary Chain (IMC)



Tumour site and Lymphatic mapping

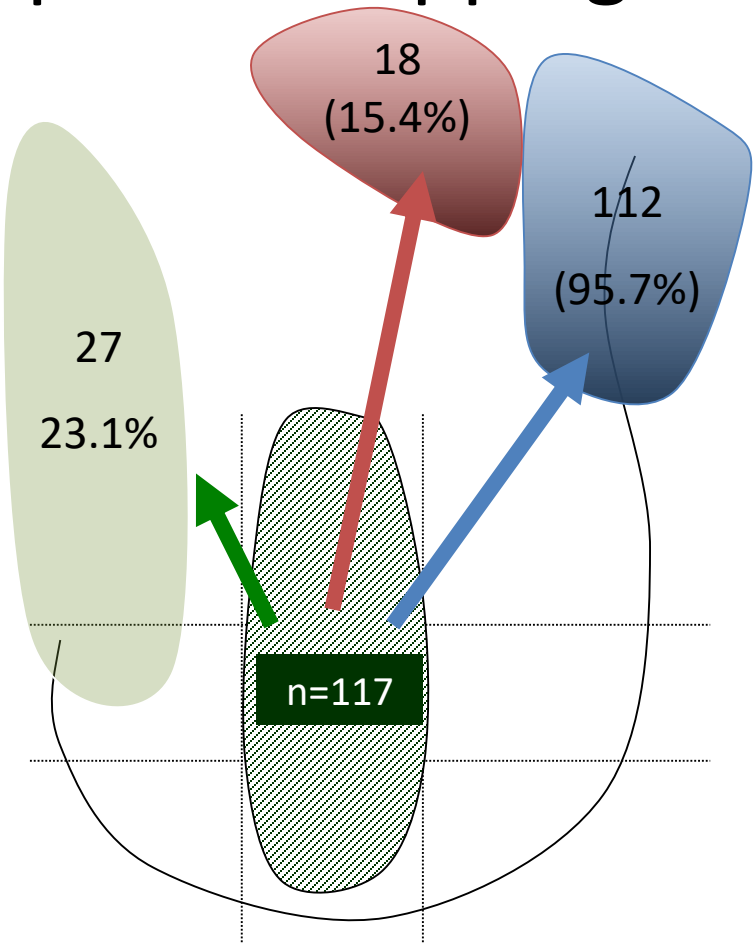
- Inner tumours n=98
- Mapped according to nodal basins
  - Most mapped to axilla L1
  - ¼ mapped to IMC

Values exceed total number of pts because patients often mapped to two or more nodal basins



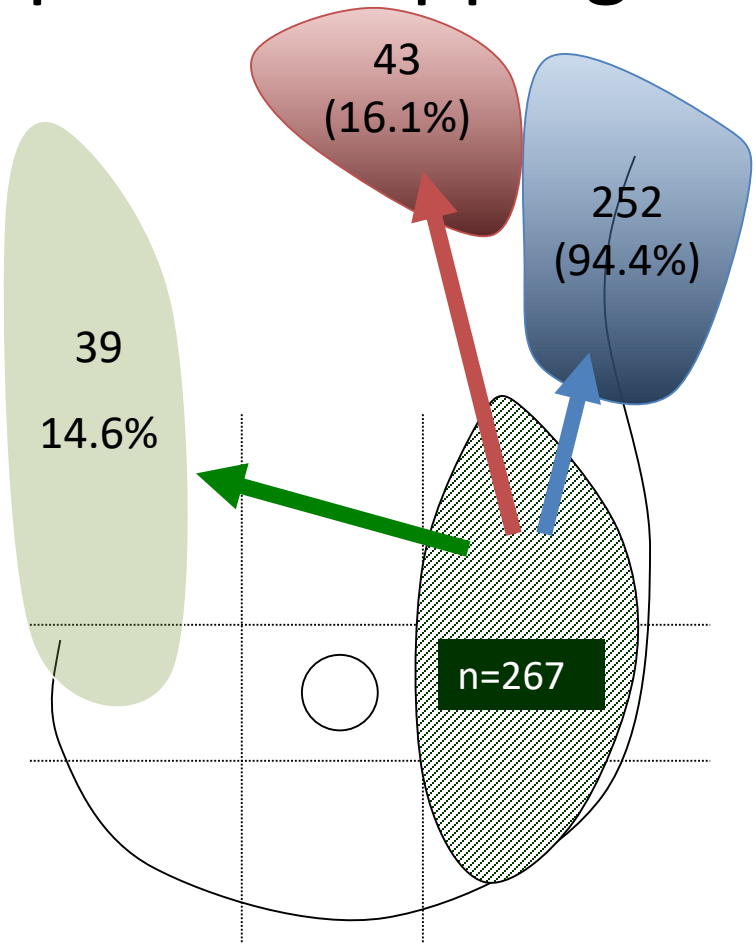
Tumour site and Lymphatic mapping

- Central tumours n=117
- Mapped according to nodal basins
  - Most mapped to axilla L1
  - ¼ mapped to IMC



Tumour site and Lymphatic mapping

- Outer tumours n=267
- Mapped according to nodal basins
  - Most mapped to axilla L1
  - 15% still map to IMC



Node positivity by basin

Nodal basins dissected	Number of patients	Number positive node basins	%
Level 1	462	145	31.4
Beyond L1	79	10	12.7
IMC	90	20	22.2

Impact of non-axillary sentinel node biopsy on staging and treatment of breast cancer patients

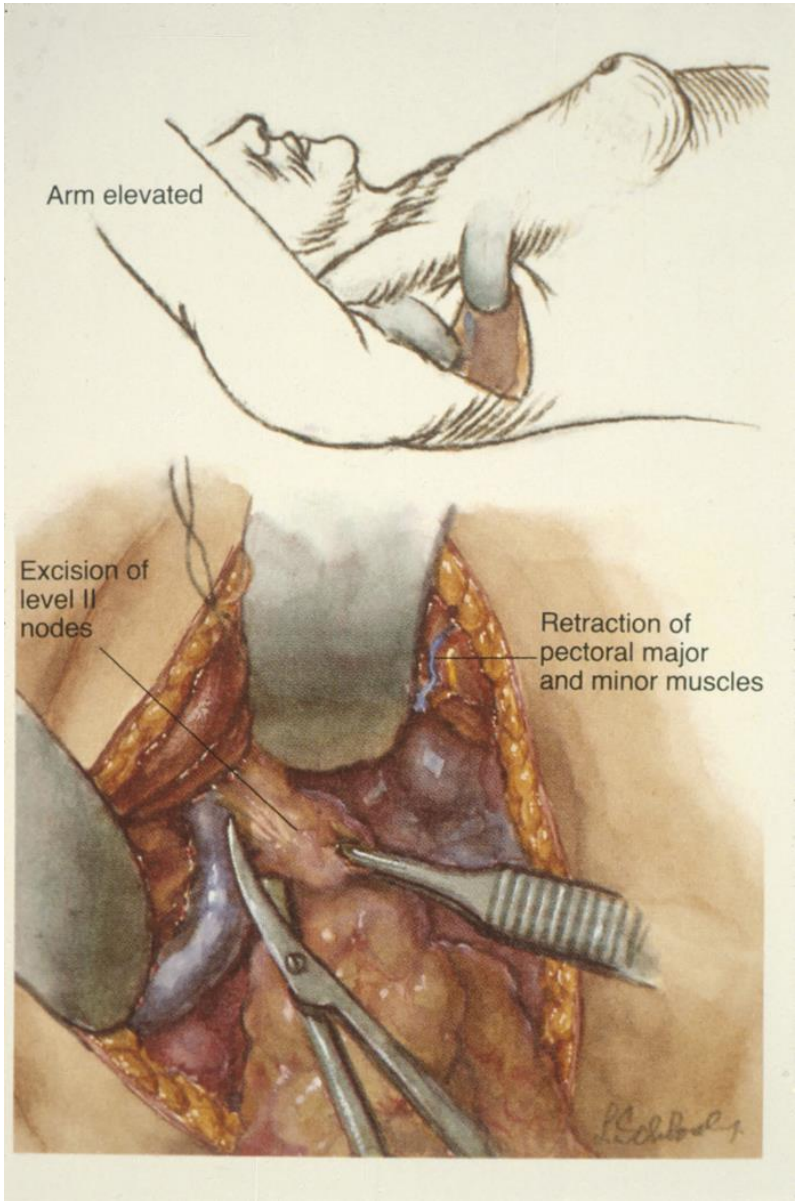
- 549 breast cancer patients underwent lymphoscintigraphy
- A sentinel node outside level the axilla - 149 patients (27%)
  - internal mammary sentinel node - 86 patients (16%)
  - other non-axillary sentinel nodes in 44
  - both internal mammary and other non-axillary sentinel nodes in 19
- The intra-operative identification rate was 80%
- **Staging improved in 13% of patients with non-axillary sentinel lymph nodes**
- **treatment strategy was changed in 17%.**

