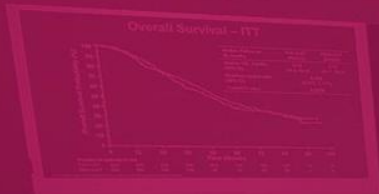
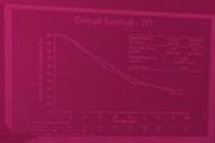


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REALIZAÇÃO



EDUARDO MILLEN

MD-PhD

SEM CONFLITOS DE INTERESSES

Recurrence-free survival following sentinel node-positive breast cancer without completion axillary lymph node dissection – first results from the international randomized SENOMAC trial

Jana de Boniface, M.D., Ph.D., Associate Professor

Department of Molecular Medicine and Surgery, Karolinska Institutet, Stockholm, Sweden

Breast Unit, Capio St. Göran's Hospital, Stockholm Sweden



**Karolinska
Institutet**

- ACOSOG Z0011 results first published in 2010 & 2011
- EORTC 10981-22023 AMAROS in 2014
- Uncertainties regarding
 - Statistical power
 - Radiotherapy target volumes
- Under-representation of relevant subgroups
 - Older patients, patients receiving mastectomy, larger tumors, SLN macro- versus micrometastases


SENOMAC Trial Design

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December 5-9, 2023 | San Antonio, TX | @SABCSSanAntonio

- Prospective 1:1 randomized clinical non-inferiority trial
 - **Standard of Care:** Completion axillary dissection
 - **Intervention:** No completion axillary dissection
- Primary endpoint: Overall Survival
- Non-inferiority margin 2.5% (HR upper limit of CI below 1.44)
- Target accrual **3000 patients**
 - **190 events required for statistical power**
- **Secondary endpoint: Recurrence-Free Survival**

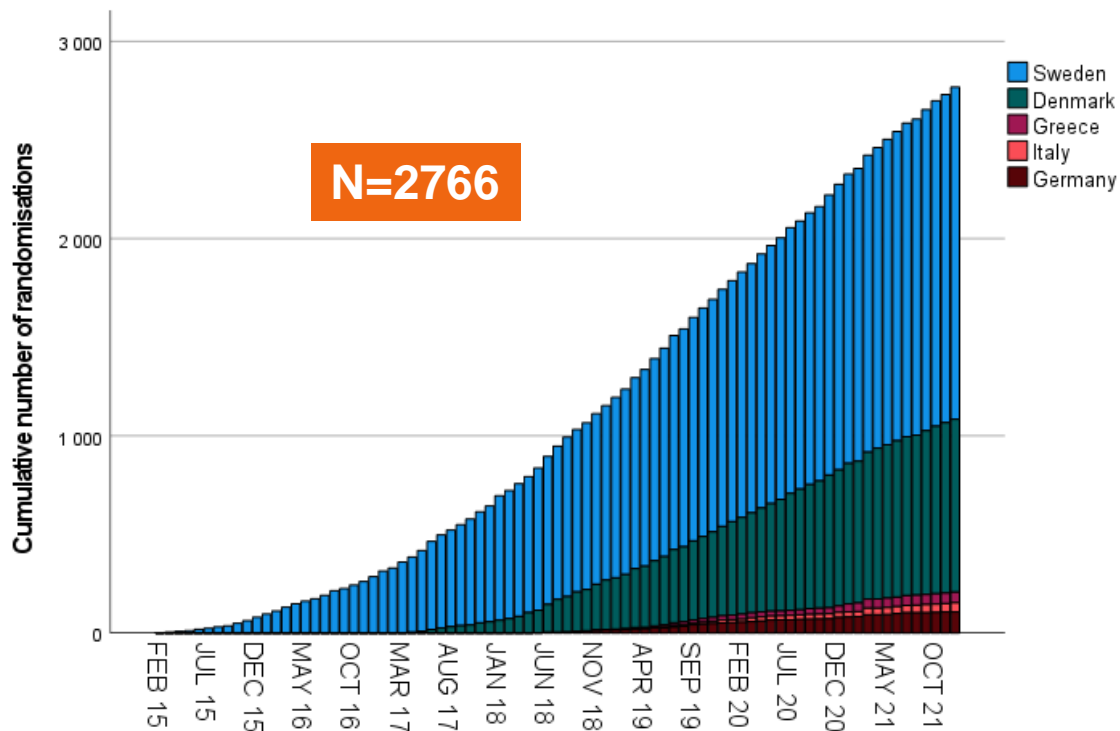
Patient Selection

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- T1-T3 primary invasive breast cancer
- Clinical node negativity (palpation)
 - Mandatory preoperative axillary ultrasound  US + PAAF +: cN0 included
- Male & female patients
- Breast-conserving surgery and mastectomy
- Up to 2 sentinel lymph node macrometastases
- No medical contraindications to adjuvant radiotherapy or relevant systemic treatment

Enrolment

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Results: Population

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- Per-protocol population N=2540
 - **Standard of Care** N=1205
 - **Intervention** N=1335
- Median follow-up 47 months (2-95)
- Median age 61 years (20-94)
 - **Age 65 years or above in 1025 patients (40%)**
- Ten male patients (0.4%)

Results: Tumor

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- Median tumor size 20 mm (0.2-155 mm)
 - T3 in 147 patients (5.8%)
- Lobular carcinoma in 504 patients (19.8%)
- Estrogen receptor positive & HER2 negative in 2200 patients (86.6%)

Results: Axilla

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- 1 sentinel lymph node macrometastasis in 2151 patients (84.7%)
- Extranodal extension in 870 patients (34.3%)
- Removed lymph nodes median 15 (1-51) *versus* 2 (1-15)
- Additional sentinel lymph node micrometastases in 261 patients (10.2%)

Results: Axilla

- Non-sentinel lymph node (SLN) metastases on axillary dissection in 403 patients (34.5%)
 - If 1 SLN met: 31.3%
 - If 2 SLN met: 51.3%
- Pathological nodal stage (primary surgery)

| | Standard of Care | Intervention |
|-----|------------------|--------------|
| pN1 | 1016 (84.3%) | 1311 (98.2%) |
| pN2 | 116 (9.6%) | 7 (0.5%) |
| pN3 | 35 (2.9%) | 0 (0%) |

Results: Treatment

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- **Mastectomy in 920 patients (36.2%)**
- Adjuvant radiotherapy including nodal target volumes in
 - **Standard of Care** N=1058 (88.4%)
 - **Intervention** N=1192 (89.9%)
- Systemic treatment in all but 27 patients
 - Chemotherapy N=1649 (64.9%)
 - Endocrine treatment N=2335 (91.9%)
 - HER2-targeted therapy N=224 (8.8%)

Recurrence-Free Survival

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191 Recurrence-Free Survival (RFS) events

- **Standard of Care** N=96 (8.0%)
- **Intervention** N=95 (7.1%)



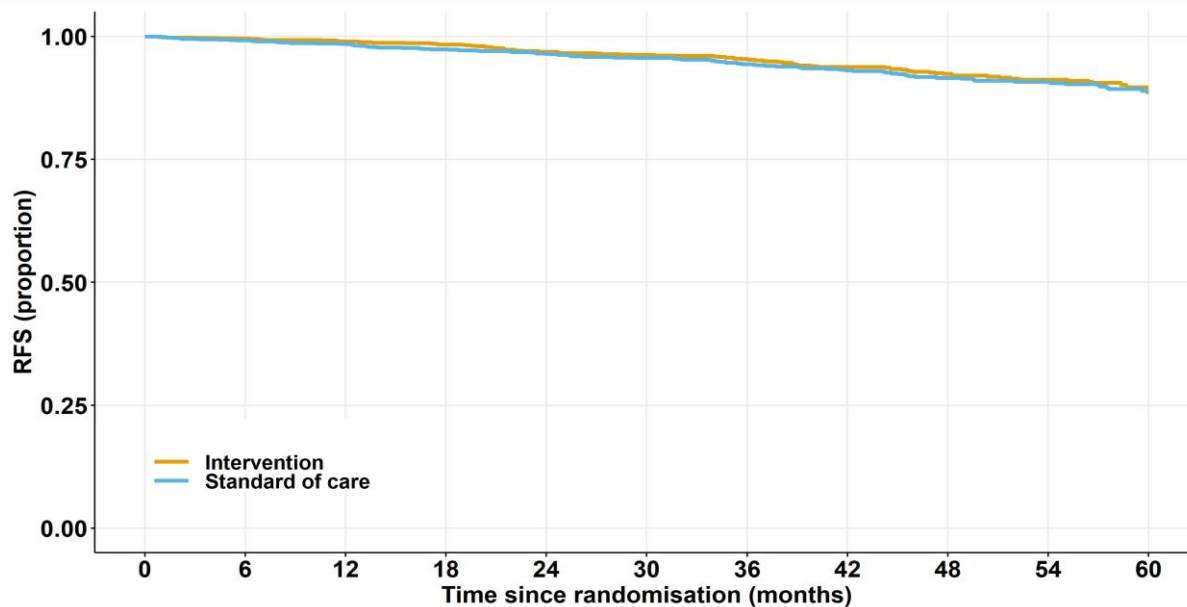
Pre especificado:
190 eventos

Estimated 5-year RFS

- **Standard of Care** 88.7% (86.3-91.1)
- **Intervention** 89.7% (87.5-91.9)

