Highlights 2018 San Antonio Breast Cancer Symposium: New Developments

Sheldon M Feldman, M.D., FACS
Chief Breast Surgical Oncology
Director Breast Cancer Services
Professor of Surgery
Montefiore Medical Center
Albert Einstein College of Medicine
Acknowledgements and Topics for Discussion

Best of San Antonio 1/20/2019  NYC

- Dr. Joseph Sparano (Montefiore) - tumor biology, endocrine rx and genomic profile
- Dr. Sheldon Feldman (Montefiore) - axillary nodal Rx, decision making and quality of life
- Dr. Larry Solin (U of Penn) - radiation
- Dr. Francesco Esteva (NYU) - chemotherapy
- Dr. Charles Shapiro (Mt. Sinai) - survivorship
FERN FELDMAN ANOLICK
(1942-1979)
Precision Medicine: Role of Biomarkers in Breast Cancer

1st generation: protein expression ~ 1970
   - ER/PR IHC

2nd generation: gene amplification ~ 1990
   - HER2/neu FISH

3rd generation: gene expression ~ 2004
   - Oncotype DX, Mammaprint, BCI
   - PAM50, Endopredict

4th generation: mutational profiling ~ 2010
   - Commercial and academic assays
Breast Cancer Phenotypes

Invasive Ductal Carcinomas
~ 80% of invasive breast cancers

Unclassified

Luminal A
ER+, PR+, HER2-

Luminal B
ER+, PR+, HER2+

HER2+
ER-, PR-, HER2+

Basal-like
ER-, PR-, HER2-, CK5/6 and/or EGFR+

ER+, PR+

ER-, PR-
Gene Expression Profiling in Breast Cancer

- Breast cancer is heterogeneous
- Distinct subtypes
- Prognosis varies by subtype

PNAS 2003; 100(14): 8418-8423
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<td>Predictive - chemotherapy benefit</td>
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<td>Predictive - extended</td>
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21-Gene Expression Recurrence Score Assay and Algorithm

**Proliferation**
- Ki67
- STK15
- Survivin
- CCNB1 (cyclinB1)
- MYBL2

**HER2**
- GRB7
- HER2

**Estrogen**
- ER
- PGR
- BCL2
- SCUBE2

**Invasion**
- MMP11
- CTSL2

**GSTM1**

**CD68**

**BAG1**

**Reference**
- ACTB (B-actin)
- GAPDH
- RPLP0
- GUS
- TFRC

RS = +0.47 x HER2 Group Score
- 0.34 x ER Group Score
+ 1.04 x Proliferation Score
+ 0.10 x Invasion Group Score
+ 0.05 x CD68
- 0.08 x GSTM1
- 0.07 x BAG1

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<th>Category</th>
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<td>Intermediate risk</td>
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<td>High Risk</td>
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Reference: NEJM 2004; 351(27): 2817-26
Prognosis: Prospective Validation of 21-Gene Assay (B14)
(N=668 ER+, node-neg - tamoxifen x 5 years enrolled between January, 1982- October 1988)

Multivariate cox model with distant recurrence as outcome revealed a statistically significant association for RS that was independent of age and tumor size.

NEJM 2004; 351(27): 2817-26
TAILORx Methods: Treatment Assignment & Randomization

Accrued between April 2006 – October 2010

**Key Eligibility Criteria**
- Node-negative
- ER-pos, HER2-neg
- T1c-T2 (high-risk T1b)

**Statistical Design**
- Non-Inferiority - IDFS
- HR 1.332 (90 vs. 87% 5-yr DFS)
- Type I 10%, type II 5%
- Full info – 835 IDFS events

Preregister - Oncotype DX RS (N=11,232)

Register (N=10,273)

**ARM A**: Low RS 0-10
(N=1629 evaluable)

**ARM B**: Experimental Arm
(N=3399)

**ARM C**: Standard Arm
(N=3312)

**ARM D**: High RS 26-100
(N=1389 evaluable)

**Mid-Range RS 11-25**
(N=6711 evaluable)

**RANDOMIZE**

Stratification Factors: Menopausal Status, Planned Chemotherapy, Planned Radiation, and RS 11-15, 16-20, 21-25

**RS = 11 (B14 Study)**
- 7.3% distant recurrence rate at 10 years
- 95% CI 5%, 10%

**RS = 25 (B14 Study)**
- 16.1% distant recurrence rate at 10 years
- 95% CI 13%, 20%

**RS 11-25 (B20 Study)**:
5% distant recurrence rate at 10 years

Endocrine Therapy (ET)

ET Alone

ET + Chemo

Sparano et al. *N Engl J Med* 2018
Tailorx Low Risk Registry: RS 0-10 - Endocrine Therapy Alone

Prospective Validation of a 21-Gene Expression Assay in Breast Cancer


5 year iDFS Rate
93.8%
(95% CI 92.4%, 94.9%)

5 year RFI Rate
98.7%
(95% CI 97.9%, 99.2%)

5 year DRFI Rate
99.3%
(95% CI 98.7%, 99.6%)

5 year OS Rate
98.0%
(95% CI 97.1%, 98.6%)

Primary Endpoint - RS 0-10

Original Article

Adjuvant Chemotherapy Guided by a 21-Gene Expression Assay in Breast Cancer

TAILORx Results - ITT Population: RS 11-25 (Arms B & C)

836 IDFS events (after median of 7.5 years), including 338 (40.3%) with recurrence as first event, of which 199 (23.8%) were distant.

Primary Endpoint
Invasive Disease-Free Survival

- CHEMO + ET
- ET Alone

Secondary Endpoint
Distant Relapse-Free Interval

- CHEMO + ET
- ET Alone

Number at risk

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<th>Arm B ET Alone</th>
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Number at risk

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<td>554</td>
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Sparano et al. *N Engl J Med* 2018
### TAILORx Subgroup Analysis - 50 or Younger:
Chemotherapy Associated with Fewer Earlier & Later Distant Recurrences within RS 16-25 Range (Especially 21-25)

<table>
<thead>
<tr>
<th>Freedom from recurrence of breast cancer at a distant site</th>
<th>5 Years</th>
<th>9 Years</th>
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<tr>
<td>Score of (\leq 10), endocrine therapy</td>
<td>99.7±0.3</td>
<td>98.5±0.8</td>
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<tr>
<td>Score of 11–15, endocrine therapy</td>
<td>98.8±0.6</td>
<td>97.2±1.0</td>
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<tr>
<td>Score of 11–15, chemoendocrine therapy</td>
<td>98.5±0.7</td>
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<tr>
<td>Score of 16–20, endocrine therapy</td>
<td>98.1±0.7</td>
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<td>Score of 16–20, chemoendocrine therapy</td>
<td>98.9±0.5</td>
<td>95.2±1.3</td>
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<td>Score of 21–25, endocrine therapy</td>
<td>93.2±1.7</td>
<td>86.9±2.9</td>
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<tr>
<td>Score of 21–25, chemoendocrine therapy</td>
<td>96.4±1.2</td>
<td>93.4±2.3</td>
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<tr>
<td>Score of (\geq 26), chemoendocrine therapy</td>
<td>91.1±1.6</td>
<td>88.7±2.1</td>
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Δ 0.8%  Δ 1.6%  Δ 3.2%  Δ 6.5%
RxPONGDER Trial
(Accrual completed, awaiting results)

ER+/HER2-
LN: 1-3+

Trial Sponsored
Oncotype Dx testing

RS>25
RS≤25

Discuss Alternatives

Oncotype Dx already performed, and RS≤25

Randomize
Stratified by:
RS<14 vs. 14-25
Menopause status
ALND vs. SLNB

Hormone therapy
Chemotherapy + Hormone therapy
Cancer Mortality Declining in U.S.

Breast Cancer Symptoms/Diagnosis/Philosophy

• Over 80% of patients with breast cancer are asymptomatic when diagnosed
• Typically diagnosis made on screening mammogram or noticing a new lump
• Needle biopsy of the lump confirms the diagnosis and leads to a specific treatment plan for that particular type of breast cancer
• Important that we strive for Minimally Effective not Maximally Tolerated treatment
• Goal for patients to be cured of cancer while avoiding side effects from treatment
• You cannot improve on being asymptomatic from a disease!!!!!
Sequelaes of Breast Cancer Treatment

The benefits of current treatment strategies are effective, many cancer survivors are at risk for developing physiologic and psychological late effects of cancer treatment that might lead to premature mortality and morbidity and compromise their quality of life. Psychological symptoms include anxiety, depression, fatigue, difficulty sleeping, and loss of self-esteem. Physiologic changes include pain, numbness, cognitive impairment, weight gain, loss of sexual interest, spontaneous menopause, and peripheral neuropathy. LYMPHEDEMA is a major QOL issue!!

National Lymphedema Network
Arm symptoms after axillary lymph node surgery

- Pain
- Numbness
- Weakness
- Limitation of range of movement
- Seroma
- Cording (axillary web syndrome)
- Swelling: LYMPHEDEMA
WHAT IS LYMPHEDEMA?