PJ Taniset al, British Journal of Cancer (2002) 87, 705 – 710

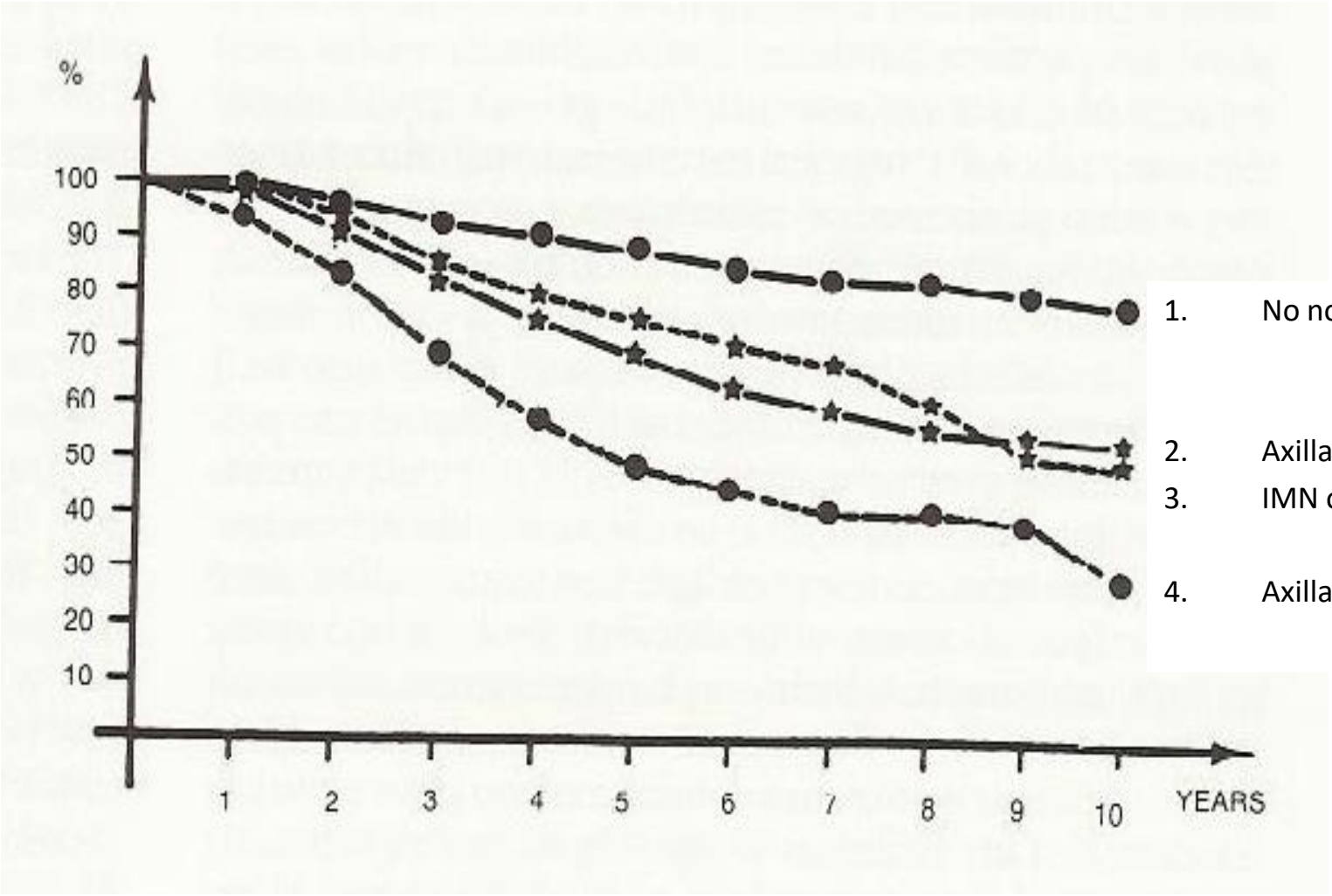
The Axilla – Lymph nodes

Some patients will still need an axillary clearance:

- **Significant Node +ve**
- To stage disease more accurately and determine adjuvant therapy



Prognosis of breast cancer patients after mastectomy and dissection of internal mammary lymph nodes



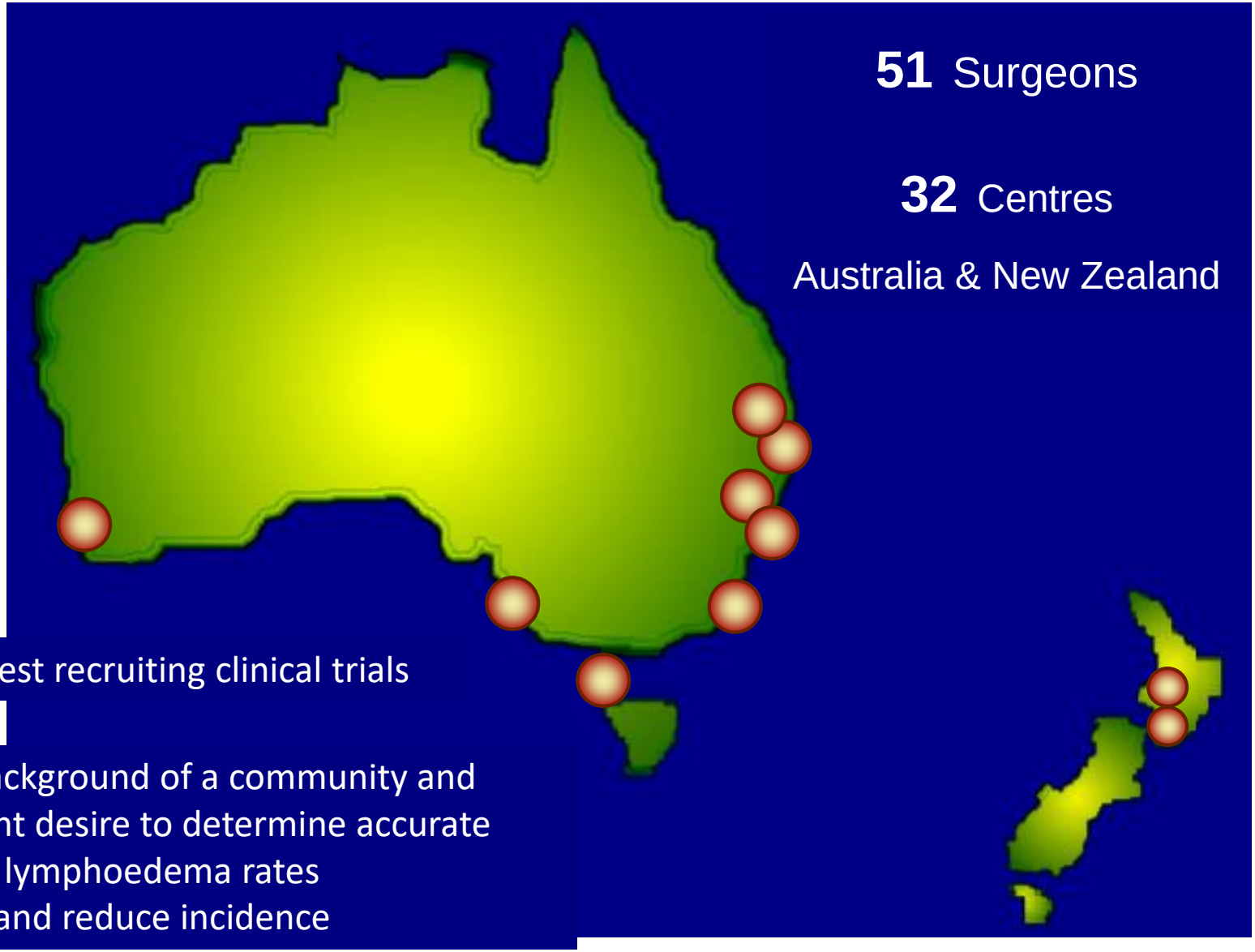
1. No nodal involvement
2. Axillary node only
3. IMN only
4. Axilla + IMN ($p=10^{-9}$)