Recurrence-Free Survival

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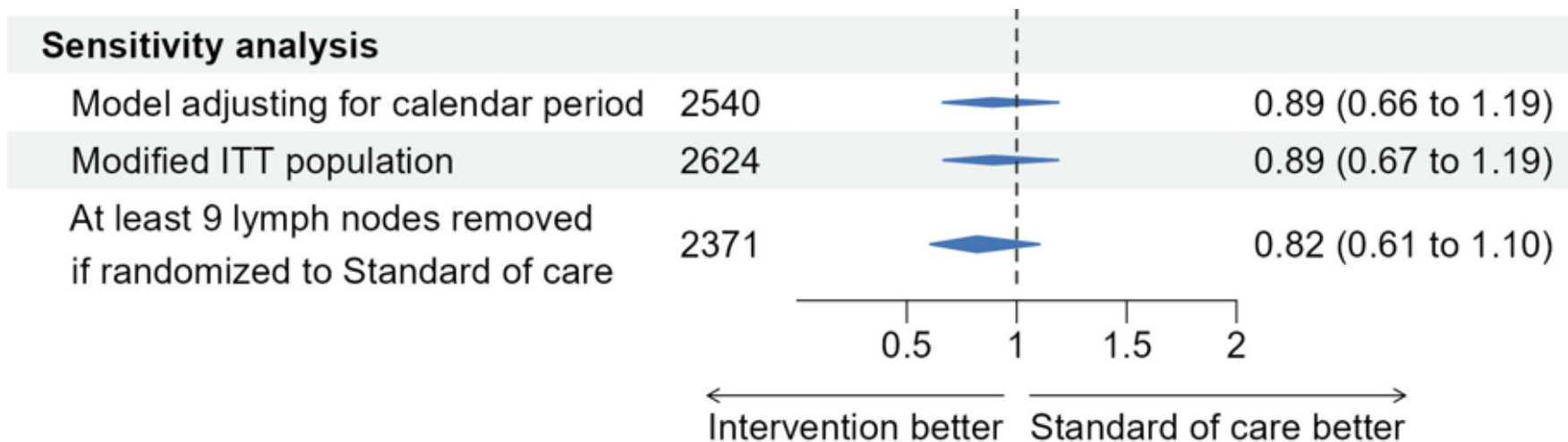
Number at risk

| | 0 | 6 | 12 | 18 | 24 | 30 | 36 | 42 | 48 | 54 | 60 |
|------------------|------|------|------|-----|-----|-----|----|----|----|----|----|
| Intervention | 1335 | 1276 | 1069 | 832 | 577 | 307 | | | | | |
| Standard of care | 1205 | 1159 | 1009 | 772 | 544 | 274 | | | | | |

Results: Non-inferiority

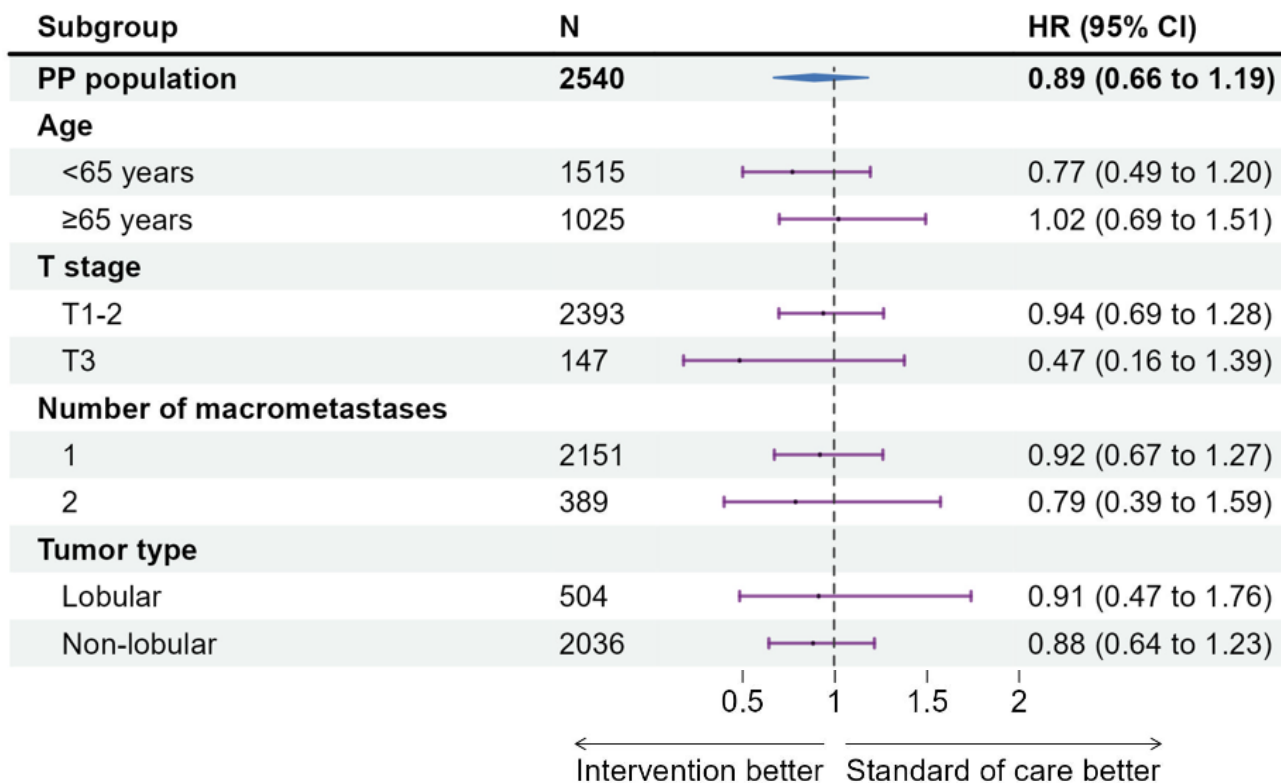
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- Hazard ratio 0.89 (0.66-1.19)
- Test of non-inferiority $p < 0.001$



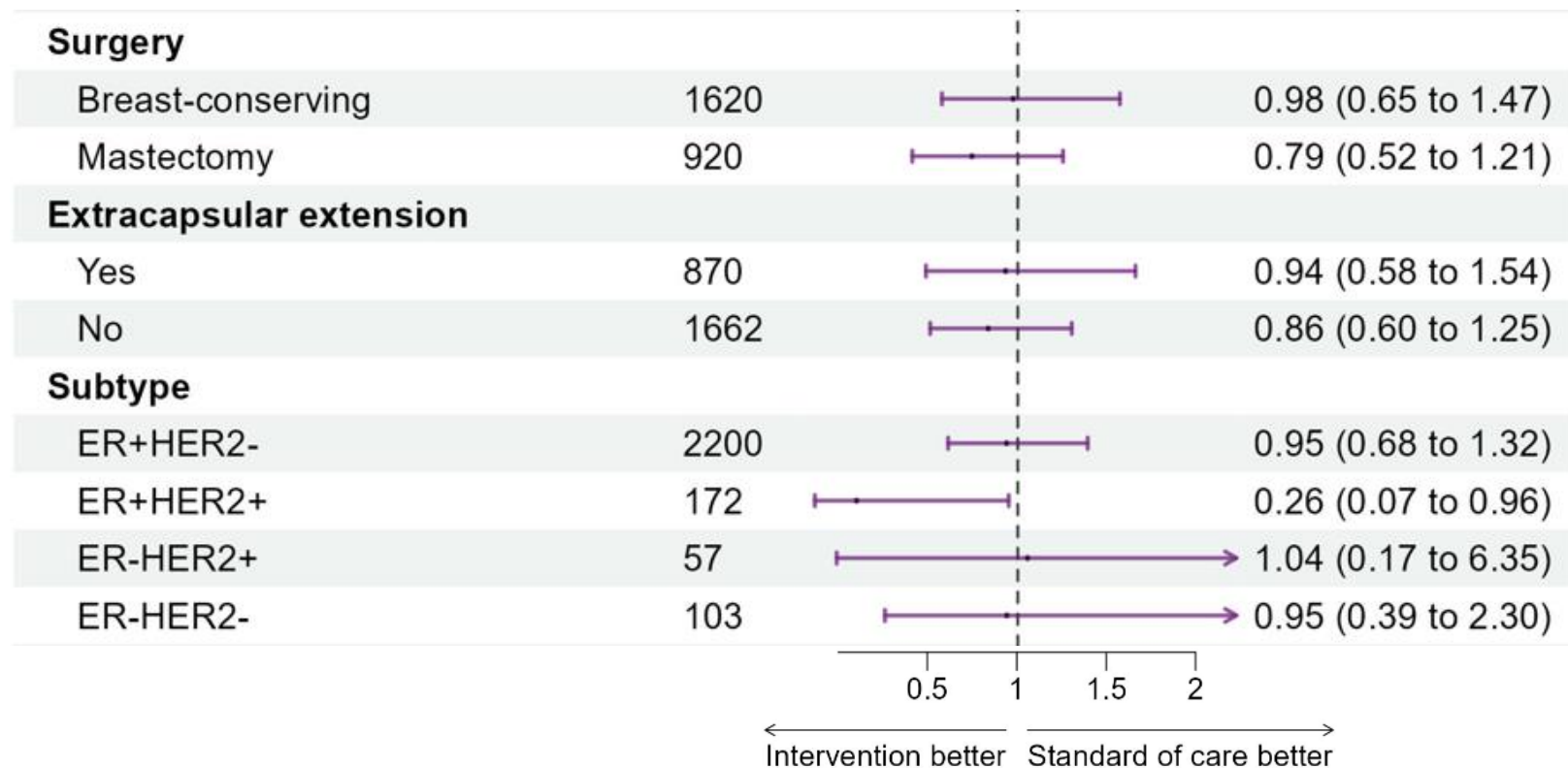
Subgroup analyses

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Subgroup analyses

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Conclusion

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- SLN biopsy alone non-inferior to axillary dissection
 - High proportion of nodal irradiation & systemic treatment
- Clinically relevant subgroups well represented
 - Mastectomy
 - Patients aged ≥ 65 years
 - Larger tumors
- Next step is to evaluate omission of nodal RT in the ongoing randomized T-REX trial

