INCIDENCE OF LYMPHEDEMA A LITERATURE REVIEW

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Wide Range of Estimates

- Changing cancer diagnosis & treatment
- Lack of standard clinical criteria
- Prolonged clinical course of toxicity
- Therapeutic interventions during study
- Physician viewpoint and knowledge
- Inadequate contemporary documentation
- Selection criteria of patients for study
- Non-use of actuarial estimates

Systematic Reviews

- 2004. Hinrichs, Watroba, et. al., 12 Studies, 77 References,1967-2004
- 2004. Okeke, Bates, Gillatt, 54 References, 1962-2002
- 2001. Erickson, Pearson, et. al., 10 Studies, 115 References, 1985-1999
- 2000. Pain & Purushotham, 145 References, 1908-1999
- 1998, 2000. Petrek & Heelan, 7 Studies, 22 References, 1991-1997
- 1997. Schünemann & Willich, 40 References, 1972-1995
- 1996. Mortimer & Bates
- 1995. Logan
- 1992. Moffat, Senofsky, et. al., 10 Studies, 40 References, 1981-1991
- 1986. Casley-Smith, 63 References 1956-1985
- 1985. Smeltzer, Stickler, et al., 154 References
- 1966. Hughes & Patel, 11 Studies, 37 References, 1940-1961
- 1962. Britton & Nelson, 14 Studies, 30 References 1908-1950

Lymphedema Risk Factors

Treatment-Related Factors
- Axillary surgery
- Axillary radiation
- Radiation dose level, schedule and distribution
- Chemotherapy, hormonal
- Interaction between modalities
- Infection
- Delayed wound healing
- Seroma

Tumor Characteristics
- Advanced stage at diagnosis
- Pathologic node status
- Location of tumor

Patient-Related Factors
- Advanced age/Youth?
- Obesity
- Weight gain after treatment
- Hypertension
- Genetic determination of lymphatics
- History of infections/inflammation
- Presence of co-morbidities
- Physical activities in relation to conditioning

Incidence of Lymphedema–A Literature Review by Robert Weiss, M.S.
6th International NLN Conference *New Frontiers in LE Research & Therapy*

Etiology of Arm Lymphedema

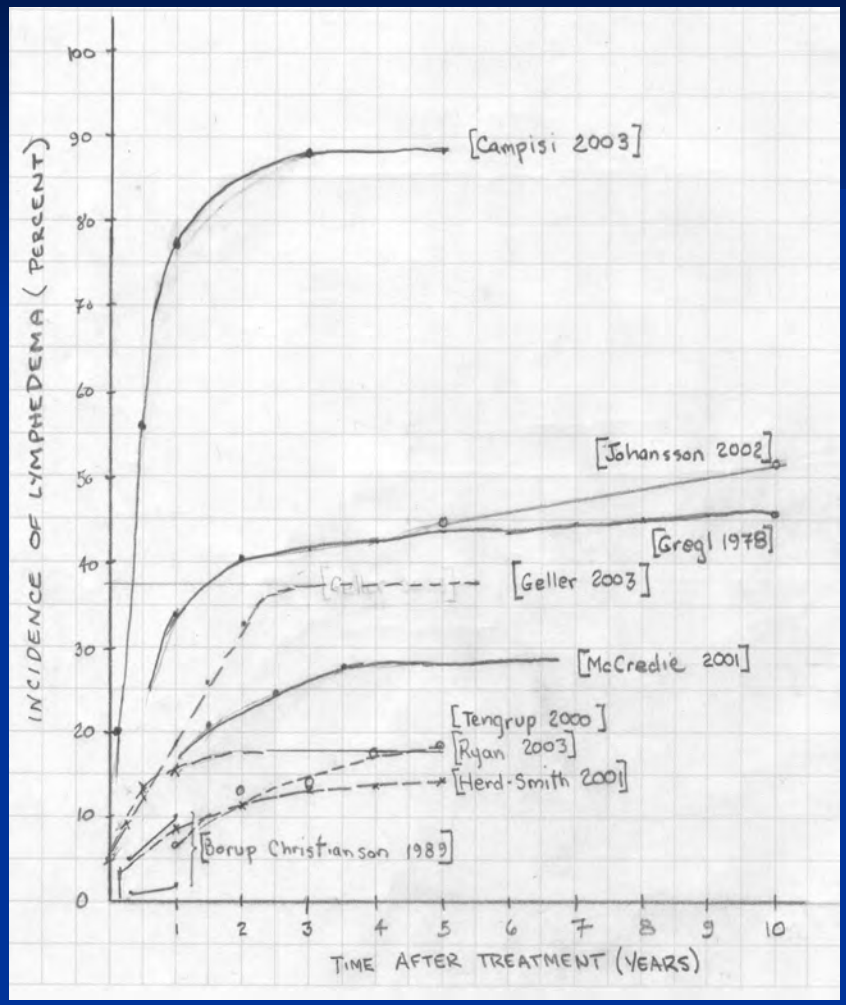
- Removal of lymphatic channels
- Infection of lymphatics
- Lymphatic obstruction due to scarring
- Occlusion of axillary vein
- Inhibited venous and lymphatic regeneration
- Post-radiation axillary scarring
- Local cancer

Ref. Britton RC & Nelson PA: "Causes and Treatment for Postmastectomy Lymphedema of the Arm: Report of 114 Cases", *JAMA* 1962;180:95-102.

Onset of Lymphedema

Time to onset of LE

- 3-6(<1-24) Mo. [Campisi 2003]
- 36 (±29 s.d.) Mo. [Dewar 1987]
- 478(±356s.d.) D. [Hinrichs 2004]
- 14(2-92) M, 97% within 4 Yr. [Werner 1991]
- 7(7-37) Mo. surgery alone,
- 12(1-52) Mo. surgery + RT,
- 25(6-156) Mo. RT alone [Pierquin 1986]
- 17(1-109) Mo. [Meric 2002]
- 77% in 3 Yr. [Petrek 2001]
- 73% in 1 Yr. [Guedes Neto 1997]
- 75% in 1 Yr. [Clark 1997][Mozes 1982] per Pain 2000]



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Length of Evaluation

- "It is obvious that 5 years is too short an observation time for assessment of some complications [of radiotherapy]…" The incidence of oedema at ,5 years was 65%, rising to 70% at <10 years in this series. [Johansson 2000]
- "Lymphedema may, however, develop months or years after [treatment] (an interval of over 20 years has been reported) with around 75 percent of cases occurring in the first year…" (references to Clark 1997 and Mozes 1982) [Pain 2000]

Measurement Methods

- Circumferential
- Volumetric
  - Water Immersion
  - Calculated based on circumferential measurements
  - Computed based on electro-optical inputs
- Tissue Tonometry
- Bioelectrical Impedance
- Measurement of Skin Thickness
- MRI/CT Scanning
- Lymphoscintigraphy
- Differential Absorptiometry
- Clinical Assessment
- Functional Assessment

Refs: Mikes 1999, Gerber 1998, Casley-Smith 1994, Hoe 1992, Kissin 1986

SWELLING LOCATION

■ Any Swelling	35.8	27.1
■ Side of chest wall	13.5	
■ Front of chest wall	10.1	
■ Remaining breast tissue	13.5	
■ Back	10.1	
■ Armpit	22.6	
■ Shoulder/Upper arm	18.2	20.7
■ Forearm	18.9	15.0
■ Wrist	12.8	
■ Hand	13.5	12.1
■ Fingers	14.2	

Ref. Bosompra, Ashikaga, O'Brien, Nelson, Skelly & Beatty
Patient Education and Counseling 2002;47:155-163

[Haid 2002]

Objective or Subjective Measures?

