2016 San Antonio Breast Cancer Symposium: Local Therapy Highlights

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Abstracts

1. Sentinel Node Dissection after Neoadjuvant Chemotherapy in Patients without Previous Axillary Node Involvement (GANEA 2 Trial): Follow-up of a Prospective Multi-institutional Cohort (S2-07)

2. Impact of Radiotherapy on Complications and Patient-Reported Outcomes after Breast Reconstruction: Findings from the Prospective Multicenter MROC Study (S3-07)

3. Radioactive Seed Localization versus Wire Guided Localization of Nonpalpable Invasive and In Situ Breast Cancer: A Danish Multicenter Randomized Control Trial (S3-08)
Abstracts

4. DCIS Biological Risk Profile Predicts Risk of Recurrence after Breast Conserving Surgery in a Kaiser Permanent NW Population (S5-01)

5. Low-fat Dietary Pattern and Breast Cancer Overall Survival in the Women’s Health Initiative Dietary Modification Randomized Controlled Trial (S5-04)

6. Randomized, placebo-controlled trial of Duloxetine for Aromatase Inhibitor (AI)-associated Musculoskeletal Symptoms (AIMSS) in Early Stage Breast Cancer (SWOG 1202) (S5-06)

Sentinel node detection after neoadjuvant chemotherapy (GANEA 2 trial):
Follow-up of a prospective multi-institutional cohort

Pr Jean-Marc Classe, MD, PhD
Institut de Cancérologie de l’Ouest – Centre Gauducheau – Nantes - France
GANEA 2 trial
Prospective Multi-institutional French Cohort

Breast cancer
T1-T3
N0-N1
From: 07-2010
To 07-2014
From 15 institutions

NAC
pN+
Axillary sonography
+/- fine needle
pN-

Group 1:
SLN
+ Axillary lymphadenectomy
No follow-up

Group 2:
SLN
+/- Axillary lymphadenectomy
follow-up

Axillary assessment
pN+
pN+

pN+ before NAC

Group 1:
SLN + Axillary lymphadenectomy

GANEA 2 trial
Group 1
GANEA 2 trial
Group 1

307 Patients
1 exclusion: no ALND

Identification rate 79.8%
244 SLN successful mapping
103 SLN Not involved

19 ALND involved FNR 12%
PCR 27%
(n=84)

GANEA 2 trial
Group 2

Axillary assessment

pN-

pN-
before NAC

Group 2:
SLN +/- Axillary lymphadenectomy
## Patients’ characteristics

<table>
<thead>
<tr>
<th>Patients characteristics</th>
<th>SLN alone n=418</th>
<th>SLN pN+ (+ Lymphadenectomy) n=120</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBR Scoring III</td>
<td>255 (61%)</td>
<td>31 (26%) (p&lt;10⁻³)</td>
</tr>
<tr>
<td>Hormonal Receptor: RO</td>
<td></td>
<td></td>
</tr>
<tr>
<td>neg.</td>
<td>212 (51%)</td>
<td>23 (19%) (p&lt;10⁻³)</td>
</tr>
<tr>
<td>RP neg.</td>
<td>262 (62%)</td>
<td>32 (26%) (p&lt;10⁻³)</td>
</tr>
<tr>
<td>HERb2 3+</td>
<td>73 (17%)</td>
<td>10 (8%) (p=0.016)</td>
</tr>
</tbody>
</table>

## Results: Breast surgery

<table>
<thead>
<tr>
<th>Patients characteristics</th>
<th>SLN alone n=418</th>
<th>SLN pN+ (+ Lymphadenectomy) n=120</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conservative surgery</td>
<td>379 (90%)</td>
<td>98 (81.5%)</td>
</tr>
<tr>
<td>mastectomy</td>
<td>39 (10%)</td>
<td>22 (18.5%)</td>
</tr>
</tbody>
</table>

P=0.006
Results: axillary nodes

<table>
<thead>
<tr>
<th>Patients characteristics</th>
<th>SLN alone n= 418</th>
<th>SLN pN+ (+ Lymphadenectomy) n=120</th>
</tr>
</thead>
<tbody>
<tr>
<td>SLN</td>
<td>pN-</td>
<td>pN+ (macro= 79/micro=41)</td>
</tr>
<tr>
<td>ALND</td>
<td>Not done</td>
<td>pN+=29 (24%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>pN-=88 (73%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(NA:3)</td>
</tr>
</tbody>
</table>