ESTUDOS RANDOMIZADOS LN+ SEM DISSECÇÃO AXILAR

| ESTUDOS | FOLLOW UP ANOS | US AXILAR | LN + ADICIONAIS | RECORRÊNCIA AXILAR |
|---------|----------------|----------------|---|--------------------|
| 2301 | 10 | NÃO | 13% | 1% |
| AATRM | 6 | NÃO | 13% | 1% |
| Z011 | 10 | NÃO | 27,2% 20% > 3 LN+ 13,7% > 4 LN+ | 1,3% |
| AMAROS | 10 | NÃO | 33% 8,4 > 4 LN+ | 1,19% |
| OTOASOR | 8 | SIM | 38,5% 22% > 4LN+ | 1,7% |
| SINODAR | 3 | SIM | 44% 13% > 4 LN+ | < 0,5% |
| SENOMAC | 47 MESES | SIM < 2 LN+ | 34,5% 1 SLN met: 31.3% 2 SLN met: 51.3% | |



The OPBC05/EUBREAST-14R/ICARO study

Are nodal isolated tumor cells (ITCs) after neoadjuvant chemotherapy an indication for axillary dissection?



Speaker: **Giacomo Montagna, MD, MPH**

Breast Service, Department of Surgery, Memorial Sloan Kettering Cancer Center

Giacomo Montagna MD, MPH, Alison Laws MD, MPH, Massimo Ferrucci MD, PhD, Mary M. Mrdutt MD, MS, Susie X. Xun MD, Sung Gwe Ahn MD, PhD, Mariacarla Andreozzi PhD, Suleyman Bademler MD, Hakan Balbaloglu MD, Nora Balint-Lahat MD, Maggie Banyas-Paluchowski MD PhD, Daniel Meirelles Barbalho MD, PhD, Andrea V. Barrio MD, Nuran Bese MD, Jean François Boileau MD, MSc, Judy Boughey MD, Marissa Boyle MD, Flavia Vidal Cabero MD, MSc, Daniela Cocco MD, Fabio Corsi MD, Angelena Crown MD, Elco de Bree MD, PhD, Maria del Mar Vernet-Tomas MD, Christine Deutschmann MD, Emilia J. Diego MD, Nina Ditsch MD, Claire Eden MD, Ruth Eller MD, Emanuela Esposito MD, PhD, Oluwadamilola Fayanju MD, MPH, Franziska Fick MD, Forian Fitzal MD, Meghan R. Flanagan MD, MPH, Damiano Gentile MD, Oreste D. Gentilini MD, Maite Goldschmidt MSc, Mehmet Ali Gulcelik MD, Callie Hlavin, MD, MPH, Martin Heidinger MD, Jörg Heil MD, PhD, Justyna Jelinska MD, PhD, Güldeniz Karadeniz Cakmak MD, FEBS, Susan Kesmodel MD, Natalia Krawczyk MD, Henry M. Kuerer MD, PhD, Thorsten Kühn MD, PhD, Sherko Kümmel MD PhD, Cornelia Leo MD, Julie Loesch MD, Francesco Milardi MD, Dawid Murawa MD, PhD, Tracy Ann Moo MD, Tehillah S. Menes MD, Valentina Nekljudova PhD, Lisa A. Newman MD MPH, Daniele Passeri MD, PhD, Jessica M. Pastoriza MD, Andraz Perhavec MD, PhD, Melissa Pilewskie MD, Nina Pislar MD, Natália Polidorio MD, PhD, Fiorita Poulakaki MD, PhD, Avina Rami, Fabian Riedel MD, Nicola Rocco MD PhD, Jai Min Ryu MD, PhD, Freya R. Schnabel MD, Alexandra Schulz MSc, Emily L. Siegel MD, Colin Simonson MD, Christian Singer MD, PhD, Leonardo Soares MD, PhD, Varadan Sevillamedu, MBBS, DrPH, Christoph Tausch MD, Ekaterini Christina Tampaki MD, PhD, Athanasios Tampakis MD, PhD, Marios Konstantinos Tasoulis MD, PhD, M. Umit Ugurlu MD, Cihan Uras MD, Cicero Urban, MD, PhD, Astrid Botty Van den Bruele MD, Annemiek van Hemert MSc, Glenn Vergauwen MD, PhD, Denise Vorburger MD, Fredrik Wärnberg, Anna Weiss MD, Austin D. Williams MD, MSc, Kerstin Wimmer MD, PhD, Stephanie M Wong MD, MPH, Steven G. Woodward MD, Tae-Kyung Robyn Yoo MD, Jennifer Q. Zhang MD, Firdos M. Ziauddin MD, Tari King MD, Hasan Karanlik MD, Neslihan Cabioğlu MD, Marie-Jeanne Vrancken Peeters MD, PhD, Monica Morrow MD, Walter P. Weber, MD

Background: Nodal Burden in Patients with Residual Nodal Disease After NAC

- Patients with a positive sentinel lymph node (SLN) after neoadjuvant chemotherapy (NAC) have a high residual nodal burden, and axillary lymph node dissection (ALND) is currently considered standard of care

| | ACOSOG Z1071 | SN FNAC | MSKCC |
|-----------|--------------------------|----------------------|-----------------------|
| Micromets | 164/273 (60.1%) | 3/8 (37%) | 34/61 (56%) |
| Macromets | | 28/44 (64%) | 75/121 (62%) |

Residual Isolated Tumor Cells

- Residual isolated tumor cells (ITCs) are found in ~1.5% of patients undergoing neoadjuvant chemotherapy
- Data on the likelihood of finding additional positive lymph nodes in patients with residual ITCs are scarce, and the benefit of ALND is unclear

| | ACOSOG Z1071 | SN FNAC | MSKCC | OVERALL |
|------|--------------|---------|-------|---------------------|
| ITCs | 4/11 | 4/7 | 1/6 | 9/24 (37.5%) |

- As a consequence, surgical management of the axilla in these patients is not standardized 

Aims

- To determine how often additional positive LNs are found in patients with residual ITCs
- To evaluate rates of axillary and any invasive recurrence
- To compare outcomes in patients treated with and without ALND