- Self-reported symptoms result in higher incidence than clinical measurements [Tengrup 2000], [Edwards 2000], [Moffatt 2003] or lower incidence [Kissin 1986].
- Attempt to correlate subjective and objective criteria [Ververs 2001]
  - Severe oedema reported by 9% of responders: $\Delta c \geq 2cm$ on 71%
  - No or slight oedema reported by 90%: $\Delta c \geq 2cm$ on 17%
- "Incidence of lymphedema seems to be underestimated clinically, as we found only 14 out of 21 patients with registered lymphedema when looking through the patients' records." [Tengrup 2000]
- The overall subjective percentage for lymphedema (23.4%) was considerably higher than the objective rate (11%). Of the 47 women who reported noticing swelling, only 14 (30%) exceeded the 10% volume threshold for definition of lymphedema. The objective rate matched the subjective rate when the cut-off was lowered to 6%. [Edwards 2000]

Standard Definition or Measure ?

- Any differential defines "swollen" [Lobb 1949]
- "Significant" is Δc >0.5cm [Deland 1950]
- Swelling is Δc> 0.72cm [MacDonald 1955]
- Lymphedema is Δc ≥2cm @ any of 3 points [Ozaslan 2004]
- Presence of LE Δc ≥2cm [Armer 2004]
- Lymph Edema "Present or Absent" [Schijven 2003]
- Arm lymphedema present when Δv ≥200mL [Kwan 2002][Beaulac 2002], or when Δvc≥10% [Kuehn 2000],[Tengrup 2000]
- Sum of Δc/c% measured at 6 places >5% defines lymphedema [Herd-Smith 2001]
- LE present if Δc >2cm @ 2 points and if tissue consistency was typical of edema [Haid 2002]
- Skin thickness Δt > 2mm [Rönkä 2004]
- Ratio of extracellular to intracellular fluid volumes [Cornish 2002]

Grading Lymphedema

- MASS criteria: None, Mild or Moderate/Severe/Very Severe [Swenson 2002]
- LENT-SOMA objective criteria for the Breast- Lymphedema Arm:

Grades 1/2/3/4: Δc=2-4cm/ >4-6cm/ >6cm/ Useless Arm. [Fehlauer 2003][Højris 2000]; Δv=200-499mL/500-999mL/≥1000mL/ Useless Arm [Højris 2000]

- Grades 1/2/3/4: Δc <3cm above elbow/ >3cm below elbow/ Impaired function/ Total Loss of function [Meric 2002]; Δvc=11-20%/ 21-30%/ 31-40%/ >40% [Kuehn 2000]
- Moderate: Δc>2cm @ 1 point /Severe >4cm with symptomatic restriction of arm movement. [Coen 2003]
- Mild/Moderate/Severe: Δc<3cm/ 3-5/ >5cm @ any of 5 points. "Clinically significant LE" Δc≥3cm [Deo 2004][Brennan 1996]
- None/Mild/Moderate/Severe: Δc<0.5in with no report of swelling or heaviness/ Δc<0.5in with self-report/ Δc≥0.5-2in/Δc≥2in [Petrek 2001]
- Slight/Moderate/Severe is Δv=150-400/400-800/>800mL [Göltner 1988], Δv=200-400/400-700/>700mL [Duff 2001]; 150-400/400-700/>700mL [Brennan 1996]
- Mild/Moderate/Severe: Δv<20%/21-40%/>40% [Sener 2001]; Δv=10-20%/ 20-40%/ >40% [Edwards 2000]

