

Appropriate Concept of Prevention of Lymphedema at the Initial Treatment

Zisun Kim

Department of Surgery, Soonchunhyang University Bucheon Hospital,
Soonchunhyang University College of Medicine, Korea

Introduction

- Lymphedema
 - ✓ Abnormal accumulation of protein-rich fluid in the interstitial space
 - ✓ A progressive disorder
 - ✓ Treatment-induced mechanical insufficiency of the lymphatic system



Incidence and risk factors

- Breast cancer associated treatments: the most common causes of upper extremity lymphedema
- The overall incidence of lymphedema: 17%
 - ✓ systematic review (72 studies, 29,612 women)
- Risk factors for breast cancer related lymphedema (BCRL)
 - ✓ axillary lymph node dissection (ALND)
 - ✓ radiation therapy (RT)
 - ✓ local infection, hematoma/seroma
 - ✓ obesity, medication effects (taxane)



ORIGINAL ARTICLE – BREAST ONCOLOGY

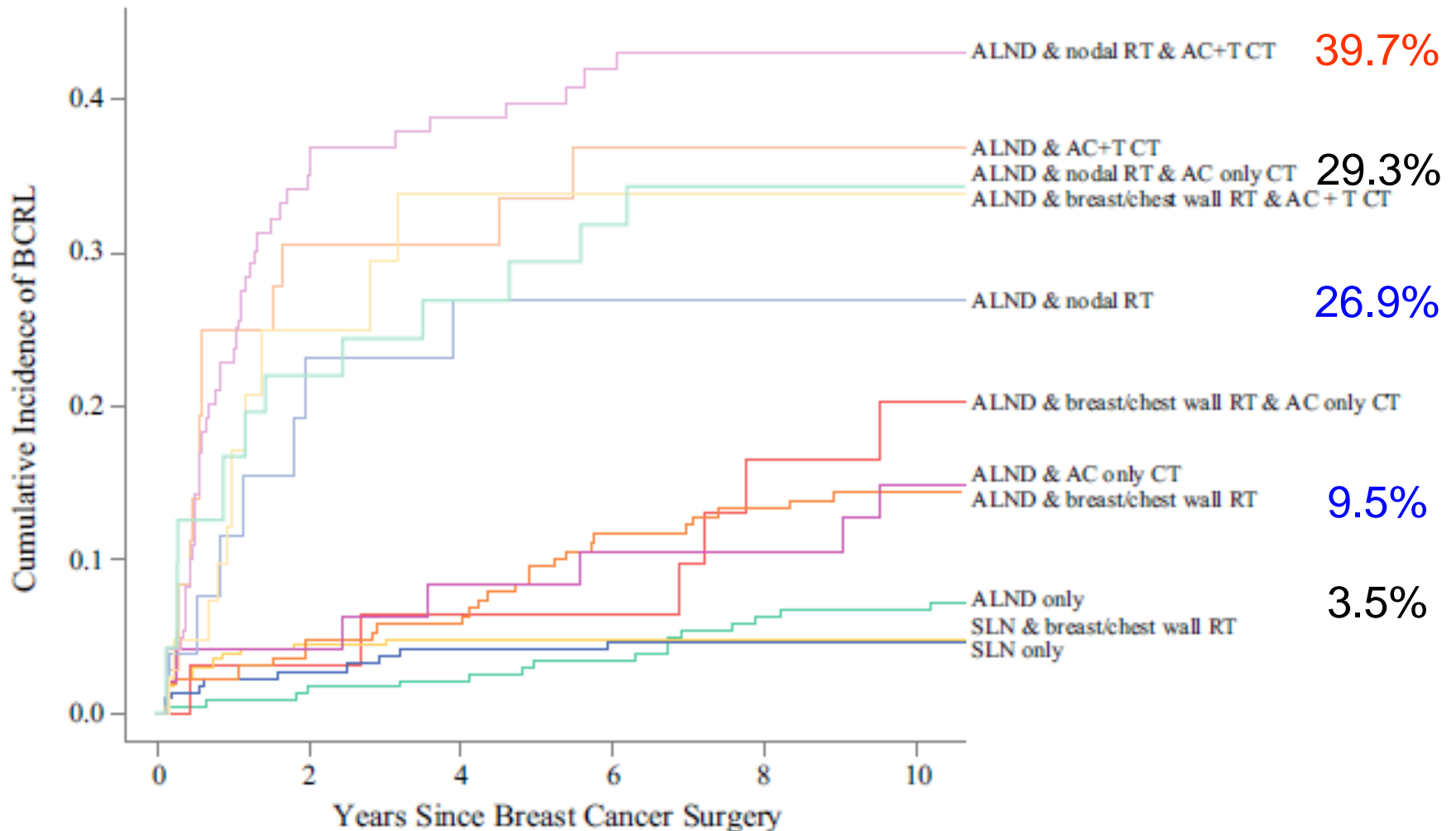
Breast Cancer-Related Lymphedema Risk is Related to Multidisciplinary Treatment and Not Surgery Alone: Results from a Large Cohort Study

