For doctors and nurses

6th Aarhus Workshop in:

Breast Surgery

May 17-18, 2017

AMAROS trial and beyond

(Has axillary clearance become obsolete?)

Emiel Rutgers

NKI-AVL

No financial disclosures

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Question for you

Lady, 45 yrs, self detected breast cancer left breast, 1.5 cm, ER 90%, PgR 90%, unifocal. Ultrasound axilla: normal nodes

- Who would advice breast conservation and SN procedure?

Next question

Lady, 45 yrs, self detected breast cancer left breast, 1.5 cm, ER 90%, PgR 90%, unifocal, Ultrasound axilla normal nodes

- Who would do intraoperative examination of SN?

Next question

Histology: 16 mm gr 2 IDC, complete margins, Ki67 15%, SN meta 3 mm, 2nd node -ve

- Who would advice ALND?

Next question

Histology: 16 mm gr 2 IDC, complete margins, Ki67 15%, SN meta 3 mm, 2nd node -ve

- Who would advice wait and see?

Next question

Histology: 16 mm gr 2 IDC, complete margins, Ki67 15%, SN meta 3 mm, 2nd node -ve

- Who would advice RT to the axilla?

Next question
Other pathology!

Histology: 22 mm gr 2 IDC, complete margins, Ki67 30%, SN meta 7 mm, 2nd node 1 mm meta.

- Who would advice W & S, RT to the axilla, ALND?

Lymph nodes & breast cancer
Why knowing the lymph nodes status?
The old paradigm

- Provide for prognostic information to guide adjuvant systemic and regional treatment: surgery, radiotherapy, chemo/hormonal Rx

➢ Improved regional control

➢ Improved survival

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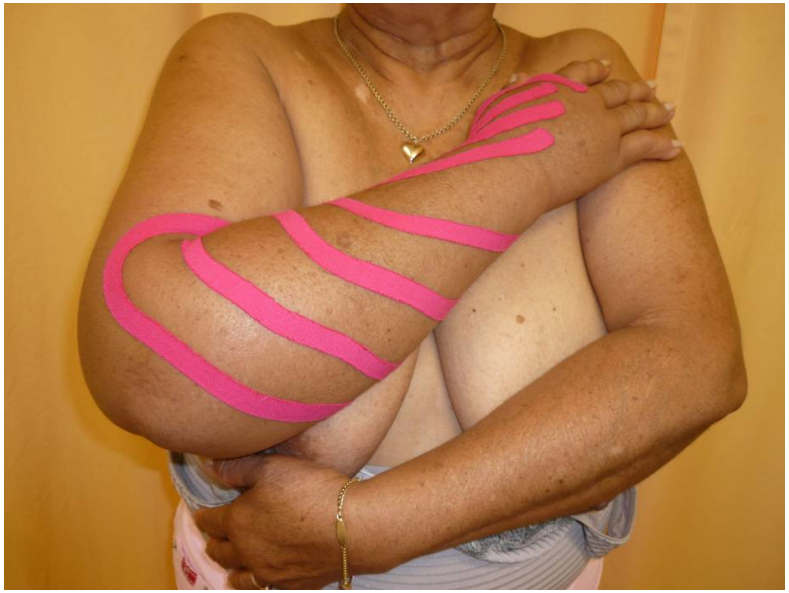
Lymph nodes & breast cancer
Why knowing the lymph node status?
Improving regional control?

Yes, no doubt, but…

- At what price? Is this what we want?



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Occurrence axilla after –ve SN

remind +/- 7% false positive if back up ALND is done!

studies	34
patients	14959
Occurrences (‘relapses’)	67
➢ Risk	0.3%!

After ALND

Risk axillary relapse **0.8 – 2.3**

van der Ploeg IM, et al. Axillary recurrence after a tumour-negative sentinel node biopsy in breast cancer patients: A systematic review and meta-analysis of the literature. Eur J Surg Oncol. 2008.

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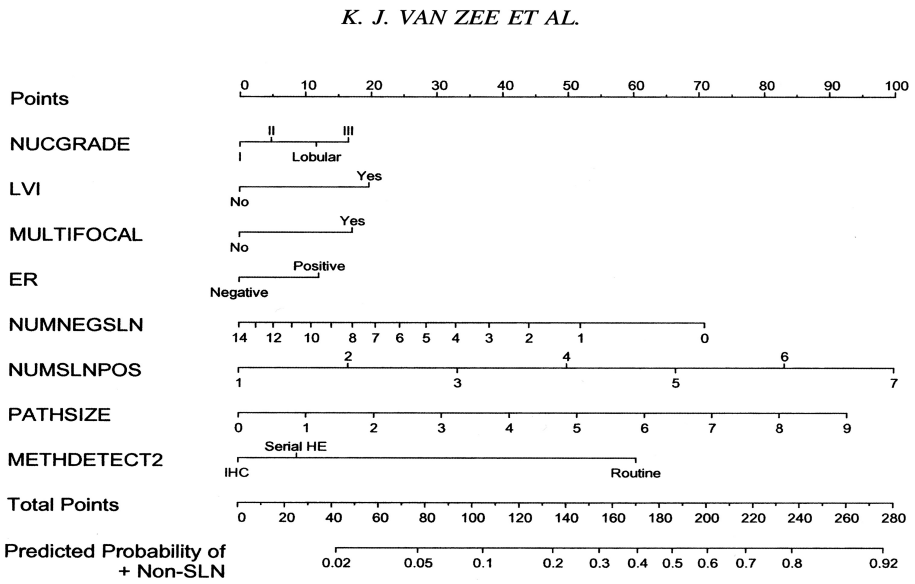
+ ve Sentinel lymph nodes & further nodal involvement.

The nomograms: a complete new science



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+ve Sentinel lymph nodes & further nodal involvement.

- I am not interested in the risk of further nodal involvement at ALND, but in the clinical relapse rate

Clinically node negative disease & +ve SN
Level 1 evidence

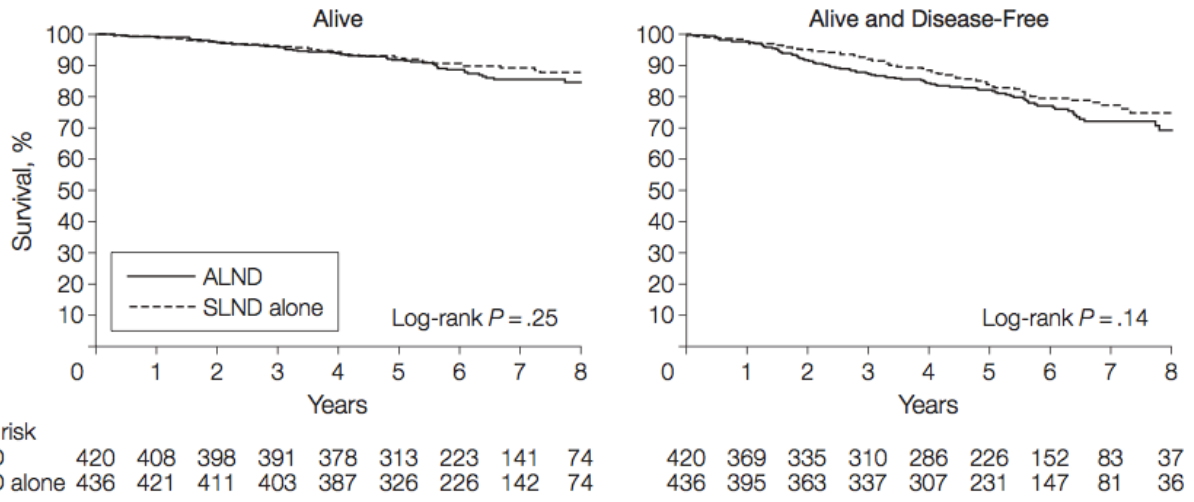
- ACOSOG Z-11: Giuliano 2010, 2016
- IBCSG 027: Galimberti 2013
- AMAROS: Donker et al 2014
- OTOSAOR: ECCO 2017/EJSO 2017

ACOSOG Z0011

After a median follow-up of 6.3 years:

Survival:

Figure 2. Survival of the ALND Group Compared With SLND-Alone Group



No. at risk

ALND	420	408	398	391	378	313	223	141	74
SLND alone	436	421	411	403	387	326	226	142	74

ALND	420	369	335	310	286	226	152	83	37
SLND alone	436	395	363	337	307	231	147	81	36

ALND indicates axillary lymph node dissection; SLND, sentinel lymph node dissection.

Regional control:

Conclusions: Despite the potential for residual axillary disease after SLND, SLND without ALND can offer excellent regional control and may be reasonable management for selected patients with early-stage breast cancer treated with breast-conserving therapy and adjuvant systemic therapy.

Giuliano, JAMA 2011 Feb 9; 305(6); Giuliano, Ann Surg 2010; 252: 426-433;

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ACOSOG Z0011

After a median follow-up of 9.25 years:

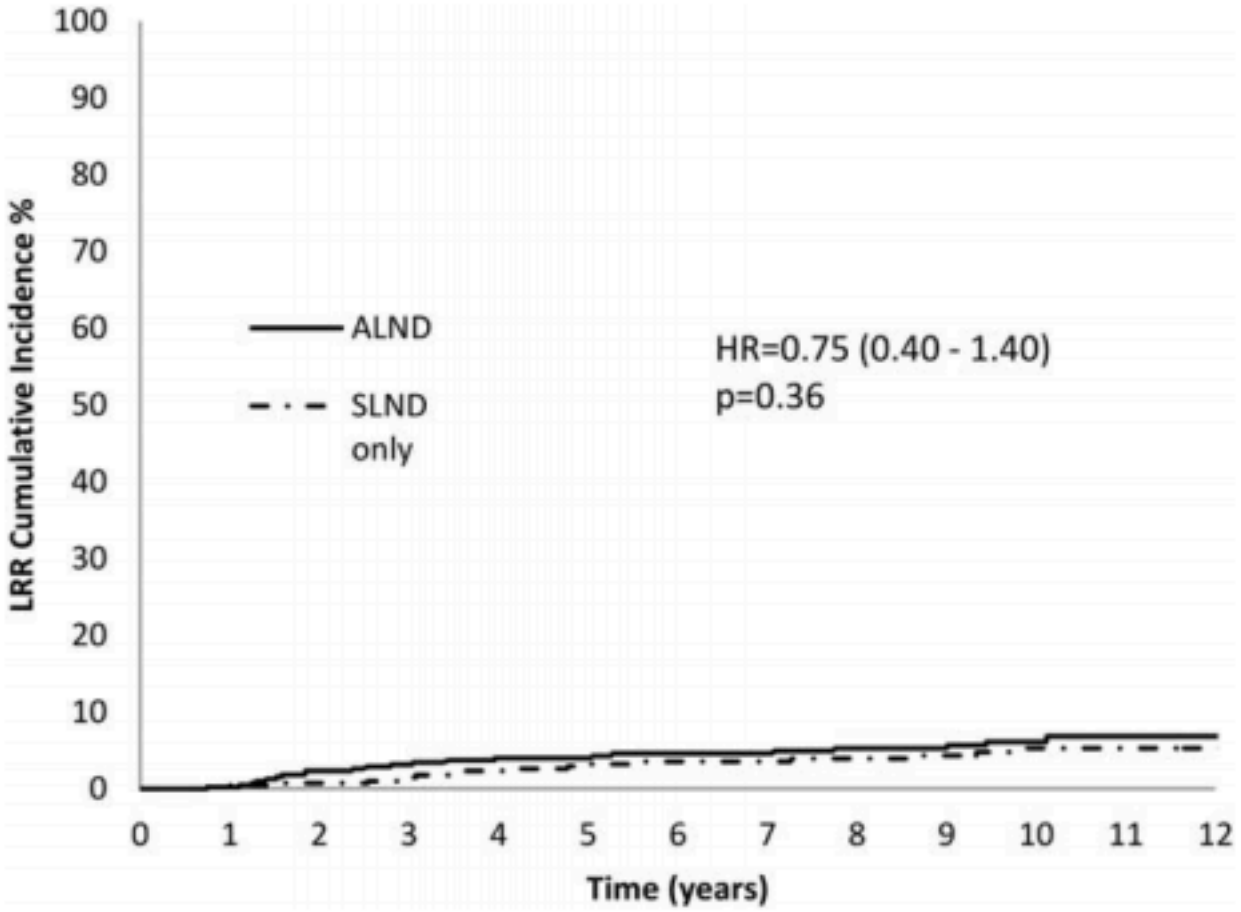

FIGURE 2. Cumulative incidence of locoregional recurrence by treatment arm.

Giuliano, Ann Surg 2016 Sep;263(3)

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Radiotherapy or surgery of the axilla after a positive sentinel node in breast cancer patients: final analysis of the EORTC AMAROS trial

By the EORTC Breast Cancer Group and
Radiation Oncology Group
In collaboration with the Dutch BOOG Group
and ALMANAC Trialists' Group

Donker, Lancet Oncol 2014 Nov;15(12)

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Hypothesis (in 1999)

Axillary radiotherapy provides local control and survival comparable to ALND with fewer side effects in women with a positive axillary SN

Eligibility Criteria

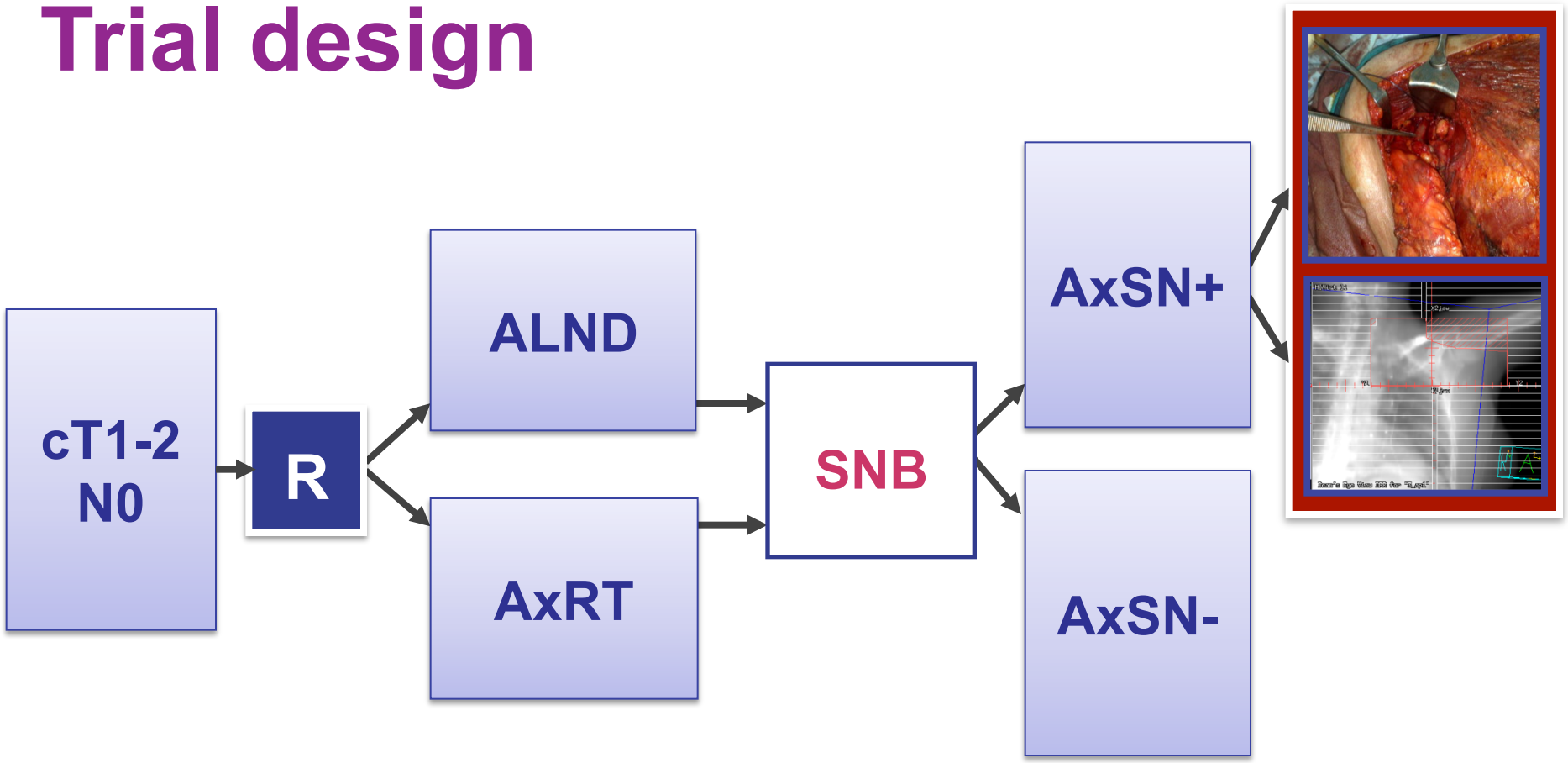
Inclusion

- Invasive breast cancer 0.5-5 cm
- Clinically N0
- BCT or mastectomy
- Any age
- Informed consent

Exclusion

- Multicentric disease
- Neoadjuvant systemic treatment
- Previous axillary treatment
- Prior malignancy

Trial design



Stratification: institution
Adjuvant systemic therapy by choice

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Objectives

Primary: To demonstrate non-inferiority in axillary recurrence rate

Secondary:

1. To compare overall survival (OS) and disease-free survival (DFS)
2. To compare lymphedema, shoulder function and Quality of Life (QoL)

Endpoints and statistical design

Primary: 5-years axillary recurrence free rate

Non inferiority hypothesis (design):

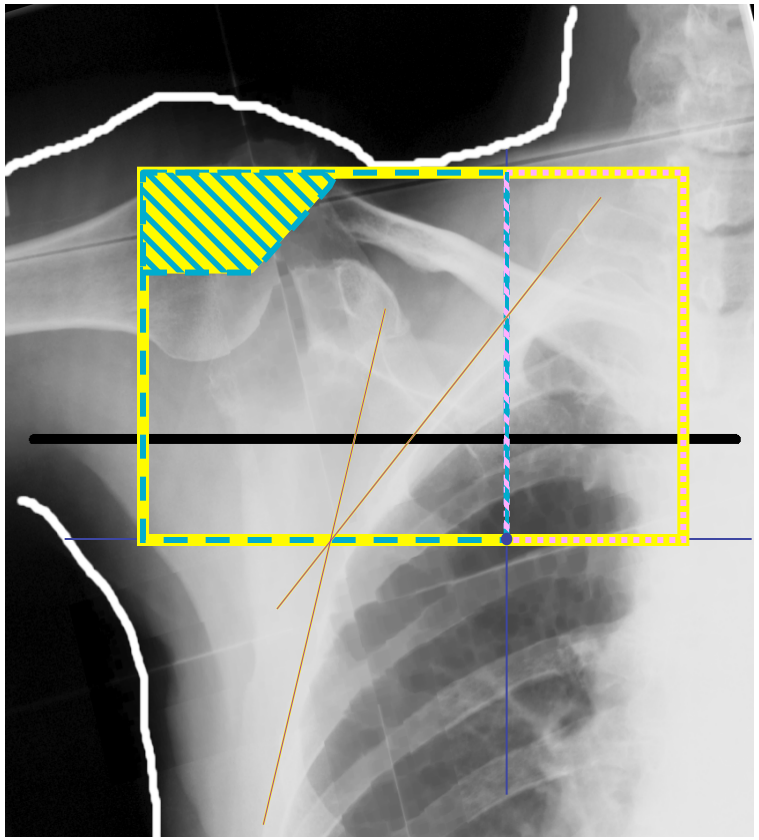
- assumption: ALND 98%; ART >96%
- one-sided log-rank; alpha = 0.05; power = 80%
- 52 events needed

Secondary:

- Efficacy: OS and DFS
- Safety: shoulder function, lymphedema, QoL

ART

- Timing:
  Start < 12 weeks after SNB
- Extent:
  level I + II + III + medial SC
- Dose & schedule:
  25 x 2 Gy or equivalent
- Quality control:
  dummy run



Hurkmans et al, Radiother Oncol 2003

ALND

- Timing:

  < 12 weeks after SNB

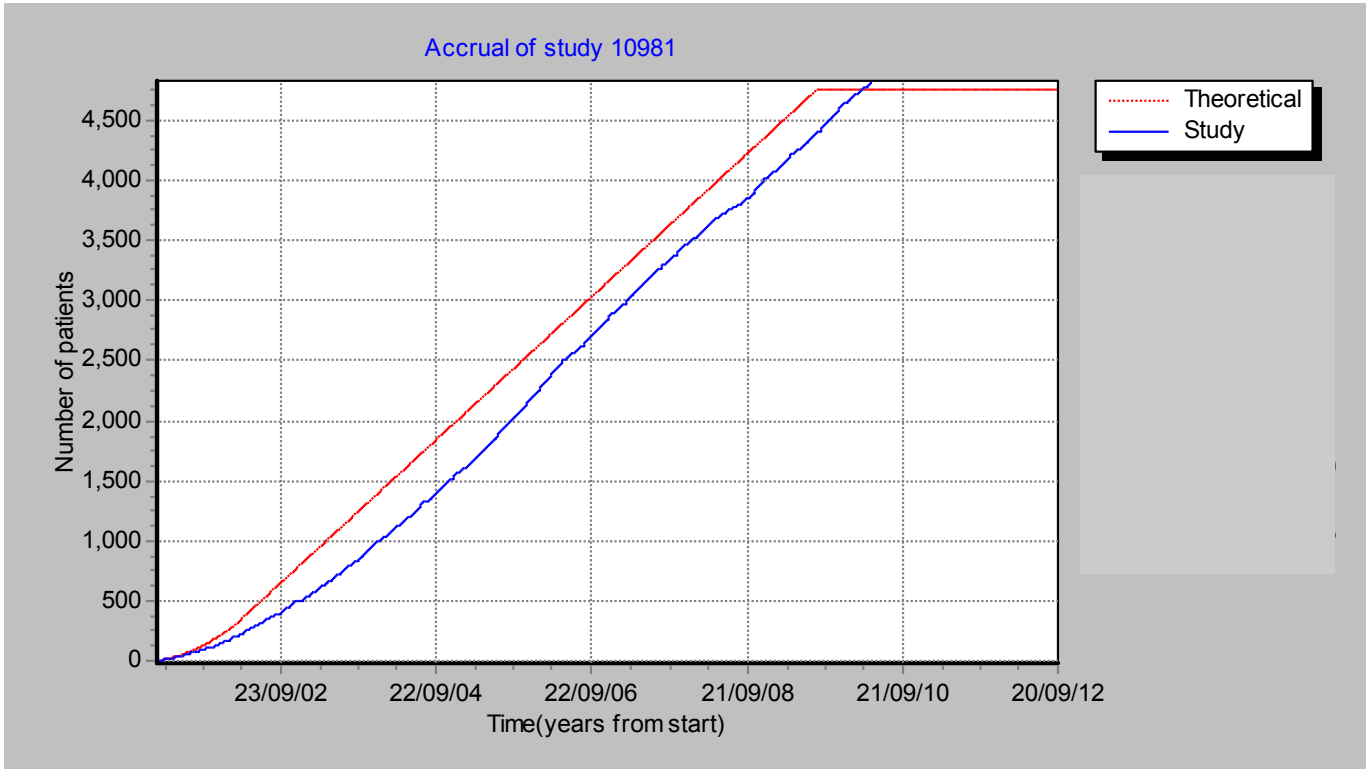
- Extent:

  Level I + II mandatory
  Level III optional

- Additional ART:

  ≥ 4 positive nodes

RESULTS



2001- 2010: 4806 patients enrolled (4766 required)

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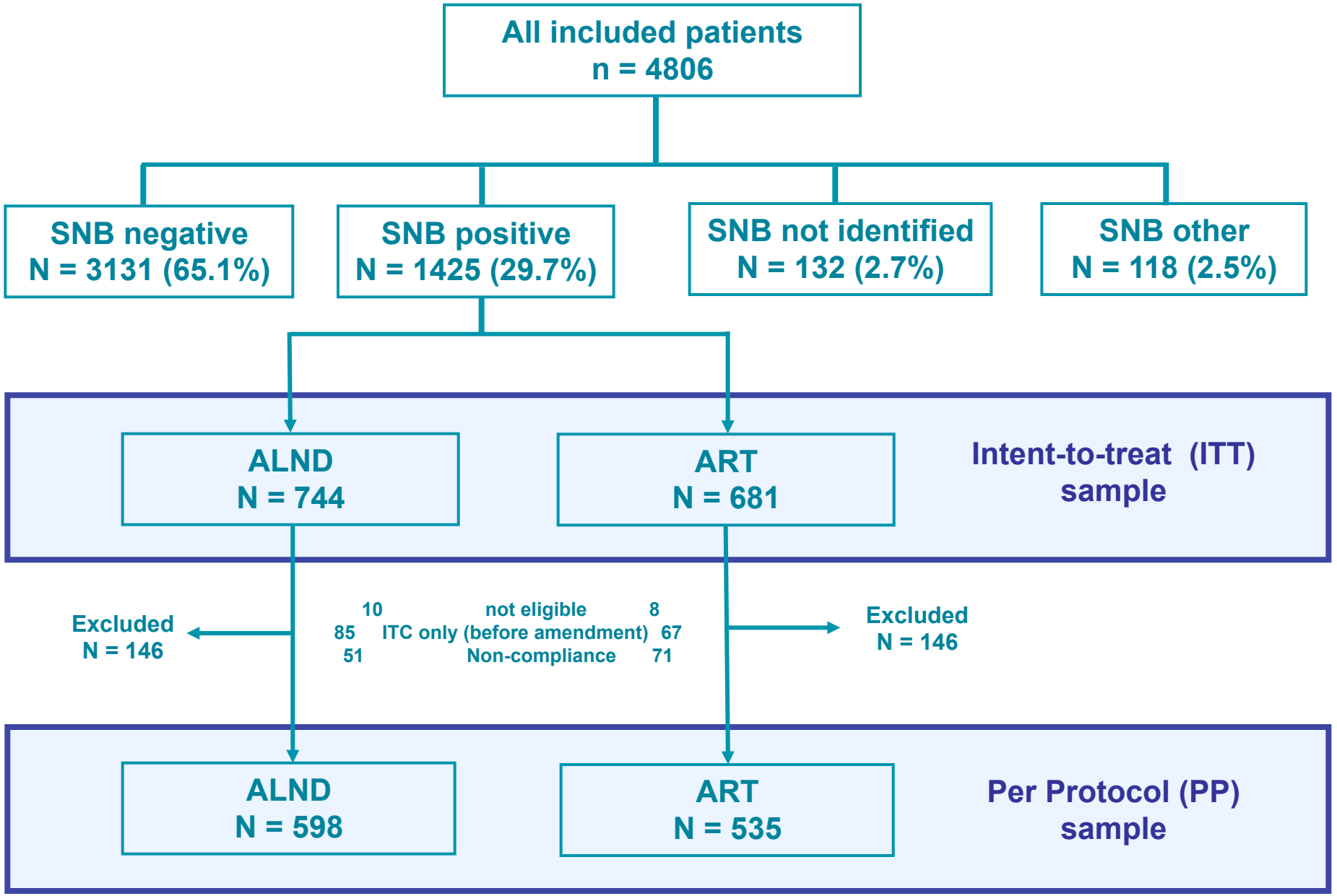
All included patients
n = 4806
SNB negative
N = 3131 (65.1%)
SNB positive
N = 1425 (29.7%)
SNB not identified
N = 132 (2.7%)
SNB other
N = 118 (2.5%)
ALND
N = 744
ART
N = 681
Intent-to-treat (ITT) sample
Excluded
N = 146
10 not eligible 8
85 ITC only (before amendment) 67
51 Non-compliance 71
Excluded
N = 146
ALND
N = 598
ART
N = 535
Per Protocol (PP) sample

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Baseline clinical

	ALND (744 pts)	ART (681 pts)
Median age (Q1-Q3)	56 (48 - 64)	55 (48 - 63)
Menopausal stage		
pre-menopausal	38.1 %	42.5 %
post-menopausal	57.7 %	54.5 %
Median tumor size (Q1-Q3)	17 mm (13 - 22)	18 mm (13 - 23)
Grade		
1	24.1 %	22.6 %
2	47.8 %	45.7 %
3	25.8 %	29.4 %
Pre-operative ultrasound axilla	59.2 %	61.5 %

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Treatment compliance

	ALND (744 pts)	AxRT (681 pts)
Randomized treatment	631 (84.8 %)	590 (86.6 %)
Both treatments	41 (5.5 %)	1 (0.1 %)
Cross-over	46 (6.2 %)	68 (10.0 %)
No axillary treatment	24 (3.2 %)	22 (3.2 %)

Baseline treatment

	ALND (744 pts)	AxRT (681 pts)
Breast surgery		
BCS	81.9 %	81.8 %
Mastectomy	17.1 %	17.8 %
Systemic treatment		
chemotherapy	60.9 %	61.3 %
hormonal therapy	78.6 %	77.1 %
immunotherapy	6.0 %	6.4 %
no systemic treatment	9.0 %	9.4 %
RT breast/chest wall	84.8 %	87.7 %

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SN results

	ALND (744 pts)	AxRT (681 pts)
Median number of SN removed (Q1-Q3)	2 (1-3)	2 (1-3)
Size of metastases in SN		
macrometastases	59.4 %	61.5 %
micrometastases	28.9 %	28.6 %
ITC	11.7 %	9.8 %

Straver et al, Ann Surg Oncol 2010

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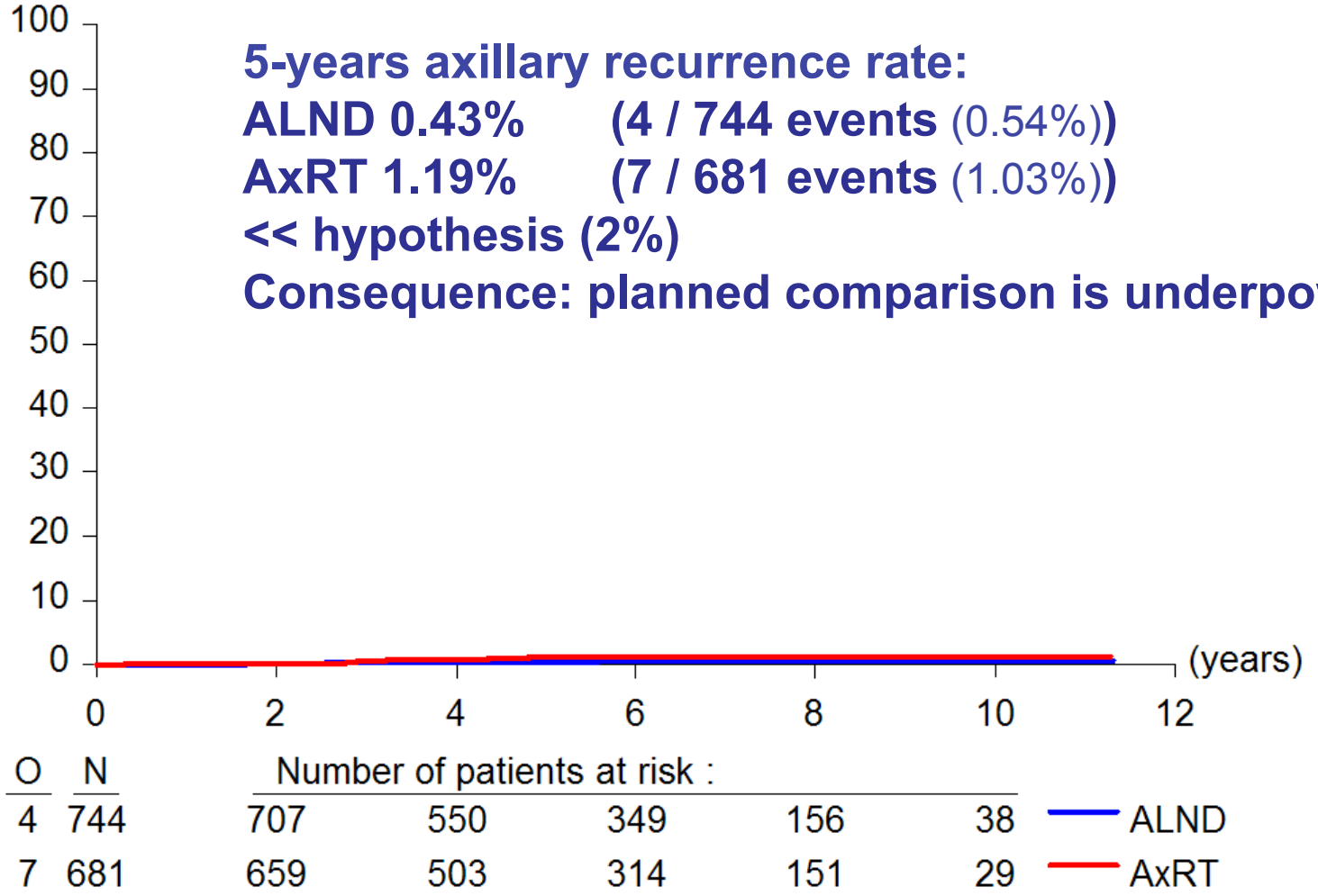
ALND results

