WELCOME to Boston
ASTRO’s 54th Annual Meeting
“Key Studies in Breast Cancer” News Briefing

Tuesday, October 30, 2012
7:00 – 7:45 a.m.

Bruce Haffty, MD, FASTRO
President-elect, ASTRO 2014
Improved Survival with Adjuvant Radiation in Elderly Women with Early-Stage Breast Cancer

Randi Cohen, MD, MS
University of Maryland School of Medicine
Assistant Professor
Background

• **Cancer and Leukemia Group B (CALGB):** women >70 yrs with favorable, early stage breast cancer who do not get radiation have an increased risk of the cancer returning in the breast, but did not affect how long the women lived.

• **Early Breast Cancer Trialists’ Collaborative Group (EBCTCG):** meta-analysis demonstrated that for every 4 breast cancer recurrences prevented, ~1 breast cancer death is avoided by 15 years.
Methods & Results

• Surveillance, Epidemiology, and End Results (SEER) database was queried to identify elderly women with the same favorable breast cancer features as in the CALGB study treated with breast conserving surgery +/- radiation.
• 29,949 women identified
• Median follow-up of 66 months
• 76% of all patients received radiation. By age groups, percent of patients receiving surgery + radiation:
  – Ages 70-74: 80%
  – Ages 75-79: 74%
  – Ages 80-84: 61%
### Results: Overall Survival

#### Multivariate Analysis – Overall Survival

<table>
<thead>
<tr>
<th>OS Variable</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>80-84</td>
<td>2.39</td>
<td>2.24-2.55</td>
</tr>
<tr>
<td>75-79</td>
<td>1.48</td>
<td>1.40-1.57</td>
</tr>
<tr>
<td><strong>No Radiation</strong></td>
<td><strong>1.56</strong></td>
<td><strong>1.48-1.64</strong></td>
</tr>
<tr>
<td>Tumor size:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>16-20mm</td>
<td>1.50</td>
<td>1.36-1.65</td>
</tr>
<tr>
<td>11-15mm</td>
<td>1.26</td>
<td>1.15-1.38</td>
</tr>
<tr>
<td>Race:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>1.39</td>
<td>1.18-1.65</td>
</tr>
<tr>
<td>White</td>
<td>1.28</td>
<td>1.13-1.46</td>
</tr>
<tr>
<td>Hispanic</td>
<td>1.23</td>
<td>1.03-1.46</td>
</tr>
<tr>
<td>Asian</td>
<td>1.00</td>
<td>--</td>
</tr>
<tr>
<td>Ductal histology</td>
<td>1.09</td>
<td>1.01-1.19</td>
</tr>
<tr>
<td>Lymph nodes examined</td>
<td>0.99</td>
<td>0.98-0.99</td>
</tr>
<tr>
<td>Married</td>
<td>0.82</td>
<td>0.78-0.86</td>
</tr>
</tbody>
</table>

#### Univariate Analysis – Overall Survival

<table>
<thead>
<tr>
<th>Radiation</th>
<th>No Radiation</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 yrs</td>
<td>88.6%</td>
</tr>
<tr>
<td>10 yrs</td>
<td>65.0%</td>
</tr>
<tr>
<td>15 yrs</td>
<td>39.6%</td>
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</tbody>
</table>
Results: Breast Cancer Survival

Multivariate Analysis

<table>
<thead>
<tr>
<th>CSS Variable</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumor size:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>16-20mm</td>
<td>4.22</td>
<td>3.02-6.06</td>
</tr>
<tr>
<td>11-15mm</td>
<td>2.49</td>
<td>1.79-3.57</td>
</tr>
<tr>
<td>6-10mm</td>
<td>1.60</td>
<td>1.15-2.31</td>
</tr>
<tr>
<td>Age: 80-84</td>
<td>1.47</td>
<td>1.22-1.78</td>
</tr>
<tr>
<td>No Radiation</td>
<td>1.41</td>
<td>1.20-1.66</td>
</tr>
<tr>
<td>Lymph nodes examined</td>
<td>0.98</td>
<td>0.97-0.99</td>
</tr>
<tr>
<td>Right sided breast cancer</td>
<td>0.82</td>
<td>0.71-0.95</td>
</tr>
<tr>
<td>Married</td>
<td>0.78</td>
<td>0.67-0.90</td>
</tr>
<tr>
<td>PR positive</td>
<td>0.76</td>
<td>0.64-0.91</td>
</tr>
</tbody>
</table>

Univariate Analysis – Breast Cancer Survival

<table>
<thead>
<tr>
<th></th>
<th>Radiation</th>
<th>No Radiation</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 yrs</td>
<td>98.3%</td>
<td>97.4%</td>
</tr>
<tr>
<td>10 yrs</td>
<td>95.5%</td>
<td>93.3%</td>
</tr>
<tr>
<td>15 yrs</td>
<td>91.4%</td>
<td>89.5%</td>
</tr>
</tbody>
</table>
Conclusions

• The use of radiation after breast conserving surgery was an independent predictor of overall survival & breast cancer specific survival.