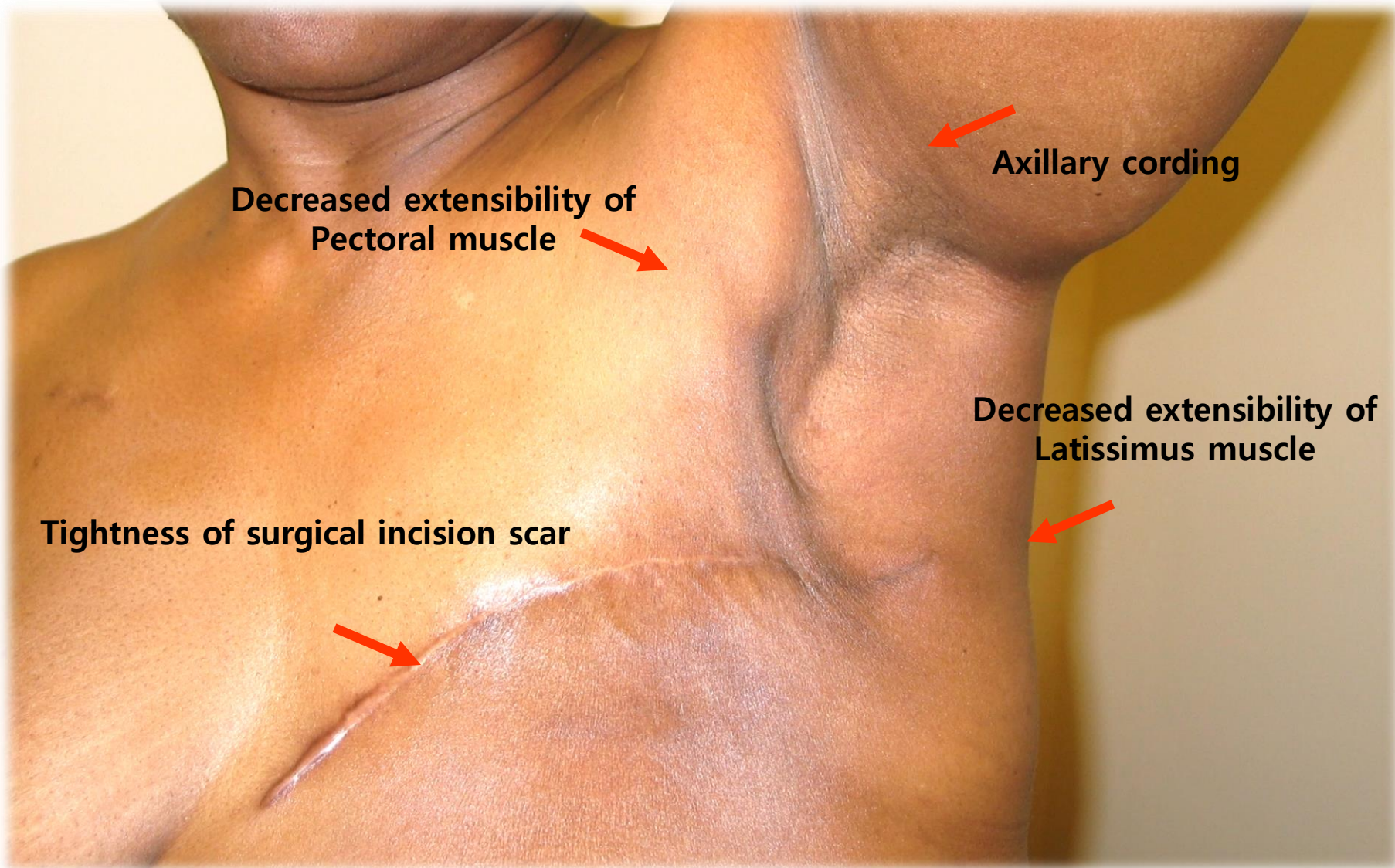
Toan T. Nguyen, MD¹, Tanya L. Hoskin, MS^{2,3}, Elizabeth B. Habermann, PhD^{1,3}, Andrea L. Cheville, MD⁴, and Judy C. Boughey, MD¹

¹Department of Surgery, Mayo Clinic, Rochester, MN; ²Department of Health Sciences Research, Mayo Clinic, Rochester, MN; ³The Robert D. and Patricia E. Kern Center for the Science of Health Care Delivery, Mayo Clinic, Rochester, MN; ⁴Department of Physical Medicine and Rehabilitation, Mayo Clinic, Rochester, MN

- 1,794 patients, Stage 0-3 breast cancer, median 10 yrs f/u
- 5 yr cumulative incidence of BCRL: 9.1% [95% CI 7.8–10.5%]
- 5 yr incidence of BCRL: 5.3% (SLNB) vs. 15.9% (ALND) ($p < 0.001$)
- Breast/chest wall RT: 3.5% (surgery) vs. 9.5% (surgery+RT) ($p = 0.01$)

BCRL is related to multimodal treatment, and not surgery alone





Decreased extensibility of Pectoral muscle

Axillary cording

Tightness of surgical incision scar

Decreased extensibility of Latissimus muscle

Adverse impact

- Secondary shoulder dysfunction
 - ✓ Myofascial syndrome
 - ✓ Impingement syndrome
 - ✓ Pain and decreased muscle strength
- Psychological morbidity
- Diminished quality of life/lower patient reported outcome
- Higher medical costs and more productive days lost

Pasket E, et al. J Clin Oncol 2012;30:3726-33.

Land, et al. J Clin Oncol 2010;28:53929-36.

Hayes, et al. Cancer 2012;118:2237-49.

Helms, et al. Eur J Surg Oncol 2009;35:696-701.

Prevalence and time of onset

- Insidious onset, slowly progressive swelling of the upper extremity
- Most patients become symptomatic within 8 months of surgery.
- 23.1%: waxing and waning lymphedema symptoms in the first 3yrs
- The greatest risk for developing lymphedema: ≤ 2 yr after treatment
- Freedom from progression: 79% (1yr), 66% (3yr), and 52% (5yr)
- Higher risk of progression: morbidly obese, positive axillary lymph nodes, supraclavicular irradiation

Bar Ad V, et al. Int J Radiat Oncol Biol Phys 2010;76:85-90.

Norman S, et al. J Clin Oncol 2009;27:390-7.

Petrek JA, et al. Cancer 2001;92(6):1368-77.