BC Therapy in Japan 1946-2000

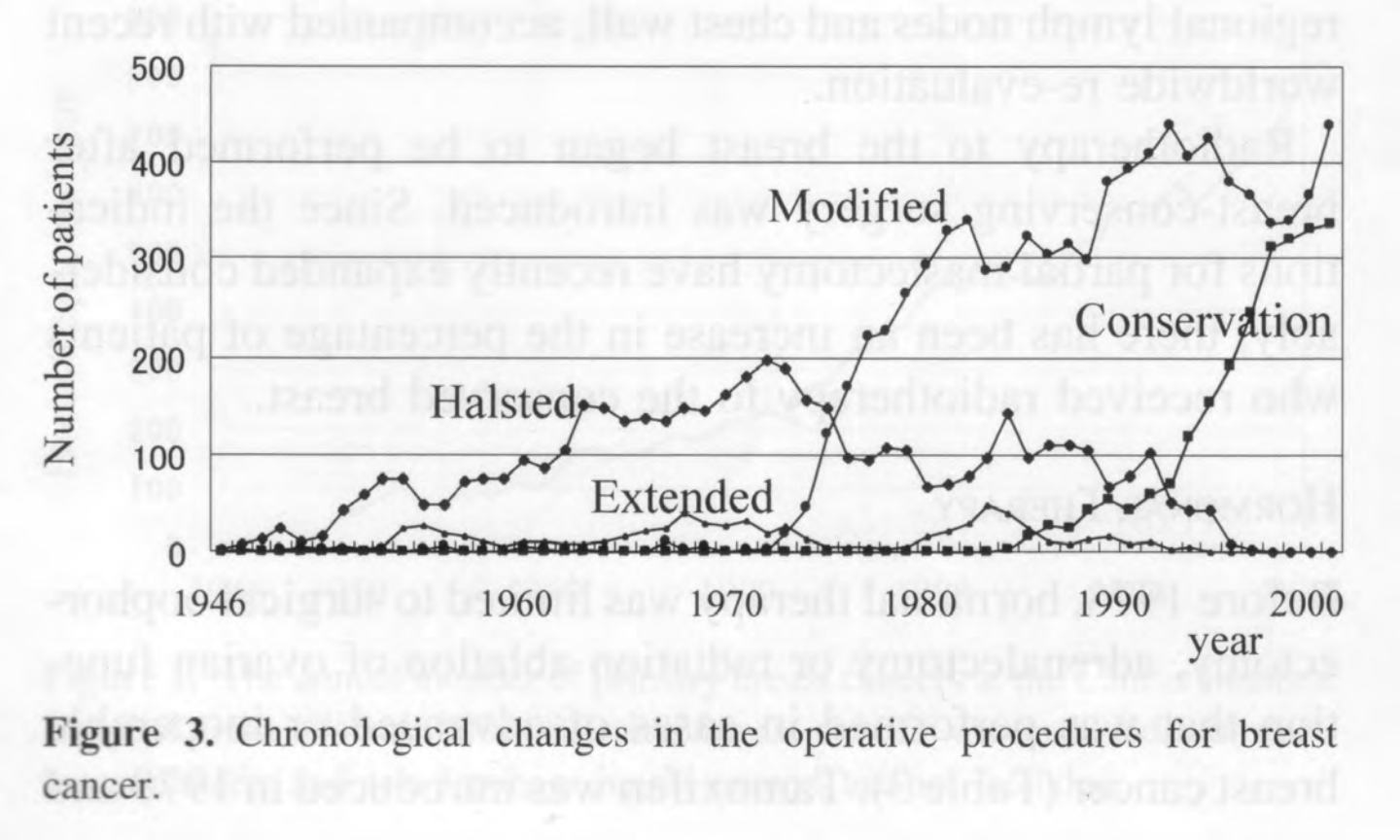

Figure 3. Chronological changes in the operative procedures for breast cancer.

Ref. Yoshimoto M, Tada K, Hori H, Morota A, Tanabe M, Nishimura S, Takahashi K, Makita M, Iwase T, Kasumi F, Takahashi S, Ito Y, Oguchi M, Yamashita T Akiyama F & Sakamoto G: "Improvement in the prognosis of Japanese breast cancer patients from 1946 to 2001–an institutional review" *Jpn J Clin Oncol* 2004;34(8):457-62.

BC Therapy in the U.S. 1997-2000 (3003 Patients)

	1997-2000	1997	2000
■ Type of definitive surgery		(Stage 1 BC)	
■ Breast Conserving Surgery	59%	(N=1763)	
■ Mastectomy (RM, MRM, SM)	41%		
■ Type of Axillary Surgery			
■ SLNB alone	13%	8%	58%
■ SLNB + ALND	22%	23%	23%
■ ALND alone	59%	58%	13%
■ None	6%	11%	6%

Edge SB, Niland JC, Bookman MA, Theriault RL, Ottesen R, Lepisto E & Weeks JC: "Emergence of Sentinel Node Biopsy in Breast Cancer as Standard-of-care in academic comprehensive care centers" *J Nat Cancer Inst.* 2003;95(20)1514-21

Cumulative Survival Japanese BC Patients

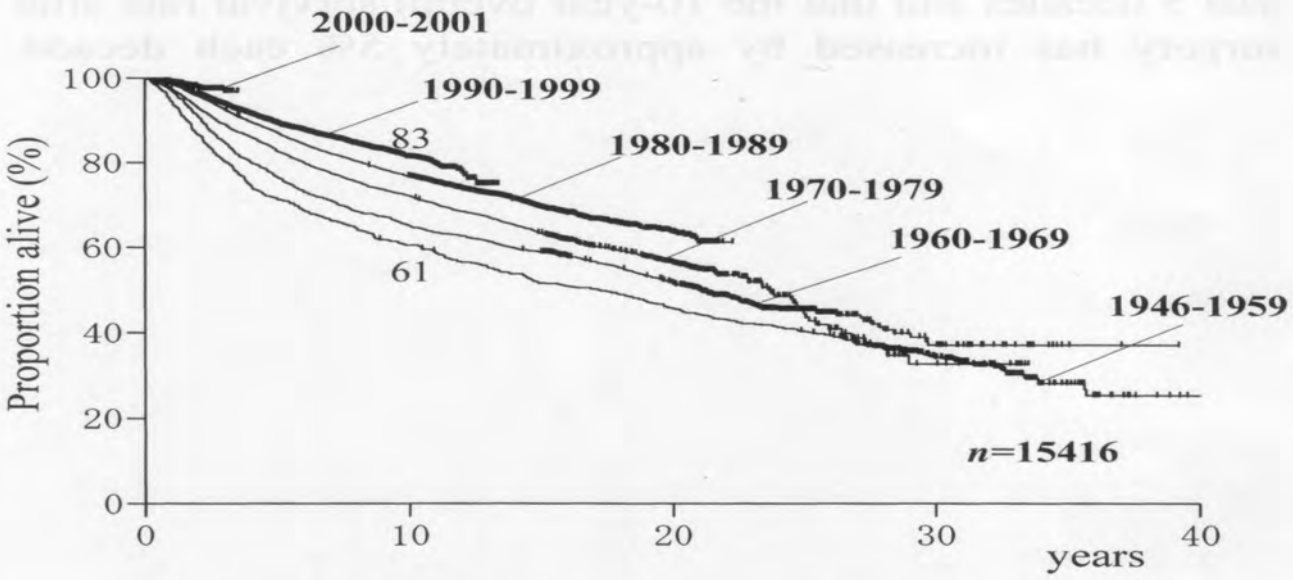

Figure 4. Chronological changes in the cumulative survival curve for Japanese women with breast cancer after the first operation by decades.

Ref. Yoshimoto M, Tada K, Hori H, Morota A, Tanabe M, Nishimura S, Takahashi K, Makita M, Iwase T, Kasumi F, Takahashi S, Ito Y, Oguchi M, Yamashita T Akiyama F & Sakamoto G: "Improvement in the prognosis of Japanese breast cancer patients from 1946 to 2001–an institutional review" *Jpn J Clin Oncol* 2004;34(8):457-62.