Veronesi U. Ann Surg 202:702-707, 1985

Some patients will still need an axillary clearance

- If local control is important
- To limit the incidence of lymphoedema for treated node positive disease - avoid the combination of axillary dissection and XRT
- There is still a role for level III clearance of the axilla for sentinel node positive cases

The RACS SNAC I Trial



51 Surgeons

32 Centres

Australia & New Zealand

One of the fastest recruiting clinical trials

On the background of a community and government desire to determine accurate lymphoedema rates and reduce incidence

The RACS SNAC I Trial

Endpoints

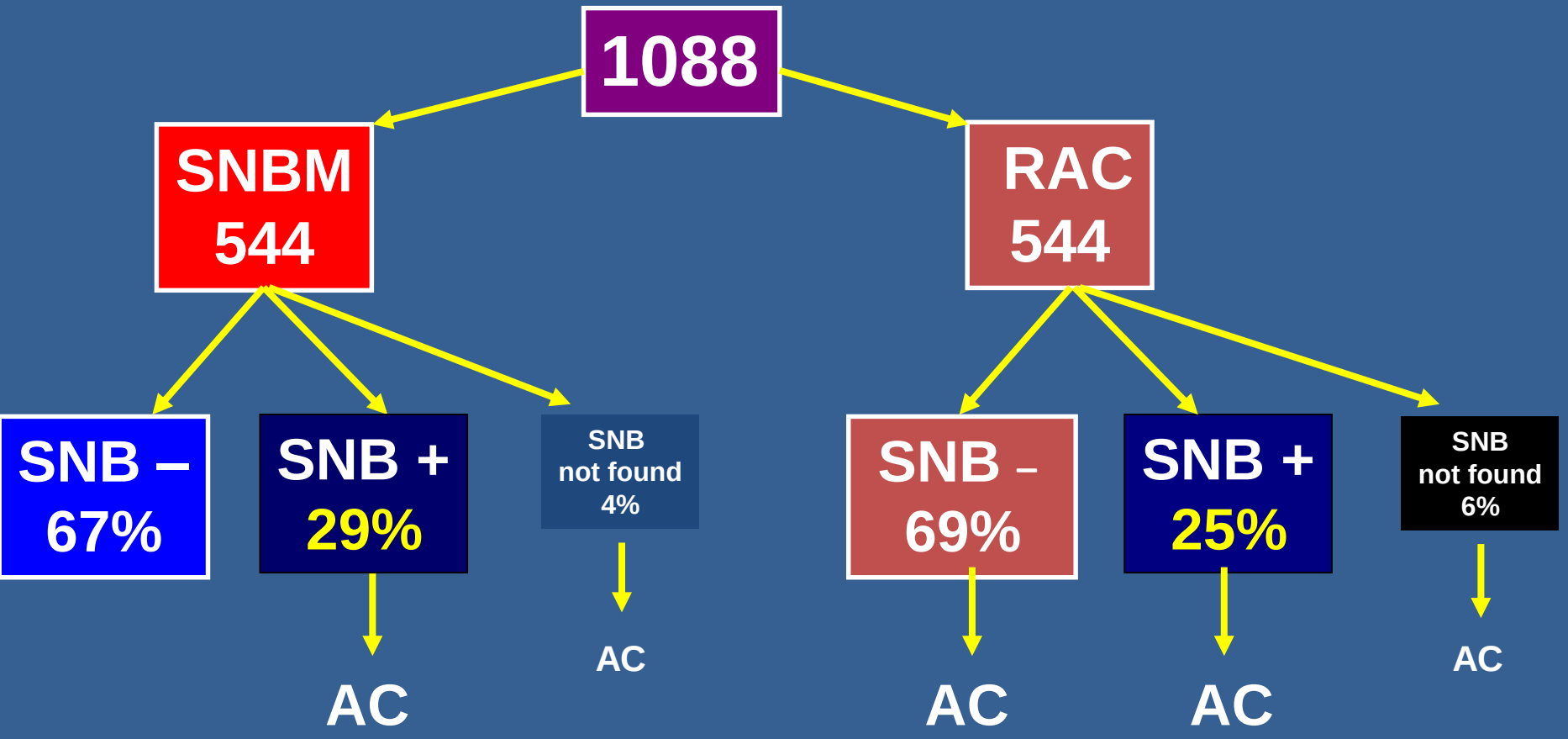
Clinician rated outcomes

- Percent increase in arm volume
- Proportion with >15% increase in arm volume
- Shoulder movements (goniometer)

Patient rated outcomes

- Change in total SSSS score (primary analysis)
- Quality of Life Measures

RACS SNAC trial



sentinel node biopsy (SNB)

vs

routine axillary clearance (AC)

The RACS SNAC I Trial

Clinician ratings of arm swelling
> 15% arm volume
NODE NEGATIVE Patients

	RAC	SNBM	p value
Visit	> 15 % Change	>15 % Change	
1 month	**1.1 %**	**0.3 %**	
6 months	**4.8 %**	**2.8 %**	
1 Year	**8.4 %**	**4.0 %**	0.019
2 Years	**14.3 %**	**7.9 %**	0.010
3 Years	**15.5 %**	**8.3 %**	0.006
4 Years	**15.4 %**	**10 %**	0.0499
5 Years	**15.9 %**	**11.7 %**	0.147

SNAC – 5yr

Clinician ratings of arm swelling
> 15% arm volume- NODE NEGATIVE
Non-Operated Arm

	RAC Op Arm	RAC Non treated Arm	SNBM Op Arm	SNBM Non treated Arm
Visit				
1 month	1.1 %	0.4 %	0.3 %	0.4 %
6months	4.8 %	2.7 %	2.8 %	3.4 %
1 Year	8.4 %	4.3 %	4.0 %	5.6 %
2 Years	14.3 %	8.5%	7.9 %	8.3%
3 Years	15.5 %	11.2 %	8.3 %	11.4 %
4 Years	15.4 %	12.5%	10 %	10.9%
5 Years	15.9 %	12.8 %	11.7 %	11.9 %

RACS SNAC trial - Lymphoedema

When a correction is made for volume change in the operated arm by subtracting the volume change in the non-operated arm the real incidence of true arm swelling due to increase fluid in the arm is seen

- 22% of patients have only minor swelling (26% after RAC)
- 7.7% have moderate swelling (>10%) (11% in RAC)
- Only 3.3% have significant swelling >15% (5% in RAC)
- SNB with few nodes removed results in negligible swelling

Predictors of significant swelling are: Treatment (RAC);
Increased weight and BMI; and palpable tumours

Moderate to Severe Arm Oedema

Treatment of Axilla	Incidence
Sampling or sentinel node biopsy	negligible
Dissection	6%-8%
Radiotherapy	6%-8%
Sampling and radiotherapy	6%-8%
Dissection and Radiotherapy	29%-36%

Axillary surgery and radiotherapy
lymphoedema

- Sample and radiotherapy - 6-8%
- Dissection and radiotherapy - 25-30%
- Independent of nodal status

Can we substitute radiotherapy for surgery?