BCRL prevention 1: SLNB

Incidence of BCRL after ALND

Author	Year	No. of patients	Measurement	Lymphedema, %
Sackey	2014	194	Water displacement	45
Sagen	2014	204	Water displacement	17
Rutgers	2013	744	NR	28
Ashinkaga	2010	1975	Water displacement	14
Teshome	2014	853	Circumference	40
Lucci	2007	445	Circumference	11
Langer	2007	210	Circumference	19
Francis	2006	73	Circumference	47
Mansel	2006	403	Circumference	13
Haid	2002	140	Circumference	27
Swenson	2002	78	Subjective	17
Schrenk	2000	35	NR	57

12 studies
5,354 patients
Pooled incidence
: **22.3%**

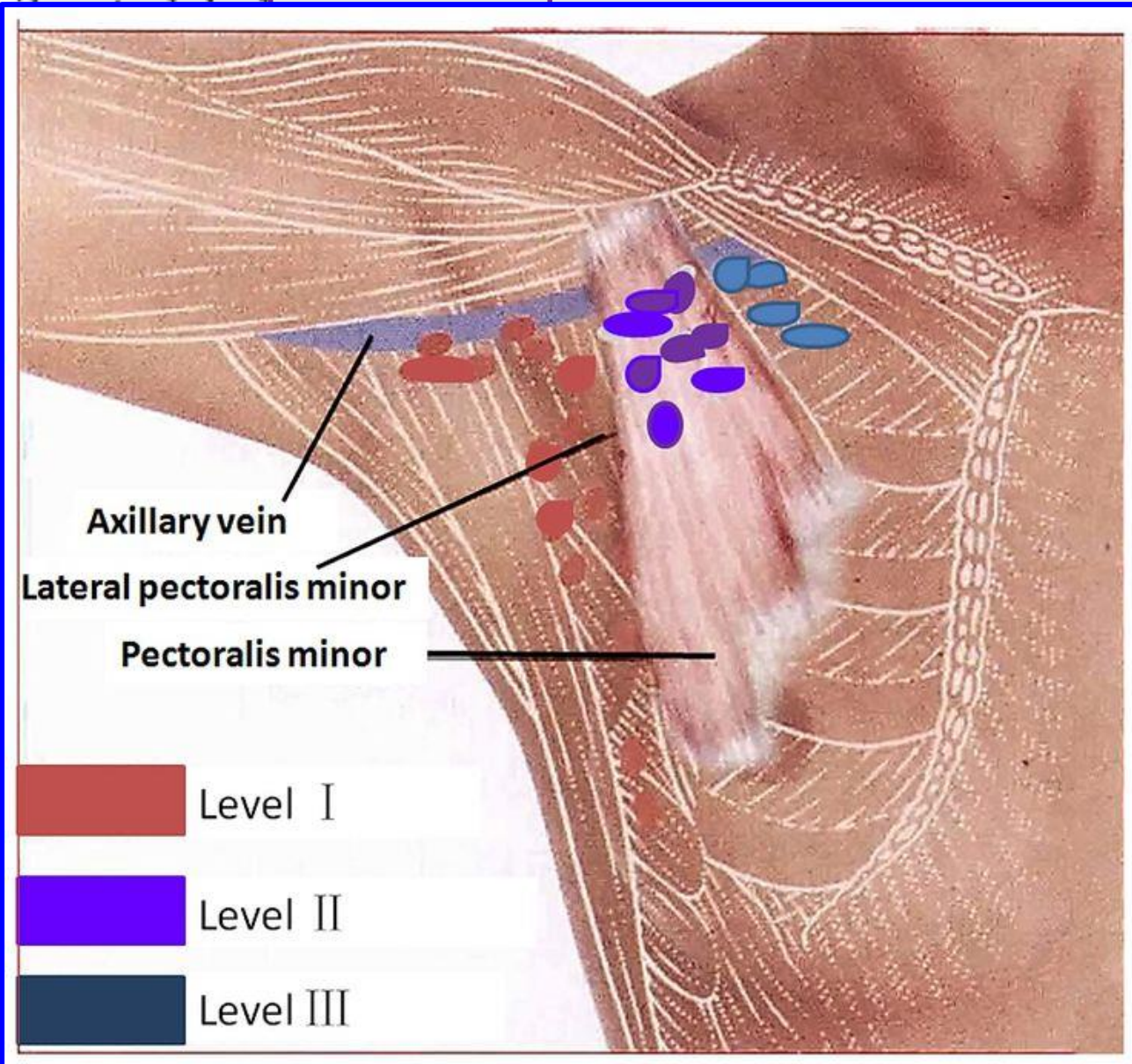
Incidence of BCRL after SLNB

Author	Year	No. of patients	Measurement	Lymphedema, %
Sackey	2014	140	Water displacement	20
Sagen	2014	187	Water displacement	3
Velloso	2011	45	Circumference	4
Goldberg	2010	600	Circumference	5
Lucci	2007	446	Circumference	7
Langer	2007	449	Circumference	4
Mansel	2006	478	Circumference	5
Francis	2006	26	Circumference	17
Wilke	2006	2904	Circumference	7
Leidenius	2004	92	NR	4
Ronka	2004	57	NR	23
Langer	2004	40	NR	0
Blanchard	2003	683	Circumference	6
Haid	2002	57	Circumference	4
Swenson	2002	169	Subjective	9
Sener	2001	303	NR	3
Schrenk	2000	35	NR	0