Follow-up organization:

Clinical visit / 6 months:
Clinical breast and axillary assessment +/- axillary sonography if necessary AND Mammography/ year

<table>
<thead>
<tr>
<th>3 years survival</th>
<th>N= 418 (SLN alone)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall survival</td>
<td>97.8% [94.9-99.1]</td>
</tr>
<tr>
<td>Disease free survival</td>
<td>94.8% [91.0-97.1%]</td>
</tr>
</tbody>
</table>
Take Home Message

- Axillary ultrasound with biopsy to prove nodal involvement prior to NACT is necessary to differentiate surgical approach to the axilla following NACT.
- In patients without axillary nodes involved before NACT, SLNbx alone is acceptable without axillary lymph node dissection.
- In patients who are initially node positive, the clinical implications of a false negative rate of 12% in SLNbx alone following NACT is unknown.
Limitations

• Variety of techniques for identifying sentinel lymph node
• All patients with positive lymph node received ALND and these patients were not followed
• Did not provide data on SLN involved among Group 2 patients (all had ALND)
Integrating Post-Mastectomy Radiation and Reconstruction

• Evidence to date has been limited
  – Primarily retrospective single-institution data
  – Few multi-center studies limited
    • failure to include sufficient numbers of radiated pts
    • failure to include patients treated with different reconstruction techniques for comparison
    • failure to measure covariates
    • limitation to populations substantially different from those treated in the US

Practice varies widely
  – reflects historical traditions and institutional culture rather than shared decision-making informed by high-quality evidence
Approach

- **Design:**
  - prospective multicenter cohort study

- **Study Population:**
  - 553 radiated and 1461 non-radiated patients who received either implant or autologous reconstruction (at any time point before or after radiation in irradiated patients) at 11 institutions 2012-15

- **Endpoints:**
  - Complications, failure, and patient-reported outcomes
    - PROs measured using BREAST-Q
      - validated, condition-specific HR-QOL measure
      - specifically developed for breast reconstruction patients
      - measures multiple domains

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Approach

- **Mixed-effects regression models assessed impact of reconstruction type, radiotherapy, and the interaction of reconstruction and radiotherapy on outcomes after adjusting for relevant covariates**
  - **Covariates:**
    - Reconstruction timing
    - Age
    - Extent of disease
    - Bilateral vs unilateral reconstruction
    - Chemotherapy receipt
    - Nodal management
    - BMI
    - Smoking
    - Diabetes
    - Race
    - Ethnicity
    - Education
    - Employment
    - Income
    - Marital status
    - Hospital site

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Sample Characteristics

• Median age 49
• Bilateral mastectomy received by 45.6% of radiated & 53.3% of non-radiated pts (p=0.002)
• Autologous reconstruction more commonly received by radiated pts (38.3% vs 25.1%, p<0.001)
  – ~62% of radiated patients had implants and 70-80% of these implants were tissue expanders
• Immediate reconstruction less common in radiated pts (82.6% vs 95.6%, p<0.001)
  – Immediate reconstruction was most commonly implant based with tissue expander
• 70-80% of implant cohort were tissue expanders who had exchange by 1 year post-op

Complications

• By two years, at least one complication (e.g. hematoma, wound infection, etc.) occurred in 33.4% of radiated pts and 23.5% of non-radiated pts
Complications

• MVA: bilateral treatment and higher BMI predictive of developing a complication, with significant interaction between RT receipt and reconstruction type
  – RT associated with 2.64 (p=<0.001) times higher odds of complication by 2 years in implant pts, while showing no significant difference in autologous pts (OR=1.12, p=0.67)
  – Among radiated patients, autologous reconstruction associated with lower 2-year risk of complications than implant-based reconstruction (OR=0.47, p=0.007)

Reconstruction Failure

• By two years, reconstructive failure occurred in 11.4% of radiated pts and 3.4% of non-radiated pts
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Results: PROs at 2 Years

![Graph showing Satisfaction with Breast and Outcome at 2 Years for Implant and Autologous with and without radiation.]

San Antonio Breast Cancer Symposium – December 6-10, 2016

Results: PROs at 2 Years

![Graph showing Psychosocial and Physical Well-Being for Implant and Autologous with and without radiation.]