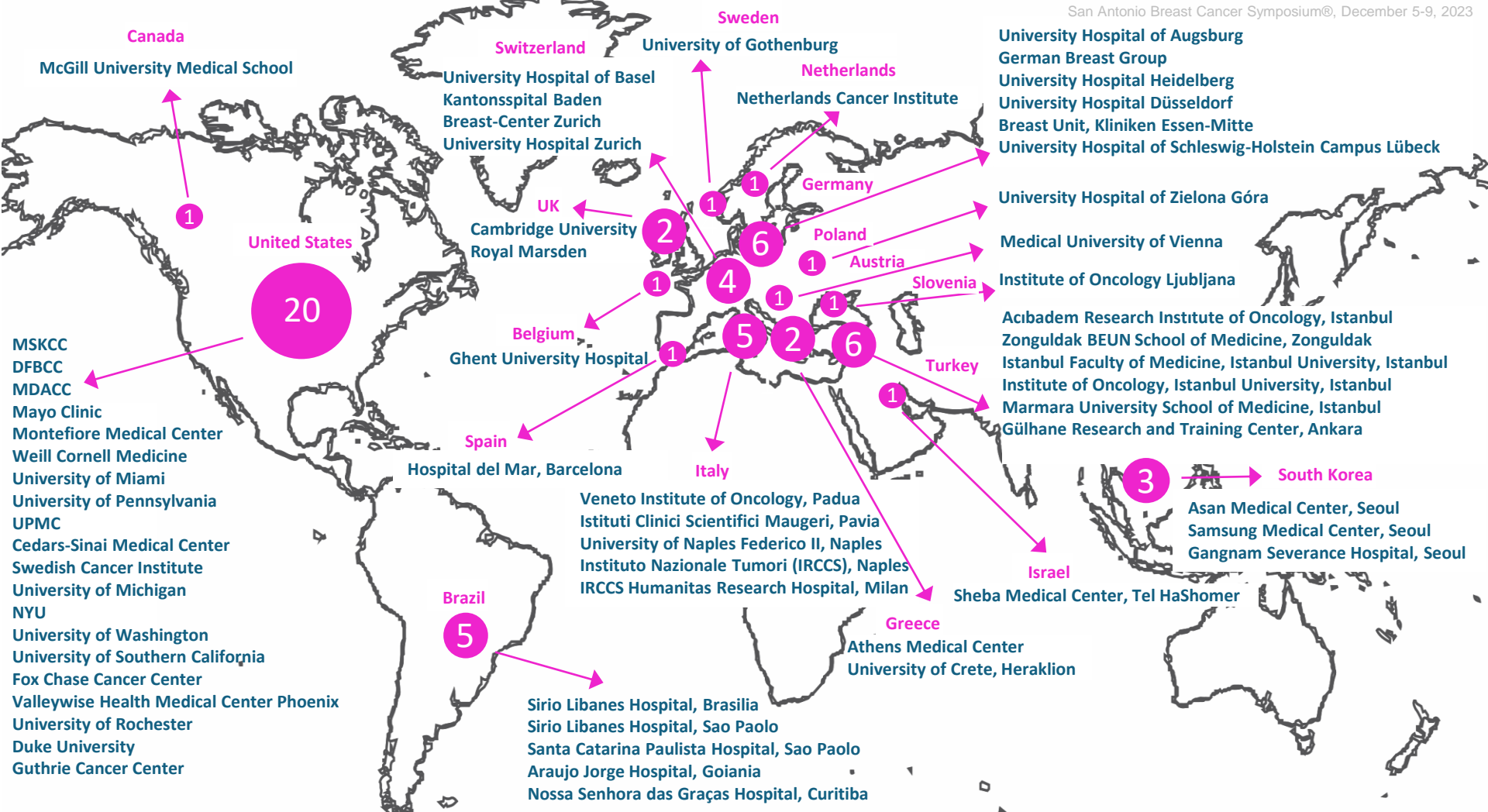
Study Population

Inclusion criteria

- T1-4 N0-3 BC patients
- Surgery after NAC with detection of ITCs [ypN0(i+)] at frozen section or final pathology
- SLNB performed with dual-tracer mapping *or* TAD *or* MARI for N+ and with single tracer for N0
- Detection of ITCs by H&E or IHC

Exclusion criteria

- No SLNB/TAD
- Inflammatory breast cancer
- Stage IV
- NET
- Detection by OSNA (quantitative measurement of target mRNA) due to lack of standardized cut-off



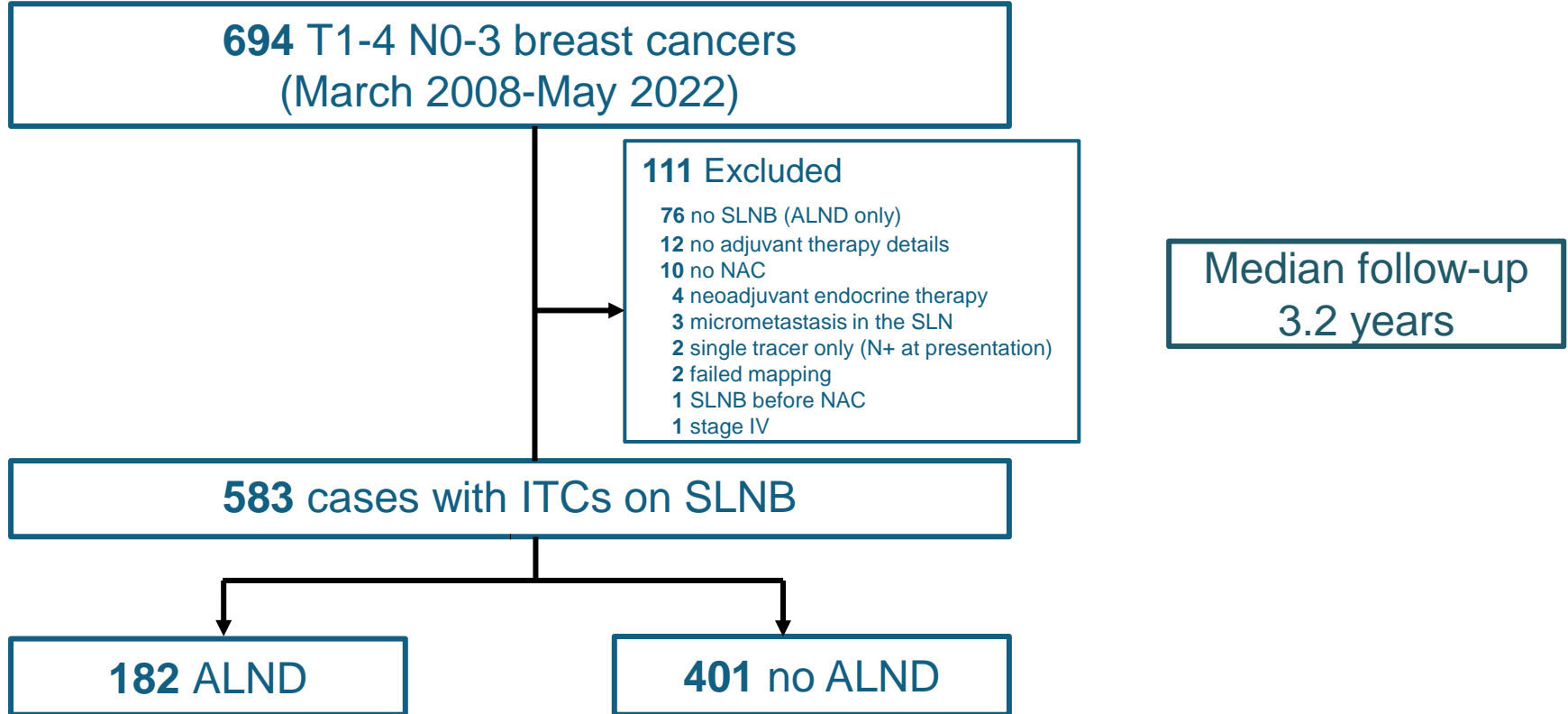
Data Collection

- Clinical and treatment variables, including pathologic characteristics of the primary tumor, surgery, radiation, and systemic therapy were collected from institutional databases

Statistical Analysis

- Clinicopathologic characteristics were compared between surgical groups using the Wilcoxon rank sum test, Pearson's Chi-squared test, and Fisher's exact test
- Competing risk analysis was performed to assess the cumulative incidence rates of axillary recurrence and any invasive recurrence (locoregional or distant)
- 5-year cumulative incidence rates were compared between patients treated with and without ALND using Gray's test

Flow Diagram



Clinical Characteristics

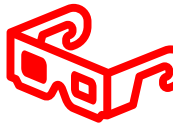
| | Overall n = 583 | No ALND n = 401 | ALND n = 182 | p value |
|------------------|--------------------|--------------------|-----------------|------------------|
| Age, years (IQR) | 48 (41, 57) | 48 (40, 57) | 49 (43, 58) | 0.11 |
| Race/Ethnicity | | | | 0.5 |
| Asian | 11% | 10% | 13% | |
| Black | 5% | 6% | 3% | |
| Hispanic | 5% | 6% | 4% | |
| White | 77% | 76% | 77% | |
| Other/unknown | 2% | 3% | 2% | |
| Clinical T stage | | | | 0.15 |
| 1 | 16% | 17% | 15% | |
| 2 | 57% | 55% | 62% | |
| 3 | 23% | 25% | 19% | |
| 4 | 3% | 3% | 4% | |
| X | 0.2% | 0% | 0.5% | |
| Clinical N stage | | | | <0.001 |
| 0 | 26% | 30% | 16% | |
| 1 | 64% | 63% | 67% | |
| 2 | 8% | 5% | 13% | |
| 3 | 2% | 2% | 4% | |

Pathological Characteristics

| | Overall n = 583 | No ALND n = 401 | ALND n = 182 | p value |
|-----------------------|--------------------|--------------------|-----------------|------------------|
| Tumor differentiation | | | | 0.13 |
| Well | 6% | 8% | 3% | |
| Moderately | 39% | 39% | 40% | |
| Poorly | 54% | 53% | 57% | |
| unknown | 49 | 27 | 22 | |
| Histology | | | | 0.02 |
| Ductal | 89% | 88% | 92% | |
| Lobular or mixed | 9% | 11% | 5% | |
| Other | 2% | 2% | 3% | |
| unknown | 2 | 1 | 1 | |
| Receptor subtype | | | | 0.6 |
| HR+/HER2- | 41% | 40% | 43% | |
| HR+/HER2+ | 28% | 27% | 29% | |
| HR-/HER2+ | 10% | 10% | 10% | |
| HR-/HER2- | 21% | 22% | 18% | |
| LVI | | | | <0.001 |
| Yes | 29% | 24% | 38% | |