BC Therapy in Germany 1972-1995

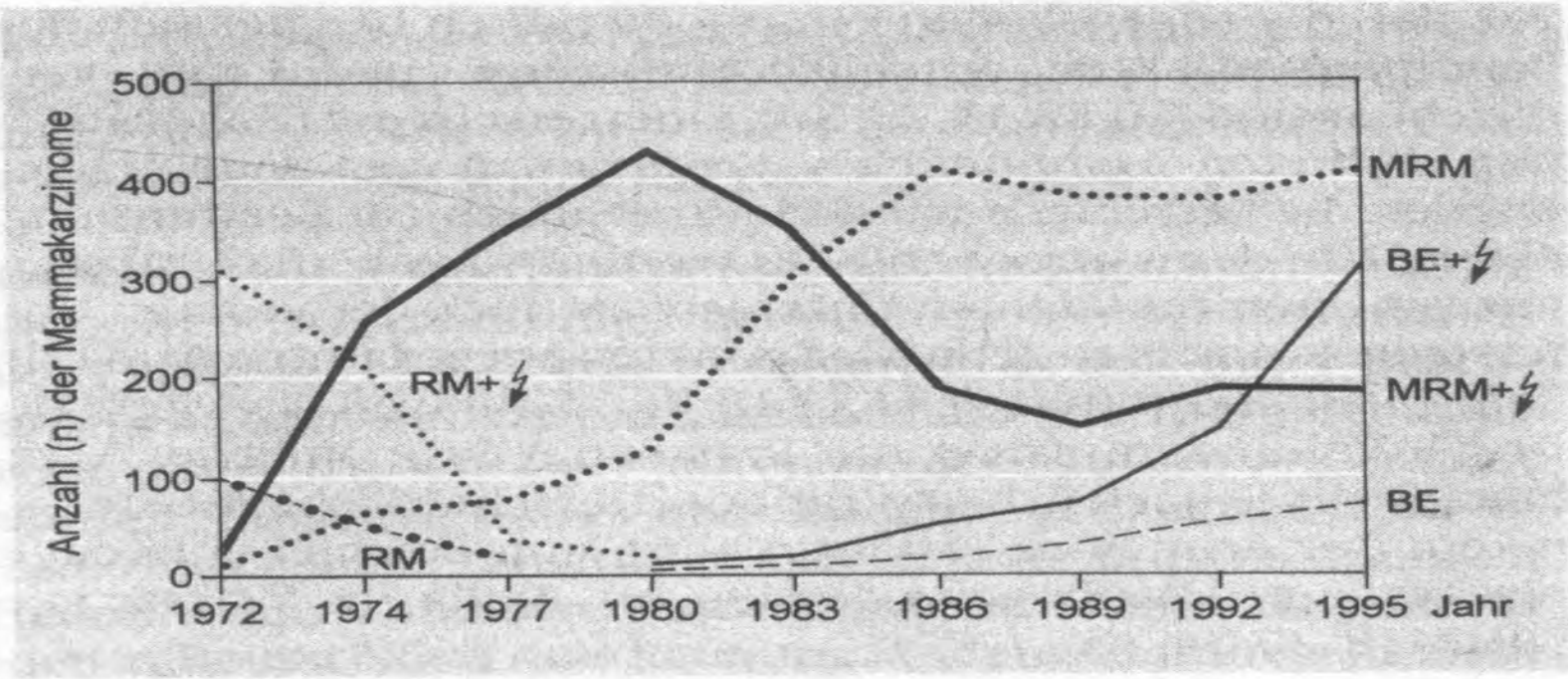

Abb. 1 Wandel der Primärtherapie von Mammakarzinomen (n = 5868) im Zeitspiegel 1972 – 1995. RM = radikale Mastektomie, MRM = modifiziert radikale Mastektomie, BE = brusterhaltende Operation, + = mit Strahlentherapie.

Ref. Schünemann H & Willich N: "Lymphödeme nach Mammakarzinom: Eine Studie über 5868 Falle" *Dtsch. Med. Wschr.* 1997;122:536-41

Decrease in Incidence of LE over the period 1972-1995

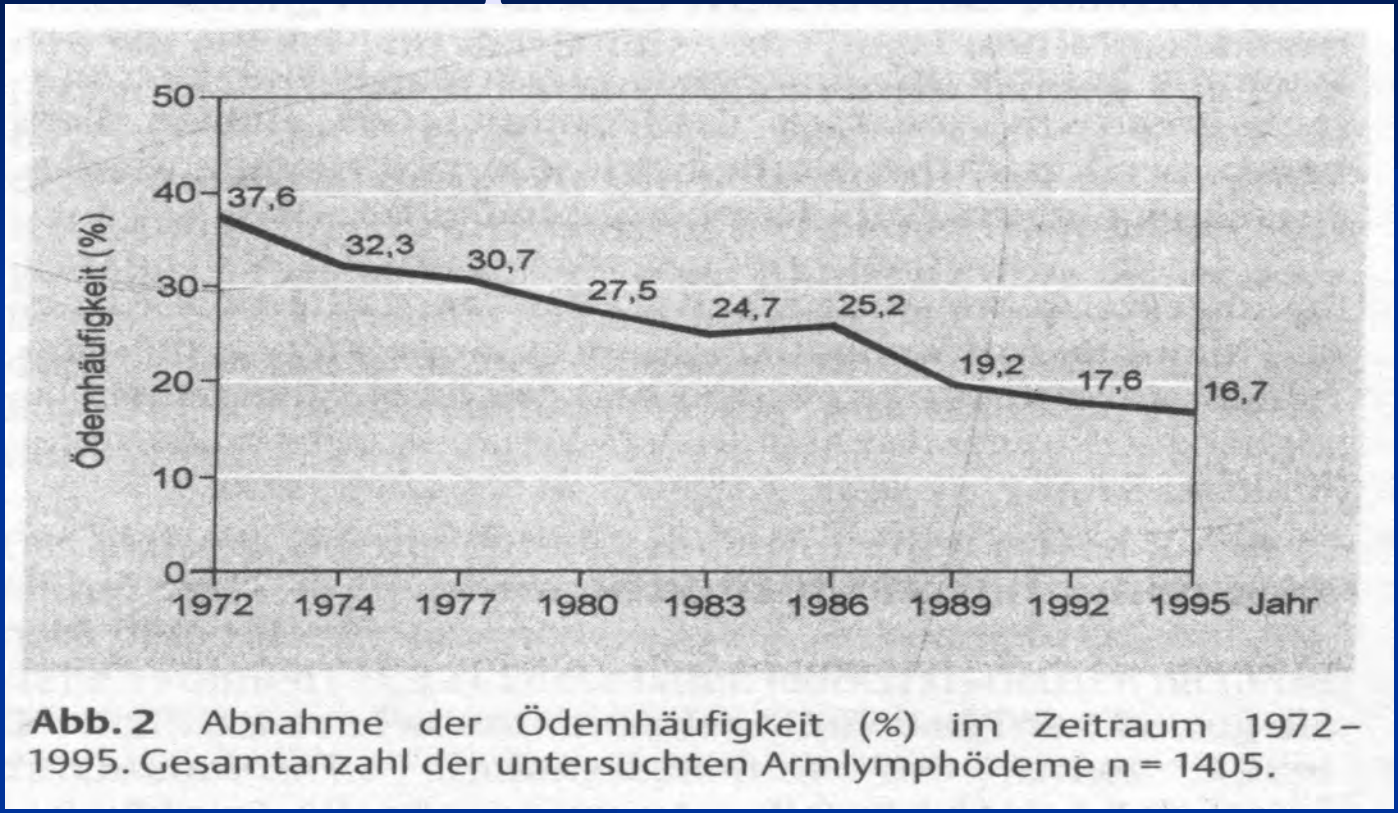

Abb. 2 Abnahme der Ödemhäufigkeit (%) im Zeitraum 1972–1995. Gesamtanzahl der untersuchten Armlymphödeme n = 1405.