Yes - but…

Still results in similar rates of lymphoedema

Do not obtain prognostic information

EORTC 10981-22023 AMAROS

- Positive sentinel node (1425) randomised to axillary node dissection(744) or radiotherapy (681)
- 5-year axillary recurrence - 0.43% (95% CI 0.00–0.92) after ALND vs 1.19% (0.31–2.08) after axillary XRT
- No statistically significant and clinically relevant differences in QoL were noted between groups for any of the selected scales: arm symptoms, pain, or body image
- >10% circumference – numerically greater ALND compared XRT group; however, the difference was only significant at 5 years
- 39 (6%) of 655 ALND vs 11 (2%) of 586 XRT received both radiation and surgery to the axilla

www.thelancet.com/oncology Vol 15 November 2014

EORTC 10981-22023 AMAROS

	Axillary lymph node dissection	Axillary radiotherapy	p value
Clinical sign of lymphoedema in the ipsilateral arm			
Baseline	3/655 (<1%)	0/586 (0%)	0·25
1 year	114/410 (28%)	62/410 (15%)	<0·0001
3 years	84/373 (23%)	47/341 (14%)	0·003
5 years	76/328 (23%)	31/286 (11%)	<0·0001
Arm circumference increase ≥10% of the ipsilateral upper or lower arm, or both			
Baseline	33/655 (5%)	24/586 (4%)	0·497
1 year	32/410 (8%)	24/410 (6%)	0·332
3 years	38/373 (10%)	22/341 (6%)	0·080
5 years	43/328 (13%)	16/286 (6%)	0·0009

Data are n/N (%), unless otherwise specified.

Table 2: **Lymphoedema**

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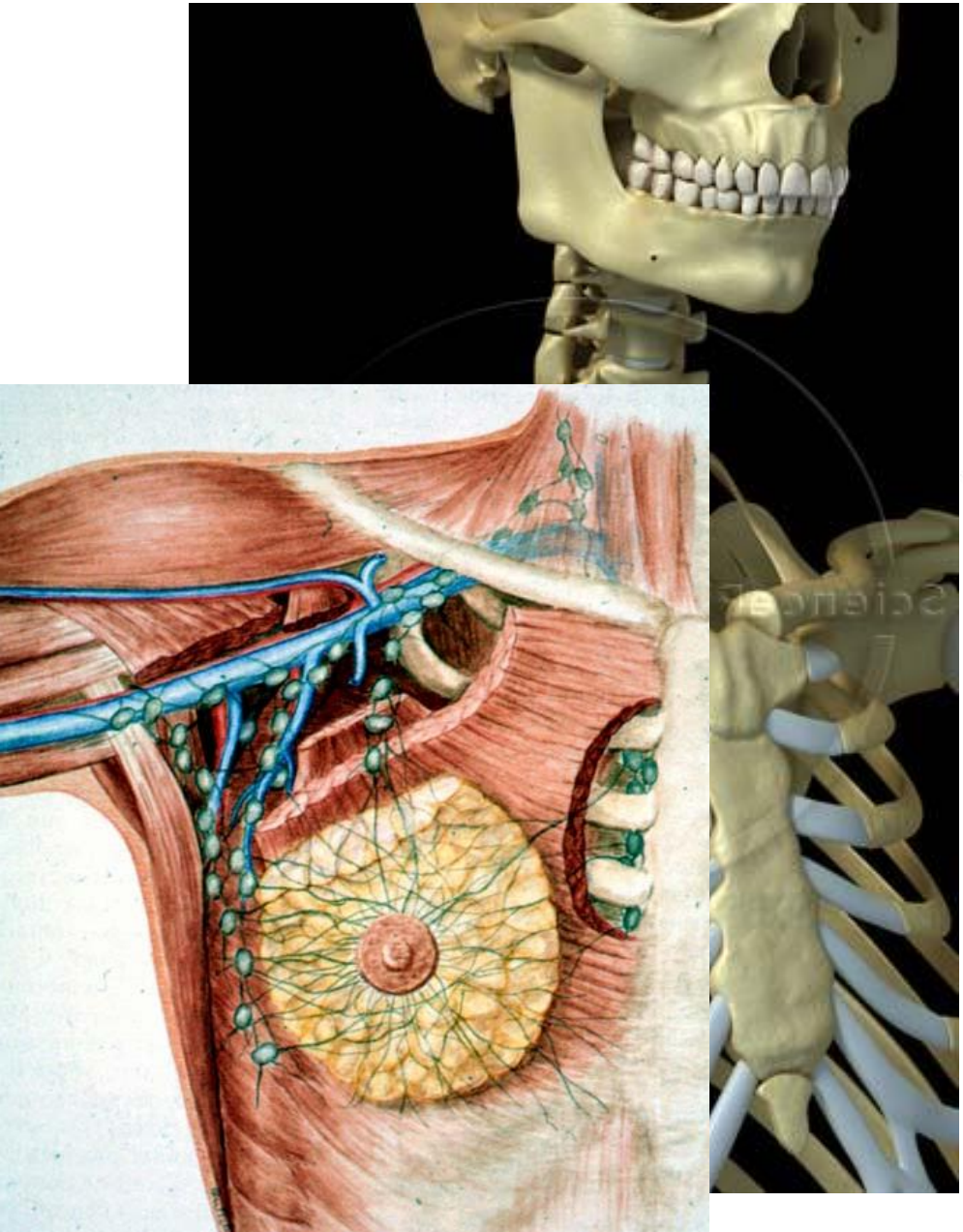
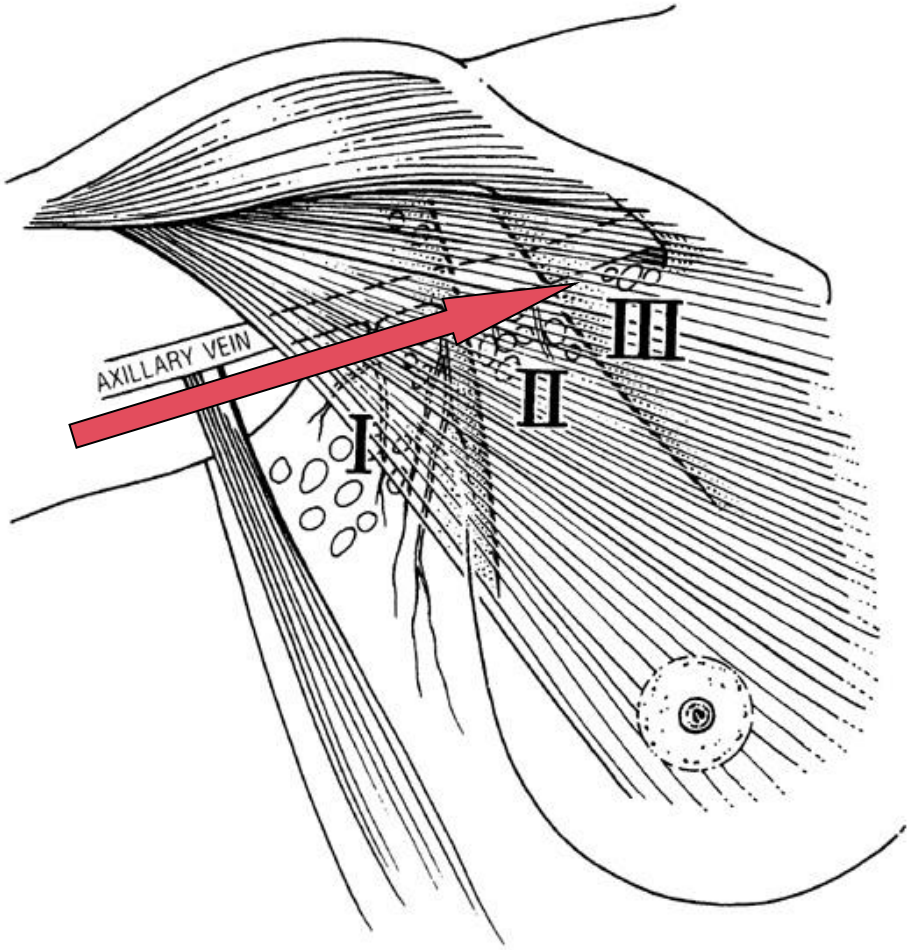
SNAC 1 - lymphoedema - patients that had axillary dissection