• Limitation: Recurrence rates, margin status, and hormonal therapy data not available in SEER database.

• We anticipate the improvement of breast cancer specific survival is a result of decreased recurrence rates.

• The improvement in breast cancer survival with the addition of radiation suggests that in healthy, elderly women, adjuvant radiation should be strongly considered as part of their breast cancer treatment.
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Alexandra Hanlon, PhD
WELCOME to Boston
ASTRO’s 54th Annual Meeting
Implications of Omitting Radiation after Breast Conserving Surgery in Elderly Women with Low Risk Invasive Breast Cancer

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Departments of \textsuperscript{1}Radiation Oncology, \textsuperscript{2}Medicine, and \textsuperscript{3}Surgery
Introduction

• Standard management for early stage breast cancer consists of breast conserving surgery (BCS) and radiation (RT).
• The CALGB C9343 and Fyles et al randomized controlled trials (RCTs) identified older women with early estrogen receptor positive (ER+) breast cancer as a low risk group in whom RT may be omitted.
• The RCTs failed to show a survival advantage with RT after BCS in women who received tamoxifen.
• The NCCN amended its practice guidelines to reflect that RT may be omitted in women >70 years with ER+, stage I breast cancer who receive adjuvant hormonal therapy.
Specific Study Aims

• To assess changes in patterns of care in clinical practice with regard to utilization of RT after BCS in older patients with low risk invasive breast cancer

• To determine cancer specific (CSS) and overall survival (OS) outcomes with and without RT after BCS in a large population based cohort of favorable risk patients
Materials & Methods

• The Surveillance, Epidemiology, and End Results (SEER) database was queried for women ≥age 70 years diagnosed with T1 or T2, N0 M0 ER+ breast cancer that underwent BCS from 2000-2009.
  – Included patients were required to have:
    • Diagnosis of breast cancer as the first and primary malignant indicator
    • ICD-0-3 histology groupings for ductal and lobular neoplasms (8500-8549)
    • Active ongoing follow-up (minimum of 3 months )
  – Patients in whom RT administration was unknown or uncertain were excluded.
The proportion of patients receiving RT declined by 5.5% in the latter study period. On multivariate analysis, patients were less likely to undergo RT if diagnosis occurred between 2005-2009 (p<0.001).
Results: Breast Cancer-Specific Survival

Hazard ratio: 0.51 (95% CI 0.45-0.57)  
$p<0.001$

1045 deaths attributed to cancer

<table>
<thead>
<tr>
<th>Cause-specific survival</th>
<th>5y</th>
<th>8y</th>
</tr>
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<tbody>
<tr>
<td>BCS</td>
<td>95%</td>
<td>91%</td>
</tr>
<tr>
<td>BCS + RT</td>
<td>97%</td>
<td>95%</td>
</tr>
<tr>
<td>Absolute Difference</td>
<td>2%</td>
<td>4%</td>
</tr>
</tbody>
</table>
Results: Overall Survival

Overall survival

<table>
<thead>
<tr>
<th>Overall survival</th>
<th>5y</th>
<th>8y</th>
</tr>
</thead>
<tbody>
<tr>
<td>BCS</td>
<td>68%</td>
<td>50%</td>
</tr>
<tr>
<td>BCS + RT</td>
<td>87%</td>
<td>73%</td>
</tr>
</tbody>
</table>

Absolute Difference

| Absolute Difference | 19% | 23% |

Hazard ratio: 0.41 (95% CI 0.39-0.43)  
$p<0.001$

6056 total deaths
Conclusions

• RT delivery after BCS was associated with a reduction in the risk of breast cancer specific death.
• An evolution in the patterns of care was noted after 2004 with a 6% drop in RT utilization, even after adjustment for relevant factors.
• The perceptible shift in practice paradigm dovetailed the publication of the aforementioned RCTs.
• Treatment recommendations should be guided by a synthesis of best available aggregate evidence.
Cardiac Toxicity is Not Increased 25 Years After Treatment of Early-stage Breast Carcinoma with Mastectomy or Breast Conservation Therapy from the National Cancer Institute Randomized Trial

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Christopher Sibley, Tu D. Dan, Danielle M. Boyce, Sharon Smith, Marc Lippman, Eli Glatstein, David A. Bluemke, Kevin Camphausen, Nicole L. Simone

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October 29, 2012
NCI Breast Conservation Trial

Trial Registration Number: 79-C-0111

6 major randomized trials show BCT = MRM for outcomes for early stage breast cancer

NCI Breast Conservation Trial

- 237 patients with stage I-II breast cancer randomized from 1979-1986
  - Arm 1: Modified radical mastectomy + axillary dissection (level I/II)
  - Arm 2: Lumpectomy + axillary dissection (level I/II) → radiation
    - RT: 45-50.4 Gy whole breast +/- regional nodes, 15-20 Gy boost (Ir-192 or electrons)
    - CT simulation with dose inhomogeneity corrections
  - Node (+) patients (40%): AC (6-11 cycles)
  - TAM for postmenopausal N+ patients after 1985