• Lymphedema is a chronic lymphatic disease that results in disfiguring swelling in one or more parts of the body. It can be hereditary (Primary Lymphedema) or it can occur after a surgical procedure, infection, radiation or other physical trauma (Secondary Lymphedema). In breast cancer, for example, it can appear in the arm on the same side as the cancer, after lymph nodes are removed from the armpit region for cancer staging. Primary Lymphedema often occurs in the lower extremities. Lymph is the protein-rich body fluid that accumulates when the lymphatic system for fluid transport is damaged.
PATIENT’S POINT OF VIEW

“LYMPHEDEMA WORSE THAN MASTECTOMY”

“I FEAR LYMPHEDEMA MORE THAN CANCER”

“LYMPHEDEMA REMINDS ME I HAVE CANCER EVERY DAY”
LYMPHEDEMA: SCOPE OF THE PROBLEM

• 3.1M breast cancer survivors in the US, (NCI estimates >4M by 2024)
• Worldwide: 1.7M women dx with breast cancer annually
• Lymphedema rates
  SLNB: 5-7%
  ALND: 15-20%
  ART: 10-15%
  ALND +XRT: 24-40%
Complicated breast cancer–related lymphedema: health care resource utilization and associated costs of management

- 56,075 women
- IRR for admission if LE: 5.02 (4.76 to 5.29)
- Health care charges: $58,088 vs $31,819, p<0.001

Two-year standardized all-cause hospitalizations cumulative per patient charges ($) with and without complicated lymphedema.

Impact of LE on work and career after breast cancer

<table>
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<th>Breast cancer impact</th>
<th>Yes</th>
<th>No</th>
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<tr>
<td>BREAST CANCER (BC) (106)</td>
<td>51%</td>
<td>49%</td>
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<tr>
<td>BC + LYMPHOEDEMA (109)</td>
<td>63%</td>
<td>37%</td>
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<tr>
<th>Lymphedema impact</th>
<th>Yes</th>
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<tr>
<td>BC + LYMPHOEDEMA (103)</td>
<td>42%</td>
<td>58%</td>
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<th>Severity impact</th>
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<td>SUB-CLINICAL (9)</td>
<td>22%</td>
<td>78%</td>
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<td>MILD (53)</td>
<td>32%</td>
<td>68%</td>
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<td>MODERATE (37)</td>
<td>57%</td>
<td>43%</td>
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<tr>
<td>SEVERE (4)</td>
<td>75%</td>
<td>25%</td>
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- Annual number of days off work for subclinical/mild vs moderate/severe LE: 1.4 vs 8.1 ($p=0.003$)
OVERVIEW OF LYMPHEDEMA ISSUE

• Major morbidity of breast cancer treatment
• Impacts quality of life and survivorship
• Often life long chronic therapy
• Many patients poorly controlled- infectious complications and secondary malignancy
• Risk factors; number nodes removed, BMI>30 radiation, advanced age, limited ROM, taxol
• Incidence 40% high risk group
Is lymph node removal important?

- Overall survival-NO
- Disease free survival: loco-regional control
- Prognosis TNM staging
- Guide for systemic treatment-LESS SO
- Complications: lymphedema, chronic pain, shoulder mobility, nerve injury
Rationale for Cancer Staging

CLINICAL CARE

• Define extent and prognosis of cancer
• Guide appropriate treatment
• Basis for guidelines (NCCN and others)

COMMUNICATION ABOUT PATIENT GROUPS

• Population impact of cancer; changes over time
• Group similar cases for clinical trials
Anatomic stage is a key predictor of cancer outcome; 10 year data NCDB (cancer vol 83,1988)
ANATOMIC STAGE

CLINICAL

PATHOLOGICAL

TNM

Still can used when biomarkers and genomic scores are not available

PROGNOSTIC STAGE (PREFERRED)

• BASED ON PATIENTS TREATED WITH ENDOCRINE AND OR SYSTEMIC CHEMOTHERAPY

• TNM

• BIOMARKERS - ER, PR, HER2

• TUMOR GRADE

• GENOMIC SCORE – ONCOTYPE DX
# AJCC 8th Edition - NODE POSITIVE - HR+

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**NOTE:** IMPACT OF GRADE AND HER 2 NEU on Prognostic Stage T3N2 Grade 3 TP= 1B
Sentinel (Primary) Lymph Node Concept
-Breast Cancer-

Cancer cells must travel here first
SENTINEL NODE VS ALND
LYMPH NODE METASTASES; “INDICATORS NOT GOVERNORS OF SURVIVAL” Arch Surg 1984

“Biology is King; selection of cases is Queen, and the technical details of surgical procedures are princes and princesses of the realm who frequently try to overthrow the powerful forces of the King and Queen, usually to no long-term avail, although with some temporary apparent victories.” 1997
DE-ESCALATION OF AXILLARY SURGERY

No axillary surgery
SOUND

SLN biopsy
NSABP B-32
ALMANAC

SLN biopsy
after NACT
ACOSOG Z1071
SLN biopsy
(macrometastases)
Z0011, AMAROS, POSNOC
SLN biopsy (micrometastases/ITCs)
IBCSG 25-01, AATRM

No node

NODE NEGATIVE

NODE POSITIVE

Axillary sampling (targeted)

Axillary sampling (blind)

Axillary lymph node dissection (level 2)

Axillary lymph node dissection (level 3)
Sentinel Node Biopsy; Major Improvement!

- Replaces ALND for pts with healthy sent node
- Marked reduction BCRL(5-7%)
- ACOSOG Z11 study: not necessary to do ALND if limited cancer involvement of sent node when pts have lumpectomy surgery since will receive radiation and systemic therapy. 27% of patients have additional lymph nodes with cancer that were not removed and no difference in survival
- NOT yet proven to avoid ALND in patients having mastectomy-since the number of lymph nodes involved with cancer determine the benefit of post-mastectomy radiation
Overall survival
86.3% (SN) vs 83.6% (ALND)

Disease-free survival
80.2% (SN) vs 78.2% (ALND)
Axillary Surgery Options

• SO PATIENTS MUST UNDERSTAND THAT IF THEY CHOOSE MASTECTOMY OVER LUMPECTOMY THEY ARE INCREASING THE LIKELIHOOD THAT THEY WILL UNDERGO AN ALND WITH AN INCREASED RISK OF DEVELOPING LYMPHEDEMA

• Very relevant point of discussion since mastectomy rates have been increasing among patient who are eligible for breast conservation surgery(lumpectomy)
Radiotherapy or surgery of the axilla after a positive sentinel node in breast cancer patients: 10-year results 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

Emiel J Rutgers
The Netherlands Cancer Institute,
Amsterdam

Clinical trial information: NCT00014612
Trial design

Stratification: institution
Adjuvant systemic therapy by choice
Axillary recurrence rate

AxSN+ ITT population

10-year cumulative incidence rate of axillary recurrence:
ALND 0.93% (95%CI: 0.18; 1.68) (7 / 744 patients)
AxRT 1.82% (95%CI: 0.74; 2.94) (11 / 681 patients)

HR: 1.71; 95%CI: 0.67-4.39
P = 0.365

Cumulative incidence analysis considers death as a competing risks. HR and Wald p-value based on Fine & Gray model.
Disease-free survival

AxSN+ ITT population

HR: 1.19; 95% CI: 0.97-1.46
P = 0.105

Events: local recurrence (incl. ipsilateral DCIS), axillary recurrence, distant metastasis, second primary (including contralateral DCIS), death. If multiple events occurred within a 1-month time window, the following prioritization was applied: distant progression, axillary recurrence, local recurrence, second primary, death. HR and Wald p-value based on Cox proportional hazard model.
Distant metastasis free survival

AxSN+ ITT population

Events: distant metastasis, death. HR and Wald p-value based on Cox proportional hazard model.
Overall survival

AxSN+ ITT population

**Overall survival**

HR: 1.17; 95% CI: 0.89-1.52  
P = 0.258

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<th>ALND (N=744)</th>
<th>ART (N=681)</th>
<th>Total (N=1425)</th>
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<tr>
<td>Breast cancer</td>
<td>67 (9.0)</td>
<td>70 (10.3)</td>
<td>137 (9.6)</td>
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<td>Other malignancy</td>
<td>14 (1.9)</td>
<td>22 (3.2)</td>
<td>36 (2.5)</td>
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<td>Other</td>
<td>17 (2.3)</td>
<td>9 (1.3)</td>
<td>26 (1.8)</td>
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<td>6 (0.8)</td>
<td>11 (1.6)</td>
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Number of patients at risk:

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<th>N</th>
<th>Number of patients at risk</th>
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</tr>
<tr>
<td>112</td>
<td>681</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Lymphedema of the arm

Measured: 1, 3 and 5 years after treatment

Items:
1. Clinical observation
2. Measurement
Lymphedema: clinical observation and/or treatment

Years after sentinel node biopsy

- 1 (n = 821):
  - ALND: 39.9%
  - AxRT: 21.7%
  - P < 0.0001

- 3 (n = 758):
  - ALND: 31.0%
  - AxRT: 17.9%
  - P < 0.0001

- 5 (n = 789):
  - ALND: 29.4%
  - AxRT: 14.6%
  - P < 0.0001

P-value from exact Fisher’s test
Conclusion

• Both ALND and AxRT provide excellent and comparable locoregional control in AxSN+ patients after 10 years, and no differences in DFS and OS

• Diagnosis of axillary lymph node recurrence after 5 yrs is a very rare event

• Significantly less lymphedema after AxRT after 5 years
Conclusion

- AxRT can be considered standard treatment for patients with Amaros eligibility criteria
- Too few mastectomy patients for statistical significance but likely applies
- Radiation fields used more extensive than current approach
The concept of axillary reverse mapping (ARM)

- Involves mapping the lymphatic drainage form the upper extremity, determine anatomic variation and ensure preservation

- Reverse mapping – blue dye, radioisotope or ICG
Axillary Reverse Mapping

- ARM, preserves upper extremity lymphatics
- Avoid inadvertent injury to arm related nodes

Courtesy Klimberg
IF SENTINEL NODE (Isotope) is the ARM NODE (Blue) - about 5%, can resect and reconstruct lymphatics.
E V O L U T I O N  O F  L Y M P H A

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, MD¹, Fatih Balci, MD¹,⁵, 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