17 studies
6,711 patients
Pooled incidence
: **6.3%**

Lateral group

Deltoid



Central
Subscapular

Axillary vein

Lateral pectoralis minor

Pe

Pectoralis minor

Cutane
front

Level I

Level II

Level III

Systemic
semination

Lymphatic
in
glands

axillary group

collecting
s

axillary plexus

axillary
internal
glands

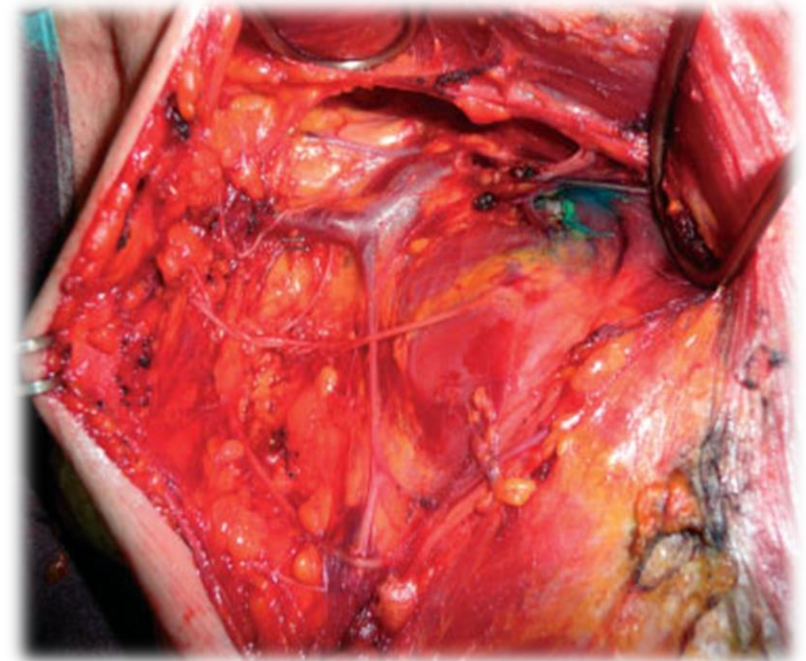
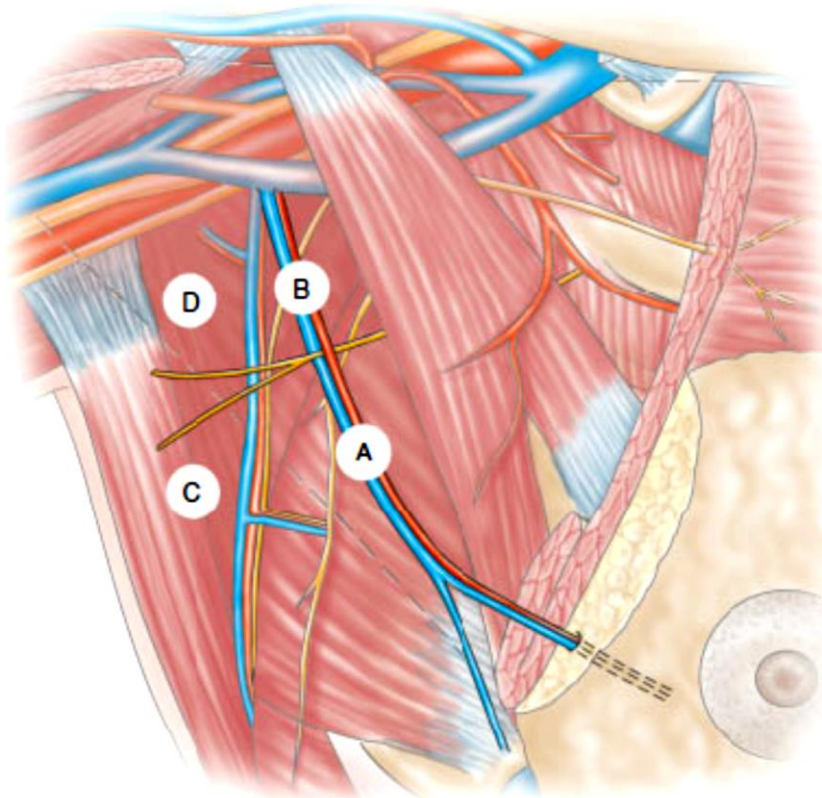
Henry Gray, Anatomy of the Human Body, 1918.

New anatomical classification of the axilla with implications for sentinel node biopsy

K. B. Clough, R. Nasr, C. Nos, M. Vieira, C. Inguenault and B. Poulet

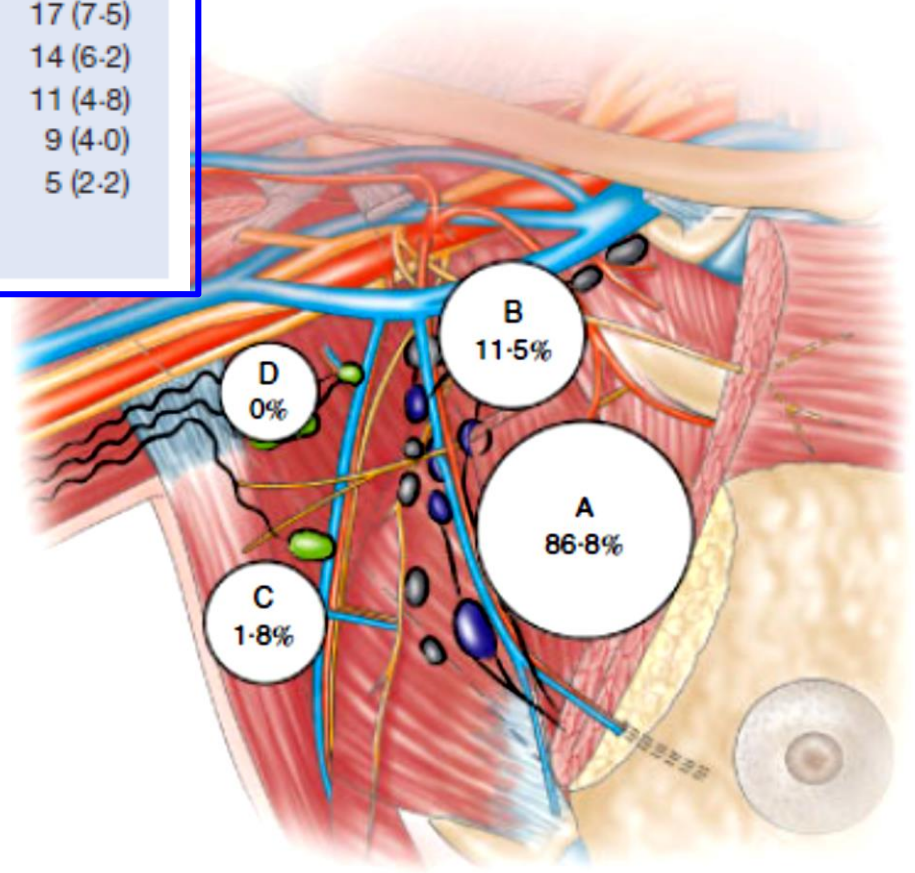
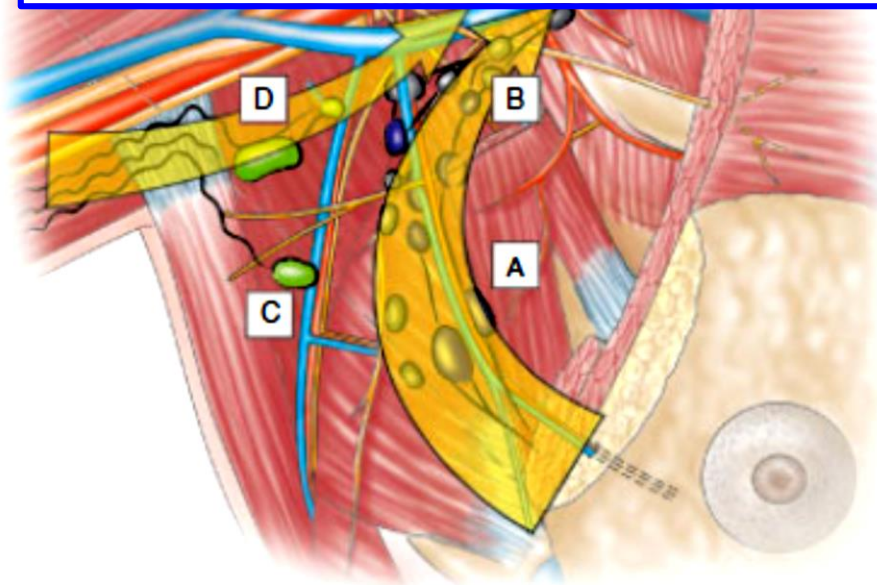
The Paris Breast Centre (L'Institut du Sein), 7 Avenue Bugeaud, 75116 Paris, France