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Conclusions

• In the largest prospective multicenter study of outcomes of breast reconstruction to date, RT appears to compromise outcomes of implant reconstruction without clear impact on autologous reconstruction.

• Autologous reconstruction appears to yield superior patient-reported outcomes and lower risk of complications than implant-based approaches among patients receiving PMRT.

• These data are critical to inform the growing number of patients who are considering PMRT and may desire reconstruction, so that they may make informed, preference-concordant decisions.

Take Home Message

• In patients who receive post mastectomy radiation, implant based (with tissue expanders) vs. autologous reconstruction is associated with more complications and worse patient reported quality of life outcomes.
Limitations

- No information on cancer outcomes or how reconstruction may impact radiation technique
- Does not address optimal timing of reconstruction. 170 patients had delayed reconstruction and received radiation to the unreconstructed chestwall. They then received autologous reconstruction after radiation and were grouped in the autologous cohort. Separate analysis looking at timing of reconstruction is pending.
- 70-80% of “implant” patients had temporary tissue expanders during radiation that were replaced with permanent implant after radiation
- Vast majority of immediate reconstruction patients had tissue expander during radiation

Radioactive Seed Localization vs. Wire-Guided Localization of Nonpalpable Invasive and In Situ Breast Cancer: A Danish Multicenter Randomized Controlled Trial

Rigshospitalet & Herlev Hospital, University of Copenhagen, Denmark
Study Design

Randomized controlled trial of radioactive seed localization vs. wire-guided localization of nonpalpable invasive and in situ breast cancers:

- Primary Endpoint: Positive margin rate defined as < 2.0mm for invasive or DCIS
- Secondary Endpoint:
  a) Patient’s pain perception following seed placement or wire
  b) Duration of surgical procedure – time from skin incision to complete excision of specimen
  c) Weight of excised specimen
Patients

- Nonpalpable lesions
- Invasive breast cancer (IBC) or ductal carcinoma in situ (DCIS)
- Visible on ultrasound
- Eligible for breast conserving surgery

Trial profile

- 444 (RSL)
- 409/413
- 35

Allocation

- 206
- 207

Intention-to-treat

- 195
- 195

Per-protocol

- 192
- 186
Results

- Inclusion period was Jan 1, 2014 to Feb 4, 2016
- Baseline characteristics were alike
- Significantly more patients with DCIS in the WGL group (p=0.006)

<table>
<thead>
<tr>
<th>Margin status</th>
<th>RSL n (%)</th>
<th>WGL n (%)</th>
<th>P-value</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intention-to-treat</td>
<td></td>
<td></td>
<td>0.65</td>
<td>1.15 (0.83-2.10)</td>
</tr>
<tr>
<td>Negative</td>
<td>172 (88.2%)</td>
<td>169 (86.7%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>23 (11.8%)</td>
<td>26 (13.3%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Per-protocol</td>
<td></td>
<td></td>
<td>0.62</td>
<td>1.17 (0.64-2.14)</td>
</tr>
<tr>
<td>Negative</td>
<td>164 (88.2%)</td>
<td>166 (86.5%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>22 (11.8%)</td>
<td>26 (13.5%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IBC</td>
<td></td>
<td></td>
<td>0.997</td>
<td>1.0 (0.53-1.89)</td>
</tr>
<tr>
<td>Negative</td>
<td>172 (88.7%)</td>
<td>164 (88.6%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>22 (11.3%)</td>
<td>21 (11.4%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Secondary outcomes

<table>
<thead>
<tr>
<th></th>
<th>RSL</th>
<th>WGL</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight total (g)</td>
<td>29 (18.5-43.0)</td>
<td>26 (18.0-40.0)</td>
<td>0.54</td>
</tr>
<tr>
<td>Duration (min)</td>
<td>19 (7-12)</td>
<td>19 (7-15)</td>
<td>0.12</td>
</tr>
<tr>
<td>Pain Perception</td>
<td></td>
<td></td>
<td>0.28</td>
</tr>
<tr>
<td>No</td>
<td>13 (7.9%)</td>
<td>4 (2.5%)</td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>88 (53.3%)</td>
<td>76 (55.1%)</td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>48 (29.1%)</td>
<td>41 (29.7%)</td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td>16 (9.7%)</td>
<td>17 (12.3%)</td>
<td></td>
</tr>
</tbody>
</table>