Axillary Staging Characteristics

| | Overall n = 583 | No ALND n = 401 | ALND n = 182 | p value |
|---|--------------------|--------------------|-----------------|-------------------|
| Staging technique (cN+ only) | n = 433 | | | |
| SLNB with dual tracer mapping | 58% | 52% | 69% | < 0.001 |
| TAD | 34% | 37% | 28% | |
| MARI | 8% | 11% | 3% | |
| Entire cohort (cN0 and cN+) | | | | |
| # of SLNs removed (mean, min, max) | 3.3 (0, 16) | 3.5 (1, 16) | 2.8 (0, 10) | < 0.001 |
| # of SLNs with ITCs (mean, min, max) | 1.2 (0, 6) | 1.2 (0, 6) | 1.2 (0, 6) | 0.6 |
| ITCs detected on frozen section | | | | < 0.001 |
| Yes | 25% | 8% | 62% | |
| Not performed/unknown | 20 | 11 | 9 | |
| Total # of LNs removed (mean, min, max) | 7 (1,37) | 4 (1, 16) | 15 (4, 37) | < 0.001 |



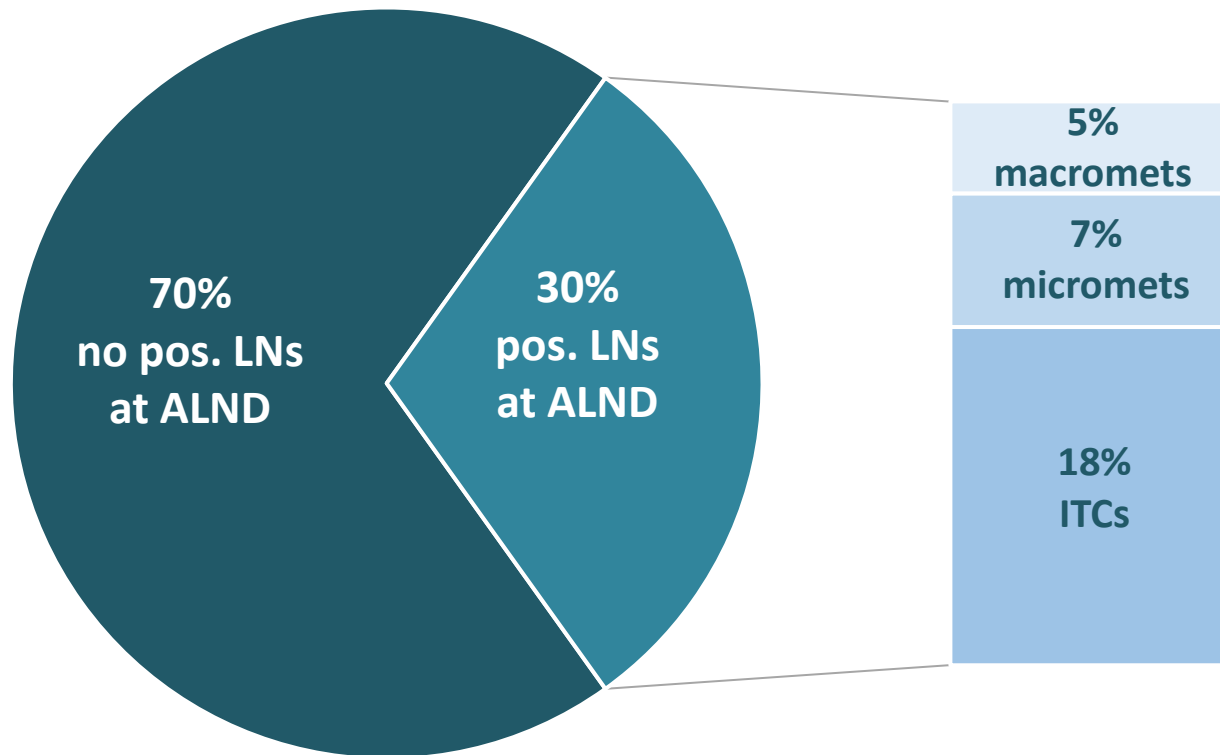
Treatment Characteristics

| | Overall n = 583 | No ALND n = 401 | ALND n = 182 | p value |
|---------------------------------|--------------------|--------------------|-----------------|---------|
| NAC regimen | | | | |
| HER2- | n = 362 | | | 0.8 |
| AC-T | 79% | 78% | 81% | |
| AC-T + Carbo | 6.6% | 6.0% | 8.1% | |
| AC-T + Carbo with pembrolizumab | 2.8% | 2.8% | 2.7% | |
| Anthracycline-free regimen | 2.8% | 3.2% | 1.8% | |
| Other | 8.6% | 9.6% | 6.3% | |
| HER2+ | n = 221 | | | 0.068 |
| AC-TH | 22% | 20% | 27% | |
| AC-THP | 29% | 29% | 31% | |
| TC-H | 1.8% | 1.3% | 2.8% | |
| TC-HP | 30% | 36% | 18% | |
| Other | 16.5% | 13.7% | 18% | |

Treatment Characteristics

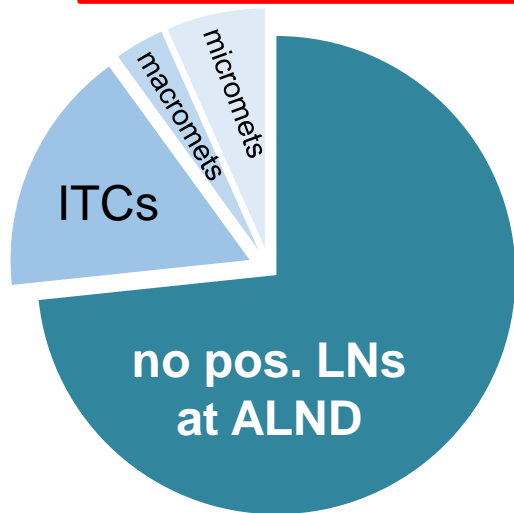
| | Overall n = 583 | No ALND n = 401 | ALND n = 182 | p value |
|------------------------|--------------------|--------------------|-----------------|--------------|
| Type of breast surgery | | | | 0.13 |
| Breast conservation | 46% | 48% | 41% | |
| Mastectomy | 54% | 52% | 59% | |
| Radiation therapy (RT) | | | | |
| Breast (n = 267) | 98% | 97% | 100% | 0.3 |
| Chest wall (n = 316) | 82% | 78% | 89% | 0.024 |
| Nodal RT | | | | 0.038 |
| Yes | 77% | 75% | 82% | |

Additional Positive Lymph Nodes in the ALND Group (n=182)

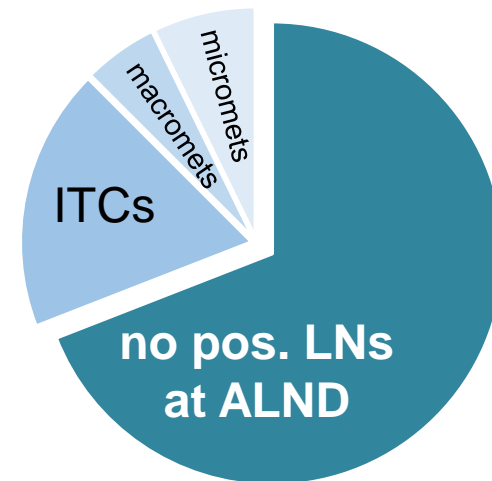


Additional Positive Lymph Nodes at ALND by Nodal Status at Presentation

cN0 (n= 30)



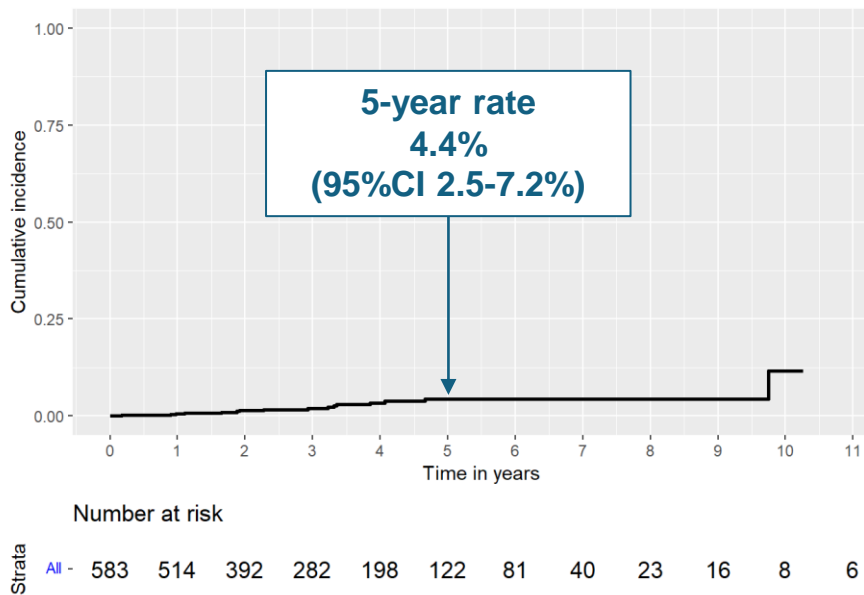
cN+ (n = 152)