Correspondence to: Dr K. B. Clough (e-mail: krishna.clough@orange.fr)



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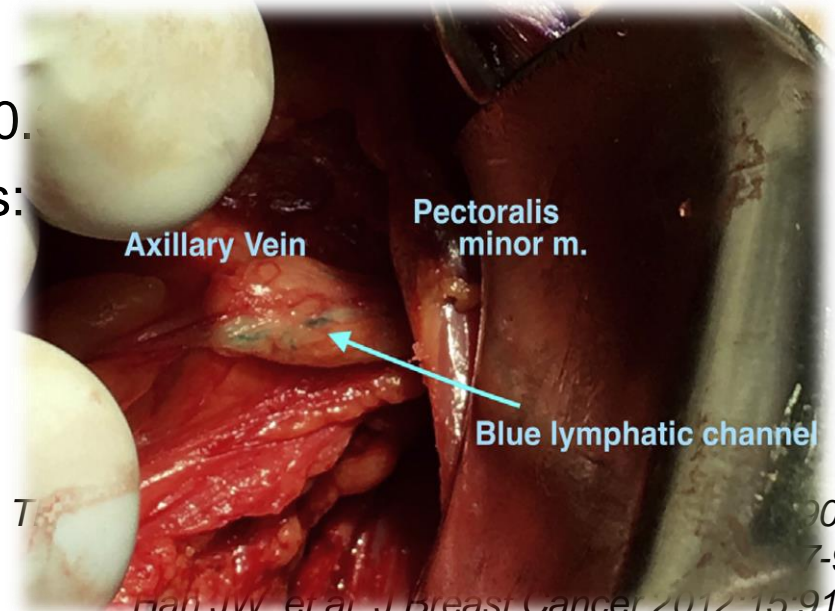
	Zone A	Zone B	Zone C	Zone D	Tumour location
UOQ	80	10	1	0	91 (40.1)
UIQ	27	6	0	0	33 (14.5)
JUQ	24	3	2	0	29 (12.8)
JOQ	16	1	1	0	18 (7.9)
LOQ	16	1	0	0	17 (7.5)
LIQ	13	1	0	0	14 (6.2)
RA	9	2	0	0	11 (4.8)
JLQ	8	1	0	0	9 (4.0)
JIQ	4	1	0	0	5 (2.2)
SLN location	197 (86.8)	26 (11.5)	4 (1.8)	0 (0)	



BCRL prevention 2: ARM

Axillary Reverse Mapping (ARM)

- Klimberg and colleagues (2007)
- Modified lymph node mapping technique for identifying the SLN
- Preserve the functioning upper extremity lymphatics
- Hypothesis: the arm and breast has distinct lymphatic channels
- blue dye (2~5mL) injected into the ipsilateral upper inner arm along the intramuscular groove





A Prospective Study to Assess the Feasibility of Axillary Reverse Mapping and Evaluate Its Effect on Preventing Lymphedema in Breast Cancer Patients

Tao Yue, Dayong Zhuang, Peng Zhou, Luming Zheng, Ziyi Fan, Jian Zhu, Lei Hou, Fang Yu, Xuefeng Dong, Lei Xiao, Qingqing He

- 265 patients, ALND (n=127) vs. ALND+ARM (n=138)
- Identification rate of ARM node: 93.48% (129/138)
- 1 ARM node 75.2%, 2 ARM nodes 19.38%, 3 ARM nodes 5.43%
- FNAC assessment of ARM node metastasis
- ARM nodes metastasis: 8.53% (11/129)
- No nodal relapse during follow-up
- 20 month LE: **33%(ALND) vs. 5.93% (ALND+ARM) ($p<0.001$)**

Table 2 Additional ARM Nodes Metastases

Stage	Number of Patients Identified ARM Nodes and Lymphatics	ARM Nodes Metastases, n (%)	P ^a
Overall	129	11 (8.53)	
pN1	56	2 (3.57)	.021
pN2	49	4 (8.16)	
pN3	24	5 (20.83)	

Table 4 The Lymphedema of the Control and Experimental Groups

Stage	Control Group, n (%)	Experimental Group, n (%)	P ^a
Overall	42 (33.07)	7 (5.93)	<.001
pN1	17 (30.91)	3 (5.57)	.001
pN2	16 (32.65)	3 (6.67)	.002
pN3	9 (39.13)	1 (5.26)	.028 ^b

- ARM is a feasible technique to identify upper arm nodes.
- The incidence of LE can be decreased with ARM procedure.