Results

- Complication rate (p=0.89)
- Sentinel node identification rate (p=1.00)
Conclusions

No significant difference in:

- Margin status
- Duration of the surgical procedure
- Weight of the excised specimen
- Patients’ pain perception

Perspectives

- 2 previous randomized trials with similar results on margin status
- RSL offers a major logistic advantage
- Do we have enough evidence to safely implement RSL as standard procedure?
Take Home Message

• In this randomized trial, radioactive seed placement for nonpalpable breast cancer lesions did not lead to a higher rate of positive margins, more time in the operating room, or more breast tissue removed than traditional wire guided localization procedures.
• Radioactive seed placement has the potential to increase operating room throughput and convenience, as the seed may be placed several days ahead of the operating room procedure.

Limitations

• Data is lacking quantifying patient perceptions of time spent having seed placed and returning for a second visit to the operating room procedure versus time and inconvenience spent in mammography suite and operating room with the wire localization procedure.
• Majority of patients in this study had invasive breast cancer and very few had DCIS.
• Less than 2mm margins on invasive or DCIS was considered a positive margin.
Take Home Message

• DCIS biological risk signature appears to be both prognostic and predictive of benefit of radiation in DCIS patients treated with lumpectomy

Limitations

• Validation studies are ongoing
• Unclear how the clinical factors were incorporated with the biological factors and how they were weighted
• No detailed data presented on risk of invasive recurrences although presenter said it was half and half
• Unclear how the cutoff scores of 3 was determined or how biomarkers were selected
Low-Fat Dietary Pattern and Breast Cancer Mortality in the Women’s Health Initiative Dietary Modification (WHI DM) Trial


Los Angeles BioMedical Research Institute at Harbor-UCLA Medical Center for the Women’s Health Initiative


Country-by-Country Breast Cancer Death Rate by Estimated Dietary Fat Intake

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WHI Dietary Modification Randomized, Controlled, Primary Breast Cancer Prevention Clinical Trial Analysis Plan

**Postmenopausal Women**

- N=48,835
- Age 50-79 years
- No prior breast cancer
- Fat intake ≥ 32% calories
- Mammogram normal
- Entry: 1993-1998

**Comparison**

- N=29,294

**Dietary Intervention**

- N=19,541
- 8.5 Years (median) (intervention)
- 16.1 Years (median) (cumulative)

Analysis Endpoints:
- Deaths from breast cancer
- Deaths after breast cancer
- Clinical follow-up plus National Death Index queries

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**WHI DM: Dietary Intervention**

- Dietary Intervention Goals:
  - Reduce dietary fat intake (target 20% calories from fat)
  - Increase vegetables and fruit servings (target 5/day)
  - Increase grains servings (target 6/day)
  - Weight loss not an intervention target
  - Diet Group: Year 1: 18 group sessions, then quarterly maintenance
  - Control Group: received dietary guideline report only

Baseline Demographics by Randomization Group

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Diet [N=19541]</th>
<th>Control [N=29294]</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N (%)</td>
<td>N (%)</td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>50-59</td>
<td>7206 (37%)</td>
<td>10797 (37%)</td>
<td>&gt;.99</td>
</tr>
<tr>
<td>60-69</td>
<td>9086 (47%)</td>
<td>13626 (46%)</td>
<td></td>
</tr>
<tr>
<td>70-79</td>
<td>3249 (17%)</td>
<td>4871 (17%)</td>
<td></td>
</tr>
<tr>
<td>Race/ethnicity</td>
<td></td>
<td></td>
<td>.76</td>
</tr>
<tr>
<td>White</td>
<td>15869 (81%)</td>
<td>23890 (82%)</td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>2137 (11%)</td>
<td>3129 (11%)</td>
<td></td>
</tr>
<tr>
<td>Hispanics</td>
<td>755 (4%)</td>
<td>1099 (4%)</td>
<td></td>
</tr>
<tr>
<td>Asian/Pacific Islander</td>
<td>433 (2%)</td>
<td>674 (2%)</td>
<td></td>
</tr>
<tr>
<td>Other/Unknown</td>
<td>362 (2%)</td>
<td>502 (1%)</td>
<td></td>
</tr>
</tbody>
</table>

