Regional Radiotherapy
in the Wake of Z11 and MA.20

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Conflict of Interest

- P.I. NIH R01
- P.I. DOD Multi-Team Award
- P.I. KOMEN Scholar Grant
- P.I. BCRF
- Varian Speakers Bureau
- BMS Scientific Advisory Board

Local Recurrence and Survival after Mastectomy: with vs without RT

Every 4 local recurrences avoided 1 BC death over the following 15 years, is avoided.
RT vs no RT after lumpectomy

Radiotherapy: Impact on mortality
(N+ Breast Cancer)

Chemo vs no Chemo  RT vs no RT

Post-mastectomy  Post-BCT


These results were achieved with standard axillary dissection and post-operative regional radiotherapy, in node positive patients.
Regional Radiotherapy in the Wake of Z11 and MA.20

Evidence from randomized trials

Current surgical practices and consequences to radiotherapy

NYU approach to regional radiotherapy

From the surgeon’s point of view:

s/p SNL vs LAND

RT ~ to LAND
NSABP B-04: 25 y follow up
N0: 1) Total mastectomy + ALND; 2) Total mastectomy + XRT; 3) Total mastectomy only

NCIC-CTG MA.20
post-BCS, high risk N- or N+
RT to breast alone
RT to breast and regional nodes (SC, Axilla and IM)

NCIC-CTG MA.20
1832 women enrolled
Median follow-up 62m

<table>
<thead>
<tr>
<th>Mean age</th>
<th>53.3 years</th>
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<tbody>
<tr>
<td>Nodal Status</td>
<td>5-year risk</td>
</tr>
<tr>
<td>N0</td>
<td>10%</td>
</tr>
<tr>
<td>1-3 LN+</td>
<td>85%</td>
</tr>
<tr>
<td>&gt; 3 LN+</td>
<td>5%</td>
</tr>
<tr>
<td>Adjuvant Systemic Therapy</td>
<td>90%</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>71%</td>
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<tr>
<td>Endocrine Therapy</td>
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5-year risk
Isolated locoregional DFS: 94.5% vs 96.8% (p = 0.02)
Distant DFS: 87.0% vs 92.4% (p = 0.002)
DFS: 84.0% vs 89.7% (p = 0.003)
OS: 96.7% vs 92.3% (p = 0.07)
Gr2+ pneumonitis: 0.2% vs 1.3% (p = 0.01)
Gr2+ lymphedema: 4.1% vs 7.5% (p = 0.004)
Positive SNL in early BC: is further axillary treatment necessary?

US: Z11 trial
Europe: EORTC AMAROS trial

Giuliano et al. JAMA 2011
ACOSOG Z0011

- A randomized trial of axillary node dissection vs none in patients with a positive SLN
- A non-inferiority trial (skipping ax dissection not inferior to doing it in SLN positive patients)
- 177 institutions, 813 patients
- The trial closed early

ACOSOG Z0011: STUDY DESIGN

Eligibility
- Clinical T1/T2 N0 M0 breast ca
- H & E detected mets in SN
- Lumpectomy WITH whole breast irradiation (WBI)
- Adjuvant systemic tx by choice

Ineligibility
- Nodal irradiation or APBI
- Mets on SN by IHC
- Matted nodes
- 3 or more involved nodes
- T3/T4 tumors
- Palpable lymph nodes

RESULTS

- For both groups: ~ 69% were T1
- 83% were ER +
- ~68% were PR+
- 35-40% had LVI
- Majority were Grade II
- Mean tumor size was 1.6-1.7cm
- Median age 55
RESULTS

• 27.4% of ALND patients had additional positive nodes, removed beyond SN
• SN-only patients had a median of 2 LN removed (range 1-4)
• 96% ALND and 97% SN had either chemo or hormone tx.

Median follow up 6.3 years

<table>
<thead>
<tr>
<th></th>
<th>ALND</th>
<th>SN</th>
</tr>
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<tbody>
<tr>
<td>Local</td>
<td>3.6%</td>
<td>1.8%</td>
</tr>
<tr>
<td>Regional</td>
<td>0.5%</td>
<td>0.9%</td>
</tr>
<tr>
<td>Combined</td>
<td>4.1%</td>
<td>2.8%</td>
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</table>

27% of SN+ALND had additional N+, yet regional recurrence very low, different than NSABP=04 or MA.20

SLND ALND P

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<thead>
<tr>
<th></th>
<th>SLND</th>
<th>ALND</th>
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<tbody>
<tr>
<td>LR (%)</td>
<td>1.8</td>
<td>3.6</td>
</tr>
<tr>
<td>DFS (%)</td>
<td>83.9</td>
<td>82.2</td>
</tr>
<tr>
<td>OS (%)</td>
<td>92.5</td>
<td>91.8</td>
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MULTIVARIATE ANALYSIS