Does Axillary Reverse Mapping Prevent Lymphedema After Lymphadenectomy?

Evan Tummel, MD, Daniela Ochoa, MD,* Soheila Korourian, MD,† Richard Betzold, MD,*
Laura Adkins, MS,* Maureen McCarthy, OCN, RN, Stephanie Hung, MD,* Kyle Kalkwarf, MD,*
Kristalyn Gallagher, DO,* Jeannette Y. Lee, PhD,‡ and V. Suzanne Klimberg, MD*†*

- 654 patients prospectively underwent ARM+SLNB and/or ALND
- **Objective LE: 0.8% (SLNB) and 6.5% (ALND)**, 26-month median f/u
- Blue lymphatics identification: 29.2% (SLNB) and 71.8% (ALND)
- Crossover: 3.8% (18/472) of SLNB and 5.6% (12/213) of ALND
- Blue node metastases rate: 4.5% (2/44)
- Axillary recurrence rate: 0.2% (SLNB) and 1.4% (ALND)
- Lymphedema rates are dramatically reduced using ARM when compared with accepted standards.

Axillary Reverse Mapping (ARM)

- The ARM technique is applicable in surgical axillary staging, early breast cancer patients are better candidates.
- Preserving nodes using ARM decrease the occurrence of upper limb lymphedema after SLNB or ALND.
- Larger samples and longer follow-up times are needed to evaluate the oncological safety of ARM node (4~12% metastasis).
- Longitudinal studies using objective measurement could determine the primary benefit of ARM in LE prevention.

BCRL prevention 3: LYMPHA

Lymphatic microsurgical preventive healing approach (LYMHPA)

- Boccardo, et al. (2009)
- Surgical approach for the primary prevention of LE after ALND
- ALND + lympho-venous anastomosis

- Blue dye injected into the volar aspect of the ipsilateral upper arm
- The blue lymphatics are identified and the afferent lymphatics are clipped near insertion into the node.
- The afferent lymphatics are directly anastomosed into a collateral branch of the axillary vein with microsurgical technique.

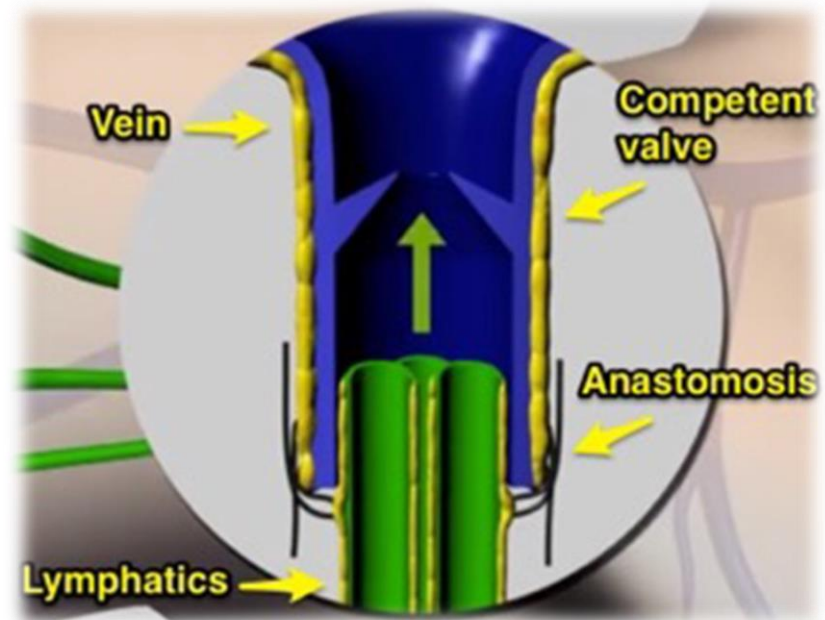
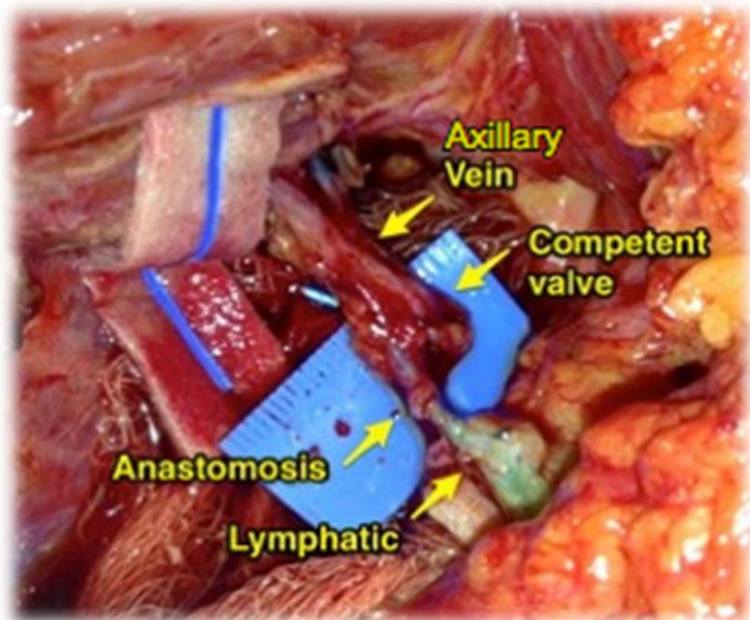
- Significant reduction in LE at 18 months (30% vs 4.05%, $p < 0.01$)