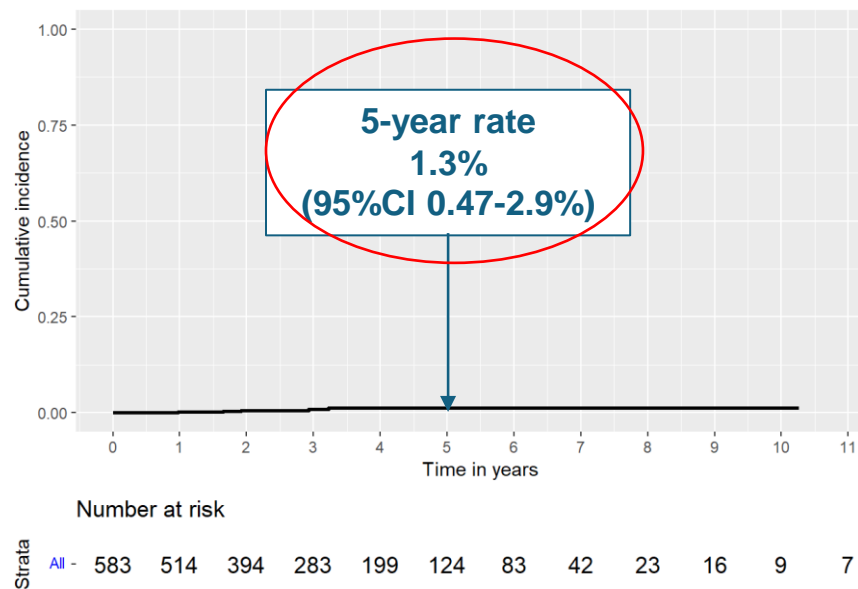
27% (cN0) vs 31% (cN+)
p = 0.6

Axillary Recurrence

Any (Isolated or Combined with Local and Distant Recurrence)



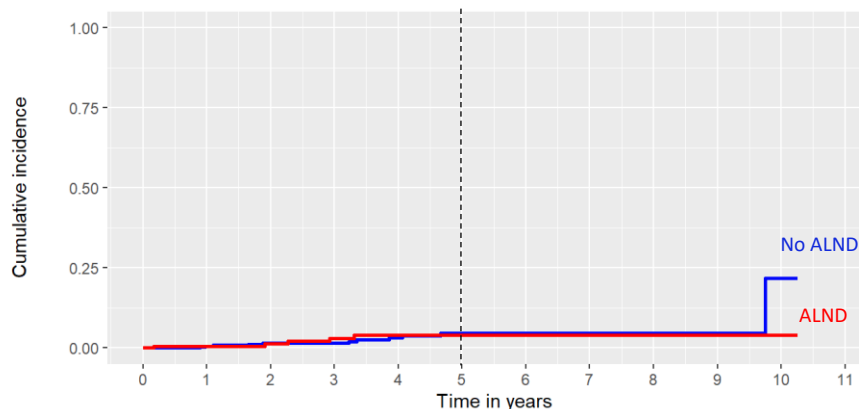
Isolated



Axillary Recurrence (No ALND vs ALND)

Isolated or Combined with Local and Distant Recurrence

5-year rate of any axillary recurrence
no ALND vs ALND
4.6% vs 4.1%, p = 0.8

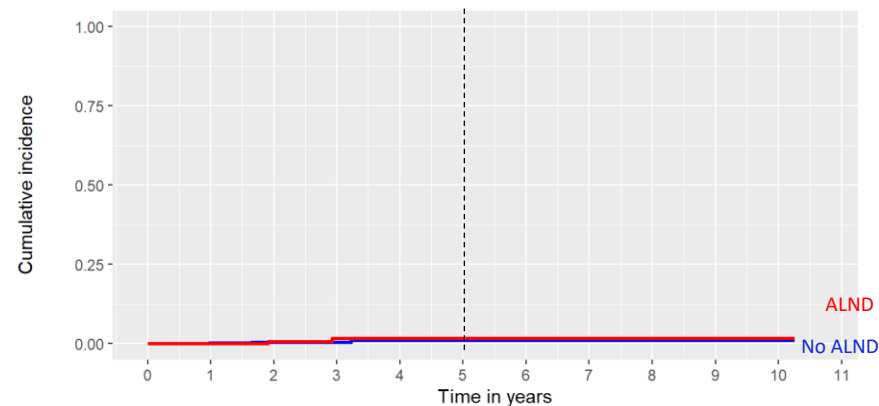


Number at risk

| Strata | No ALND | 401 | 349 | 266 | 187 | 131 | 73 | 45 | 21 | 10 | 6 | 3 | 3 |
|--------|---------|-----|-----|-----|-----|-----|----|----|----|----|---|---|---|
| ALND | 182 | 165 | 126 | 95 | 67 | 49 | 36 | 19 | 13 | 10 | 5 | 3 | |

Isolated

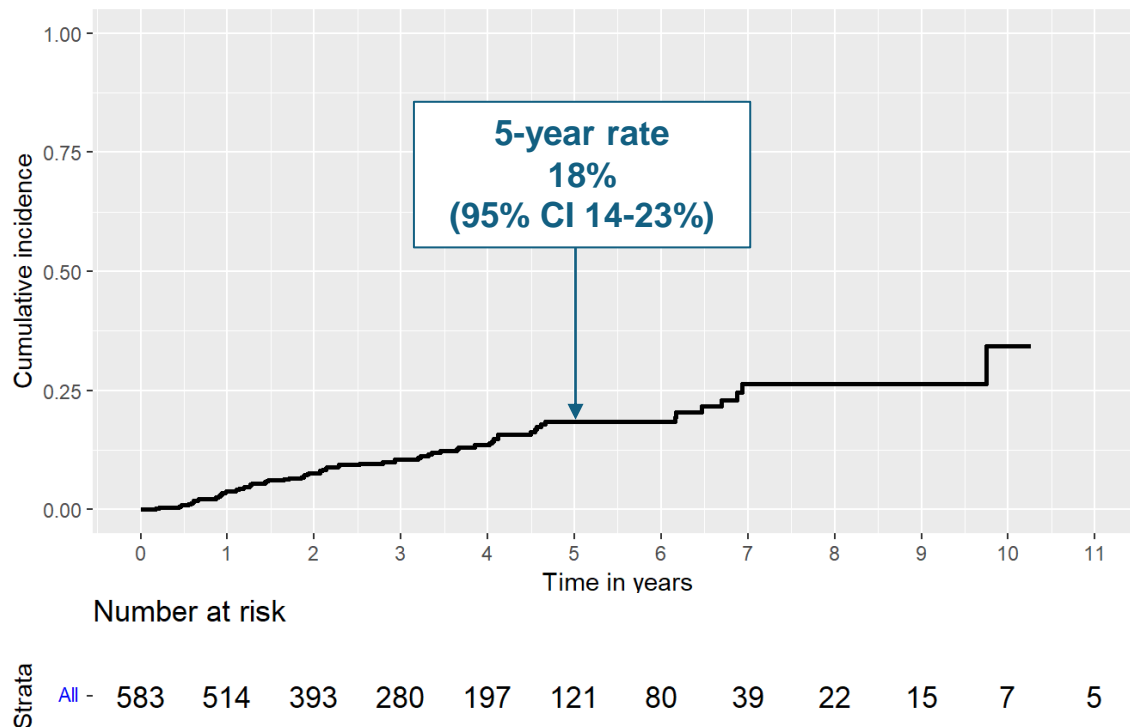
5-year rate of isolated axillary recurrence
no ALND vs ALND
1.1% vs 1.7%, p = 0.7



Number at risk

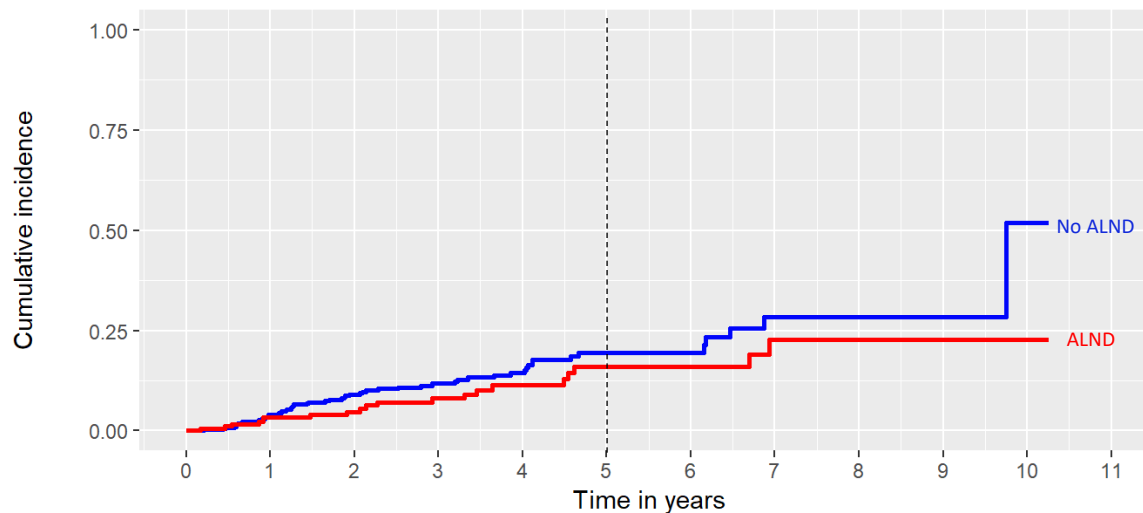
| Strata | No ALND | 401 | 349 | 266 | 187 | 131 | 73 | 45 | 21 | 10 | 6 | 3 | 3 |
|--------|---------|-----|-----|-----|-----|-----|----|----|----|----|---|---|---|
| ALND | 182 | 165 | 126 | 95 | 67 | 49 | 36 | 19 | 13 | 10 | 5 | 3 | |