Baseline Demographics of WHI DM Trial Participants Did not Differ by Randomization Group

<table>
<thead>
<tr>
<th>Age</th>
<th>Body Mass Index</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mammogram within 2 years</td>
</tr>
<tr>
<td>Race/ethnicity</td>
<td>History of estrogen plus progestin use</td>
</tr>
<tr>
<td>Breast cancer family</td>
<td>History of estrogen alone use</td>
</tr>
<tr>
<td>history</td>
<td></td>
</tr>
<tr>
<td>Gail 5y breast cancer</td>
<td></td>
</tr>
<tr>
<td>risk</td>
<td></td>
</tr>
<tr>
<td>Reproductive history</td>
<td>Treated diabetes</td>
</tr>
</tbody>
</table>
Dietary Intake Change in the Diet Group:
Types of Fat

Overall decrease in percent calories from fat of 13.9% at year 1 and 8.2% at year 5 (both P < 0.001)

WHI DM: Change in Body Weight by Randomization Group

Decrease in weight of -2.2 kg at year 1
DM Trial: Breast Cancer Incidence during 8.5 year (median) Dietary Intervention Period

HR 0.91 (0.83-1.01)
1,727 breast cancers,
P =0.07
3.5% of all DM participants

For deaths from breast cancer
27 vs 53, HR 0.77 (0.48-1.22)

Low-Fat Dietary Pattern and Deaths from and after 1767 Breast Cancers During the 8.5 year (median) Dietary Intervention Period

HF (95% CI) = 0.67 (0.43, 0.106)
P-value = 0.08
Deaths from Breast Cancer

HF (95% CI) = 0.64 (0.44, 0.93)
P-value = 0.02
Deaths after Breast Cancer
Low-Fat Dietary Pattern and Deaths from and after 3034 Breast Cancers During 16.1 Years (Median) Cumulative Follow-up

Deaths from Breast Cancer

111(0.035%) vs 184(0.039%)
HR(95%CI) = 0.91(0.72, 1.15)
N= 295
P-value = 0.44

Deaths after Breast Cancer

234(0.085%) vs 443(0.11%)
HR(95%CI) = 0.82(0.70, 0.96)
N= 677
P-value = 0.01

Subgroup Analysis/Deaths After Breast Cancer:
Cumulative Follow-up

Greater dietary effect in women with waist circumference ≥ 88 cm
Subgroup Analysis: Cases Diagnosed During Dietary Intervention, Deaths After Breast Cancer, Cumulative

Greater dietary effect in women with higher baseline dietary fat intake

Ϯ From breast cancer cases with 4 day food records collected.

Breast Cancer Characteristics (n=3034) of Cases Diagnosed Throughout Cumulative 16.1 year (median) Follow-up

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Diet [N=1177] N (%)</th>
<th>Control [N=1857] N (%)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>STAGE</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LOCAL</td>
<td>871 (75.5)</td>
<td>1375 (75.3)</td>
<td>0.91</td>
</tr>
<tr>
<td>REGIONAL/DISTANT</td>
<td>283 (24.5)</td>
<td>451 (24.7)</td>
<td></td>
</tr>
<tr>
<td>TUMOR SIZE</td>
<td></td>
<td></td>
<td>0.95</td>
</tr>
<tr>
<td>&lt;1</td>
<td>307 (28.6)</td>
<td>504 (29.5)</td>
<td></td>
</tr>
<tr>
<td>1-&lt;2</td>
<td>482 (44.8)</td>
<td>728 (42.7)</td>
<td></td>
</tr>
<tr>
<td>≥2</td>
<td>286 (26.6)</td>
<td>474 (27.8)</td>
<td></td>
</tr>
<tr>
<td>POSITIVE NODES</td>
<td>790 (75.5)</td>
<td>1254 (75.9)</td>
<td>0.98</td>
</tr>
</tbody>
</table>

For breast cancer incidence HR 0.96 95% CI 0.90-1.04, p=0.33
Breast Cancer Characteristics (n=3034) of Cases Diagnosed Throughout Cumulative 16.1 yr (median) Follow-up