		Level 3 clearance			<L3 clearance	
visit		<15%	≥15%		<15%	≥15%
1 month		76 (100%)	0 (0.0%)		612 (98.9%)	7 (1.1%)
6 months		71 (97.3%)	2 (2.7%)		553 (93.6%)	38 (6.4%)
1 year		70 (92.1%)	6 (7.9%)		530 (90.1%)	58 (9.9%)
2 years		69 (92.0%)	6 (8.0%)		484 (83.2%)	98 (16.8%)
3 years		64 (87.7%)	9 (12.3%)		454 (81.8%)	101 (18.2%)
4 years		62 (84.9%)	11 (15.1%)		429 (80.8%)	102 (19.2%)
5 years		58 (81.7%)	13 (18.3%)		407 (81.6%)	92 (18.4%)

Surgical technique can avoid lymphoedema

Stay off the axillary vein



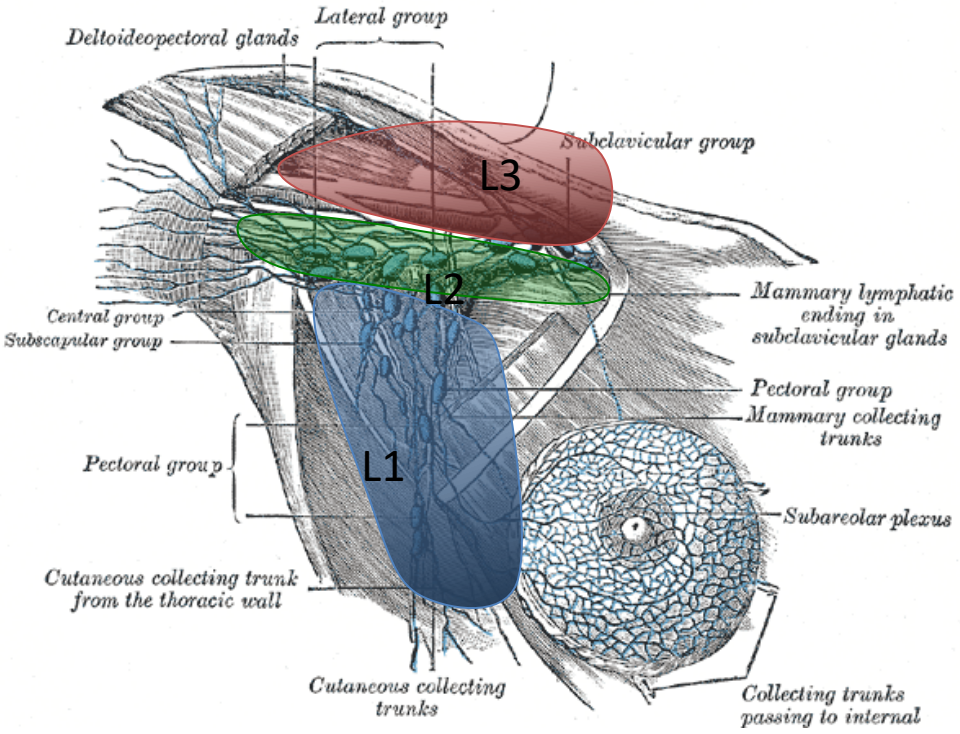


Axilla – alternate description of levels

(Ung)

Risk of moderate to severe lymphoedema (>15%)

- Level 1
  - Below axillary vein (1cm)
    - *Negligible risk (~0%)*
- Level 2
  - Along the axillary vein
    - *5-7%*
- Level 3
  - Above the axillary vein (supraclavicular)
  - Or combine with XRT
    - *30%*



Un-anatomical nomenclature has

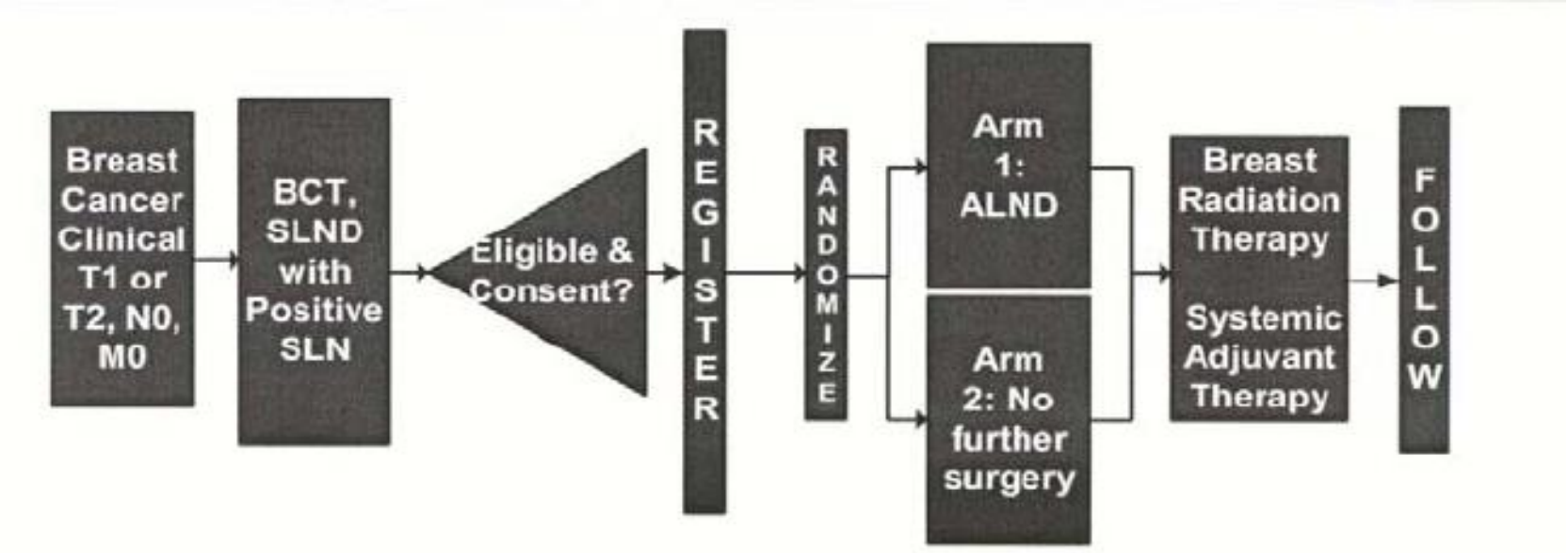
- results in misinformation about the surgical risks of lymphoedema
- distorts scientific analysis and may impact treatment recommendations

Risks and Benefits -

Can Axillary Dissection be Omitted?

ACOSOG Z0011 (Guiliano)
ASCO/NEJM 2010

Randomize all sentinel positive patients between an ALND and no further treatment



No significant difference in local recurrence after 6yrs FU

25% Adverse effects 70%

Are Z11 Results Reliable?

- Trial underpowered 891/1900 recruited
- Survival endpoint lacks power
- Only applies to BCS patients with <3 nodes
- Opposing tangential fields will irradiate the SLND operative field, much of the level I axilla, and a portion of the level II axilla
- Is the local control due to XRT and Chemo?
- Patients are a selected good prognosis group

What are the consequences of omitting axillary dissection?

- all patients with invasive breast cancer

Axillary Recurrence after SNB

Milan Negative SN	FU 38 months	No 3,000 +	LR 0.3%
MSKCC Negative SN	31 months	2,340	0.12%
Moffitt series Negative SN	60 months	1,800	0.26%
MSKCC Positive SN no ANC (Pt choice)	31 months	210	1.4%

practice changing studies?

- Z0011
- Small numbers incomplete accrual
- 27.3% of patients undergoing ALND had positive non-sentinel nodes
- But compelling results
  - limited by their inclusion criteria
  - applies to 9.3% of breast cancer cases in Australian setting (Ngui *et al*.)

- IBSCG 2101 – only micromets – does this study enhance Z0011 – represents a smaller subgroup – predictable result!