2015 – Feldman, Bansil, et. al. report Columbia’s experience with LYMPHA in the Annals of Surgical Oncology.²⁵
LYMPHA Procedure

- Average diameter of anastomosed vessels was 1-2 mm. Average 1.5 lymphatics
- LYMPHA added about 45 minutes of OR time.
- No LVA-related complications.
FIRST COLUMBIA
LYMPHA
PATIENT:
74yo Woman (Nun)
Stage 2B Left
Invasive Lobular
Carcinoma. Left
Modified Radical
Mastectomy with
Implant: Feb 2013
Severe arthritis-
ambulates with
walker. Major
concern mobility
issues if
developed
lymphedema. Arm
measurements
and 18 month f/u
lymphoscintigram
normal
Sequence of treatment decision

• Essentially all patients with breast cancer require local therapy (surgery - lumpectomy or mastectomy), axillary nodal evaluation and possible radiation

• Essentially all patients with invasive breast cancer require systemic therapy with antiestrogen medicine and/or chemotherapy to treat cancer cells that may be spread to organs outside the breast

• KEY QUESTION WHICH GOES FIRST??
Based on the subtype of the cancer, size of tumor and lymph node involvement, many patients benefit from systemic therapy prior to surgery (neoadjuvant) for the following reasons:

a. Tumor gets smaller or disappears (complete response) so can remove less breast tissue—more normal breast appearance

b. Cancer containing axillary lymph nodes can become cancer free allowing avoidance of ALND

c. Can assess the effectiveness of the medical treatment
Complete pathological response by subtype after neoadjuvant chemotherapy

<table>
<thead>
<tr>
<th>References</th>
<th>No. of Patients</th>
<th>SLNB Success Rate (%)</th>
<th>Axillary pCR (%)</th>
<th>Molecular Subtype (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mamtami et al 13</td>
<td>195</td>
<td>98</td>
<td>49</td>
<td>21 70 97 47</td>
</tr>
<tr>
<td>Park et al 14</td>
<td>178</td>
<td>95</td>
<td>41</td>
<td>24 52 52 59</td>
</tr>
<tr>
<td>Dominici et al 15</td>
<td>109</td>
<td>—</td>
<td>—</td>
<td>— 67 79 —</td>
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<tr>
<td>Boughey et al 16</td>
<td>689</td>
<td>93</td>
<td>40</td>
<td>— — — —</td>
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<tr>
<td>Yagata et al 17</td>
<td>95</td>
<td>85</td>
<td>33</td>
<td>— — — —</td>
</tr>
<tr>
<td>Newman et al 18</td>
<td>54</td>
<td>98</td>
<td>32</td>
<td>— — — —</td>
</tr>
<tr>
<td>McVeigh et al 19</td>
<td>78</td>
<td>—</td>
<td>37</td>
<td>— — — —</td>
</tr>
<tr>
<td>Total [n/N (%)]</td>
<td>—</td>
<td>1067/1144 (93)</td>
<td>497/1236 (40)</td>
<td>33/148 (22)</td>
</tr>
</tbody>
</table>

pCR indicates pathologic complete response; ER; estrogen receptor; HER2, human epidermal growth factor receptor 2; SLNB, sentinel lymph node biopsy.
Current approach lymphedema prevention:

- Less axillary surgery - sentinel node bx, preop chemotherapy for node + patients
- No sentinel node bx if will not effect systemic Rx, SSO choosing wisely - pts > age 70
- Preserve arm nodes with Axillary Reverse mapping technique
- LYMPHA procedure if extensive residual disease requiring complete axillary dissection
- Monitor for pre-clinical volume increase with bioimpedence spectroscopy (L-Dex)
- Patient education and awareness key
- Early physical therapy
- Multidisciplinary team to evaluate patients refractory to conservative management - LVA, LNT, Liposuction
POSNOC TRIAL-opened 7/2014

• POSITIVE SENTINEL NODE-ADJUVANT THERAPY ALONE VS ADJUVANT THERAPY PLUS AXILLARY CLEARANCE OR AXILLARY RADIATION

• PATIENT HAVING BREAST CONSERVATION WITH 2 OR LESS MACROMETS IN SENTINEL NODE

• ELUCIDATE VALUE OF AXILLARY SPECIFIC TREATMENT IN SETTING OF SYSTEMIC THERAPY
Surgical treatment after neoadjuvant systemic therapy in young women with breast cancer: Results from a prospective cohort study

Hee Jeong Kim¹,², Laura Dominici¹,³, Shoshana Rosenberg¹, Linda Ma Pak¹,³, Phillip D. Poorvu¹, Kathryn Ruddy⁴, Rulla Tamimi³, Lidia Schapira⁵, Steven Come⁶, Jeffrey Peppercorn⁷, Virginia Borges⁸, Ellen Warner⁹, Hilde Vardeh⁶, Laura Collins⁶, Rachel Gaither¹, Tari King¹,³, Ann H. Partridge¹

¹Dana-Farber Cancer Institute, Boston, MA; ²Asan Medical Center, Seoul, South Korea; ³Brigham and Women’s Hospital, Boston, MA; ⁴Mayo Clinic, Rochester, MN; ⁵Stanford University, Palo Alto, CA; ⁶Beth Israel Deaconess Medical Center, Boston, MA; ⁷Massachusetts General Hospital, Boston, MA; ⁸University of Colorado Cancer Center, Aurora, CO; ⁹Sunnybrook Health Science center, Toronto, ONT
Background

- Randomized controlled trials (RCTs) have demonstrated that eligibility for breast conserving surgery (BCS) can be increased after neoadjuvant chemotherapy (NAC).

- Despite eligibility for BCS, analyses from large pre-operative RCTs have revealed many women are undergoing mastectomy:
  - 76% of BCS eligible patients had mastectomy in CALGB 40601 (HER2+).
  - 69% of BCS eligible patients had mastectomy in CALGB 40603 (TNBC).
Background

• Young women are more likely to present with large tumors and may benefit from a neoadjuvant systemic approach

• Recent data suggest that response rates, including pathologic complete response (pCR), are higher in women <40 years than in older women

• Little is known about how response to NAC influences surgical decision making in young women
Objectives

• To describe the use of and response to NAC among young women with breast cancer

• To evaluate choice of surgical procedure considering:
  - Before- and after- NAC eligibility for BCS
  - Clinical and pathological response to NAC

• To evaluate reasons for not undergoing BCS when BCS eligible after NAC
Methods

• The Young Women`s Breast Cancer Study (YWS)
  - Multicenter prospective cohort
  - Women age ≤40 at diagnosis of breast cancer identified through pathology record review
  - 12 participating hospitals (academic and community)
  - 1302 women enrolled from October 2006 to June 2016

• The study was established to explore biological, medical and psychosocial issues in young breast cancer patients
Methods

• BCS eligibility before and after NAC and clinical response to NAC were abstracted from the medical records by two trained surgeons and reviewed by a third investigator in instances of discrepancy.
Initial surgical procedure among BCS-eligible patients after NAC (N=133)

- 41% of BCS-eligible patients after NAC chose mastectomy
- The proportion of patients with BCS as first surgical procedure was not influenced by response to NAC
  - 42% of BCS-eligible patients with clinical CR chose mastectomy and 35% had a pCR
Reasons for choosing mastectomy in BCS-eligible patients (N=55)

- The most common documented reason that BCS-eligible patients chose mastectomy was patient preference (53%)

- 40% chose mastectomy because of carrying a BRCA 1 or 2, or p53 mutation or having a strong family history

- 75% who chose mastectomy underwent bilateral mastectomy

- Among BCS-eligible patients with cCR and/or ultimately pCR who chose mastectomy, these reasons were similar
Conclusions and Implications

• NAC increased the proportion of young women with breast cancer who were eligible for BCS, yet 40% of eligible patients chose mastectomy regardless of response to NAC in a large multicenter cohort
  - Personal preference (without known high risk predisposition) was most common reason

• While rates of NAC have increased over time and response rates have improved, rate of BCS as first surgical procedure is not increasing

• Surgical decisions among young women with breast cancer appear driven by factors beyond the extent of disease and response to NAC

• Focused efforts to optimize surgical decision-making are needed
Local therapy and quality of life outcomes in young women with breast cancer

Laura Dominici, Jiani Hu, Tari King, Kathryn J. Ruddy, Rulla M. Tamimi, Jeffrey Peppercorn, Lidia Schapira, Virginia F. Borges, Steven E. Come, Ellen Warner, Ann Partridge, Shoshana Rosenberg
Background

- More than 13,000 women ≤40 years of age are diagnosed with breast cancer each year
  - ~7% of new breast cancers diagnosed in the United States

- Despite equivalent local regional control and survival with breast conservation and mastectomy, rates of (bilateral) mastectomy are increasing in young women
  - 3.6% in 1998 → 33% in 2011
Background

• Previous studies of women of all ages treated for breast cancer found no clinically meaningful differences in QOL related to surgical procedure
  • Some QOL domains improved after CPM

• Young women are at increased risk for poorer psychosocial outcomes following a breast cancer diagnosis and in survivorship

• Little is known about the impact of surgery, particularly in the era of increasing bilateral mastectomy, on QOL in young survivors
Objectives

• Using a multicenter prospective cohort of young women with breast cancer, we sought to:
  
  • Evaluate differences in QOL among women who had breast conserving surgery (BCS), unilateral mastectomy and bilateral mastectomy
  
  • Identify demographic and treatment-related factors that impact QOL
Methods

• This analysis used a cross-sectional study design

• BREAST-Q was administered to all eligible YWS participants in active follow-up in 2016-2017, either as a stand-alone survey or as part of their 10-year follow-up

• Median time from diagnosis to BREAST-Q completion: 5.8 (range: 1.9-10.4) years

• Demographics and treatment information were obtained from serial surveys and chart review
BREAST-Q