	ALND (744 pts)
Median number of all nodes removed (Q1-Q3)	15 (12-20)
Number of additional positive nodes (besides SN)	
0	67.1 %
1-3	25.0 %
≥ 4	7.8 %

Axillary recurrence rate



5-years axillary recurrence rate:
ALND 0.43% **(4 / 744 events** (0.54%)**)**
AxRT 1.19% **(7 / 681 events** (1.03%)**)**
<< hypothesis (2%)
Consequence: planned comparison is underpowered

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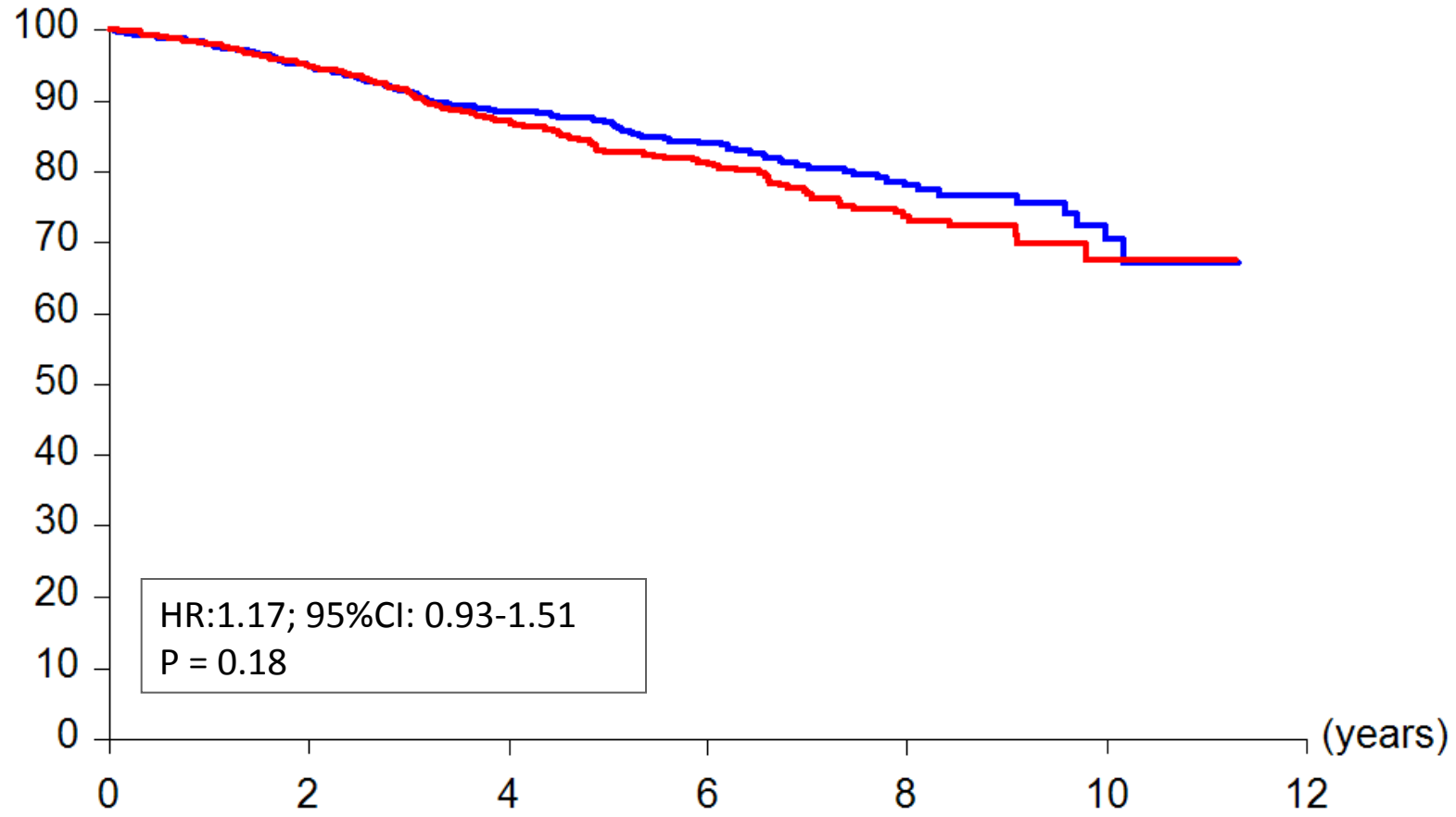
Disease-free survival



O	N	Number of patients at risk :					
124	744	686	511	322	140	33	ALND
134	681	633	468	284	131	24	AxRT

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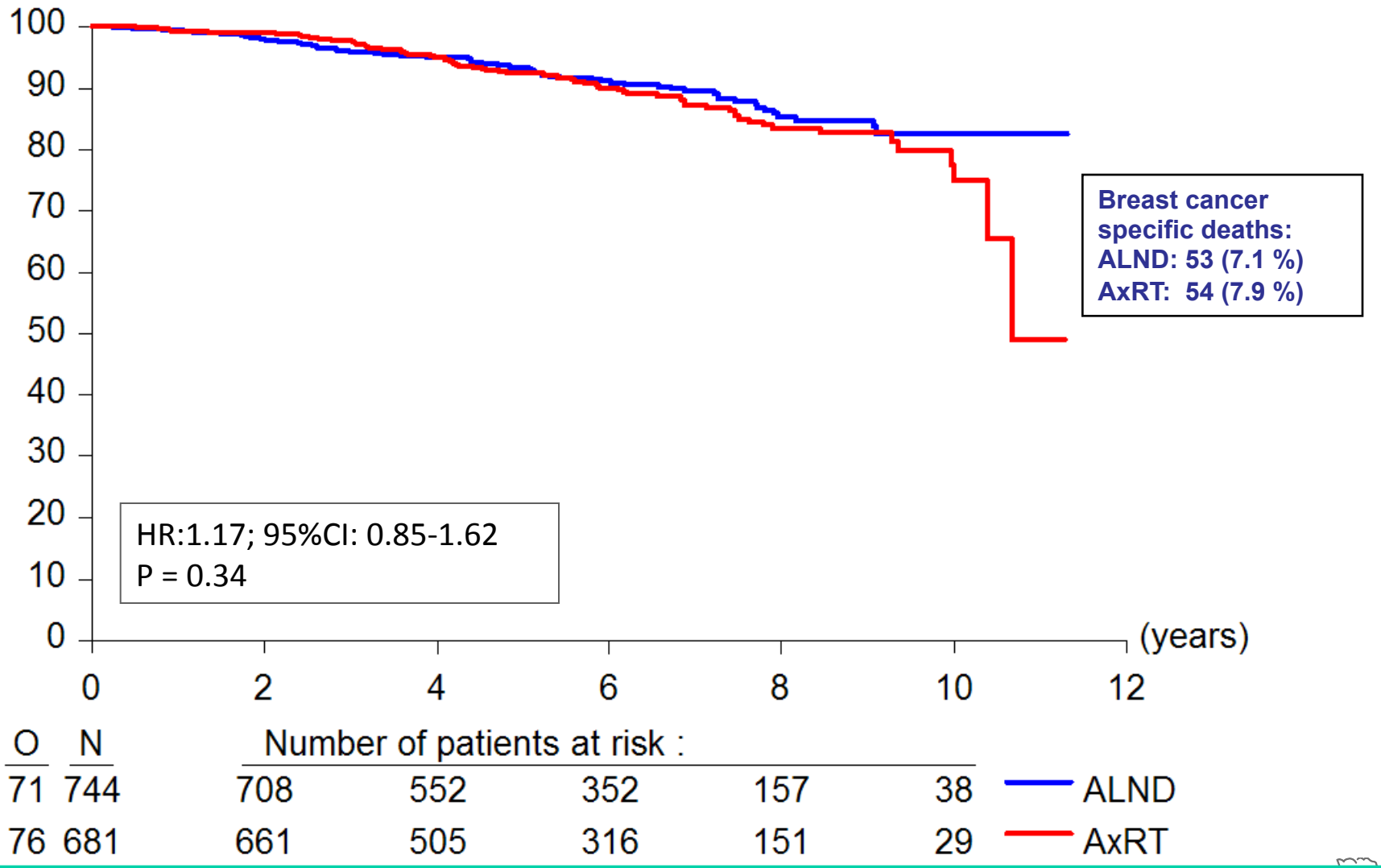
Overall survival