Any Invasive Recurrence (Locoregional or Distant)



Any Invasive Recurrence (No ALND vs ALND)

5-year rate of any invasive recurrence no ALND vs ALND
19% vs 16%, $p = 0.13$



Number at risk

| Strata | No ALND | 401 | 349 | 266 | 185 | 129 | 71 | 43 | 20 | 9 | 5 | 2 | 2 |
|--------|---------|-----|-----|-----|-----|-----|----|----|----|----|---|---|---|
| ALND | 182 | 165 | 127 | 95 | 68 | 50 | 37 | 19 | 13 | 10 | 5 | 3 | |

Strengths and Limitations

Strengths

- First study to compare outcomes in patients with residual ITCs treated with and without ALND
- Large number of patients to examine residual nodal burden in patients with ITCs
- Multicenter
- All settings (public, private academic, and community hospitals)

Limitations

- Retrospective
- Relatively short median follow-up (3.2 years)
- Pathological assessment was not standardized

Conclusions

- The likelihood of finding additional positive lymph nodes in patients with residual ITCs is lower than in patients with residual micro- and macrometastases
 - macrometastases were found at ALND in 5% of cases
 - no impact of nodal status at presentation
- Detection of ITCs on frozen section was strongly associated with ALND
- Rates of axillary and invasive recurrence did not statistically differ based on the use of ALND

Conclusions

- These results do not support routine ALND in patients with residual ITCs after NAC
- Randomized trials (NASBP-B51) will provide further insight to whether nodal RT is needed in this setting

Surgical Treatment of Women with Breast Cancer and a *BRCA1* Pathogenic Variant: An International Analysis of the Impact of Bilateral Mastectomy on Survival

Kelly A. Metcalfe, RN, PhD, FAAN, FCAHS, FCAN
Senior Scientist, Women's College Research Institute, Toronto, ON
Professor, University of Toronto, Toronto, ON



Introduction

- Germline genetic testing has been integrated into clinical care for women with breast cancer prior to treatment
- Pathogenic variants in *BRCA1* and *BRCA2* are found in 3-4% of women with breast cancer
- Treatment can be personalized based on genetic test results
- Treatment options include consideration of index cancer and increased risks of ipsilateral and contralateral breast cancer, and ovarian cancer
- Surgical options include breast conserving treatment and mastectomy

Study Objective

To evaluate the **risk of contralateral breast cancer** and **breast cancer specific mortality** by surgical treatment in women with *BRCA1* pathogenic variant and non-metastatic breast cancer

Methods

- Eligible subjects identified from **international cohort**
- Clinical and treatment data collected through **medical chart review**
- Demographic data collected through patient questionnaire
- Women were followed from date of breast cancer diagnosis to
 - **Date of last follow-up**
 - OR
 - **Date of death**

Eligibility Criteria

- **Breast cancer stage I to III**
- **BRCA1 pathogenic variant**

Excluded:

- DCIS or Stage IV breast cancer
- Synchronous bilateral breast cancer
- No follow-up

Study Cohort

- 2482 eligible participants
- 26 centers
- 11 countries

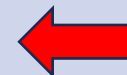
| Variable | Mean (range) / frequency (%) |
|--------------------------|------------------------------|
| Date of diagnosis | 2011.1(1995-2021) |
| Follow up (years) | 8.9 (0.0-26.0) |
| Age at Diagnosis (years) | |
| Mean | 43.1 (18-70) |
| <=40 | 1049 (42.3) |
| 40-50 | 833(33.6) |
| 50+ | 600(24.2) |
| Surgery | |
| BCT | 852 (34.3) |
| Mastectomy | 1141 (46.0) |
| Bilateral Mastectomy | 489(19.7) |

76% < 50 anos



20% mastectomia

Results: Participant Characteristics

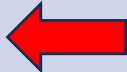

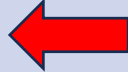

| Variable | BCT N=852 | Unilateral mastectomy N=1141 | Bilateral Mastectomy N=489 | P-value |
|------------------|-------------------|------------------------------------|----------------------------------|---------|
| Date of dx | 2010.9(1995-2021) | 2009.9(1996-2021) | 2014.1(1997-2021) | <0.0001 |
| Follow-up years | 9.2(0.2-26.0) | 9.6 (0.1-25.7) | 6.5 (0.0-23.5) | <0.0001 |
| Age at Diagnosis | | | | |
| Mean | 43.5 (20-70) | 43.5 (18-69) | 41.3 (23-70) | <0.0001 |
| <=40 | 356 (41.8) | 443 (38.8) | 250 (51.1) | <0.0001 |
| 40-50 | 270 (31.7) | 415 (36.4) | 148 (30.3) | |
| 50+ | 226 (26.5) | 283 (24.8) | 91 (18.6) | |



Results: Clinical Characteristics

| Variable | BCT N=852 | Unilateral mastectomy N=1141 | Bilateral Mastectomy N=489 | P-value |
|------------------|--------------------------|--|-------------------------------|---------|
| Size (cm) | | | | |
| <=2 | 2.1 (0-20) 506 (59.4) | 3.0 (0-40) 451 (39.5) | 2.2 (0-27) 263 (53.8) | <0.0001 |
| 2-5 | 277 (32.5) | 508 (44.5) | 188 (38.4) | <0.0001 |
| 5+ | 24 (2.8) | 101 (8.9)  | 21 (4.3) | |
| Nodes | | | | |
| Neg | 647 (78.1) | 683 (62.4) | 354 (75.6) | |
| Pos | 182 (21.9) | 412 (37.6)  | 114 (24.4) | 0.03 |
| Grade | | | | |
| I | 20 (2.5) | 22 (2.2) | 23 (2.6) | |
| II | 173 (22.1) | 243 (24.1) | 75 (16.1) | 0.05 |
| III | 591 (75.4) | 744 (73.7) | 380 (81.4) | |
| ER | | | | |
| Neg | 614 (72.2) | 826 (73.4) | 360 (74.2) | |
| Pos | 233 (27.4) | 300 (26.6) | 124 (25.6) | 0.52 |

Results: Other Treatments

| Variable | BCT N=852 | Unilateral mastectomy N=1141 | Bilateral Mastectomy N=489 | P-value |
|---------------------|--------------|--|--|---------|
| Oophorectomy | | | | |
| No | 347 (41.7) | 555 (49.4) | 170 (35.4) | <0.0001 |
| Yes | 485 (58.3) | 569 (50.6) | 310 (64.6)  | |
| Radiotherapy | | | | |
| No | 159 (18.9) | 506 (44.7) | 287 (60.7) | <0.0001 |
| Yes | 683 (81.1) | 627 (55.3)  | 186 (39.3) | |
| Chemotherapy | | | | |
| No | 117 (15.5) | 246 (23.1) | 225 (52.9) | <0.0001 |
| Yes | 640 (84.5) | 819 (76.9)  | 200 (47.1) | |
| Tamoxifen | | | | |
| No | 667 (78.3) | 844 (74.0) | 406 (83.0) | 0.0002 |
| Yes | 185 (21.7) | 297 (26.0) | 83 (17.0)  | |