- Six domains:
  - Satisfaction with breasts
  - Psychosocial well-being
  - Physical well-being
  - Sexual well-being
  - Overall outcome
  - Process of care
BREAST-Q Mean Scores

Higher score = Better QOL

<table>
<thead>
<tr>
<th>Satisfaction with breasts</th>
<th>Physical well-being</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bilateral mastectomy</td>
<td>60.4</td>
</tr>
<tr>
<td>Unilateral mastectomy</td>
<td>59.3</td>
</tr>
<tr>
<td>Breast conserving surgery</td>
<td>65.5</td>
</tr>
<tr>
<td>Bilateral mastectomy</td>
<td>78.7</td>
</tr>
<tr>
<td>Unilateral mastectomy</td>
<td>78.9</td>
</tr>
<tr>
<td>Breast conserving surgery</td>
<td>78.9</td>
</tr>
</tbody>
</table>

p = 0.008

p = 0.8

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BREAST-Q Mean Scores

Higher score = Better QOL

psychosocial well-being

68.4
70.6
75.9

60.4
78.7
59.3
78.9
65.5
78.9

p<0.001
p<0.001

Bilateral mastectomy
Unilateral mastectomy
Breast conserving surgery

Satisfaction with breasts
Physical well-being
Limitations

• One time survey of women enrolled in an observational cohort study
  • Preoperative QOL likely drives surgical choices

• Findings may have limited generalizability to more diverse populations
  • Majority of participants are white and of a high socio-economic status
Conclusions

• Local therapy decisions are associated with a persistent impact on QOL in young breast cancer survivors

• Compared to BCS, unilateral or bilateral mastectomy is associated with significant decreases in QOL domains for:
  • Satisfaction with breasts
  • Psychosocial well-being
  • Sexual well-being
Abs GS03-01. Randomized trial of low dose tamoxifen to prevent recurrence of breast intraepithelial neoplasia. Study TAM01


EudraCT Number 2007-007740-10
ClinicalTrials.gov NCT01357772
Women aged <75 yrs with IEN (ADH or LCIS or ER+ve or unk DCIS) R

Tamoxifen 5 mg/day

Placebo

Primary endpoint: Incidence of invasive breast cancer or DCIS

- 500 participants enrolled from 14 centers in Italy
- Visit and QoL every 6 months, Mx every year
- Median follow up = 5.1 years (IQR 3.9-6.3)
- Primary events: 42
Effect of 10 mg on alternate days on ipsilateral recurrence in high risk DCIS>50 yrs

- No tamoxifen (n=420)
- Low dose tamoxifen (n=208)

Based on patient preference

Annual rate (%): 4.2 (3.5-4.9) vs 3.1 (2.6-3.8)

HR=0.43 (0.26-0.72), P=0.001

Guerrieri Gonzaga et al. *Int J Cancer* 139:2127-34, 2016
Log-rank p=0.024

All breast events, 28 vs 14
HR=0.48, 95%CI: 0.26-0.92
Rate: 23.9 vs 11.6/1000 py

Log-rank p=0.018

Contralateral BrCa, 12 vs 3
HR=0.24, 95%CI: 0.07-0.87
## Serious adverse events

<table>
<thead>
<tr>
<th></th>
<th>Tamoxifen</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Endometrial cancer</strong></td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td><strong>DVT or PE</strong></td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td><strong>Other neoplasms</strong></td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td><strong>Coronary heart disease</strong></td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td><strong>Other</strong></td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td><strong>Death</strong></td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>12</td>
<td>16</td>
</tr>
</tbody>
</table>

20 mg/d, expected Endometrial Cancer: 2.7; DVT+PE: 2.4

1. NSABP-P1 trial (Fisher et al. *JNCI* 90:1371-88, 1998)
Daily hot flashes frequency

Daily hot flashes score
Frequency by Intensity

Sloan, Loprinzi et al. JCO 19:4280, 2001

San Antonio Breast Cancer Symposium®, December 4-8, 2018

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Vaginal dryness or pain at intercourse

P = 0.57

Musculoskeletal pain/Arthralgia

P = 0.84

BCPSC, Stanton et al. JNCI 97:448-456, 2005
Log-rank p=0.39

Tam=64.8%, Pla=60.7%

*Persistent use >2.5 years

Log-rank p=0.39

Number at risk

Placebo 247 (29) 218 (23) 195 (15) 180 (18) 162 (12) 149 (0) 109
Tamoxifen 253 (25) 228 (24) 204 (22) 182 (9) 173 (9) 163 (0) 114
Conclusions

• Tamoxifen 5 mg/day for 3 years halves the recurrence of breast intraepithelial neoplasia in line with 20 mg/day (HR=0.58, 95% CI, 0.42-0.81)\(^1\)

• Low dose Tamoxifen decreased contralateral breast cancer by 75%, suggesting a strong preventive potential

• Rate of endometrial cancer and DVT/PE on 5 mg (0.85/1000 py) not different from placebo and 2.5 times lower than 20 mg\(^2\)

• Menopausal symptoms not worsened except for a borderline effect on hot flashes

• Our results have external validity and are generalizable

• Tamoxifen 10 mg every other day is applicable in clinical practice from tomorrow!

\(^1\)Allred et al. NSABP B-24 trial. JCO 30:1268-73, 2012

\(^2\)Fisher et al. NSABP-P1 trial. JNCI 90:1371-88, 1998
Extended Aromatase Inhibitor treatment following 5 or more years of endocrine therapy: a meta-analysis of 22,192 women in 11 randomised trials

Early Breast Cancer Trialists’ Collaborative Group
Extended AI treatment after 5+ years of prior endocrine therapy: methods

Meta-analysis of individual patient data on postmenopausal women with ER-positive (99%) or ER-unknown (1%) tumours in trials of:

Any third-generation AI (exemestane, anastrozole, letrozole) vs no further adjuvant therapy following:

- a) ≈ 5 years of tamoxifen alone (n=7,500)
- b) ≈ 5-10 years of tamoxifen then AI (n=12,600)
- c) ≈ 5 years of AI alone (n=4,800)

Intellectual property of the author/presenter. Contact them at richard.gray@ndph.ox.ac.uk for permission to reprint and/or distribute
(a) Trials of AI after ≈5 years of Tamoxifen alone

Any recurrence (distant, local or new primary)

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>AI</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-y gain</td>
<td>10.7%</td>
<td>7.1%</td>
</tr>
<tr>
<td>RR</td>
<td>0.67 (0.57–0.79)</td>
<td>0.67 (0.57–0.79)</td>
</tr>
</tbody>
</table>

Distant Recurrence

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>AI</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-y gain</td>
<td>6.7%</td>
<td>5.2%</td>
</tr>
<tr>
<td>RR</td>
<td>0.77 (0.63–0.93)</td>
<td>0.77 (0.63–0.93)</td>
</tr>
</tbody>
</table>

Breast cancer mortality

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>AI</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-y gain</td>
<td>3.6%</td>
<td>2.7%</td>
</tr>
<tr>
<td>RR</td>
<td>0.77 (0.59–1.00)</td>
<td>0.77 (0.59–1.00)</td>
</tr>
</tbody>
</table>

Intellectual property of the author/presenter. Contact them at richard.gray@ndph.ox.ac.uk for permission to reprint and/or distribute.
(b) Trials of Extended AI following 5-10 years of Tamoxifen then AI

Any recurrence

RR 0.82 (0.73–0.93)
Logrank 2p = 0.002
5-y gain 2.1% (CI 1.0 – 3.2)

Distant Recurrence

RR 0.92 (0.80–1.07)
Logrank 2p = 0.29
5-y gain 1.0% (CI 0.0 – 1.9)

Breast cancer mortality

RR 0.93 (0.77–1.12)
Logrank 2p = 0.45
5-y gain 0.2% (CI -0.5 – 0.8)

11387 women

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(c) Trials of Extended AI following 5 years of AI alone

Any recurrence

Distant Recurrence

Breast cancer mortality

3322 women

RR 0.76 (0.61–0.95)
Logrank 2p = 0.02
5-y gain 1.2% (CI 0.6–3.1)

3322 women

RR 0.78 (0.59–1.04)
Logrank 2p = 0.09
5-y gain 0.3% (CI 1.2–1.7)

3322 women

RR 0.99 (0.68–1.44)
Logrank 2p = 0.97
5-y loss 0.2% (CI 0.9–1.3)

Intellectual property of the author/presenter. Contact them at richard.gray@ndph.ox.ac.uk for permission to reprint and/or distribute.
### Effect on recurrence by prior endocrine therapy

<table>
<thead>
<tr>
<th>Prior therapy</th>
<th>Allocated AI</th>
<th>Allocated control</th>
<th>Logrank O-E</th>
<th>Variance of O-E</th>
<th>Ratio of annual event rates</th>
</tr>
</thead>
<tbody>
<tr>
<td>(a) Tamoxifen alone</td>
<td>272/3718 (7.3%)</td>
<td>383/3765 (10.2%)</td>
<td>-61.7</td>
<td>155.5</td>
<td>0.67 (0.55–0.83)</td>
</tr>
<tr>
<td>(b) Tamoxifen then AI</td>
<td>510/5664 (9.0%)</td>
<td>606/5723 (10.6%)</td>
<td>-51.6</td>
<td>267.7</td>
<td>0.82 (0.70–0.97)</td>
</tr>
<tr>
<td>(c) AI alone</td>
<td>134/1661 (8.1%)</td>
<td>174/1661 (10.5%)</td>
<td>-20.4</td>
<td>74.4</td>
<td>0.76 (0.56–1.02)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>916/11043 (8.3%)</td>
<td>1163/11149 (10.4%)</td>
<td>-133.7</td>
<td>497.6</td>
<td>0.764 (0.700–0.835)</td>
</tr>
</tbody>
</table>