Ref. Schünemann H & Willich N: "Lymphödeme nach Mammakarzinom: Eine Studie über 5868 Falle" *Dtsch. Med. Wschr.* 1997;122:536-41

Incidence of LE by Treatment

Tab. 2 Häufigkeit des Armlymphödems bei 5868 Mammakarzinomen in Abhängigkeit von Operation und Strahlentherapie im Zeitraum von 1972 – 1995

Therapie	Anzahl der Mamma-karzinome	Ödemhäufigkeit	
		n	%
RM	166	37	22,3
RM + ϟ	579	257	44,4
MRM	2170	415	19,1
MRM + ϟ	2148	621	28,9
BE	179	12	6,7
BE + ϟ	626	63	10,1
Summe	5868	1405	23,9

RM = radikale Mastektomie, MRM = modifiziert radikale Mastektomie, BE = brusterhaltende Therapie, + ϟ = mit Strahlentherapie

Ref. Schünemann H & Willich N: "Lymphödeme nach Mammakarzinom:
Eine Studie über 5868 Falle" *Dtsch. Med. Wschr.* 1997;122:536-41

Breast Lymphedema

- 1-9% subjective [Fehlauer 2003][Højris 2000] [Senofsky 1991] [Kissin 1982] 712 cases
- 10-19% clinical examination [Fehlauer 2003][Goffman 2004] 285 cases
- 20-48% clinical examination [Rönkä 2004] [Senofsky 1991] [Read 1987] 402 cases
- 25% (combined with truncal) [Martlew 1998] 250 cases
- 30-70% skin thickness [Rönkä 2004] [Hayward 1984] [Clarke 1983] [Clarke 1982] 349 cases

Genital Lymphedema

- 2-5% [Gaarenstroom 2003][Nelson 2004] 123 cases
- 18% (combined with leg) [Lieskovsky 1980] 82 cases
- 43% of pump users [Boris 1998] 53 cases

Lower Limb Lymphedema

- 0-4% [Coblenz 2002] [Levi D'Ancona 2004] [Zhang 2000] [Hagen 1994] [Sivanesaratnam 1993] [Greshkovich 1990] [Webb 1982] [Perez 1979] 963 cases
- 5-9% [Samlal 1996] [Baas 1992] [Cavanagh 1990] [Urist 1983] [Benedet 1979] [Rutledge 1965] 1352 cases
- 10-19% [Ryan 2003] [Gerdin 1995] [Rotmensch 1990] [Lieskovsky 1980] [Webb 1979] 1365 cases
- 20-29% [Nesvold 2002][Bevan-Thomas 2002] [Nelson 2004] [Gaarenstroom 2003] [Martin Martinez 1995] [Ravi 1993] [Baas 1992] [Höyer 1990] [Karakousis 1983] [Martinbeau 1978] [Holmes 1977] 1522 cases
- 30-39% [Gould 2001] [Hinrichs 2004] [Zhang 2000] [Hughes 2000] [Levi D'Ancona 2004] 251 cases
- 40-50% [Hughes 2000] [Ryan 2003] [Karakousis 1996] [Werngren-Elgstrom 1994] [Haberthür 1993] [Johnson 1984] 472 cases
- 60-80% [Balzer 1993] [James 1982] [Papachristou 1977] 224+ cases

Prevalence Estimates*

- Rochester, Minnesota Primary Lymphedema 1.15/100,000 of the under-20 year old population [Smeltzer 1985]
- South West London 1.33/1,000, 5.4/1,000 age >65years, 2.15/1,000 women, 0.47/1,000 men [Moffatt 2003]
- There are an estimated 2 Million BC survivors in the U.S. Assuming a conservative incidence of 10%, means there are 200,000 women with lymphedema. [Petrek 2001]

*The incidence of the different morbidities was defined as the percentage of the treated patients who developed the syndrome. The prevalence was defined as the percentage with the syndrome among the patients still alive. [Johansson 2002]

RESULTS

- Over 200 selected journal citations are tabulated
- Majority of estimates relate to breast cancer treatment protocols
- Survey includes pelvic and inguinal treatment protocols
- Incidence of lymphedema compared and contrasted
- An attempt is made to explain the dispersion between references.
- Attempt to derive consistent estimates for individual procedures or causes
- Estimates cited of primary lymphedema prevalence

INCIDENCE OF LYMPHEDEMA A LITERATURE REVIEW Part 2 Results

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SUMMARY MATRIX COLUMN LEGEND

- 1: Date of publication
- 2: Principal author
- 3: Treatment protocols
- 4: Number of patients in study
- 5: Incidence of lymphedema
- 6: Time of observation mean(range)
- 7: Years of treatment of study patients
- 8: Site of lymphedema
- 9: Method of measurement of swelling or limits

Breast Cancer Treatment Protocols

- Radical Mastectomy (RM)
- Modified Radical Mastectomy (MRM)
- Simple Mastectomy (SM)
- Breast Conserving Surgery, Quadrantectomy (BCS)
- Axillary Lymph Node Dissection (ALND)
- Axillary Lymph Node Sampling (ALNS)
- Sentinel Lymph Node Biopsy (SLNB)
- Radiotherapy (RT)
  - Local–Breast only (BrRT)
  - Local/Regional–Breast & Axilla (BrRT & AxRT)
  - Superclavicular (ScvRT)

Groin Lymphadenectomies

- Inguinal LND (External Inguinal) (ILND)
- Inguinofemoral LND (Inguinal + Femoral) (IFLND)
- InguinoFemoroIliac LND (Inguinal + Femoral + Iliac) (IFILND)
- Ilioinguinal LND (Inguinal + Iliac + Obturator) (IILND)
- Pelvic LND (Common & External Iliac + Obturator + Hypogastric) (PLND)
- Combined Inguinal + Pelvic LND (CLND)
- Sentinel LNB (Sentinel)

Groin Surgery

- Radical Hysterectomy (RH)
- Radical Penectomy (RP)
- Radical Prostatectomy (RPr)
- Prostate Resection (PrR)
- Radical Vulvectomy (RV)
- Modified Radical Vulvectomy (MRV)
- Vascular Surgical Reconstruction (VSR)