Might treatment toxicity be causing separation of curves?
Cardiac Assessment

- Detailed history and physical exam
- Cardiac labs:
  - Lipid, CRP, homocysteine, HbA1c
  - ProBNP, creatinine, cystatin-c
- Imaging:
  - Cardiac MRI - evaluate anatomy and function
  - CT angiogram – evaluate coronary artery disease and coronary arterial calcium (CAC) score

50/102 (26 BCT, 24 MRM) remaining patients returned for follow-up
Results

• Arms similar for pt characteristics, exam, and labs

• Cardiac MRI
  – Left ventricular mass in BCT pts (91 gm vs. 110 gm, p=0.02)
    • Not significant after adjusting for systolic blood pressure
  – Peak midwall strain and chamber mass, volume and function all similar between arms

• CT Angiogram
  – Median CAC was similar [BCT 25 (IQR 0, 86) vs. MRM 0 (IQR 0, 354), p=0.65]
  – Atherosclerosis - no significant difference
    • MRM vs. BCT
    • Left vs. right side no change in LAD or any other vessel
  – Visible atherosclerosis with chemo (HR 2.4, 95% CI 0.94-6.32, p=0.07)
Conclusions

• 25 yrs after breast radiation, cardiac toxicity does not seem to be responsible for slight decrease in patient survival in the BCT arm

• No difference noted for left-sided vs. right-sided tumors

• Cardiac morbidity has been attenuated in patients treated with CT simulation and 3D planning

Patients with early-stage breast cancer treated with radiotherapy do not have a higher risk of long-term cardiac morbidity compared with patients having mastectomy
Conclusions

• Sildenafil citrate was associated with improved sexual function outcomes after radiotherapy when given to patients during and after RT for patients with prostate cancer.

• When controlled for baseline IIEF and age of patient significant improvement of the post-treatment IIEF and overall satisfaction of function was observed for those who took sildenafil citrate.

• Differences between the treatment groups became less apparent beyond 12 months from treatment.

• No benefit for this intervention was noted among patients treated with ADT.
Interim Toxicity Results From RAPID: A Randomized Trial of Accelerated Partial Breast Irradiation (APBI) Using 3D Conformal External Beam Radiation Therapy (3D-CRT)

TJ Whelan, I Olivotto, S Parpia, T Berrang, DH Kim, I Kong, P Truong, B Cochrane, JA Julian and the RAPID Trial Investigators

For the Ontario Clinical Oncology Group and Trans-Tasman Radiation Oncology Group
Whole Breast Irradiation (WBI)

- Given following breast conserving surgery
- Reduces local recurrence, prevents mastectomy and improves survival
- Despite benefits, it is estimated that up to 30% of women do not receive WBI
- Investigators have evaluated alternative approaches to WBI: Hypofractionation and Accelerated Partial Breast Irradiation
Accelerated Partial Breast Irradiation (APBI)

- Delivery of large dose/fraction to the surgical cavity plus 1-2cm margin
- Smaller treated volume permits radiation to be given in shorter period of time (≤1 week)
- Several techniques have been developed:
  - Multi-catheter interstitial brachytherapy
  - Balloon-based brachytherapy (Mammosite)
  - Intra-operative therapy
  - 3D conformal radiation therapy (3D-CRT)
Accelerated Partial Breast Irradiation (APBI)

- Many of the techniques are labor and resource intensive

- 3D-CRT is attractive:
  - Non invasive
  - Standard CT planning and external beam linear accelerators to shape and deliver the multiple fields required
  - Less costly
Recruited between Feb 2006 and Jul 2011
From centers in Canada, Australia and New Zealand

Results

2135 Patients Randomized

WBI
1065 Patients

3DCRT
APBI
1070 Patients
Interim Results*

Adverse Cosmetic Outcome (Fair or Poor) Nurse Assessment at Baseline and 3 Years

<table>
<thead>
<tr>
<th></th>
<th>WBI</th>
<th>APBI</th>
<th>Difference APBI – WBI (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline (n=1995)</td>
<td>17%</td>
<td>19%</td>
<td>2% (-2 – 5%)</td>
<td>0.35</td>
</tr>
<tr>
<td>3 Years (n=850)</td>
<td>19%</td>
<td>32%</td>
<td>13% (7 – 19%)</td>
<td>&lt; 0.0001</td>
</tr>
</tbody>
</table>

*median follow-up = 2.3 years
Conclusions

- APBI was associated with an adverse cosmetic outcome at 3 and 5 years
- Accompanied by an increase in G1, G2 toxicity. G3 toxicity was very uncommon
- Increase in toxicity may have resulted from:
  - Limited conformality of 3DCRT
  - Short time between fractions
  - Asymmetric nature of partial breast irradiation
- Further research is necessary to determine if there is a group of patients who can be treated with limited toxicity
Q & A
For additional questions or interviews, please contact the ASTRO Press Office 617-954-3461 or 617-954-3462

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