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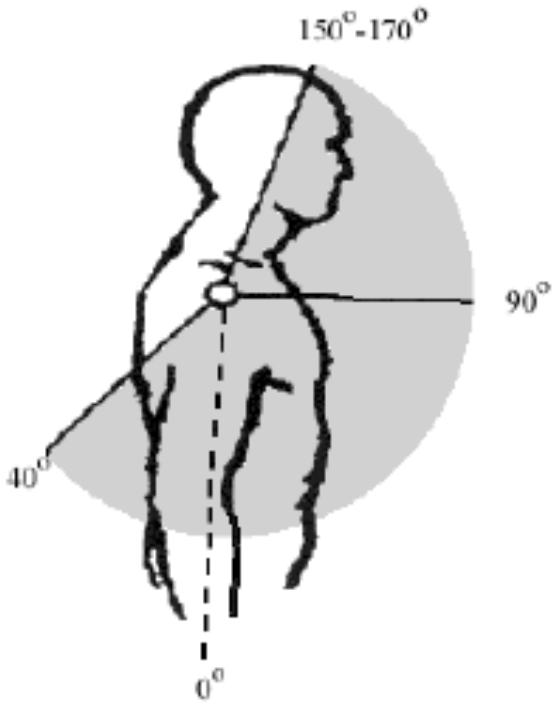
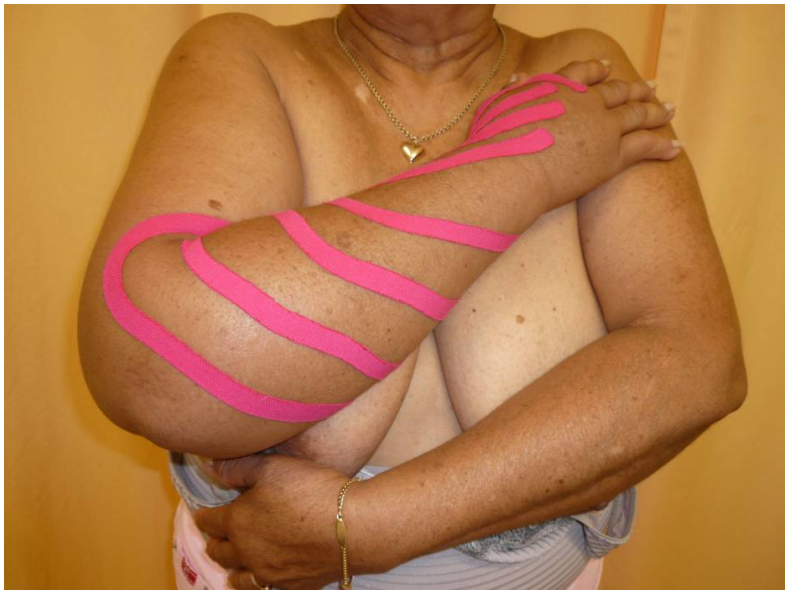
Results side effects





50-70% form compliance at all time points

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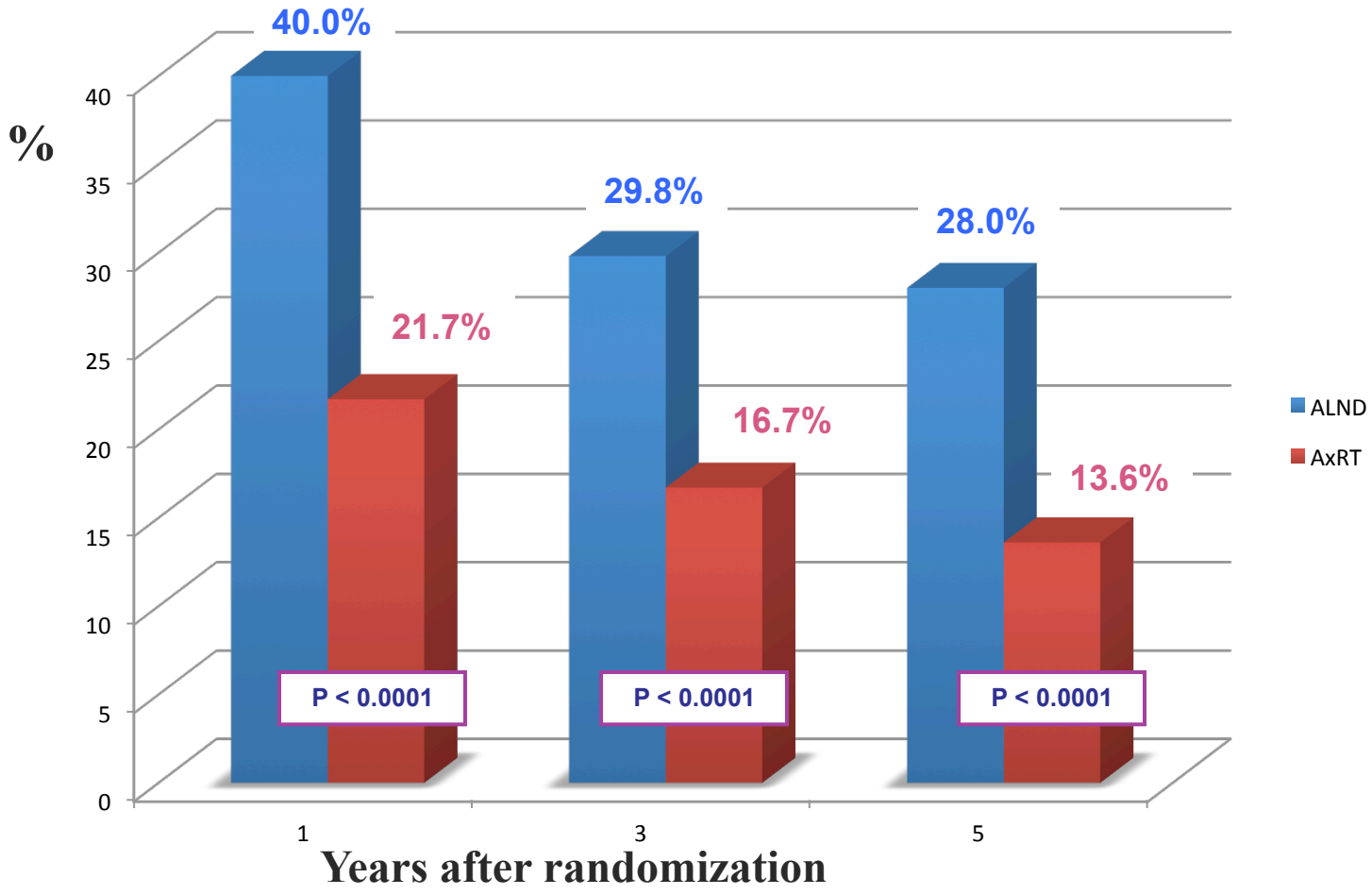
Lymphedema of the arm

Measured: 1, 3 and 5 years after treatment

Items:

1. Clinical observation
2. Treatment for edema:
   - sleeve garment
   - lymph drainage therapy
   - compression therapy

Lymphedema: clinical observation and/or treatment



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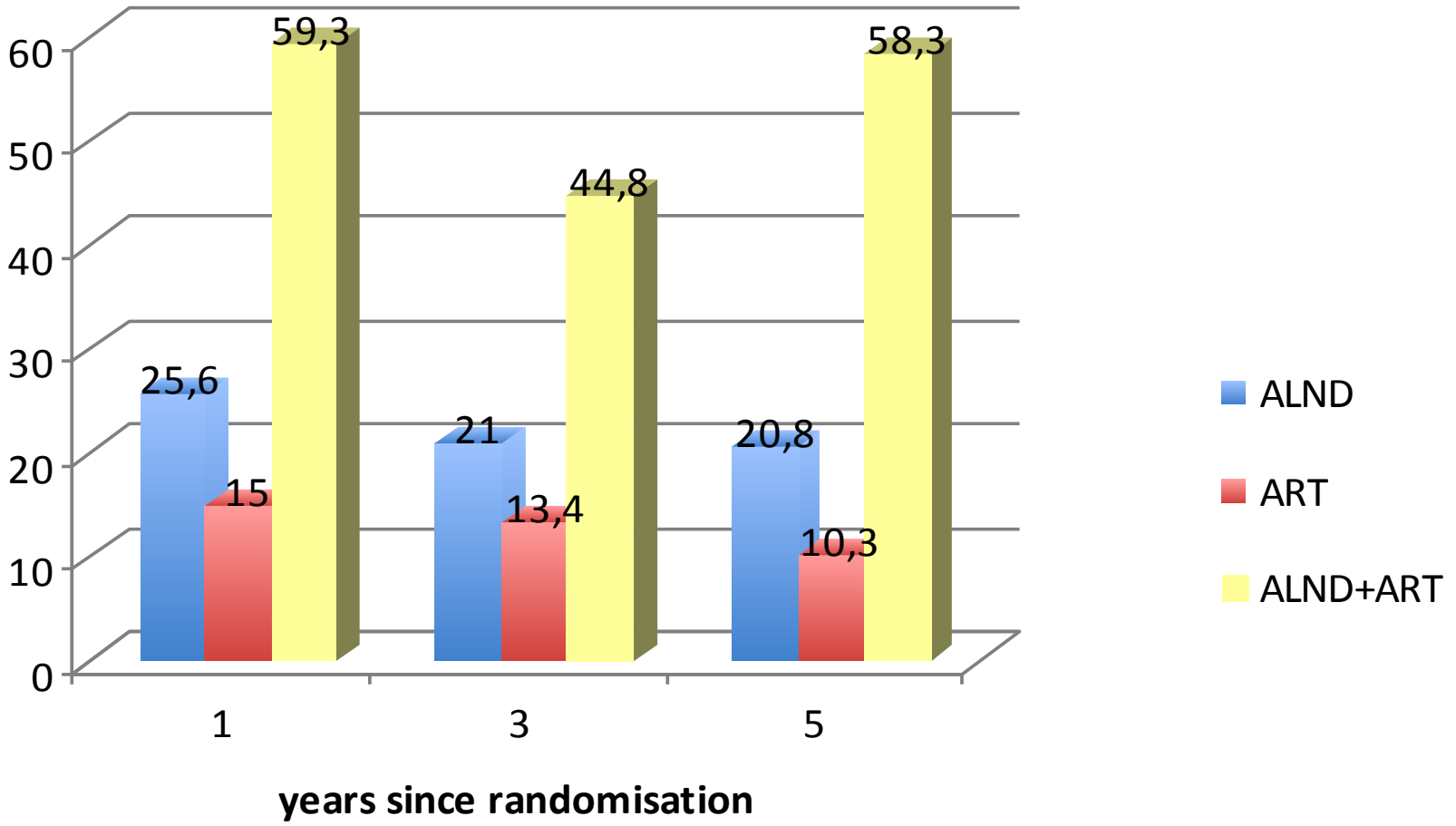
Lymphoedema: clinical observation