- 99% or ↔ 95% confidence intervals

Heterogeneity between 3 categories: $\chi^2 = 4.1; p > 0.1; \text{NS}$

Treatment effect $2p < 0.00001$
Effect on recurrence in years 0-1 after treatment divergence by prior endocrine therapy

<table>
<thead>
<tr>
<th>Prior therapy</th>
<th>Events/woman–years</th>
<th>Al events</th>
<th>Ratio of annual event rates</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Allocated</td>
<td>Allocated</td>
<td>Logrank</td>
</tr>
<tr>
<td>(a) Tamoxifen alone</td>
<td>97/7174 (1.4%/y)</td>
<td>156/7181 (2.2%/y)</td>
<td>-28.4</td>
</tr>
<tr>
<td>(b) Tamoxifen then AI</td>
<td>177/10863 (1.6%/y)</td>
<td>173/10991 (1.6%/y)</td>
<td>0.5</td>
</tr>
<tr>
<td>(c) AI alone</td>
<td>48/3201 (1.5%/y)</td>
<td>48/3202 (1.5%/y)</td>
<td>0.0</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>322/21238 (1.5%/y)</strong></td>
<td><strong>377/21374 (1.8%/y)</strong></td>
<td><strong>-27.8</strong></td>
</tr>
</tbody>
</table>

- 99% or ↔ 95% confidence intervals

Heterogeneity between 3 categories: $\chi^2 = 8.7; p = 0.01$

Treatment effect $2p = 0.03$
Effect on recurrence in years 2-4 after treatment divergence by prior endocrine therapy

<table>
<thead>
<tr>
<th>Prior therapy</th>
<th>Events/woman-years</th>
<th>Ratio of annual event rates</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Al</td>
<td>Control</td>
</tr>
<tr>
<td>(a) Tamoxifen alone</td>
<td>125/7995 (1.6%/y)</td>
<td>177/7670 (2.3%/y)</td>
</tr>
<tr>
<td>(b) Tamoxifen then AI</td>
<td>196/13767 (1.4%/y)</td>
<td>296/13756 (2.2%)</td>
</tr>
<tr>
<td>(c) AI alone</td>
<td>57/4323 (1.3%/y)</td>
<td>75/4326 (1.7%)</td>
</tr>
<tr>
<td>Total</td>
<td>378/25985 (1.5%/y)</td>
<td>548/25752 (2.1%)</td>
</tr>
</tbody>
</table>

99% or <> 95% confidence intervals

Heterogeneity between 3 categories: $\chi^2 = 0.6; p > 0.1; NS$

Treatment effect $2p < 0.00001$
Effect on recurrence in **years 5+** after treatment divergence by prior endocrine therapy

<table>
<thead>
<tr>
<th>Prior therapy</th>
<th>Events/woman-years</th>
<th>Al events</th>
<th>Ratio of annual event rates</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Allocated</td>
<td>Allocated</td>
<td>Ratio</td>
</tr>
<tr>
<td></td>
<td>Al</td>
<td>control</td>
<td>O–E</td>
</tr>
<tr>
<td>(a) Tamoxifen alone</td>
<td>50/2340 (2.1%/y)</td>
<td>50/2347</td>
<td>-3.0</td>
</tr>
<tr>
<td>(b) Tamoxifen then Al</td>
<td>137/7255 (1.9%/y)</td>
<td>137/7239</td>
<td>-0.2</td>
</tr>
<tr>
<td>(c) Al alone</td>
<td>29/2294 (1.3%/y)</td>
<td>51/2293</td>
<td>-11.3</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>216/11889 (1.8%/y)</td>
<td>238/11879</td>
<td>-14.6</td>
</tr>
</tbody>
</table>

- 99% or ↔ 95% confidence intervals

Heterogeneity between 3 categories: $\chi^2 = 5.0; p = 0.08$

<table>
<thead>
<tr>
<th>Al better</th>
<th>Al worse</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment effect 2p &gt; 0.1; NS</td>
<td></td>
</tr>
</tbody>
</table>
Summary: effect of extended AI therapy after 5-10 yrs on recurrence differs by type of prior endocrine therapy

Prior tamoxifen (a)

RR 0.67 (0.57–0.79)
Logrank 2p < 0.00001
5-y gain 3.6% (CI 2.1 – 5.1)

Prior AI (b + c)

RR 0.81 (0.73–0.90)
Logrank 2p = 0.00010
5-y gain 1.9% (CI 1.0 – 2.8)
Combined results from all trials of Extended AI following 5-10 years of any prior endocrine therapy

Any recurrence

- 22192 women
  - RR 0.76 (0.70–0.83)
  - Logrank 2p < 0.00001
  - 5-y gain 2.5% (CI 1.7 – 3.3)

Distant Recurrence

- 22192 women
  - RR 0.85 (0.77–0.95)
  - Logrank 2p = 0.004
  - 5-y gain 1.1% (CI 0.4 – 1.7)

Breast cancer mortality

- 22192 women
  - RR 0.89 (0.77–1.02)
  - Logrank 2p = 0.09
  - 5-y gain 0.3% (CI –0.2 – 0.8)

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## Recurrence by site – combined results from all trials

<table>
<thead>
<tr>
<th>Category</th>
<th>Events/Women Allocated</th>
<th>Allocated control</th>
<th>Logrank Variance</th>
<th>O–E</th>
<th>Ratio of annual event rates</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>AI</td>
<td></td>
<td></td>
<td></td>
<td>AI : Control (Ratio (CI))</td>
</tr>
<tr>
<td>Distant</td>
<td>582/11043 (5.3%)</td>
<td>671/11149 (6.0%)</td>
<td>-52.6</td>
<td>300.9</td>
<td>0.84 (0.72 – 0.97)</td>
</tr>
<tr>
<td>Isolated local</td>
<td>171/11043 (1.5%)</td>
<td>228/11149 (2.0%)</td>
<td>-29.4</td>
<td>97.1</td>
<td>0.74 (0.57 – 0.96)</td>
</tr>
<tr>
<td>Contralateral</td>
<td>163/11043 (1.5%)</td>
<td>264/11149 (2.4%)</td>
<td>-51.8</td>
<td>104.1</td>
<td>0.61 (0.47 – 0.78)</td>
</tr>
<tr>
<td>Any recurrence</td>
<td>916/11043 (8.3%)</td>
<td>1163/11149 (10.4%)</td>
<td>-133.7</td>
<td>497.6</td>
<td>0.764 (0.700 – 0.835)</td>
</tr>
</tbody>
</table>

- 99% or ↔ 95% confidence intervals

Treatment effect 2p < 0.00001
Recurrence by nodal status – all trials

Node-negative

10620 women

RR 0.82 (0.71–0.95)
Logrank 2p = 0.009
5-y gain 1.1% (CI 0.1–2.0)

Control 6.2%
5-y gain 1.1%

N 1-3

6919 women

RR 0.74 (0.64–0.85)
Logrank 2p = 0.00003
5-y gain 3.8% (CI 2.2–5.4)

Control 12.5%
5-y gain 8.7%

N 4+

1621 women

RR 0.71 (0.56–0.89)
Logrank 2p = 0.003
5-y gain 7.7% (CI 3.9–11.6)

Control 19.9%
5-y gain 12.2%
Bone fracture and death without recurrence

14026 women

Bone fracture

RR 1.24 (1.10–1.39)
Logrank 2p = 0.0003
5–y loss 1.8% (CI 0.8 – 2.8)

Death without recurrence

22192 women

RR 1.08 (0.95–1.23)
Logrank 2p = 0.24
5–y loss 0.4% (CI –0.1 – 1.0)

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Conclusions: Benefits and risks of AI after 5+ years of prior endocrine therapy

• ≈35% proportional reduction in recurrence for women who have received ≈5 years of tamoxifen
• ≈ 20% proportional reduction in risk of recurrence for women receiving AI (with or without prior tamoxifen)
• Recurrence reductions apparent in first two years following prior tamoxifen, but not until the third year following prior AI
• Absolute benefits increase the more nodes were involved
• Risk of bone fracture increased by ≈25%
KATHERINE Study Design

- cT1-4/N0-3/M0 at presentation (cT1a-b/N0 excluded)
- Centrally confirmed HER2-positive breast cancer
- Neoadjuvant therapy must have consisted of
  - Minimum of 6 cycles of chemotherapy
    - Minimum of 9 weeks of taxane
    - Anthracyclines and alkylating agents allowed
  - Minimum of 9 weeks of trastuzumab
    - Second HER2-targeted agent allowed
- Residual invasive tumor in breast or axillary nodes
- Randomization within 12 weeks of surgery

Stratification factors:
- Clinical presentation: Inoperable (stage cT4 or cN2–3) vs operable (stages cT1-3N0-1)
- Hormone receptor: ER or PR positive vs ER negative and PR negative/unknown
- Preoperative therapy: Trastuzumab vs trastuzumab plus other HER2-targeted therapy
- Pathological nodal status after neoadjuvant therapy: Positive vs negative/not done

T-DM1
3.6 mg/kg IV Q3W
14 cycles

Trastuzumab
6 mg/kg IV Q3W
14 cycles

Radiation and endocrine therapy per protocol and local guidelines

Geyer CE, et al. SABCS 2018
Invasive Disease-Free Survival

Trastuzumab T-DM1

Trastuzumab (n=743) T-DM1 (n=743)

IDFS Events, no. (%) 165 (22.2) 91 (12.2)

Unstratified HR=0.50 (95% CI, 0.39 – 0.64)