Col. 3–Treatment Protocol Abbreviations

- **ALND,ALND3**=Axillary clearance (Levels I-III)
- **ALND2=**Level I and II Axillary Dissection
- **ALNS**=Axillary Lymph Node Sampling
- **AVP**=Axillary Vein Preserved
- **AVR**=Axillary Vein Resection
- **AxRT**=Local Radiotherapy–Axillary Region
- **BCS**=Breast Conserving Surgery
- **BrRT**=Local Radiotherapy–Breast only
- **CLND**=Combined Inguinal + Pelvic LND
- **CT**=Adjuvent or Therapeutic Chemotherapy
- **GLND**=Groin LND
- **IFILND**=Inguinofemoroiliac
- **IFLND**=Inguinofemoral LND
- **IILND**=Ilioinguinal LND (Inguinal + Iliac + Obturator)
- **ILND**=Inguinal LND
- **LND**=Lymph Node Dissection
- **MILND**=Modified Inguinal LND
- **MRM**=Modified Radical Mastectomy
- **N+/N-**=Lymph Node Status Positive/Negative
- **P**=Penectomy
- **PLND**=Pelvic LND (Common & External Iliac + Hypogastric + Obturator)
- **PrR**=Prostate Resection
- **PT**=Physical Therapy
- **RH**=Radical Hysterectomy
- **RM**=Radical Mastectomy
- **RP**=Radical Penectomy
- **RPr**=Radical Prostatectomy
- **RT**=Radiotherapy
- **RV**=Radical Vulvectomy
- **ScvRT**=Local RT–Superclavicular Region
- **SLNB**=Sentinel Lymph Node Biopsy
- **SM**=Simple Mastectomy, Total Mastectomy
- **SaVP**=Saphenous Vein Preserved
- **SaVR**=Saphenous Vein Resection
- **VSR** =Vascular Surgical Reconstruction
- **2x**=Bilateral Mastectomy

Columns 6 & 8

Col. 6–Time of observation

- AE=actuarial estimate
- D=days
- M=months
- Y=years

Col. 8–Site of LE

- AA=arm
- BR=breast
- GE=genitals
- LA=lower arm
- LL=lower limb
- UA=upper arm

Col. 9– Method of Measurement of Swelling

- **asym**=asymptomatic
- **clin eval**=clinical evaluation
- **clin exam**=clinical exam
- **cm**=centimeter
- **m/m/s**=mild/moderate/severe
- **mL**=milliliter
- **mm**=millimeter
- **mod**=moderate
- **perm**=permanent
- **subj**=subjective (usually by patient questionaire)
- **sym**=symptomatic
- **Δc**=differential circumference
- **Δc/c**=normalized differential circumference
- **Δts**=differential skin thickness
- **Δv**=differential volume (water submersion)
- **Δvc**=differential calculated volume

METHODS USED

- Literature search of over 1800 lymphedema references primary and secondary lymphedema (Filarial lymphedema not included)
- 200+ references selected which cited the incidence of lymphedema
- References abstracted and relevant statistics collected into a matrix
  - Reference: Principal author
  - Procedure: Therapeutic protocols used on cohort
  - Number of cases
  - Incidence of lymphedema (percent)
  - Length of observation time since treatment
  - Years original treatment was given
  - Site of lymphedema
  - Measurement criteria

Summary Matrix 2000

Year	Reference	Procedure	# Cases	% LE	Time	Treatment	Site	Measure
2000	Edwards	BCS/SM(43/57%)+AxRT(13%)	201	11(O)-23(S)	3(2-4) Y	1994-1996	UL	Δv≥10%
2000	Edwards	BCS/SM(43/57%)+AxRT(13%)	201	30(O)-23(S)	3(2-4) Y	1994-1996	UL	Δv≥5%
2000	Edwards	ALND+RT(11%)	133	14	3(2-4) Y	1994-1996	UL	Δv≥10%
2000	Galper	BCS+RT	292	1	8-25 Y	1978-1987	UL	mod-sev
2000	Galper	BCS+ALNS+RT+CT	126	1	8-25 Y	1978-1987	UL	mod-sev
2000	Hare			25 to 58			UL	
2000	Højris	SM+ALND2+RT+CT	42	14	9(6-13) Y	1980's	UL	Δv≥200mL
2000	Højris	SM+ALND2+RT+CT	42	9	9(6-13) Y	1980's	UL	Δc≥2cm
2000	Højris	SM+ALND2+RT+CT	42	17+26	9(6-13) Y	1980's	UL	subj: some, perm
2000	Højris	SM+ALND2+CT	42	3	9(6-13) Y	1980's	UL	Δv≥200ml
2000	Højris	SM+ALND2+CT	42	12+5	9(6-13) Y	1980's	UL	subj: some, perm
2000	Højris	SM+ALND2+RT+CT	42	2+2	9(6-13) Y	1980's	BR	subj: asym, sym
2000	Hughes	ILND/CLND(45/55%)	132	26+19		1984-1998	LL	minor+major
2000	Hughes	ILND	60	23+13		1984-1998	LL	minor+major
2000	Hughes	CLND	72	28+24		1984-1998	LL	minor+major
2000	Johansen	BCS	266	11			UL	
2000	Johansen	BCS+ALND		5			UL	
2000	Johansen	BCS+ALND+AxRT		17 to 28			UL	
2000	Johansson	SM+ALND+RT	71	65/70	5/34 Y	1963-1965	UL	records
2000	Kuehn	BCS/SM(77%/23%)+ALND(85%)+CT(24%)	396	22	34(6-96) M	1990-1997	UL	subj
2000	Kuehn	BCS/SM(77%/23%)+ALND(85%)+CT(24%)	396	23/9	34(6-96) M	1990-1997	UL	Δv≥10% /30%calc
2000	Liao	CT+RT+SM+CT+RT	115	11	5.7(2-18) Y	1977-1993	UL	Δc≥3cm
2000	Schrenk	BCS,SM+SLNB +BrRT(70%)	35	0	15(4-28) M	1997-1999	UL	subj
2000	Schrenk	BCS,SM+ALND +BrRT(70%)	35	40+14	15(4-28) M	1997-1999	UL	subj: mild,moderate
2000	Schünemann	RM,MRM,BCS,RT	5868	24	11(2-25) Y	1972-1995	UL	Δc≥2cm
2000	Schünemann	RM	166	22	11(2-25) Y	1972-1995	UL	Δc≥2cm
2000	Schünemann	RM+AxRT	579	44	11(2-25) Y	1972-1995	UL	Δc≥2cm
2000	Schünemann	MRM	2170	19	11(2-25) Y	1972-1995	UL	Δc≥2cm
2000	Schünemann	MRM+AxRT	2148	29	11(2-25) Y	1972-1995	UL	Δc≥2cm
2000	Schünemann	BCS	179	7	11(2-25) Y	1972-1995	UL	Δc≥2cm
2000	Schünemann	BCS+BrRT	626	10	11(2-25) Y	1972-1995	UL	Δc≥2cm
2000	Tengrup	SM+ALND2+BrRT	75	22	5 Y	1992-	UL	Δv≥10%
2000	Tengrup	SM+ALND2	35	12	5 Y	1992-	UL	Δv≥10%
2000	Wrone	SLNB		2			UL	
2000	Zhang	MRV+ILND(SaVR)	77	70, 39, 32	6M, 2 Y, >2Y		LL	clin eval
2000	Zhang	MRV+ILND(SaVP)	62	32, 11, 2	6M, 2 Y, >2Y		LL	clin eval