Is Z0011 a modern version of NSAPB 04?

radical mastectomy vs total mastectomy +/- radiotherapy to axilla

- 1665 women, mean f/u 126 months
- 40% node positive
- total mastectomy - 18% axillary failure
- clinically node negative - OS 57%
- clinically node positive - OS 38%

Fisher B., New Eng.J.Med. Vol312 No.11 1995

NSABP 04
conclusions:

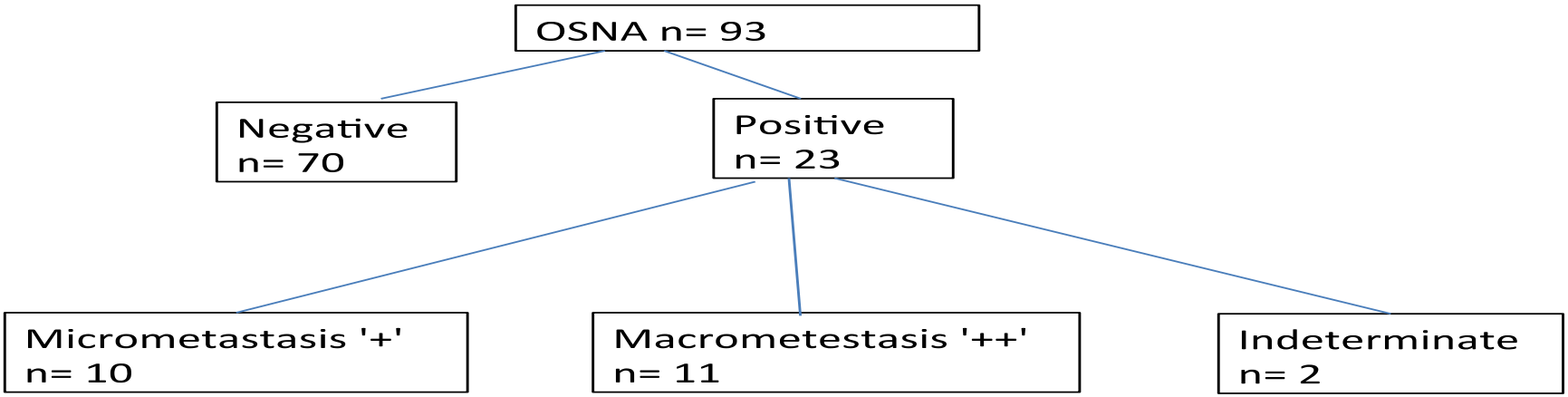
- treatment of the axilla confers no benefit in terms of overall survival
- radiotherapy and surgery provide equivalent local control of the axilla even for clinically node positive patients
- 20% of untreated axillas will progress to require treatment

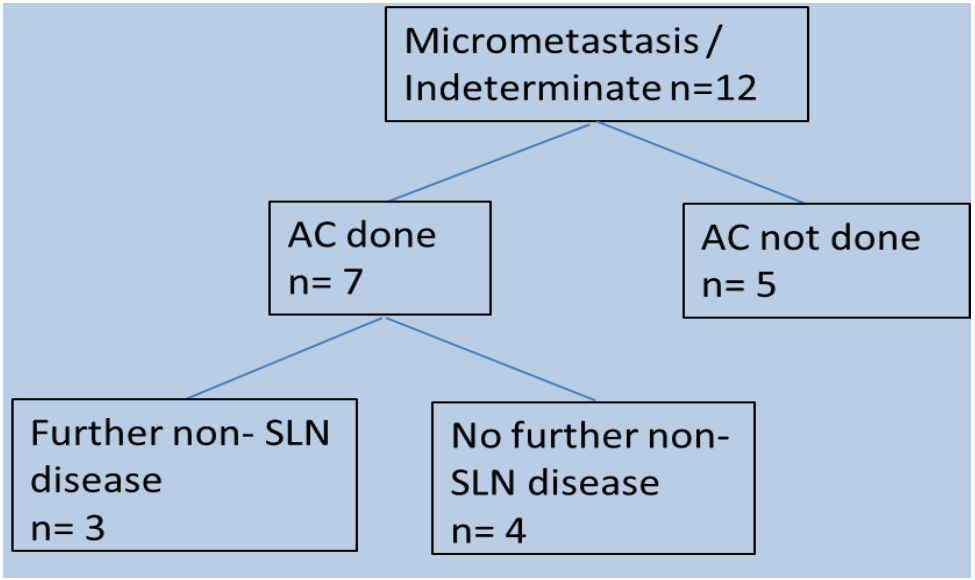
- MIRROR Ann Surg 2012;255:116-121
  - 5yr (p = 857 node neg, 795 itc, 1028 mi) LR 2%, 2.3%, 5.6% HR 1.08, 2.39, 4.39
  - ↑ size, grade 3, HR status significantly assoc LR

Not performing axillary treatment for SLN micrometastasis and unfavourable tumour characteristics is associated with ↑ 5yr LR

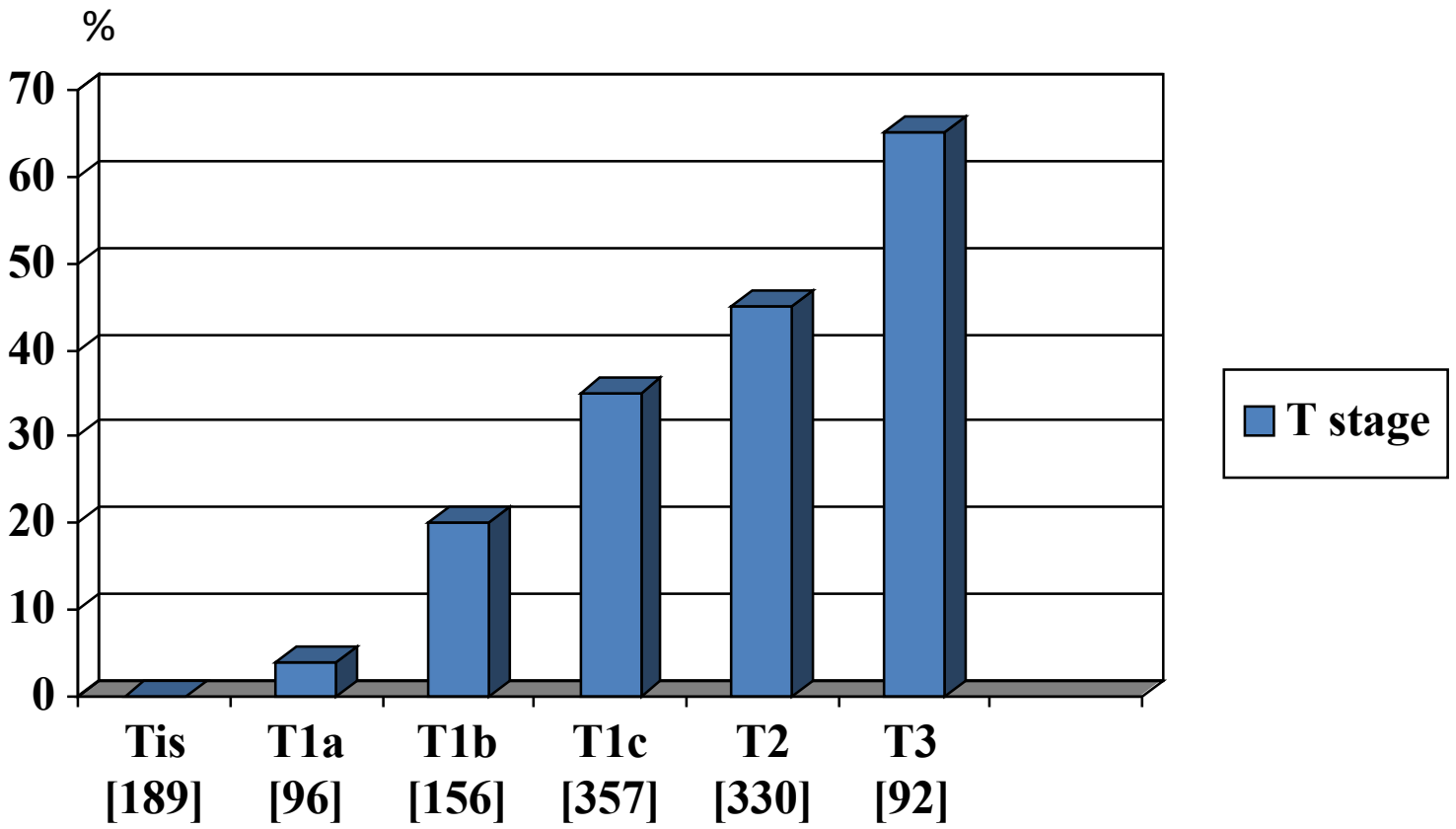
Sentinel node micrometasis

- Initial experience with OSNA at RBWH





There is a linear relationship between tumour diameter and percentage of cases with positive lymph node involvement
24740 cases, SEER DATA, NCE Carter C., Cancer 63:181-187, 1989