*Boccardo F, et al. Ann Surg Oncol 2009;16:703-8.
Feldman S, et al. Ann Surg Oncol 2015;22(10):3296-301.
Gallagher K, et al. Surg Oncol Clin N Am 2018;27:195-205.*

Single Institution Experience with Lymphatic Microsurgical Preventive Healing Approach (LYMPHA) for the Primary Prevention of Lymphedema

Sheldon Feldman, MD¹, Hannah Bansil, MD¹, Jeffrey Ascherman, MD², Robert Grant, MD², Billie Borden, BA³, Peter Henderson, MD², Adewuni Ojo, MD¹, Bret Taback, MD¹, Margaret Chen, MD¹, Preya Ananthakrishnan, MD¹, Amiya Vaz, BA¹, Fatih Balci, MD^{1,5}, Chaitanya R. Divgi, MD⁴, David Leung, MD⁴, and Christine Rohde, MD²

¹Division of Breast Surgery, Columbia University Medical Center, New York-Presbyterian Hospital, Columbia University, New York, NY; ²Division of Plastic Surgery, Columbia University Medical Center, New York-Presbyterian Hospital, Columbia University, New York, NY; ³Columbia University College of Physicians and Surgeons, New York, NY; ⁴Department of Radiology, Columbia University Medical Center, New York-Presbyterian Hospital, Columbia University, New York, NY; ⁵Department of Surgery, Atakent Hospital, Acibadem University, Istanbul, Turkey