P<0.0001

3-year IDFS 77.0% 88.3%

Geyer CE, et al. SABCS 2018
First IDFS Events

<table>
<thead>
<tr>
<th>Category</th>
<th>Trastuzumab</th>
<th>T-DM1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total patients with IDFS event</td>
<td>22.2</td>
<td>12.2</td>
</tr>
<tr>
<td>Distant recurrence</td>
<td>15.9</td>
<td>11.6</td>
</tr>
<tr>
<td>Locoregional recurrence</td>
<td>10.5</td>
<td>4.6</td>
</tr>
<tr>
<td>Contralateral breast cancer</td>
<td>4.6</td>
<td>1.1</td>
</tr>
<tr>
<td>Death without prior event</td>
<td>1.3</td>
<td>0.4</td>
</tr>
</tbody>
</table>

Patients who experience additional IDFS event(s) within 61 days of their first IDFS event are reported in the category according to the following hierarchy:


*CNS metastases as component of distant recurrence (isolated or with other sites).*

Geyer CE, et al. SABCS 2018
Distant Recurrence

No. at Risk

<table>
<thead>
<tr>
<th></th>
<th>Trastuzumab</th>
<th>T-DM1</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>743</td>
<td>743</td>
</tr>
<tr>
<td>6 months</td>
<td>679</td>
<td>707</td>
</tr>
<tr>
<td>12 months</td>
<td>643</td>
<td>682</td>
</tr>
<tr>
<td>18 months</td>
<td>609</td>
<td>661</td>
</tr>
<tr>
<td>24 months</td>
<td>577</td>
<td>636</td>
</tr>
<tr>
<td>30 months</td>
<td>520</td>
<td>564</td>
</tr>
<tr>
<td>36 months</td>
<td>359</td>
<td>412</td>
</tr>
<tr>
<td>42 months</td>
<td>233</td>
<td>254</td>
</tr>
<tr>
<td>48 months</td>
<td>126</td>
<td>143</td>
</tr>
<tr>
<td>54 months</td>
<td>41</td>
<td>45</td>
</tr>
<tr>
<td>60 months</td>
<td>4</td>
<td>4</td>
</tr>
</tbody>
</table>

Events, no. (%)

- Trastuzumab: 121 (16.3)
- T-DM1: 78 (10.5)

Unstratified HR = 0.60 (95% CI, 0.45–0.79)

3-year event-free rate

- Trastuzumab: 83.0%
- T-DM1: 89.7%

Geyer CE, et al. SABCS 2018
Overall Survival

![Graph showing overall survival rates for Trastuzumab and T-DM1.](image)

- **Trastuzumab (n=743)**
  - Events, no. (%): 56 (7.5)
  - Unstratified HR: 0.70 (95% CI, 0.47–1.05)
  - P = 0.0848

- **T-DM1 (n=743)**
  - Events, no. (%): 42 (5.7)

**Boundary for statistical significance**
- HR < 0.43 or P < 0.000032

**No. at Risk**
- **Trastuzumab**
  - 743
  - 695
  - 677
  - 657
  - 635
  - 608
  - 471
  - 312
  - 175
  - 71
  - 8
- **T-DM1**
  - 743
  - 719
  - 702
  - 693
  - 668
  - 648
  - 508
  - 345
  - 195
  - 76
  - 12

Geyer CE, et al. SABCS 2018
### AEs Leading to Treatment Discontinuation (≥1% Incidence Either Arm)

<table>
<thead>
<tr>
<th>Event</th>
<th>Trastuzumab n=720</th>
<th>T-DM1 n=740</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients discontinuing due to adverse events</td>
<td>15 (2.1%)</td>
<td>133 (18.0%)</td>
</tr>
<tr>
<td>Platelet count decreased</td>
<td>0</td>
<td>31 (4.2%)</td>
</tr>
<tr>
<td>Blood bilirubin increased</td>
<td>0</td>
<td>19 (2.6%)</td>
</tr>
<tr>
<td>Aspartate aminotransferase (AST) increased</td>
<td>0</td>
<td>12 (1.6%)</td>
</tr>
<tr>
<td>Alanine aminotransferase (ALT) increased</td>
<td>0</td>
<td>11 (1.5%)</td>
</tr>
<tr>
<td>Peripheral sensory neuropathy</td>
<td>0</td>
<td>11 (1.5%)</td>
</tr>
<tr>
<td>Ejection fraction decreased</td>
<td>10 (1.4%)</td>
<td>9 (1.2%)</td>
</tr>
</tbody>
</table>

Geyer CE, et al. SABCS 2018
All Grade AEs ≥15% Incidence in Either Arm

Geyer CE, et al. SABCS 2018
KATHERINE Summary and Conclusions

- Adjuvant T-DM1 demonstrated both a statistically significant and clinically meaningful improvement in IDFS compared with trastuzumab
  - Unstratified HR=0.50; 95% CI 0.39–0.64;  P<0.0001
  - 3-year IDFS rate improved from 77.0% to 88.3% (difference=11.3%)

- Benefit of T-DM1 was consistent across all key subgroups including HR status, extent of residual invasive disease, and single or dual HER2-targeted neoadjuvant therapy

- The safety data were consistent with the known manageable toxicities of T-DM1, with expected increases in AEs associated with T-DM1 compared to trastuzumab

- Additional follow-up will be necessary to evaluate the effect of T-DM1 on OS

- The KATHERINE data will likely form the foundation of a new standard of care in this population and increase the use of neoadjuvant therapy in HER2-positive EBC

Geyer CE, et al. SABCS 2018
Traditional whole breast radiation
Breast Conserving Therapy

• BCT = Lumpectomy + whole breast RT
  – Standard of care for early stage Breast Cancer/DCIS
  – RT typically 3- 6 weeks

• Mastectomy or Lumpectomy w/o RT remains common
  – Access to care-COMPLIANCE ISSUES!!
  – Length of treatment
  – Distance to treatment – as distance increases, BCT decreases
    • 82% <10miles
    • 69% 50-75 miles
    • 42% if >100 miles
Partial Breast Irradiation (PBI)

- Larger radiation dose/fraction
- Brachytherapy or external beam
- Complete RT in 0-5 days instead of 6-7 weeks
What is Intraoperative Radiation Therapy? (IORT)

• Technique developed since 1998
• IORT delivers dose of radiation directly to the tumor bed in the operating room
• Single dose is higher than that delivered during conventional radiation therapy, but cumulative amount of radiation is similar to conventional treatment
• Been shown to give results equivalent to weeks of whole breast radiation therapy at 6 years
• Generates and delivers a high dose of low energy (50KeV) x-rays in a precise, spherical distribution pattern around a point source
IntraBeam 50 keV Miniature X-Ray Generator

Diagram showing the components of the IntraBeam 50 keV Miniature X-Ray Generator:
- Internal Radiation Monitor
- Cathode Gun
- Accelerator Section
- Beam Deflector
- Electron Beam
- Gold Target
IORT Procedure in the OR
Intraoperative radiation (IORT)

- IORT delivers a single dose of radiation directly to the tumor bed, given at the time of surgery, greatly shortening treatment compared to the conventional 6 weeks of daily radiation.
- IORT improves patient convenience and quality of life, and same low recurrence at 5 years compared to traditional radiation.
IORT with Intrabeam

• Single procedure (lumpectomy, repair breast defect and sentinel node bx, IORT (ONE AND DONE))
• RT compliance-logistics-travel issues resolved
• Patient centered- high satisfaction
• Robust research platform
• Can allow second chance at breast conservation
IORT

- Targit-A Trial
- Age >45yo
  - Low risk IDC or DCIS
  - Randomized pre-operatively
  - Non-inferiority trial
  - 6 year follow-up
    - LR
      - 1.2% IORT(HIGHER POST PATHOLOGY!!!!)
      - 0.95% WBI
    - Equivalent toxicity
      - Grade 3-4: 3.3% vs 3.9%
NSABP B-39/RTOG 0413 Schema

Patients with Stage 0, I, or II Breast Cancer Resected by Lumpectomy
- Tumor Size ≤ 3.0 cm
- No More Than 3 Histologically Positive Nodes

STRATIFICATION
- Disease Stage (DCIS; Invasive N0; Invasive N1)
- Menopausal Status (pre- and post-)
- Hormone Receptor Status (ER and/or PR+; ER and PR-)
- Intention to Receive Chemotherapy

RANDOMIZED (n = 4,216)

Whole Breast Irradiation after Adjuvant Chemotherapy
- 50 Gy (2.0 Gy/fraction) or 50.4 Gy (1.8 Gy/fraction) to whole breast, followed by optional boost to ≥ 60 Gy

Partial Breast Irradiation prior to Adjuvant Chemotherapy
- For a total of 10 treatments given on 5 days over 5 to 10 days:
  - 34 Gy in 3.4 Gy fractions Interstitial Brachytherapy or Mammosite Balloon Catheter
  - or 38.5 Gy in 3.85 Gy fractions
  - 3D Conformal External Beam
NSABP B-39/RTOG 0413

Ipsilateral Breast Tumor Recurrence (IBTR)

Equivalence Margin for IBTR

Hazard Ratio and 90% CI for IBTR

Cumulative Incidence of IBTR

Cumulative Incidence per 100

- WBI
- PBI

Absolute difference in 10-yr rate of IBTR between PBI and WBI was 0.7%
# IBTR by PBI Method and Location in the Breast