Silverstein M., Cancer 73 [3] 1994

The RACS SNAC I Trial

Performance results of SNB in control arm of SNAC I

Tumour size	SNBM +ve SN	RAC +ve SN	False -ve SN	No. of FN
<10mm	8.9%	6.8%	**0%**	0/118
11-20mm	29.7%	23.3%	**1.6%**	5/317
21-30mm	38.4%	46.3%	**7.3%**	6/82
>30mm	63.9%	59.3%	**3.7%**	1/27
Total	29%	25%	**5.5%**	544

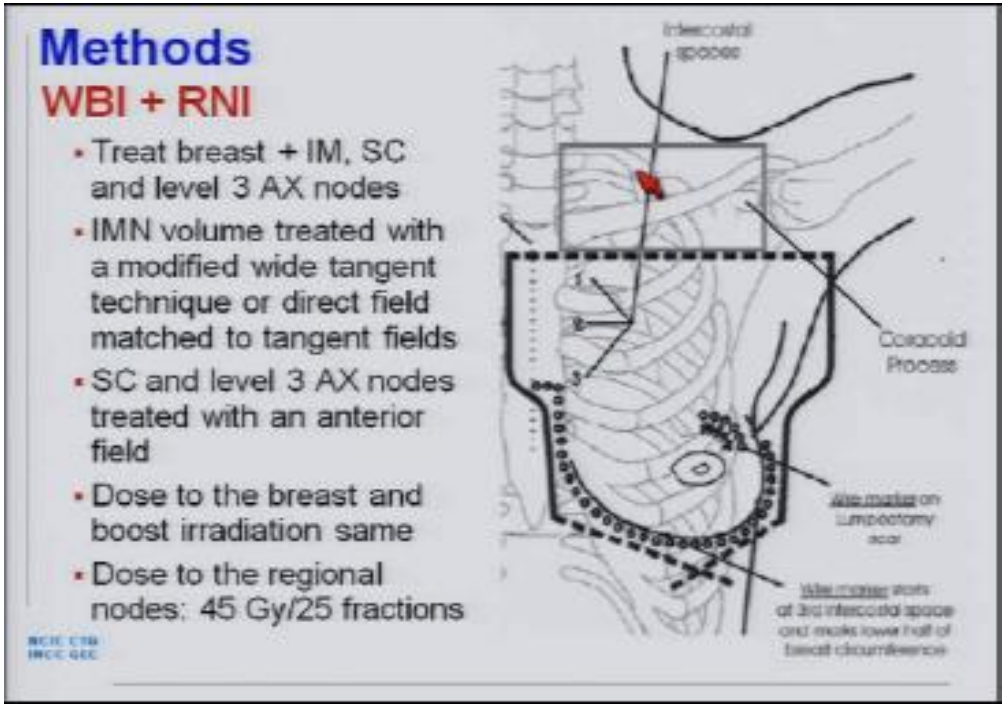
What are the concerns with node positive disease?

- Local recurrence
  - Infiltrating disease is worse than lymphoedema
- Distant recurrence
  - Seeding from persistent disease?
  - Understaging and therefore undertreating systemically

local control impacts survival

- EBCTCG Lancet Vol366 December17/24/31,2005
  - Differences in local treatment that substantially affect local recurrence rates would, in the hypothetical absence of any other causes of death, **avoid about one breast cancer death over the next 15 years for every four local recurrences avoided**
- Post Mastectomy trials showed significantly improved OS
  - Danish Breast Cancer Co-operative Group 82b/82c Trial
  - British Columbia Cancer Agency

A Phase III Study of Regional Radiation Therapy in Early Breast Cancer – MA.20



- Majority of women with early breast cancer treated with breast conservation (BCS+WBI)
- Anthracycline-based regimens
- Does targeted regional radiation add any additional benefit?

Results MA.20

	WBI + RNI	WBI	HR (*p*)
Isolated locoregional DFS	96.8%	94.5%	0.59 (0.02)
Distant DFS	92.4%	87%	0.64 (0.002)
DFS	89.7%	84%	0.68 (0.003)
OS	92.3%	90.7%	0.76 (0.07)
≥ Grade 2 pneumonitis	1.3%	0.2%	P=0.01
Lymphoedema	7.3%	4.1%	P=0.004
Patient-rated adverse cosmetic outcome	36%	29%	sig

RBWH – completion ALND following +ve sentinel node (2008-2016)

Exclusions: neoadjuvant therapy, previous ipsilateral breast cancer or axillary surgery

Baseline Characteristics	n	Proportion (%)
Non-SLN Positive	65	43.9
Level III Non-SLN Positive	8	5.9
Operation		
Mastectomy	85	57.4
WLE	63	42.6
Adjuvant Radiotherapy to Regional Nodal Basin	75	50.7

Predictors of further non-sentinel node +ve disease

Variable (n)	Proportion of Cases Positive Non-SLN (%)	Odds Ratio	95% CI	P-Value
Histological Type (148)				
IDC	39.6			0.03
ILC	31.3			
Mixed IDC/ILC	75.0			
Other	60.0			
T Stage (148)				
T1	34.0			0.16
T2	46.7			
T3	56.5			
Grade (148)				
Grade 1	42.9			0.09
Grade 2	35.1			
Grade 3	58.0			

Predictors of further non-sentinel node +ve disease

Variable (n)	Number	Proportion of Cases Positive non-SLN (%)	P-Value
ER +	130	45.4	0.33
ER -	18	33.3	
PR +	124	42.7	0.51
PR -	24	50.0	
HER-2 +	20	55.0	0.28
HER-2 -	128	42.2	
Triple Negative	14	42.9	0.93
Non-Triple Negative	134	44.0	

Predictors of further non-sentinel node +ve disease

Variable (n)	Proportion of Cases Positive Non-SLN (%)	Odds Ratio	95% CI	P-Value
Multi-focal (20)	50.0	1.92	0.83 – 4.41	0.12
Uni-focal (128)	41.4			
LVI (148)				
Present	54.3	1.52	1.08 – 2.13	0.02
Absent	34.6			
Size SLN Metastasis (116)				
Macrometastasis	35.3			0.44
Micrometastasis	32.1			
ITC	0.0			
SLN Extra-nodal Extension (95)				
Yes	34.3	1.04	0.43 – 2.52	0.93
No	33.3			
Proportion of Positive SLN (142)				
<0.5	21.4			0.02
0.5 – 0.99	33.3			
1	56.5			

Multivariate Analysis

Variable	Odds Ratio	95% CI	P-Value
Histology Mixed IDC/ILC	4.67	1.33 – 16.4	0.02
LVI	1.90	0.90 – 4.00	0.09
Proportion of Positive SLN = 1	3.73	1.30 – 10.6	0.01

Conclusions

- Thorough ALND still has a significant role in the management of patients with breast cancer post Z0011
- Rates of non-SLN positivity are influenced by tumour histology, lymphovascular invasion and the proportion of positive SLN
- Mixed IDC/ILC & all SLN being positive are the best predictors of non-SLN involvement

Axillary surgery - neoadjuvant setting

- Recent data suggest SLN biopsy is as accurate in the neoadjuvant setting for clinically node -ve
- Pre treatment node +ve patients converted to node –ve
  - false -ve rate <10% only when ≥3 sentinel nodes are identified
  - axilla recurrence rates after SLNB unknown
  - sentinel node vs routine clearance
  - case by case discussion
- Persistent positive axillary disease
  - Level III clearance