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Diet [N=672] N (%)</th>
<th>Control [N=1095] N (%)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ER/PR Status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ER+PR+</td>
<td>793 (73.5)</td>
<td>1201 (70.5)</td>
<td>0.04</td>
</tr>
<tr>
<td>ER+PR-</td>
<td>141 (13.1)</td>
<td>282 (16.5)</td>
<td></td>
</tr>
<tr>
<td>ER-PR+</td>
<td>145 (13.4)</td>
<td>221 (13.0)</td>
<td></td>
</tr>
<tr>
<td>HER2 Positive</td>
<td>146 (15.3)</td>
<td>202 (13.7)</td>
<td>0.28</td>
</tr>
<tr>
<td>Triple negative</td>
<td>76 (8.1)</td>
<td>133 (9.1)</td>
<td>0.37</td>
</tr>
</tbody>
</table>

Death after Breast Cancer During Cumulative Follow-up: Exploratory Analyses PR Status and Weight Change

<table>
<thead>
<tr>
<th>Adjustment Variable</th>
<th>Death after Breast Cancer HR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time-dependent variables for PR negative and unknown</td>
<td>0.87 (0.74-1.02)</td>
<td>0.08</td>
</tr>
<tr>
<td>Baseline weight and subsequent weight change</td>
<td>0.82 (0.70-0.96)</td>
<td>0.02</td>
</tr>
</tbody>
</table>

PR status difference provides 27% explanation of benefit seen, weight difference does not explain the benefit seen
Conclusions

- Compared to a usual diet control group, women randomized to a low-fat dietary pattern had a non-significantly reduced risk of death from breast cancer and a significantly reduced risk of death after breast cancer.
- These updated results alter the interpretation of the trial.
- A dietary effect was more likely in those with either a lifestyle (≥36.8% energy from fat) or a consequence of lifestyle (≥88 waist circumference), associated with adverse breast cancer outcome.
- Future studies of other lifestyle interventions in breast cancer settings could consider some form of a low-fat dietary pattern as a base.

Take Home Message

- Low fat diet was associated with fewer deaths after breast cancer but was not associated with fewer deaths due to breast cancer.
- Low fat diet had the greatest positive impact in women with baseline high fat intake and large waist circumference ≥ 88cm.
- In all likelihood, the deaths after breast cancer could be attributed to non-breast malignancies or cardiovascular disease which would have been impacted by low fat diet.
- Women over the age of 70 did not benefit from low fat diet.
- Low fat diet was associated with more cancers that were ER+,PR+ and fewer cancers that were ER+,PR-.
Limitations

• No data presented on causes of death after breast cancer
• No data on contribution of exercise/physical activity to their findings

Randomized, placebo-controlled trial of duloxetine for aromatase inhibitor (AI)-associated musculoskeletal symptoms (AIMSS) in early stage breast cancer (SWOG S1202)


Huntsman Cancer Institute; Fred Hutchinson Cancer Research Center; University of Michigan Comprehensive Cancer Center; Kaiser Permanente, Northern California; Metro Minnesota CCOP/Minnesota Oncology; William R. Bliss Cancer Center; Phoenixville Cancer Center; AIM Specialty Health; Heartland NCORP

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AI-Associated Musculoskeletal Syndrome (AIMSS)

- AIMSS occurs in up to 50% of AI-treated patients, and leads to early treatment discontinuation⁰.

- Premature discontinuation of AI therapy can lead to increased likelihood of breast cancer recurrence².

- Only exercise and acupuncture have been shown to improve symptoms in randomized controlled trials³,⁴.

¹Henry et al JCO 2012; ²Chirgwin et al JCO 2016; ³Irwin et al JCO 2015; ⁴Crew et al JCO 2010

Duloxetine

- Serotonin norepinephrine reuptake inhibitor (SNRI)

- FDA-approved for treatment of multiple chronic pain disorders.

- Phase II open label trial of duloxetine for treatment of AIMSS demonstrated a 61% improvement in pain¹.

¹Henry et al Cancer 2011
Hypothesis and Objectives

• Hypothesis: Treatment of AIMSS with duloxetine would improve average joint pain compared to placebo.