Summary Matrix 2001

Year	Reference	Procedure	# Cases	% LE	Time	Treatment	Site	Measure
2001	Duff	SM/BCS(64/36%)+ALND	100	8+2	1-2 Y	ca 1998	UL	Δ≥200,≥400mL
2001	Gould	RV(88%)+ILND	67	5/30	>30D		LL	early/late-clin eval
2001	Herd-Smith	RM(24%)/BCS(76%)+ALND(76%)+RT(57%)	1276	16	5 Y	1989-1997	UL	Δc/c≥5%
2001	Herd-Smith	RM	306	15	5 Y	1989-1997	UL	Δc/c≥5%
2001	Herd-Smith	BCS+ALND+BrRT	732	18	5 Y	1989-1997	UL	Δc/c≥5%
2001	Herd-Smith	BCS+ALND	240	11	5 Y	1989-1997	UL	Δc/c≥5%
2001	Herd-Smith	BCS+ALNS	76	5	5 Y	1989-1997	UL	Δc/c≥5%
2001	Lee		171	46			UL	subj
2001	McCredie	BCS(60%)+ALND(96%)+RT(66%)	809	39	3.1(1.7-4) Y	1993-1998	UL	subj
2001	Petrek	RM/MRM(57/43%)+ALND+RT(<5%)	263	19+17+13	20 Y	1976-1978	UL	Δc≤0.5,0.5-2,≥2in
2001	Petrek	RM/MRN+ALND	211	19+18+13	20 Y	1976-1978	UL	Δc≤0.5,0.5-2,≥2in
2001	Petrek	RM/MRM+ALND (2x)	52	40	20 Y	1976-1978	UL	Δc≤0.5,0.5-2,≥2in
2001	Roumen	BCS+SLNB	100	0	24(16-40)M	1997-2000	UL	subj
2001	Sener	BCS+SLNB	303	3	19 M	1997-2000	UL	Δv≤20,21-40,>40%
2001	Sener	BCS+ALND	117	17	24 M	1997-2000	UL	Δv≤20,21-40,>40%
2001	Sener	BCS+ALND	72	7	24 M	1997-1998	UL	Δv≤20,21-40,>40%
2001	Stahlberg	ALND	95	6 to 25			UL	
2001	Ververs	BCS/SM(59/41%)+ALND+BrRT/AxRT(54/17%)	400	9/22	4.7(0.3 to 28) Y	1950-1999	UL	subj/Δc≥2cm

Summary Matrix 2002

Year	Reference	Procedure	# Cases	% LE	Time	Treatment	Site	Measure
2002	Beaulac	SM+ALND2	71	28	4.8(±0.2) Y	1986-2000	UL	Δv≥200mL
2002	Beaulac	BCS+ALND2+BrRT	80	28	4.8(±0.2) Y	1986-2000	UL	Δv≥200mL
2002	Bevan-Thomas	P+ILND/CLND(62/38%)	53	23			LL	clin eval
2002	Bosompra	BCS/SM/MRM(69/25/6%)+RT(66%)+CT(40%)	148	36	to 4 Y	1997-1999	any	subj
2002	Box	ALND	65	21	24 M		UL	Δv≥200mL
2002	Box	ALND+PT		11	24 M		UL	Δv≥200mL
2002	Box	ALND		30	24 M		UL	Δv≥200mL
2002	Burak	BCS+SLNB+BrRT+CT(20%)	48		13(±4.5) M		UL	clin eval, Δc/c
2002	Burak	BCS+ALND2+BrRT+CT(58%)	48		17(±6.4) M		UL	clin eval, Δc/c
2002	Campisi	BCS+RT	25	36	>5 Y	1992-1994	UL	clin eval
2002	Campisi	BCS+RT	21	88	>5 Y	1992-1994	UL	lymphoscintigraphy
2002	Chua	ALND		10		1997-2000	UL	
2002	Chua	RT		6		1997-2000	UL	
2002	Chua	ALND+RT		31		1997-2000	UL	
2002	Coblentz	P+ILND+PLND(45%)+SaVP(86%)	11	0	9 M	1995-2001	LL	clin eval
2002	Haid	BCS/SM(49/51%)+ALND+RT(19%)+CT(36%)	140	27	5(14-60) M	1993-1996	UL	subj, Δc≥2cm
2002	Haid	BCS/SM(88/12%)+SLNB+RT(83%)+CT(28%)	57	4	18(5-30) M	1997-2000	UL	subj, Δc≥2cm
2002	Johansson	SM+ALND+RT	150	54(25-70)	34 Y	1960s	UL	subj
2002	Johansson	SM+ALND+RT	71	70	34 Y	1963-1965	UL	subj
2002	Johansson	SM+ALND+RT	23	69	34 Y	1965-	UL	subj
2002	Johansson	SM+ALND+RT	56	25	34 Y	1965-	UL	subj
2002	Kwan	BCS+ALND2(79%)+RT(28%)	112	13	2-6 Y	1993-1997	UL	Δv≥200mL
2002	Kwan	BCS	28	7	2-6 Y	1993-1997	UL	Δv≥200mL
2002	Kwan	BCS+ALND2	52	4	2-6 Y	1993-1997	UL	Δv≥200mL
2002	Kwan	BCS+ALND2+AxRT	31	32	2-6 Y	1993-1997	UL	Δv≥200mL
2002	Meric	BCS+88%ALND2+44%AxRT+CT(67%)	294	14	89(13-126) M	1990-1992	UL	self or any
2002	Meric	BCS+AxRT	130	18	89(13-126) M	1990-1992	UL	Δc>3cm
2002	Meric	BCS	164	10	89(13-126) M	1990-1992	UL	Δc>3cm
2002	Meric	BCS+ALND2+BrRT	135	12	89(13-126) M	1990-1992	UL	Δc>3cm
2002	Meric	BCS+ALND2+ScvRT	88	17	89(13-126) M	1990-1992	UL	Δc>3cm
2002	Meric	BCS+ALND2+RT	25	20	89(13-126) M	1990-1992	UL	Δc>3cm
2002	Meric	BCS	32	0	89(13-126) M	1990-1992	UL	Δc>3cm
2002	Meric	BCS+88%ALND2+44%AxRT	294	5	89(13-126) M	1990-1992	UL	Δc>3cm
2002	Nesvold	GLND	83	20			LL	subj
2002	Swenson	BCS/SM(83/11%)+SLNB+80%RT	142	4	1 Y	1999-2000	UL	subj
2002	Swenson	BCS/SM(55/37%)+ALND+71%RT	63	14	1 Y	1999-2000	UL	subj