Intra-operative sentinel lymph node evaluation

- Ability to diagnose node positive disease at initial surgery
  - Reduces number of surgical procedures for patient
  - Reduces total time required to complete treatment
    - Surgery easier
    - Potential cost savings
    - Frees theatre time for other cases
    - Complete MDT information and fast track to adjuvant therapy

Intraoperative assessment of Sentinel Node Touch Imprint Cytology (TIC)

- Sensitivity = TP / (TP + FN)

  10 / 42

  23.8%

- Specificity = TN / (TN + FP)

  92 / 92

  100%

- Accuracy = (TP+TN)/(TP+FP+TN+FN)

  (10 + 92) / (10 + 0 + 92 + 32)

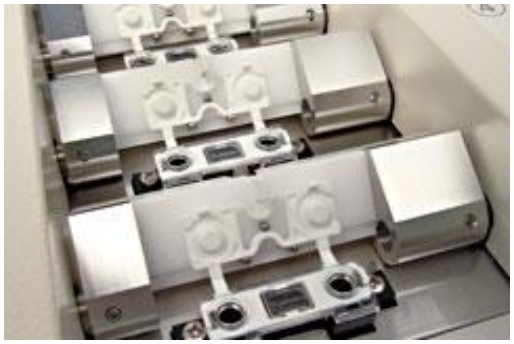
  102 / 134

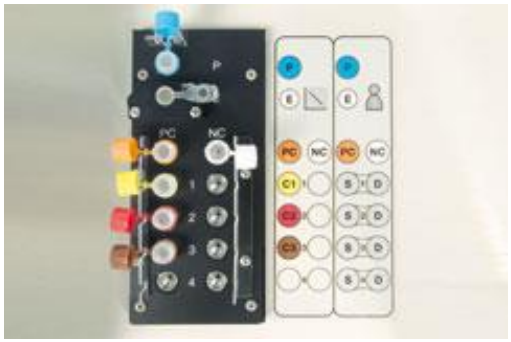
  76.1%

One Step Nucleic acid Amplification (OSNA) assay

- reverse transcription loop mediated isothermal amplification (RT-LAMP) technique
- detects the messenger RNA level of breast cancer marker - cytokeratin 19 (CK19)
- specificity and sensitivity greater than 95%
- turnaround time for assay <30 minutes
- ability to detect micrometastasis with high accuracy
- Reliably avoid second surgery to the axilla

++	**CK19 mRNA (copy number) in the sample (1) is ≥ 5000 copies/µL**
+	CK19 mRNA (copy number) in the sample (1) is < 5000 and ≥ 250 copies/µL
Reaction inhibited (+i)	CK19 mRNA (copy number) in the sample (1) is < 250 copies/µL , and CK19 mRNA (copy number) in the sample (2) (10-fold diluted solution of the sample (1)) is ≥ 250 copies/µL





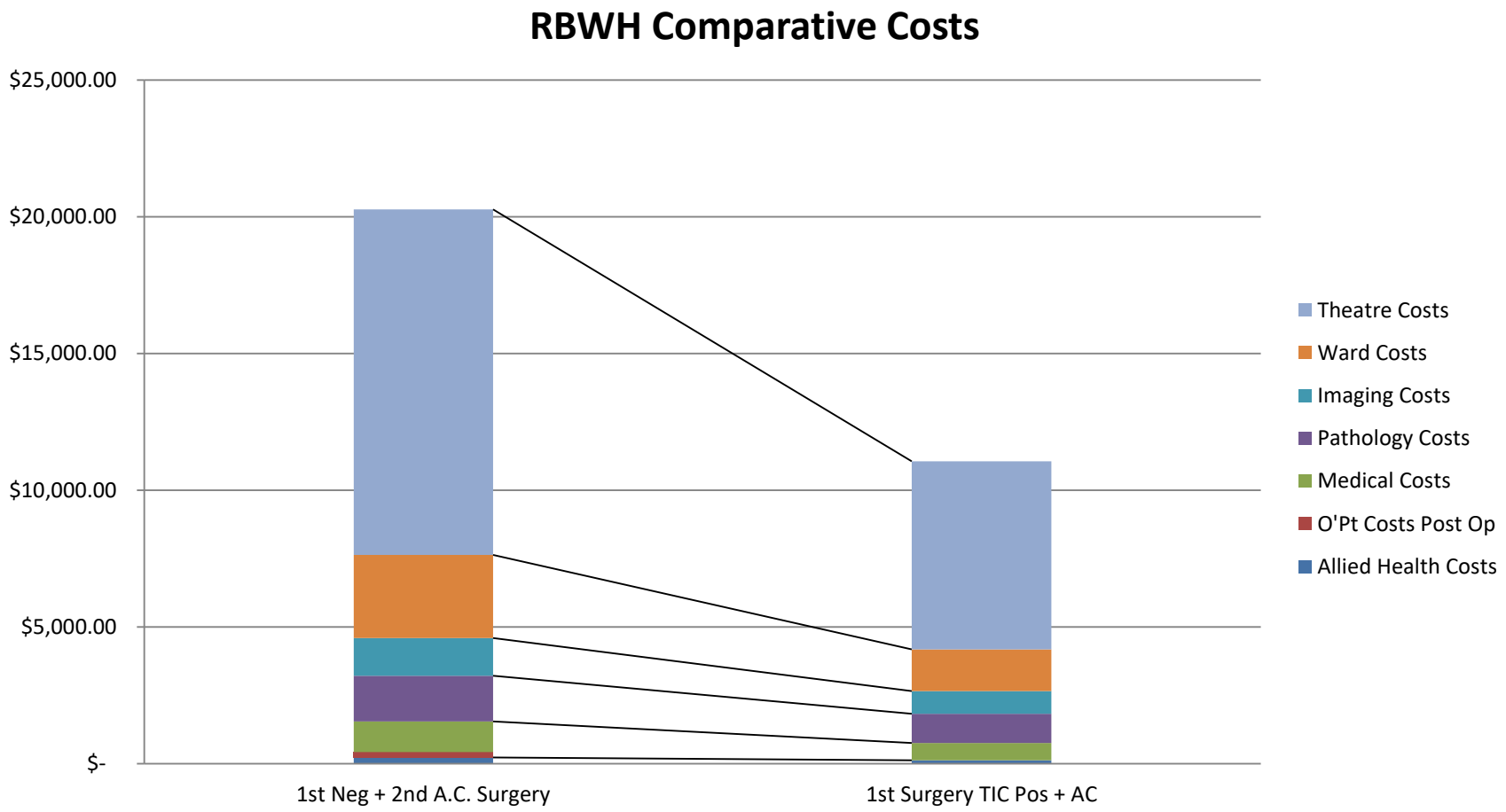
OSNA™ at RBWH

- Casemix data was collected for patients directly involved in the OSNA™ study at RBWH.
- Incremental cost of second surgery was calculated according to the following:

Cost 1st surg. (-'ve) + Cost 2nd surg (A.C) – Cost 1st surg. (+'ve)

- Ave. cost 1st surg. –'ve = AU$ 9,004.75
- Ave. cost 2nd surg. A.C. = AU$11,262.91
- Ave. cost 1st surg. A.C. = AU$11,054.89

OSNA™ at RBWH


RBWH Comparative Costs
$25,000.00
$20,000.00
$15,000.00
$10,000.00
$5,000.00
$-
1st Neg + 2nd A.C. Surgery
1st Surgery TIC Pos + AC
Theatre Costs
Ward Costs
Imaging Costs
Pathology Costs
Medical Costs
O'Pt Costs Post Op
Allied Health Costs

Challenge of defining high risk individuals

- When should the 95% rule apply?
- Not if you are one of the 5%

THE SURGEON'S ROLE: THE AXILLA

Patient with invasive breast cancer:

- Should all have axillary surgery?
  - **Yes** – snbx is gold standard
- Should all have axillary clearance?
  - **No** – most node –ve but consider high risk primary
- Should all node +ve have axillary clearance?
  - **No** – ITC and possibly micromets but consider high risk primary
- Should neoadjuvant node +ve be spared axillary clearance?
  - **Yes** – if no residual disease post treatment
- Should macroscopic node +ve have axillary clearance?
  - **Yes** – and consider level III