• Primary objective: To assess whether 12 weeks of duloxetine decreases average joint pain, assessed with Brief Pain Inventory, in women with AIMSS

• Secondary Objectives: To assess whether 12 weeks of duloxetine decreases
  • worst joint pain
  • pain interference

Eligibility Criteria

• Postmenopausal
• Stage I-III breast cancer
• Taking AI therapy for 3 weeks - 36 months
• Average musculoskeletal pain of $\geq 4/10$ that developed or worsened since AI therapy initiation
• No contraindications to duloxetine therapy
  • No concurrent SSRI/SNRI
San Antonio Breast Cancer Symposium, December 6-10, 2016

Schema

Duloxetine

<table>
<thead>
<tr>
<th>30 mg</th>
<th>60 mg</th>
</tr>
</thead>
</table>

Placebo

| 0 | 1 | 6 | 12 | 24 |

30 mg taper

Treatment

13 weeks

Stratification:

- Baseline pain (4-6 vs 7-10)
- Prior taxane (Y/N)

Pain/QOL: X X X X X

Phlebotomy: X X

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Methods

- Questionnaires completed at baseline, 2, 6, 12, and 24 weeks
  - **Joint Pain** (Brief Pain Inventory-Short Form, WOMAC, M-SACRAH)
  - **Global Ratings of Change in Joint Pain and Stiffness** (not at BL)
  - **Depression** (PHQ-9) (not at 2 or 24 wks)
  - **Quality of Life** (FACT-ES)

- Phlebotomy at baseline and 12 weeks to assess predictors of response (to be reported later)

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Statistical Methods

• Assumptions:
  • 1.0 difference in pain between the groups with a 2.3 point standard deviation at 12 weeks
  • 5% non-adherence rate, 15% drop out rate at 12 weeks, and 10% contamination rate
  • Goal sample size: 270 patients

• Analysis: linear mixed models to examine average joint pain through 12 weeks by arm, adjusting for the stratification factors and assessment time

Patient Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total (n=289)</th>
<th>Placebo (n=144)</th>
<th>Duloxetine (n=145)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median Age</td>
<td>60 (27-83)</td>
<td>60 (27-82)</td>
<td>60 (40-83)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>248 (86%)</td>
<td>120 (83%)</td>
<td>128 (88%)</td>
</tr>
<tr>
<td>Black</td>
<td>27 (9%)</td>
<td>17 (12%)</td>
<td>10 (7%)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>11 (4%)</td>
<td>6 (4%)</td>
<td>5 (3%)</td>
</tr>
<tr>
<td>Performance status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>196 (68%)</td>
<td>94 (65%)</td>
<td>102 (70%)</td>
</tr>
<tr>
<td>Breast cancer stage</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I or II</td>
<td>251 (87%)</td>
<td>119 (83%)</td>
<td>132 (91%)</td>
</tr>
<tr>
<td>III</td>
<td>38 (13%)</td>
<td>25 (17%)</td>
<td>13 (9%)</td>
</tr>
<tr>
<td>Baseline pain score</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4-6</td>
<td>220 (76%)</td>
<td>110 (76%)</td>
<td>110 (76%)</td>
</tr>
<tr>
<td>7-10</td>
<td>69 (24%)</td>
<td>34 (24%)</td>
<td>35 (24%)</td>
</tr>
<tr>
<td>Prior taxane use</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>156 (54%)</td>
<td>79 (55%)</td>
<td>77 (53%)</td>
</tr>
<tr>
<td>Prior AI duration, wk</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>51.3 (37.7)</td>
<td>50.5 (37.6)</td>
<td>52.4 (37.9)</td>
<td></td>
</tr>
</tbody>
</table>

*No sizeable imbalances between study arms
### Grade 3/4 Adverse Events

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Placebo (n=141)</th>
<th>Duloxetine (n=138)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal pain</td>
<td>0</td>
<td>1 (0.7%)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>1 (0.7%)</td>
<td>1 (0.7%)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>0</td>
<td>1 (0.7%)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>0</td>
<td>1 (0.7%)</td>
</tr>
<tr>
<td>Headache</td>
<td>1 (0.7%)</td>
<td>0</td>
</tr>
<tr>
<td>Hypersomnia</td>
<td>1 (0.7%)</td>
<td>0</td>
</tr>
<tr>
<td>Insomnia</td>
<td>1 (0.7%)</td>
<td>4 (2.9%)</td>
</tr>
<tr>
<td>Myalgia</td>
<td>0</td>
<td>1 (0.7%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>0</td>
<td>1 (0.7%)</td>
</tr>
<tr>
<td>Pain</td>
<td>1 (0.7%)</td>
<td>0</td>
</tr>
<tr>
<td>Pain in extremity</td>
<td>0</td>
<td>2 (1.4%)</td>
</tr>
<tr>
<td>ROM decreased</td>
<td>0</td>
<td>1 (0.7%)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>0</td>
<td>1 (0.7%)</td>
</tr>
<tr>
<td><strong>Total patients</strong></td>
<td><strong>5 (3.5%)</strong></td>
<td><strong>12 (8.7%)</strong></td>
</tr>
</tbody>
</table>