Summary Matrix 2003

Year	Reference	Procedure	# Cases	% LE	Time	Treatment	Site	Measure
2003	Coen	BCS+ALND+AxRT/BrRT(31/68%)	727	3	6 Y	1982-1995	UL	Δc≤2,2-4,≥4cm
2003	Coen	BCS+ALND+AxRT/BrRT(31/68%)	727	4	10 Y AE	1982-1995	UL	Δc≤2,2-4,≥4cm
2003	Coen	BCS+BrRT	37	0	10 Y AE	1982-1995	UL	Δc≤2,2-4,≥4cm
2003	Coen	BCS+RT	68	12	10 Y AE	1982-1995	UL	Δc≤2,2-4,≥4cm
2003	Coen	BCS+ALND2+BrRT	374	1	10 Y AE	1982-1995	UL	Δc≤2,2-4,≥4cm
2003	Coen	BCS+ALND2+RT	139	11	10 Y AE	1982-1995	UL	Δc≤2,2-4,≥4cm
2003	Coen	BCS+ALND3+BrRT	82	7	10 Y AE	1982-1995	UL	Δc≤2,2-4,≥4cm
2003	Coen	BCS+ALND3+RT	27	0	10 Y AE	1982-1995	UL	Δc≤2,2-4,≥4cm
2003	Deutsch	BCS+RT	265	7	6 M		UL	
2003	Engel	ALND	990	38	5 Y		UL	
2003	Fehlauer	BCS+ALND2+RT	45	4	14(13-19) Y	1983-1987	UL	Δc≥4cm
2003	Fehlauer	BCS+ALND2+RT	45	13	14(13-19) Y	1983-1987	BR	clin exam
2003	Fehlauer	BCS+ALND2+RT	345	9	9 Y	1988-1993	UL	Δc≥4cm
2003	Fehlauer	BCS+ALND2+RT	345	2	9 Y	1988-1993	BR	subj
2003	Fehlauer	BCS+ALND2+RT	200	5	6 Y	1993-1995	UL	Δc≥4cm
2003	Fehlauer	BCS+ALND2+RT	200	1	6 Y	1993-1995	BR	subj
2003	Gaarenstroom	MRV+IFLND+RT	101	28		1993-2000	LL	clin eval
2003	Gaarenstroom	MRV+IFLND+RT	101	2		1993-2000	GE	clin eval
2003	Geller	BCS(62%)+ALND(86%)+RT(68%)+CT(53%)	145	38	26(19-40) M		UL	subj
2003	Geller	RT	98	43	26(19-40) M		UL	subj
2003	Geller	no RT	47	28	26(19-40) M		UL	subj
2003	Geller	CT	77	47	26(19-40) M		UL	subj
2003	Geller	no CT	68	28	26(19-40) M		UL	subj
2003	Geller	BCS	90	34	26(19-40) M		UL	subj
2003	Geller	SM	55	44	26(19-40) M		UL	subj
2003	Rampaul	BCS,SM+ALNS1+[AxRT or ALND](<20%)	1242	<1		1973-2000	UL	subj
2003	Rampaul	BCS,SM+ALNS1+[AxRT or ALND](<20%)	677	6		1973-2000	UL	subj
2003	Ryan		490	18	5 Y	1995-2000	LL	subj
2003	Ryan	RV+ILND+RT	88	47	5 Y	1995-2000	LL	subj
2003	Schijven	BCS,SM+ALND+AxRT/BrRT(14/58%)	213	7	1.4 Y	1996-1999	UL	subj
2003	Schijven	BCS,SM+SLNB+AxRT/BrRT(8/74%)	180	1	1.9 Y	1996-1999	UL	subj

Summary Matrix 2004

Year	Reference	Procedure	# Cases	% LE	Time	Treatment	Site	Measure
2004	Armer	no ALND or SLNB	9	22			UL	subj and Δc≥2cm
2004	Armer	ALND	67	43			UL	subj and Δc≥2cm
2004	Armer	SLNB	9	22			UL	subj and Δc≥2cm
2004	Armer	SLNB+ALND	12	25			UL	subj and Δc≥2cm
2004	Deo	MRM(89%)+ALND+AxRT(79%)+CT(81%)	299	34/17	> 1 Y	<1997	UL	Δc≥3cm/≥5cm
2004	Deo	MRM+ALND+RT	202	42	> 1 Y	<1997	UL	Δc≥3cm
2004	Deo	MRM+ALND	93	13	> 1 Y	<1997	UL	Δc≥3cm
2004	Goffman	BCS/MRM(86/12%)+ALND2(77%)+RT	240	9	27 M	1998-2001	UL	clin exam
2004	Goffman	BCS/MRM(86/12%)+ALND2(77%)+RT	240	2	27 M	1998-2001	BR,AA	clin exam
2004	Goffman	BCS/MRM(86/12%)+ALND2(77%)+RT	240	11	27 M	1998-2001	BR	clin exam
2004	Hinrichs	MRM(91%)+RT+CT(90%)	105	20+6+1	24(1-81) M	1995-2001	UL	clin exam m/m/s
2004	Hinrichs	MRM+AxRT	17	47	24(1-81) M	1995-2001	UL	clin exam
2004	Levi D'Ancona	P+MILND+ILND	8	38	78(38-112) M	1994-1999	LL	clin exam
2004	Levi D'Ancona	P+MILND	18	0	78(38-112) M	1994-1999	LL	clin exam
2004	Nelson	P(95%)+ILND+PLND(45%)	22	27	34(9-69) M	1992-2003	LL	clin eval
2004	Nelson	P(95%)+ILND+PLND(45%)	22	5	34(9-69) M	1992-2003	GE	clin eval
2004	Ozaslan	MRM+ALND+RT(37%),CT(68%)	240	28/9	18-43 M	1998-2000	UL	Δc≥2cm/>4cm
2004	Ozaslan	MRM+ALND+RT	89	42	18-43 M	1998-2000	UL	Δc≥2cm
2004	Rönkä	BCS+SLNB/ALND2(36/64%)+RT+CT(26%)	160	34	1 Y	2000-2001	BR	clin exam
2004	Rönkä	BCS+SLNB+BrRT	57	23/28	1 Y	2000-2001	BR	clin exam/Δts >2mm
2004	Rönkä	BCS+ALND2(N+)+BrRT, AxRT	46	48/69	1 Y	2000-2001	BR	clin exam/Δts >2mm
2004	Rönkä	BCS+ALND2(N-)+BrRT	57	35/70	1 Y	2000-2001	BR	clin exam/Δts >2mm

The Paradox

- The determination of incidence of lymphedema with precision and accuracy requires the amassing of a large homogeneous cohort and their observation over a long period of time. After many years we would know the incidence with great precision.
- But we cannot have a large homogeneous cohort who can be followed for many years who have received the same therapeutic treatment, since treatments are continually changing.
- And even if we could, then all we would have is perfect knowledge of a treatment that is obsolete.