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th># of Pts</th>
<th># of Events</th>
<th>Hazard Ratio (HR)</th>
<th>HR 95% Confidential Interval</th>
<th>10-yr Cum Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>WBI</td>
<td>2,011</td>
<td>67</td>
<td>REF</td>
<td></td>
<td>3.8%</td>
</tr>
<tr>
<td>PBI</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multi-catheter brachytherapy</td>
<td>130</td>
<td>9</td>
<td>2.21</td>
<td>1.10 – 4.46</td>
<td>7.7%</td>
</tr>
<tr>
<td>Single-entry brachytherapy device</td>
<td>358</td>
<td>24</td>
<td>2.15</td>
<td>1.34 – 3.44</td>
<td>7.8%</td>
</tr>
<tr>
<td>3DCRT (external beam)</td>
<td>1,535</td>
<td>55</td>
<td>1.04</td>
<td>0.73 – 1.49</td>
<td>3.7%</td>
</tr>
</tbody>
</table>

This analysis used a per-protocol population, which excluded those who did not receive their randomly assigned treatment.
**NSABP B-39/RTOG 0413**

**Distant Disease-free Interval**

- **HR 1.31 (95% CI 0.91-1.91) P=0.15**
- **TRT**  N  Events  10-yr rate
  - WBI  2109  49  97.1%
  - PBI  2107  65  96.7%

<table>
<thead>
<tr>
<th>Months Since Randomization</th>
<th>% Distant Disease-free</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>12</td>
<td>90.5</td>
</tr>
<tr>
<td>24</td>
<td>80.9</td>
</tr>
<tr>
<td>36</td>
<td>71.7</td>
</tr>
<tr>
<td>48</td>
<td>62.6</td>
</tr>
<tr>
<td>60</td>
<td>53.8</td>
</tr>
<tr>
<td>72</td>
<td>45.1</td>
</tr>
<tr>
<td>84</td>
<td>36.5</td>
</tr>
<tr>
<td>96</td>
<td>28.1</td>
</tr>
<tr>
<td>108</td>
<td>19.6</td>
</tr>
<tr>
<td>120</td>
<td>11.1</td>
</tr>
</tbody>
</table>

*Based on Cox proportional hazards models stratified on disease stage, menopausal status, hormone receptor status, and intention to receive chemotherapy.

**Overall Survival**

- **HR 1.10 (95% CI 0.90-1.35) P=0.35**
- **TRT**  N  Events  10-yr rate
  - WBI  2109  174  91.3%
  - PBI  2107  199  90.6%

<table>
<thead>
<tr>
<th>Months Since Randomization</th>
<th>% Surviving</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>12</td>
<td>90.5</td>
</tr>
<tr>
<td>24</td>
<td>80.9</td>
</tr>
<tr>
<td>36</td>
<td>71.7</td>
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<tr>
<td>108</td>
<td>19.6</td>
</tr>
<tr>
<td>120</td>
<td>11.1</td>
</tr>
</tbody>
</table>

*Based on Cox proportional hazards models stratified on disease stage, menopausal status, hormone receptor status, and intention to receive chemotherapy.
Adverse Events

Toxicity:
- Grade 3 toxicity was 9.6% PBI v 7.1% WBI
- Grade 4-5 toxicity was 0.5% PBI v 0.3% WBI

Second Cancers:

<table>
<thead>
<tr>
<th>First Site of Second Primary Cancer</th>
<th>WBI</th>
<th>PBI</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Contralateral breast</td>
<td>72</td>
<td>63</td>
<td>135</td>
</tr>
<tr>
<td>All other sites</td>
<td>128</td>
<td>129</td>
<td>257</td>
</tr>
<tr>
<td>Total</td>
<td>200</td>
<td>192</td>
<td>392</td>
</tr>
</tbody>
</table>

No statistically significant differences
Conclusions

• Intent-to-treat and as-treated analyses could not refute the hypothesis that PBI is inferior and cannot declare that WBI and PBI are equivalent in controlling local in-breast tumor recurrence. However, the absolute difference in the 10-yr cumulative incidence of IBTR was only 0.7%.

• Risk of an RFI event was statistically significantly higher for PBI v WBI, but again, the absolute difference in 10-yr RFI cumulative incidence was also small (1.6%)

• Breast cancer event rates at a median follow-up of 10.2 yrs in this population were overall low: IBTR rate: ~4.5%, DM rate: ~3%, and breast cancer death rate: ~2%

• Because the differences relative to both IBTR (0.7%) and RFI (1.6%) were small, PBI may be an acceptable alternative to WBI for a proportion of women who undergo breast-conserving surgery

• Grade 3-5 toxicities were low. Additional analyses are underway to evaluate secondary endpoints of QOL and cosmesis
Regional node irradiation:
Meta-analysis of 13,500 women in 14 trials

Early Breast Cancer Trialists’ Collaborative Group (EBCTCG)

Writing Committee: David Dodwell (presenter), Carolyn Taylor, Paul McGale, Charlotte Coles, Fran Duane, Richard Gray, Thorsten Kühn, Christophe Hennequin, Robert Hills, Sileida Oliveros, Yaochen Wang, Jonas Bergh, Kathy Pritchard, Sandra Swain, Jens Overgaard, Philip Poortmans, Tim Whelan

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EBCTCG: REGIONAL LYMPH NODE RADIATION

**Regional node RT versus not**

14 trials, ~13,500 women

<table>
<thead>
<tr>
<th>Comparison</th>
<th>No. trials</th>
<th>No. women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Axilla SCF</td>
<td>2</td>
<td>652</td>
</tr>
<tr>
<td>IMC</td>
<td>3</td>
<td>4683</td>
</tr>
<tr>
<td>IMC SCF axilla</td>
<td>9</td>
<td>8069</td>
</tr>
<tr>
<td>All trials</td>
<td>14</td>
<td>13,404</td>
</tr>
</tbody>
</table>

**Regional node radiation therapy (RT)**

- **Axilla**
- **Supraclavicular (SCF)**
- **Internal mammary (IMC)**

Same treatment to breast
EBCTCG: REGIONAL LYMPH NODE RADIATION

Data analysis plan: regional node RT

1. All trials together
2. Separate older & newer trials

Target coverage better in newer trials
Heart dose: Older trials >8 Gy
Newer trials <8 Gy

Older trials (began 1961-1978)
Total with data available ≈2,500

<table>
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<th>Name</th>
<th>Women</th>
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<td>1961</td>
<td>NSABP B-03</td>
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Median FU (IQR): 9.2 (3.4 – 17.5) years

Newer trials (began 1989 onwards)
Total with data available ≈11,000

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*Data available only on overall mortality  **RT allocated by tumour laterality

Median FU (IQR): 9.1 (7.0 – 11.0) years
Data analysis plan: regional node RT

1. All trials together
2. Separate older & newer trials

Target coverage better in newer trials
Heart dose: Older trials >8 Gy
Newer trials <8 Gy

Older trials (began 1961-1978)
Total with data available ≈2,500

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*Data available only on overall mortality
**RT allocated by tumour laterality

Median FU (IQR): 9.1 (7.0 – 11.0) years

IPD Meta-analysis
EBCTCG: REGIONAL LYMPH NODE RADIATION

Any recurrence

Older trials
- 2178 women, 987 events
- 20-year gain 0.2% (95% CI -5.1 to 5.5)
- RR 0.98 (95% CI 0.85 to 1.13)
- logrank p = 0.80

Newer trials
- 9622 women, 2329 events
- 10-year gain 3.2% (95% CI 1.3 to 5.1)
- RR 0.86 (95% CI 0.79 to 0.94)
- logrank p = 0.0005

Overall mortality

Older trials
- 2178 women, 1554 deaths
- 20-year loss 2.8% (95% CI -2.1 to 7.7)
- RR 1.18 (95% CI 1.06 to 1.32)
- logrank p = 0.004

Newer trials
- 10956 women, 2713 deaths
- 10-year gain 2.9% (95% CI 1.2 to 4.6)
- RR 0.87 (95% CI 0.80 to 0.94)
- logrank p = 0.0003
EBCTCG: REGIONAL LYMPH NODE RADIATION

Breast cancer mortality

Older trials

2178 women, 957 deaths
20-year loss 0.5% (95% CI: 0.4-0.6)
RR 1.04 (95% CI: 0.90-1.20)
log rank p = 0.58

Newer trials

9622 women, 1739 deaths
10-year gain 2.8% (95% CI: 1.2-4.4)
RR 0.62 (95% CI: 0.75-0.90)
log rank p = 0.00006

Non-breast-cancer mortality

Older trials

2178 women, 597 deaths
20-year loss 5.8% (95% CI: 1.1-12.7)
RR 1.45 (95% CI: 1.21-1.74)
log rank p = 0.00006

Newer trials

9622 women, 438 deaths
10-year gain 0.2% (95% CI: 0.9-1.3)
RR 0.96 (95% CI: 0.79-1.16)
log rank p = 0.66
Breast cancer mortality did not vary according to:
Regional LNs irradiated
Breast quadrant
Use of chemotherapy
Use of endocrine therapy
All $p > .10$
Conclusions: regional node irradiation

- Older trials (began 1961-1978)
  - Breast cancer mortality – little effect
  - Overall mortality – significantly increased

- Newer trials (began 1989+)
  - Breast cancer mortality – significantly reduced
  - Overall mortality – significantly reduced
  - Absolute mortality reduction greatest in N4+
## GAINS WITH NODAL RADIATION TREATMENT