Pre-operative ultrasound of the axilla

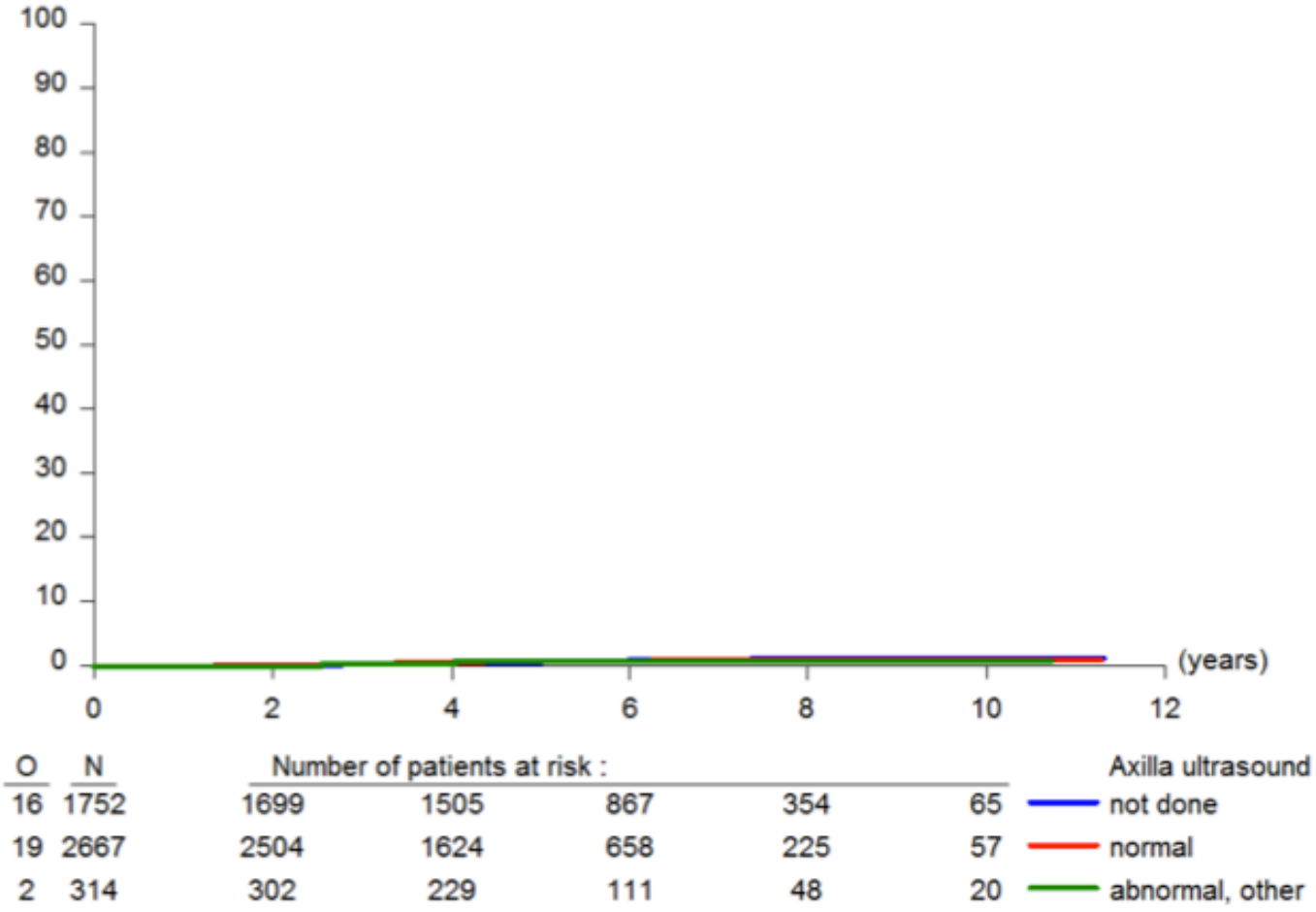
3 groups:

1. no ultrasound performed
2. ultrasound performed: no suspected nodes
3. ultrasound performed: suspected nodes, but CP negative

Results: # positive (sentinel) nodes

	Axilla ultrasound		
	Not done	Normal	Abnormal, no metatases
	(N=1752) N (%)	(N=2667) N (%)	(N=314) N (%)
SNB result			
SNB+	478 (27.3)	691 (25.9)	83 (26.4)
SNB- / ITC only	1204 (68.7)	1868 (70.0)	223 (71.0)
Additional positive nodes in ALND specimen			
No	156 (63.9)	205 (65.1)	34 (72.3)
Yes	88 (36.1)	109 (34.6)	13 (27.7)
Missing	0 (0.0)	1 (0.3)	0 (0.0)

Results: axillary recurrence rate



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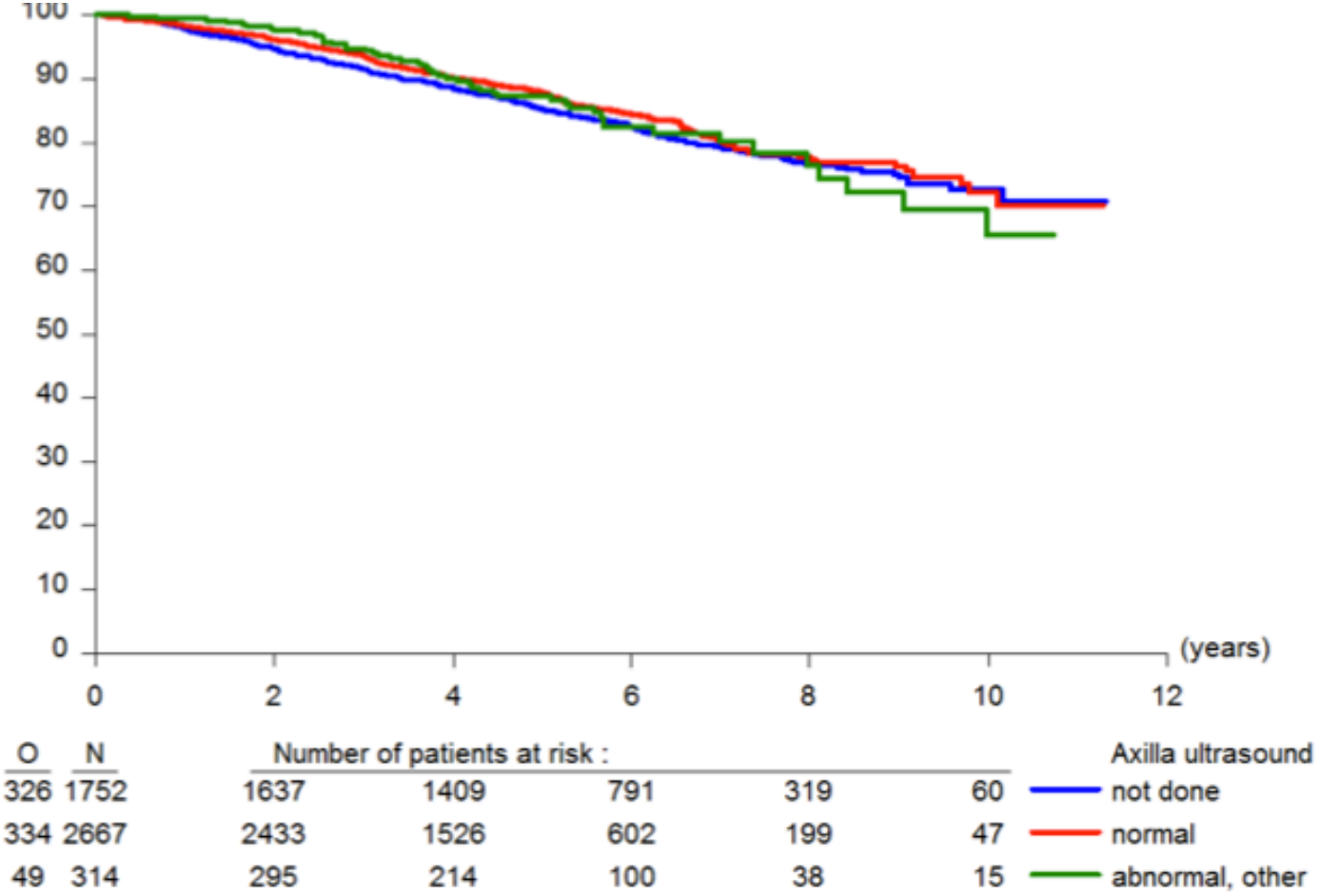
Results: disease-free survival



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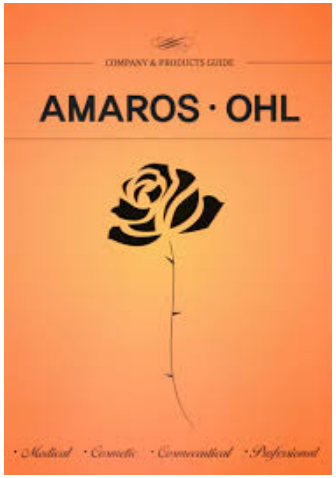
AMAROS: not bitter but sweet



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Conclusion AMAROS trial

- Both ALND and ART provide excellent and comparable locoregional control in SN+ patients
- Significantly less lymphedema after ART
- ART can be considered standard or…

  is a validated treatment for patients with SN +ve

Acknowledgement

We are very grateful to all the patients who participated in this trial

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Acknowledgement

Research fellows: Mila Donker, Marieke Straver, Philip Meijnen

Principal investigators: Cornelis van de Velde, Robert Mansel, Geertjan van Tienhoven

EORTC headquarters: Nicole Duez, Leen Slaets, Jan Bogaerts, Carlo Messina, Corneel Coens, the IDMC

EORTC Breast Cancer Group

EORTC Radiation Oncology Group

Dutch BOOG Group

ALMANAC Trialists' Group

BCT in clinically node negative disease & SN Conclusion

- Breast cancer patients with clinically node negative disease and one or two tumor-positive SLNs can be safely treated with breast conserving surgery and radiotherapy without performing ALND.

→ Therefore, intra-operative assessment of SLNs should not be performed in these patients.

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When is ALND for the treatment of breast cancer indicated? ASCO guideline update

- Women without SLN metastases should not receive ALND

Lyman, J Clin Oncol 2016 Dec

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When is ALND for the treatment of breast cancer indicated? ASCO guideline update

- Women with 1-2 metastatic SLNs who are planning to undergo breast-conserving surgery with whole-breast radiotherapy should not undergo ALND (in most cases).

Lyman, J Clin Oncol 2016 Dec

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When is ALND for the treatment of breast cancer indicated? ASCO guideline update

- Women with SLN metastases who will undergo mastectomy should be offered ALND.

Lyman, J Clin Oncol 2016 Dec

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When is ALND for the treatment of breast cancer indicated? ASCO guideline update

- Women with SLN metastases who will undergo mastectomy should be offered ALND.

→ CONTROVERSY!?

Lyman, J Clin Oncol 2016 Dec

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SN and mastectomy

- EBCTCG overview sees advantage for post mastectomy RT in patients with 1-3 positive lymph nodes: better locoregional control and breast cancer related survival

EBCTCG, Lancet 2014 Jun 21

Lymph nodes in breast cancer
RT after mastectomy?