No statistically significant differences

---

### Most Frequent Adverse Events (>10%)

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<td>15 (11%)</td>
<td>12 (9%)</td>
</tr>
<tr>
<td>Constipation</td>
<td>7 (5%)</td>
<td>17 (12%)*</td>
</tr>
<tr>
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<td>6 (4%)</td>
<td>18 (13%)*</td>
</tr>
<tr>
<td>Dizziness</td>
<td>4 (3%)</td>
<td>18 (13%)*</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>18 (13%)</td>
<td>35 (25%)*</td>
</tr>
<tr>
<td>Fatigue</td>
<td>18 (13%)</td>
<td>44 (32%)*</td>
</tr>
<tr>
<td>Headache</td>
<td>18 (13%)</td>
<td>29 (21%)</td>
</tr>
<tr>
<td>Hot flashes</td>
<td>12 (9%)</td>
<td>20 (15%)</td>
</tr>
<tr>
<td>Insomnia</td>
<td>7 (5%)</td>
<td>19 (14%)*</td>
</tr>
<tr>
<td>Myalgia</td>
<td>10 (7%)</td>
<td>21 (15%)*</td>
</tr>
<tr>
<td>Nausea</td>
<td>9 (6%)</td>
<td>42 (30%)*</td>
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*p-value < 0.05 using Fisher’s exact test
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Results

San Antonio Breast Cancer Symposium, December 6-10, 2016

Linear mixed model results

Difference in average pain: 0.82 points (95% CI: 0.4 - 1.24), p=.0002

Results: Clinically Significant (2 point) Improvement in Joint Pain
Results of secondary objectives: Improvement in average value between study arms

- Worst joint pain: 1.06 points (95% CI: 0.55-1.57), p<0.0001
- Pain interference: 0.95 points (95% CI: 0.55-1.35), p<0.0001
- WOMAC (knee/hip): 11.9 points (95% CI: 8-15.81), p<0.0001
- M-SACRAH (hand): 13.56 points (95% CI: 8.88-18.24), p<0.0001

Results of secondary objectives: Improvement in average value between study arms

- FACT-ES TOI (QOL): 3.65 points (95% CI: 1.16 – 6.13), p=0.0042
- Depression (PHQ-9): 0.52 points (95% CI: -0.19-1.22), p=0.15

- Global Rating of Change Scale
  - Pain OR 1.69 (95% CI 1.15-2.5, p=0.0085)
  - Stiffness OR 3.8 (95% CI 1.82-7.92, p=0.0004)
Conclusions

• Treatment with duloxetine met the primary endpoint.

• Duloxetine was superior to placebo for the treatment of AIMSS among women with early stage breast cancer.

• Improvement in joint pain was noted in both study arms.

Conclusions

• Duloxetine was relatively well tolerated, consistent with trials of duloxetine for other indications.

• In addition to improvements in pain, duloxetine was associated with slight improvements in quality of life.
Take Home Message

• When compared with placebo, Duloxetine improved pain symptoms in breast cancer patients who take AI. However, duloxetine is associated with insomnia, fatigue, dry mouth
• WOMAC and M-SACRAH scales have items specific for arthritis and showed larger effects of duloxetine compared with placebo

Limitations

• Did not mention which patients benefited the most from duloxetine (e.g. patients with high level of pain prior to enrollment, etc.)
• No data on whether decreasing pain level lead to higher rates of AI adherence
• Is the primary endpoint of single item rating on the BPI sensitive enough for musculoskeletal joint pain?
• Is a 1 point difference in pain at 12 weeks clinically meaningful?
• Unexpected placebo response
Thank you