<table>
<thead>
<tr>
<th></th>
<th>EORTC 22922/10925</th>
<th>NCIC MA20</th>
<th>EBCTCG (SABCS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>15-year gain with nodal RT P value</td>
<td>3.8% .0055</td>
<td>--</td>
<td>2.8%* .00006</td>
</tr>
<tr>
<td>10-year gain with nodal RT P value</td>
<td>--</td>
<td>3.6% .03</td>
<td>--</td>
</tr>
<tr>
<td></td>
<td>1.9% .03</td>
<td>--</td>
<td></td>
</tr>
<tr>
<td></td>
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<td>1.0% .38</td>
<td>2.9%* .0003</td>
</tr>
<tr>
<td>10-year gain with nodal RT P value</td>
<td>--</td>
<td>3.0% .009</td>
<td>--</td>
</tr>
<tr>
<td></td>
<td>(-0.4%)</td>
<td>--</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breast cancer mortality</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Distant metastases</td>
<td>3.4%</td>
<td>3.6%</td>
<td></td>
</tr>
<tr>
<td>Distant disease-free survival</td>
<td>1.8% .18</td>
<td>1.9% .03</td>
<td></td>
</tr>
<tr>
<td>Overall survival</td>
<td>2.2% .18</td>
<td>1.0% .38</td>
<td>2.9%* .0003</td>
</tr>
<tr>
<td>Local-regional recurrence</td>
<td>(-0.4%)</td>
<td>3.0% .009</td>
<td></td>
</tr>
</tbody>
</table>

*Newer trials
“SILVER TSUNAMI”

Changing Demographics

Figure 1: Estimated cancer prevalence by age in the US population from 1975 (216 M) to 2040 (380 M)

- 50
- 50-64
- 65-74
- 75-84
- 85+

Signifies the year at which the first baby boomers (those born 1946-1964) turned 65 years old

Shapiro CL NEJM 2018:379; 2438-50
CARDIOTOXICITY: HER2-BASED ADJUVANT REGIMENS

- No standard definition of cardiac toxicity
- Trastuzumab-induced cardiac toxicity:
  - Not dose related
  - No myocardial cell death
  - 2.3% developed CHF; 0.1% cardiac death
  - In over 50% trastuzumab retreatment
  - No late trastuzumab toxicity

**ABSTRACT GS5-1**

- **Cardiac Toxicity:**
  - Decrease in LVEF by $\geq 10\%$, $\geq 5\% \downarrow 50\%$

- **Primary Objective:**
  - Cardiac events during and the year after trastuzumab

- **Secondary objectives:**
  - Toxicity, QoL, cardiac biomarkers

- **Statistics:**
  - None presented

---

<table>
<thead>
<tr>
<th>R</th>
<th>Carvedilol 10 mg</th>
<th>Lisinopril 10 mg</th>
<th>Placebo</th>
</tr>
</thead>
</table>

N=468
Anthracyclines
Non-Anthracyclines
RESULTS

Cardiotoxicity free survival

<table>
<thead>
<tr>
<th>anthracycline cohort</th>
<th>non-anthracycline cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Carvedilol</strong> (HR 0.49, 95% CI 0.27, 0.89, p=0.009) lisinopril (HR 0.53, CI 0.30, 0.94, p=0.015)</td>
<td>N=(265)</td>
</tr>
</tbody>
</table>

(N=2
13)
CAVEATS, CONCLUSIONS

- No info on type of cardiac event, reversibility, or long term outcome
- Decreasing anthracycline use
- Until long follow-up and additional studies, lisinopril and carvedilol should NOT be used outside a clinical trial in women receiving anthracyclines
ABSTRACT GS5-2

Resource and time intensive intervention
- 120 min/week supervised, +120 min

Healthy population
- Mean age 55; BMI 25; VO2 baseline 31

Primary endpoint:
- VO2 baseline – 12 mo
Adherence and Adverse Events (AE) 
Cardiovascular capacity (VO$_{2\text{max}}$)

Adherence to the intervention

Overall cardiovascular function

**AE's:** Fatigue during CPET/exercise, one injured shoulder

This presentation is the intellectual property of Dr. Inger Thune. Contact Inger.Thune@ul.no for permission to reprint and/or distribute.
Final results - The EBBA-II (NBCG-14)

All participants (n= 545)

No chemotherapy (n=242)

This presentation is the intellectual property of Dr. Inger Thune. Contact Inger.Thune@uit.no for permission to reprint and/or distribute.
Patients receiving chemotherapy

Receiving chemotherapy (n= 295)

EEBA-IV trial
All cases receiving chemotherapy

- 0.8 % decrease
- 6.4 % decrease
- 14.3 % decrease

Receiving taxanes (n= 212)

EEBA-IV trial
All cases receiving taxanes

- 1.4 % decrease
- 7.3 % decrease
- 17.5 % decrease

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CAVEATS AND CONCLUSIONS

• Relatively young healthy population able to undergo an intensive intervention. Are the results generalizable?
• Intensive intervention results in preservation of VO2 during chemo
• What about a less intensive intervention in a more representative population?
• Do the control and intervention arms come together over time?
ABSTRACT GS5-03

- 2 year intervention- telephone based
  - 19 calls and mailings; physical activity weight
  - Formal VO2 testing
- 2292 randomized
  - Age 58; N+ 60%; postmenopausal 68%; ER+ 77%
- Primary Endpoint
  - DFS and OS
• Compliance: Only 48% completed intervention
• Completers vs. non-completers were different
  • Younger age, lower grade, higher ER+
Disease-free survival (DFS) and overall survival (OS) by lifestyle intervention arm – ITT analysis

P=0.46

P=0.56

univariate, log-rank test

P = 0.922

univariate, log-rank test

P = 0.799

This presentation is the intellectual property of the author/presenter. Contact wolfgang.janni@uniklinik-ulm.de for permission to reprint and/or distribute.
CAVEATS AND CONCLUSIONS

• Intervention was not feasible as 50% did not complete the 2 yrs.

• Ongoing trials are addressing weight loss and physical activity (BWEL trial)
HOT FLASHES
**HOT FLASHES: MAYO CLINIC**  
Randomized, Placebo Control

<table>
<thead>
<tr>
<th>Drug</th>
<th>Benefit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>20%</td>
</tr>
<tr>
<td>Clonidine/MPA</td>
<td>Pos (side effects)</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>Pos, (interferes tam)</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>Pos, (fatigue)</td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>Pos (no interference with tam)</td>
</tr>
<tr>
<td>Soy, Flaxseed</td>
<td>Neg</td>
</tr>
</tbody>
</table>

**Mechanism**  

Why Do I Have Extreme Hot Flash Episodes?

- Decreased estrogen levels can affect body temperature, which is regulated by the hypothalamus.

- Estrogen levels drop

- Body temperature up
Oxybutynin

- **Anticholinergic** (oral or transdermal).
- FDA approved for overactive bladder (5-20 mg daily).
- “Decreased sweating” common → effective for hyperhidrosis.
- **Data in refractory hot flashes:**
  - **Prospective study:** Simon et al, Menopause, 2016. Oxybutynin XR 15 mg/d improved HF but with toxicity. Investigators recommended studying lower doses.
Abstract GS6-02

Study design

Women with HF
≥28 times/week
>30 day duration
Women taking tamoxifen or AIs eligible
Concurrent antidepressants, gabapentin, pregabalin allowed
Concurrent potent anticholinergics not allowed

Treatment duration = 6 weeks, after a baseline week without medication (questionnaires)

Weekly questionnaires:
Hot Flash Diary
HFRDIS
Symptom experience questionnaire

Endpoints:
Primary: Intra-patient change in weekly HF score and frequency
Secondary: change in HFRDIS, change in self-reported symptoms

A: Oxybutynin 2.5 mg PO BID
N=40
B: Oxybutynin 5 mg PO BID
N=35
C: Placebo
N=38

This presentation is the intellectual property of the presenter. Contact Roberto Leon-Ferre at leonferre.roberto@mayo.edu for permission to reprint and/or distribute.
Results: Mean Hot Flash Score % Reduction from Baseline

HF Score = HF frequency x average severity
G1 = mild, G2 = moderate, G3 = severe, G4 = very severe

<table>
<thead>
<tr>
<th>WEEKS</th>
<th>Baseline</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
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<tbody>
<tr>
<td>Placebo</td>
<td>36</td>
<td>35</td>
<td>35</td>
<td>37</td>
<td>35</td>
<td>35</td>
<td>35</td>
</tr>
<tr>
<td>Oxybutinin 2.5 mg BID</td>
<td>40</td>
<td>40</td>
<td>38</td>
<td>36</td>
<td>35</td>
<td>35</td>
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<tr>
<td>Oxybutinin 5mg BID</td>
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<td>32</td>
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<td>31</td>
<td>31</td>
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P < 0.01
CONCLUSIONS

• Oxybutynin improved severity and frequency of hot flashes, with 5 mg > 2 mg
  • No formal comparison between doses
• HRQOL was improved except for sexuality and concentration
  • 2.5 mg BID did not improve mood and life enjoyment
• Side effects: Dry mouth, abdominal pain, difficult urination
  • 5 mg BID-dry eyes, confusion, diarrhea, headaches
• What’s the correct dosage?
Cancer and Aging Research Group (CARG) Score

Development of a Predictive Model for Tolerance to Therapy in Older Patients with Breast Cancer

Same Chronological Age; Different Functional Age
PROSPECTIVE COHORT STUDY DESIGN

CONSORT Diagram

- Patients Enrolled: N=501
- Patients Excluded (N=28) - Non-standard regimens*
- Evaluated Patients: N=473
  - Development Cohort: N=283
  - Validation Cohort: N=190

*per NCCN Guidelines
DISEASE CHARACTERISTICS

- Median Age (Range): 70 (65-85)
- Adjuvant Treatment: 82.3%
- Poly Chemotherapy: 90.1%
- Anthracycline-Based Regimen: 38.1%
- Standard Dose: 97.5%
GOODNESS OF FIT

Model Performance: Goodness of Fit

Median score (Range): 7 (0-19)
OUTCOMES
CONCLUSION

• CARG Score is a validated tool to predict chemotherapy side effects in elder women with breast ca
• Predicts dose reductions, delays, and hospitalizations
Thank you.