Effect of radiotherapy after mastectomy and axillary surgery on 10-year recurrence and 20-year breast cancer mortality: meta-analysis of individual patient data for 8135 women in 22 randomised trials

*EBCTCG (Early Breast Cancer Trialists' Collaborative Group)**

EBCTCG, Lancet 2014 Jun 21

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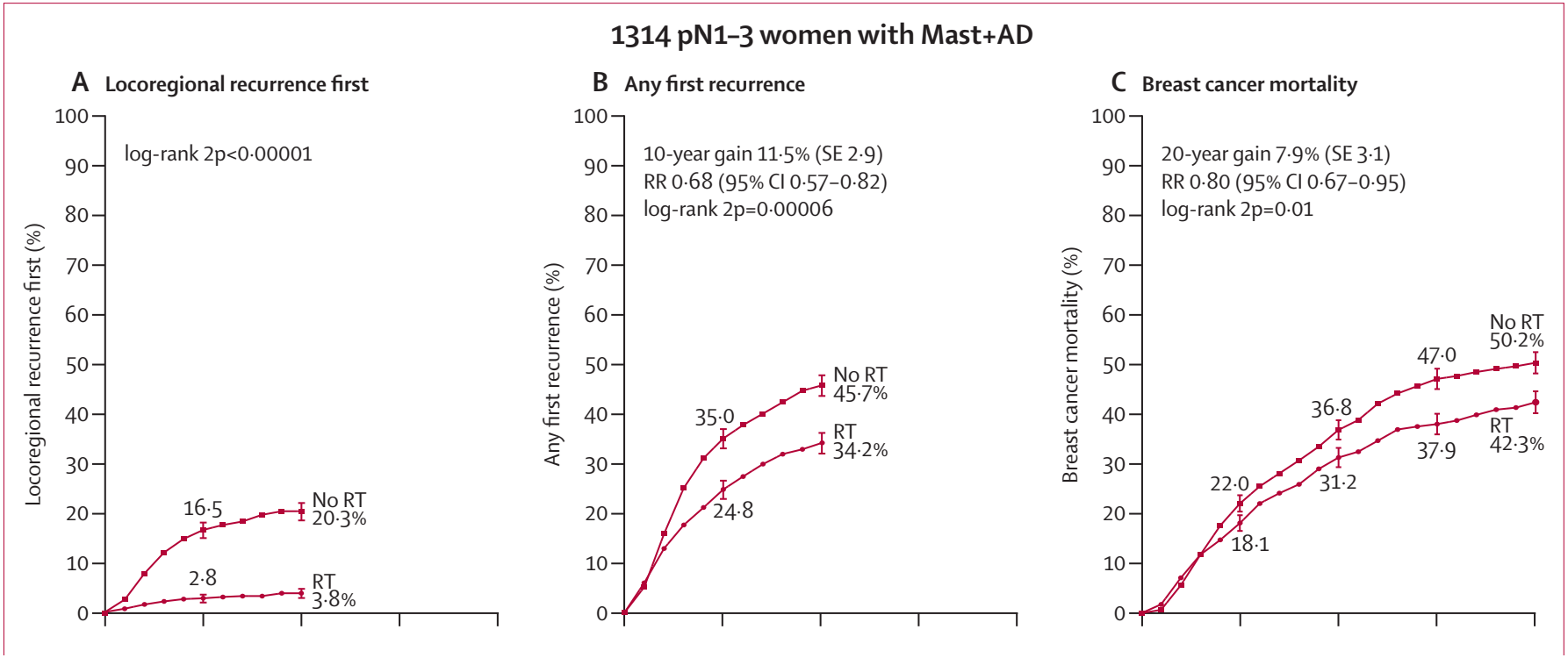
Lymph nodes in breast cancer. RT after mastectomy?



EBCTCG, Lancet 2014 Jun 21

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Lymph nodes in breast cancer. RT after mastectomy?

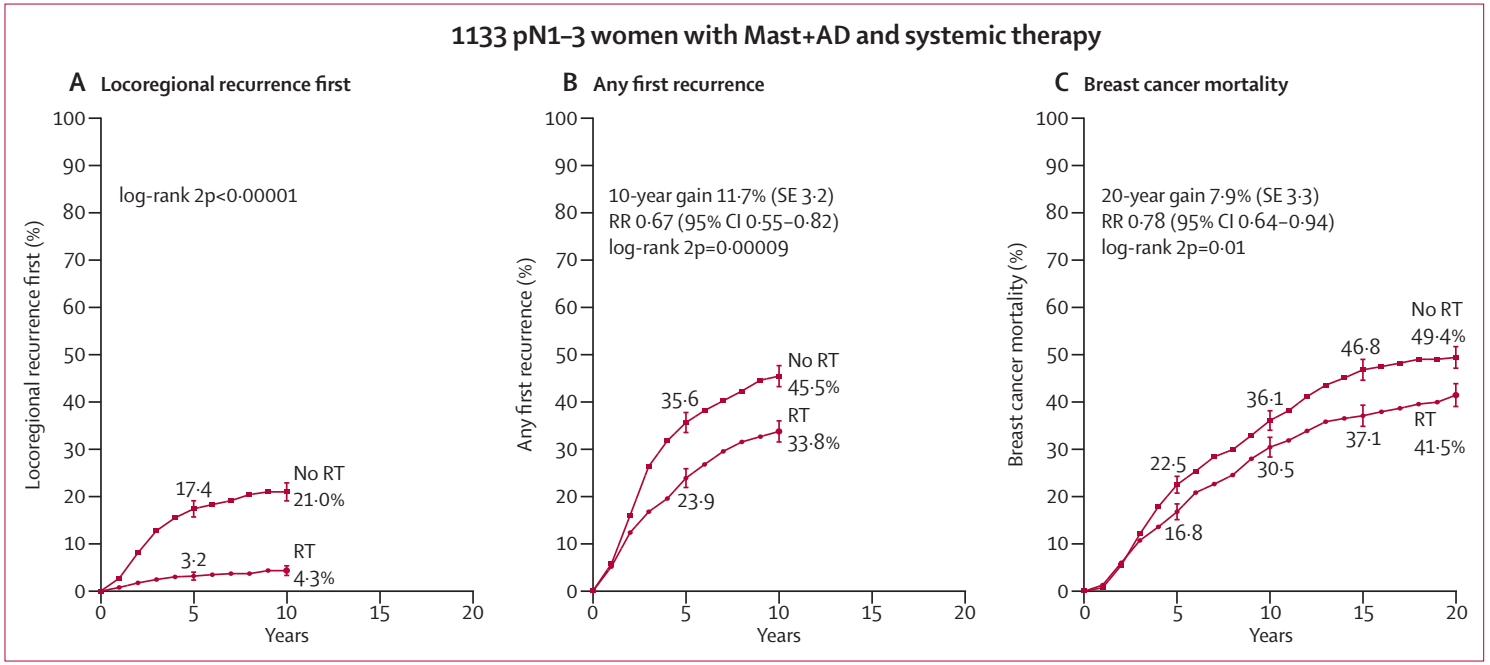

***Figure 5*: Effect of radiotherapy (RT) after mastectomy and axillary dissection (Mast+AD) on 10-year risks of locoregional and overall recurrence and on 20-year risk of breast cancer mortality in 1133 women with one to three pathologically positive nodes (pN1–3) in trials in which systemic therapy was given to both randomised treatment groups**

Analyses of locoregional recurrence first ignore distant recurrences, see appendix pp 8–9 for details. See appendix p 22 for analyses of both locoregional and distant recurrences, and appendix p 21 for analyses of overall mortality. RR=rate ratio. Vertical lines indicate 1 SE above or below the 5, 10, 15, and 20 year percentages.

EBCTCG, Lancet 2014 Jun 21

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Mastectomy, immediate reconstruction and radiotherapy

- Associated with less good cosmesis and more complications/ repeat surgeries
- Is in itself possible
- Local control appears not to be affected

SN & ALND
The controversies: our NKI team position

Positive SN & mastectomy in cN0

- First do mastectomy (incl. reconstruction if desired) and SN: then full pathology and discuss in MDM what to do: wait & see, ALND (+/- PMRT!) or PMRT

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Lymph nodes in breast cancer. Where are we now?

NO lymph node treatment:

- SN –ve
- SN itc
- SN micrometa <2 mm if systemic adjuvant treatments is given
- SN macrometa, limited involvement, favourable tumorcharacteristics, incl. adj syst Rx & Whole Breast Irradiation (Z-011 criteria)

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Lymph nodes in breast cancer. Where are we now?

Radiotherapy to the axilla (usually ‘high tangents’ will do):

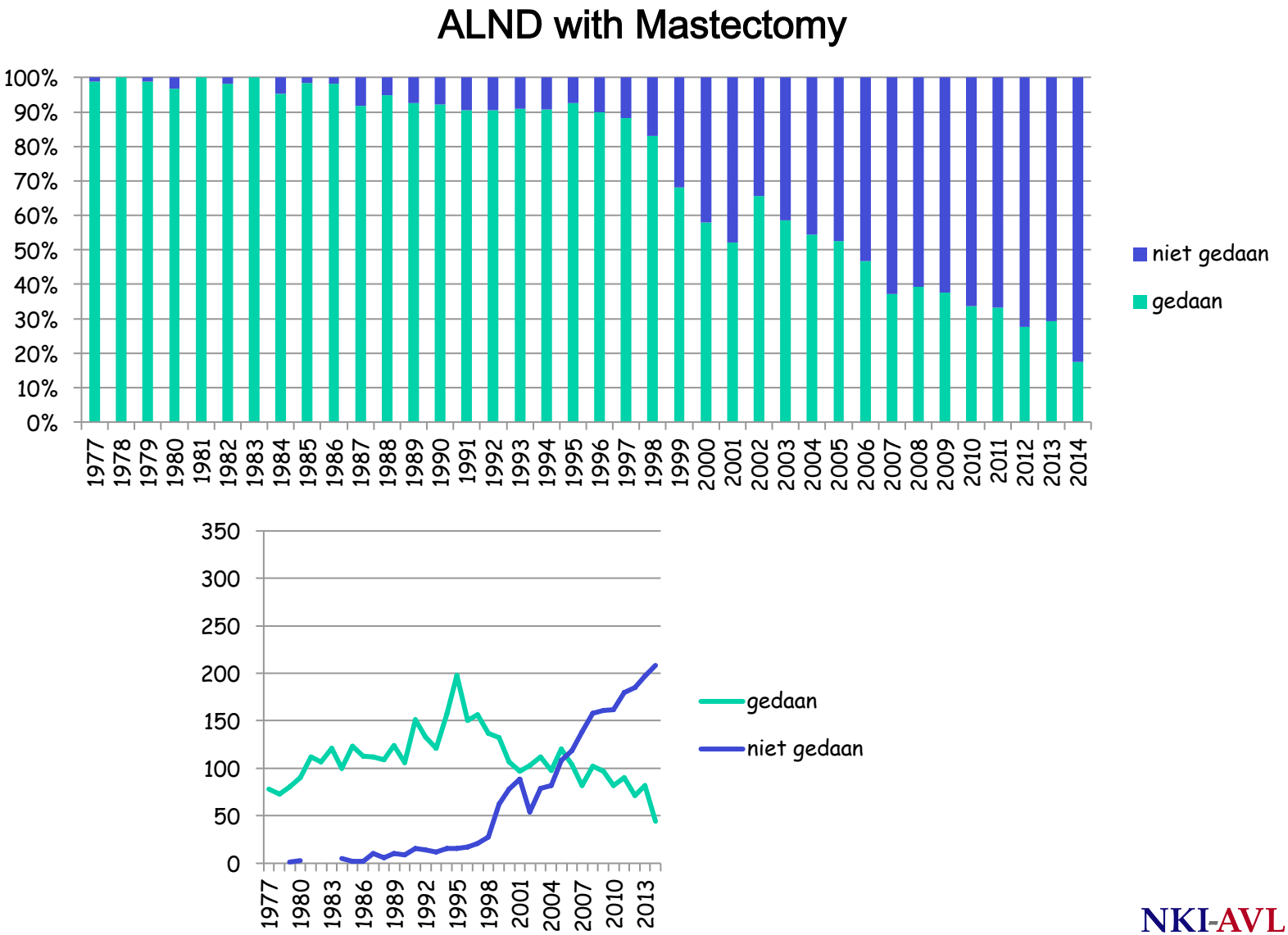
- SN macrometa high risk (multiple, larger primary)

Lymph nodes in breast cancer. Where are we now?