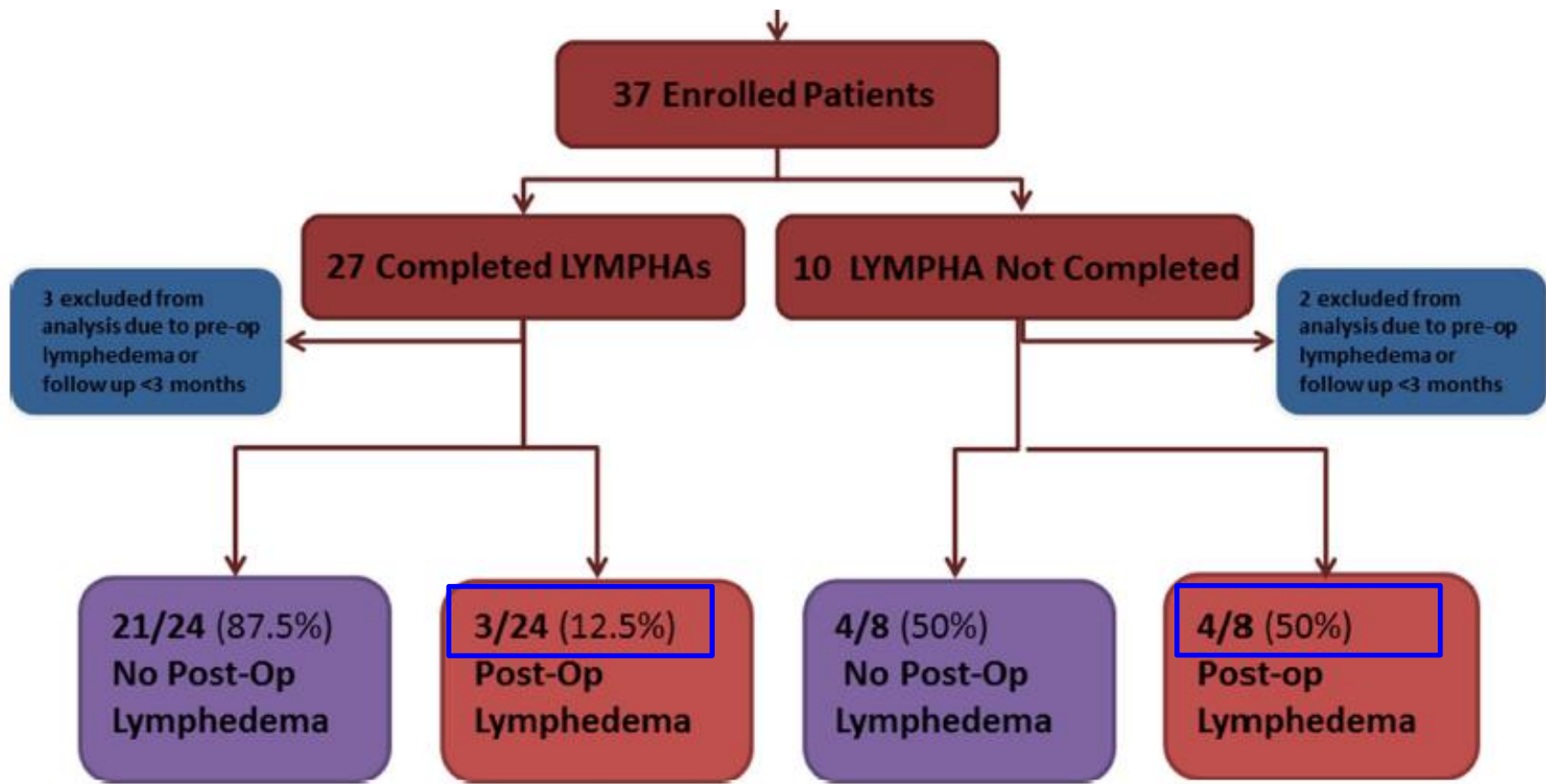


TABLE 1 Patient characteristics

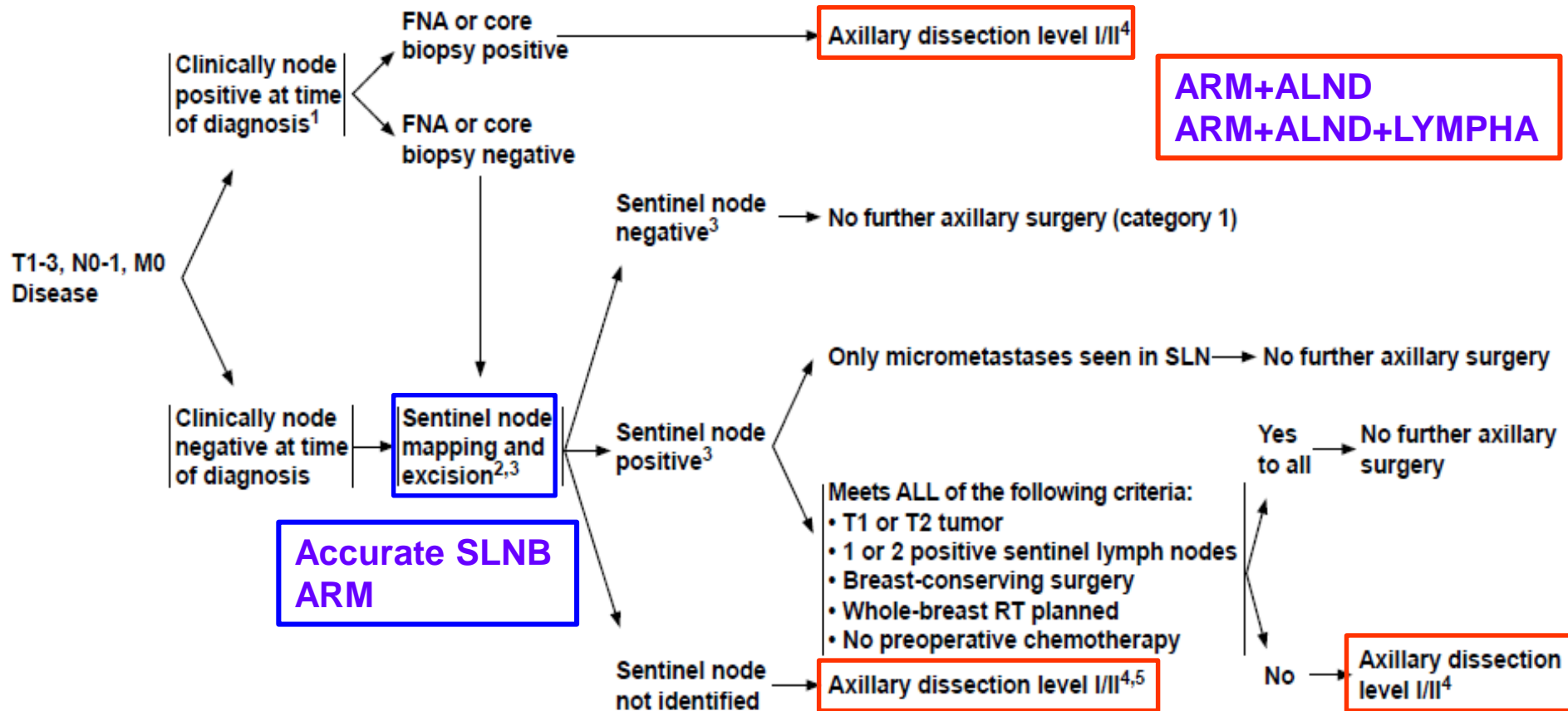
Characteristic	Incomplete LYMPHA (<i>n</i> = 8)	Completed LYMPHA (<i>n</i> = 24)	<i>p</i>
Age (years)	55.8 ± 13.1 (33–71)	58.1 ± 11.8 (33–76)	0.63 ^a
Body mass index (kg/m ²)	29.5 ± 7.1 (23.5–41.5)	28.7 ± 6.8 (17.4–47.5)	0.77
Total lymph nodes excised	14.0 ± 7.0 (4–28)	18.0 ± 8.0 (3–37)	0.26
Positive lymph nodes	5.0 ± 5.5 (1–16)	3.0 ± 3.0 (0–13)	0.26
Type of surgery (breast conservation)	1/8 (12.5)	4/24 (16.6)	1.0 ^b
Adjuvant radiotherapy	6/8 (75)	15/24 (62.5)	0.68
Chemotherapy (yes/no)	7/8 (87.5)	23/24 (95.8)	0.44

LYMHPA

- Updated data: more patients (n = 42), longer follow-up (22 months)
- LE rates: 7% (LYMPHA) vs. 31% (ALND)
- No significant complications
- 40 min of operating time
- Microsurgical technique (learning curve: 15)
- High-risk patients who require complete ALND

- LYMPHA is a promising technique for LE prevention, and should be explored further with appropriate patients.

SURGICAL AXILLARY STAGING - T1-3, N0-1, M0 DISEASE



¹Consider pathologic confirmation of malignancy in clinically positive nodes using ultrasound-guided FNA or core biopsy in determining if a patient needs axillary lymph node dissection.

²Sentinel lymph node mapping injections may be peritumoral, subareolar, or subdermal.

³Sentinel node involvement is defined by multilevel node sectioning with hematoxylin and eosin (H&E) staining. Cytokeratin immunohistochemistry (IHC) may be used for equivocal cases on H&E. Routine cytokeratin IHC to define node involvement is not recommended in clinical decision-making.

⁴[See Axillary Lymph Node Staging \(BINY-E\).](#)

⁵For patients with clinically negative axilla who are undergoing mastectomy and for whom radiation therapy is planned, axillary radiation may replace axillary dissection level I/II for regional control of disease.

Conclusion

- Breast cancer treatment places survivors at lifelong risk for the development of lymphedema.
- The true incidence of BCRL is difficult to measure (symptoms variable onset, diagnosis not standardized)
- BCRL is related to multidisciplinary treatment; ALND, nodal radiation, and chemotherapy (treatment-related factors), and obesity (patient-related factor)
- Identification of high-risk patients and application of appropriate individualized surgical strategy (SLNB, ARM, and LYMPHA) could possibly prevent BCRL. (the highest risk of developing lymphedema: first 3 years)

Thank you for your attention