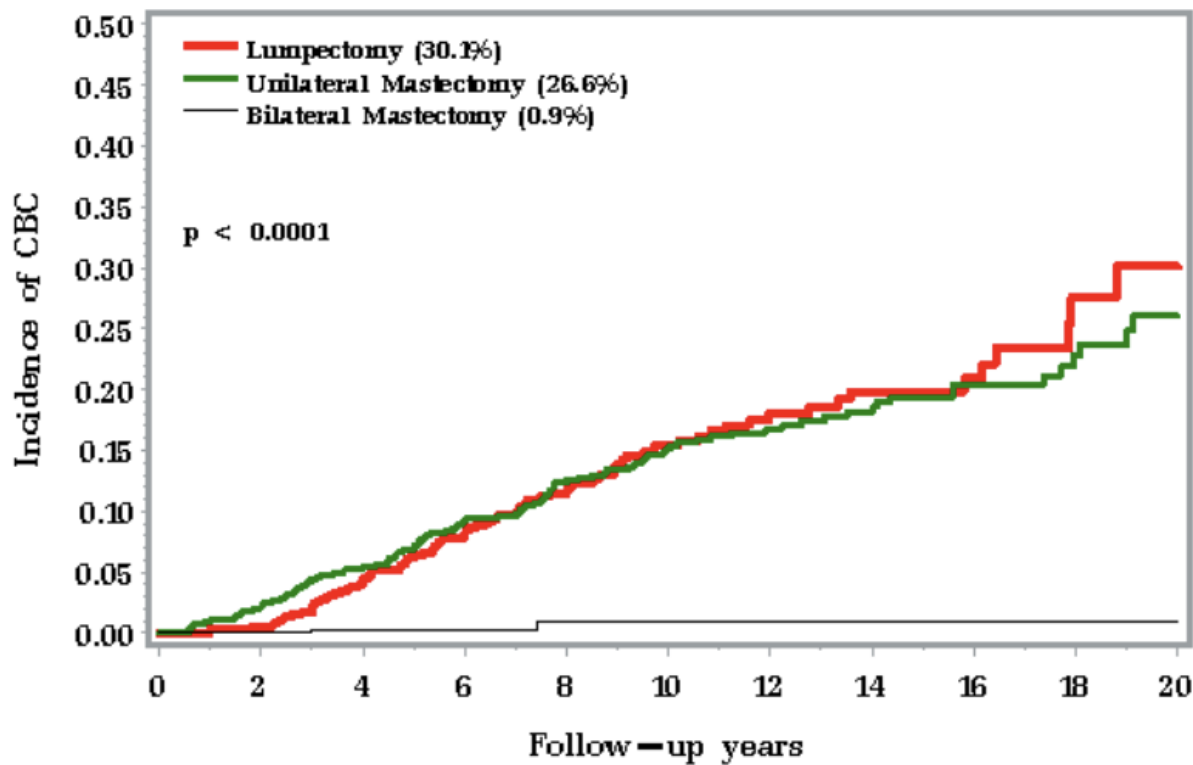
Contralateral Breast Cancer

Contralateral Breast Cancer

- 11.5% of participants diagnosed with contralateral breast cancer

| Variable | BCT N=852 | Unilateral mastectomy N=1141 | Bilateral Mastectomy N=489 | P-value |
|-------------------------|--------------|------------------------------------|----------------------------------|---------|
| Contralateral BC | | | | |
| No | 760 (89.2) | 1011 (88.6) | 485 (99.2) | |
| Yes | 92 (10.8) | 130 (11.4) | 4 (0.8) | <0.0001 |

Contralateral Breast Cancer by Surgery



Breast Cancer Mortality by Contralateral Breast Cancer

| | Univariate HR(95%CI)P | Multivariate * HR(95%CI)P |
|---|--------------------------|------------------------------|
| All subjects Contralateral BC | | |
| No | 1 | 1 |
| Yes (time dependent) | 2.20(1.48-3.28)0.0001 | 2.22(1.49-3.32) <0.0001 |
| Age ≤40 years Contralateral BC | | |
| No | 1 | 1 |
| Yes (time dependent) | 2.60(1.35-4.99)0.004 | 2.71(1.40-5.24)0.003 |
| Age >40 years Contralateral BC | | |
| No | 1 | 1 |
| Yes (time dependent) | 2.02(1.22-3.34)0.006 | 1.99(1.19-3.31)0.008 |

*adjusted by age at dx (<=40, 30-50, 50+), size (<2, 2-5, >5), nodes (Neg/Pos), surgery, oophorectomy (time dependent), tamoxifen (yes/no), er (pos/neg), and chemotherapy

Breast Cancer Mortality

Breast Cancer Mortality

- 285 (11.5%) died of breast cancer

| Variable | BCT N=852 | Unilateral mastectomy N=1141 | Bilateral Mastectomy N=489 | P-value |
|-------------------|--------------|------------------------------------|----------------------------------|---------|
| Died of BC | | | | |
| No | 667 (78.3) | 968 (84.8) | 453 (92.6) | <0.0001 |
| Yes | 76 (6.9) | 173 (15.2) | 36 (7.4) | |

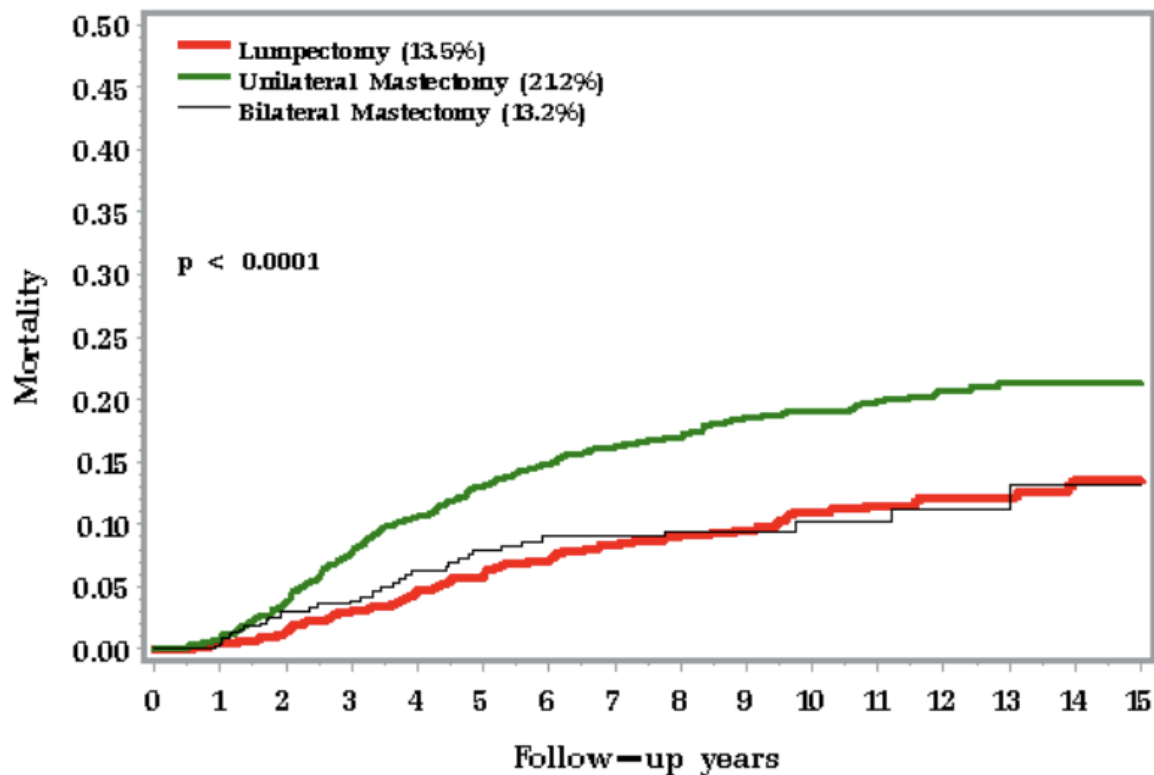


* VIÉS DE SELEÇÃO?

BRCA1 Breast Cancer-Specific Survival

- 15-year breast cancer-specific survival
 - Overall 82.9%
 - BCT 86.2%
 - Mastectomy 78.7%
 - Bilateral Mastectomy 88.7%

Breast Cancer Mortality by Surgery



Breast Cancer Mortality by Surgery Type

| | Univariate HR(95%CI)P | Multivariate * HR(95%CI)P |
|------------------------------|--------------------------|------------------------------|
| All subjects | | |
| BCT | 1 | 1 |
| Unilateral Mastectomy | 1.79(1.36-2.34)<0.0001 | 1.22(0.92-1.62)0.17 |
| Bilateral Mastectomy | 0.99(0.67-1.48)0.97 | 0.88(0.58-1.13)0.19 |
| Age ≤40 years | | |
| BCT | 1 | 1 |
| Unilateral Mastectomy | 1.68(1.08-2.63)0.02 | 1.28(0.81-2.04)0.29 |
| Bilateral Mastectomy | 1.13(0.63-2.02)0.68 | 0.94(0.51-1.72)0.84 |
| Age >40 years | | |
| BCT | 1 | 1 |
| Unilateral Mastectomy | 1.83(1.30-2.58)0.0005 | 1.15(0.80-1.65)0.44 |
| Bilateral Mastectomy | 0.89(0.51-1.55)0.68 | 0.83(0.46-1.48)0.52 |

*adjusted by age at dx (<=40, 30-50, 50+), size (<2, 2-5, >5), nodes (Neg/Pos), oophorectomy (time dependent), tamoxifen (yes/no), er (pos/neg), chemotherapy (yes/no), and preventive mastectomy for those first surgery not bilateral (time dependent)

Discussion

Conclusions

- Women with *BRCA1* PV and bilateral mastectomy
 - Significantly less likely to develop contralateral breast cancer ($p < 0.0001$)
- Women with *BRCA1* PV and contralateral breast cancer
 - Twice as likely to die of breast cancer (HR 2.22, $p < 0.0001$)
- Bilateral mastectomy not significantly associated with reduction in mortality compared to BCT (HR 0.83, $p = 0.52$)

Future Considerations

- Confirmatory studies with longer follow-up
 - Future studies with newer treatments (including Olaparib)
 - Benefit of oophorectomy
 - Compare to non-carrier population
 - Consider other genes ie *PALB2*, *Tp53*
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