Lymph node treatment (ALND):

- Residual macrometastases after upfront therapy
- Patients undergoing a mastectomy with SN involvement where there is no indication for post mastectomy RT (but according recent EBCTCG Lancet paper there is a survival benefit after RT in 1-3 +ve nodes)

The fate of ALND (NKI data)



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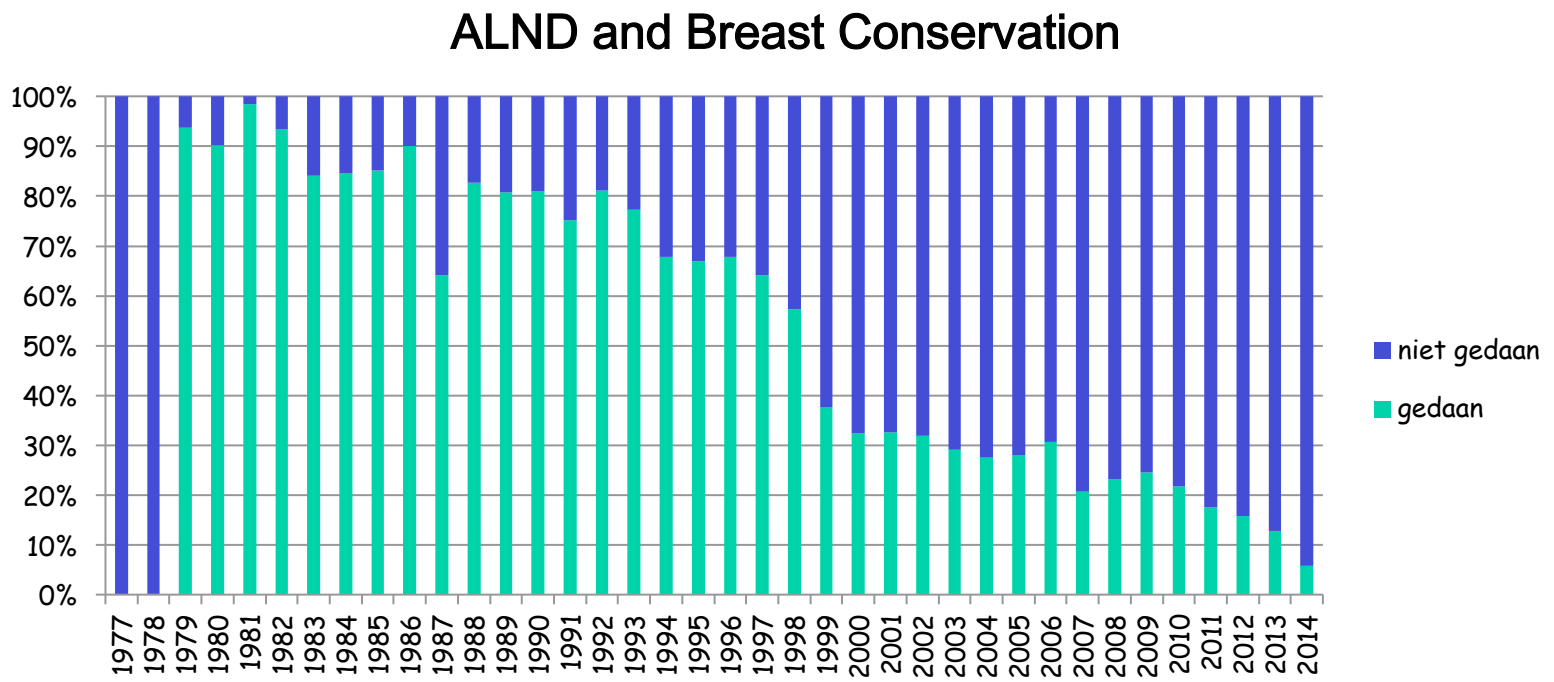
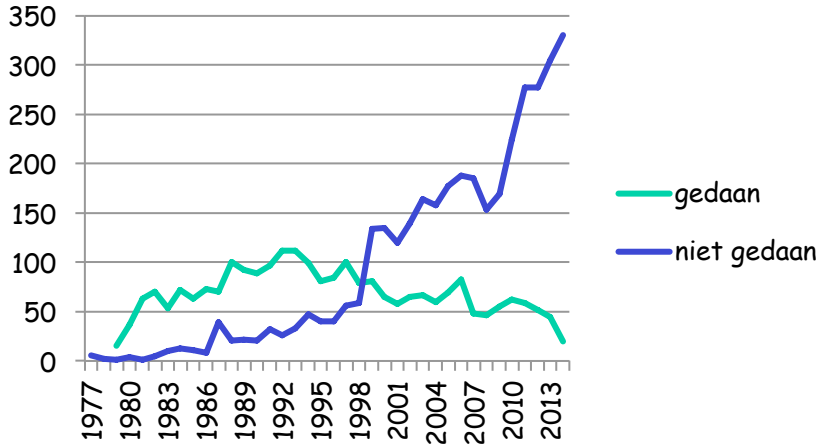
The fate of ALND NKI data





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st. gallen oncology conferences

BCC 2017

PRIMARY TREATMENT OF EARLY BREAST CANCER ST. GALLEN 2017

ESCALATING AND DE-ESCALATING TREATMENT IN EARLY BREAST CANCER ACROSS SUBTYPES AND TREATMENT MODALITIES

Consensus & Controversy

15th St.Gallen International Breast Cancer Conference 2017 Consensus

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BCC 2017

Surgery of the Axilla

13. In patients with macro-metastases in 1-2 sentinel nodes, completion of axillary dissection can safely be *omitted* following:

Mastectomy (no radiotherapy to lymph nodes planned)

(1) Yes

(2) No **86%**

(3) Abstain

15th St.Gallen International Breast Cancer Conference 2017 Consensus

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BCC 2017

Surgery of the Axilla

14. In patients with macro-metastases in 1-2 sentinel nodes, completion of axillary dissection can safely be *omitted* following:

Mastectomy (radiotherapy to lymph nodes planned)

(1) Yes **84%**

(2) No

(3) Abstain

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BCC 2017

Surgery of the Axilla

16. In patients with macro-metastases in 1-2 sentinel nodes, completion of axillary dissection can safely be *omitted* following:

Conservative resection with radiotherapy using high tangents

(1) Yes **77%**

(2) No

(3) Abstain

15th St.Gallen International Breast Cancer Conference 2017 Consensus

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Thank you!

For inviting me

Your attention

The EORTC AMAROS team

The NKI Breast Cancer Team

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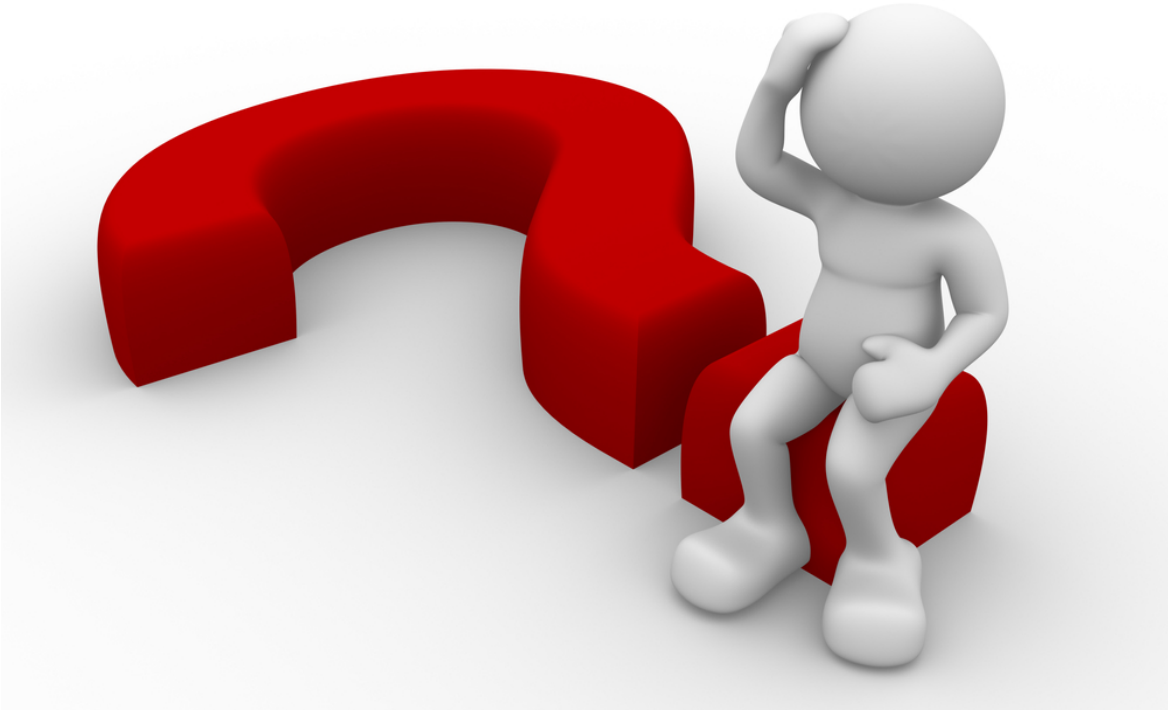

Questions?

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EBCC 11

European Breast Cancer Conference

"Estudio de luz" by **Ramón Casas**
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EBCCouncil

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