Neither number of + SN, size of SN mets, nor # of LN removed associated with LR recurrence

Older age, ER neg and no adjuvant systemic tx = worse OS
Reasons for low LRR in Z11

LN eradicated by systemic therapy
LN disease eradicated by breast radiation
LN disease “biology” may be differently explained

ACOSOG currently reviewing Z11 RT fields (with sup border below humeral head and 2 cm of lung included = 80% coverage)

Regional Radiotherapy in the Wake of Z11 and MA.20

Evidence from randomized trials
Current surgical practices and consequences to the radiotherapy
NYU approach to regional radiotherapy
658 patients with clinical T1-2 tumors planned for BC: 335 in the pre-Z11 cohort and 323 post-Z11.

Surgeons were less likely to perform intra-operative nodal assessment post-Z11 (26% vs. 69%, p < 0.001) resulting in decreased median operative times for SLN-negative patients (79 vs. 92 min, p < 0.001).
EORTC ongoing study: AMAROS trial
(Results expected for 2013)

Regional Radiotherapy in the Wake of Z11 and MA.20

Evidence from randomized trials
Current surgical practices and consequences to the radiotherapy
NYU approach to regional radiotherapy

Late morbidity of breast radiotherapy:
SEEK registry data on 300,000 women

Cardiac Mortality Ratio (L vs R): 1.58 @10-14y

Ipsilateral Lung CA death also significantly increased

Darby SC Lancet Oncology 2005
NYU 05-181:
Positioning trial to optimally spare heart and lung, while assuring same coverage of breast

Prone always better in right BC and in 85% of left BC

JAMA 2012

Current NYU prone breast technique does not cover level I-II nodes

Alonso-Basanta et al. IJROBP 2008

5Y Outcomes of 490 patients in NYU prone breast trials (with concomitant boost)

<table>
<thead>
<tr>
<th>Event</th>
<th>Number of Events</th>
<th>%</th>
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<tbody>
<tr>
<td>In breast local recurrence</td>
<td>10</td>
<td>2</td>
</tr>
<tr>
<td>Regional recurrence</td>
<td>3</td>
<td>0.6</td>
</tr>
<tr>
<td>Contralateral breast cancer</td>
<td>6</td>
<td>1.2</td>
</tr>
<tr>
<td>Distant Metastases</td>
<td>5</td>
<td>1.0</td>
</tr>
<tr>
<td>Overall Survival</td>
<td>475/490</td>
<td>97</td>
</tr>
<tr>
<td>Death from Breast Cancer</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>Death from Other Cause</td>
<td>10</td>
<td>2</td>
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(submitted for publication)
Open NYU Nodal trial:
• Post axillary dissection (at least 8 nodes) with ≤5 positive nodes
• Prone breast and level III-SCV nodal radiation

Patient Set-Up

Phase III Study of Prone Accelerated IMRT to Treat the Breast, Level III Axilla and Supraclavicular Nodes

Rajni A. Sethi MD, Gabor Jozsef PhD, Hyun-Soo No BS, Judith D. Goldberg Sc.D, and Silvia C. Formenti MD

New York University School of Medicine
2012: NYU management of regional nodes

<table>
<thead>
<tr>
<th>RT policy</th>
<th>SNL/IA ND negative</th>
<th>SNL Positive (n LAND)</th>
<th>LAND Positive ≥ 8 nodes dissected</th>
<th>LAND 1-3 N+ ≥ 8 nodes dissected</th>
<th>LAND ≥ 4 N+, or &lt; 8 nodes dissected</th>
</tr>
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<tbody>
<tr>
<td>No nodal RT (breast RT prone trials)</td>
<td>X</td>
<td></td>
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<tr>
<td>Level III and SCV RT (ONC+ prone Trial offered)</td>
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<tr>
<td>Axilla and SCV RT, supine</td>
<td>X</td>
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Are we correctly integrating the biological information?

Shall we irradiate the draining nodes in every N+ breast cancer carrier?

Stromal gene expression predicts clinical outcome in breast cancer

Cluster 1 gene set: Th1 immune responses, CD8, granzyme

Cluster 2 gene set: M2 macrophages, angiogenesis, hypoxia, (CXCL1, IL-8, endothelin-1, osteopontin..)

Finak et al., Nature Medicine, 14:518-527, 2008
Acknowledgements

Stella Lymberis
Nelly Huppert
Rajni Sethi
Keith DeWyngaert
Gabor Jozsef
Stewart Becker
Christine Hitchen
Judith Goldberg
Maria Fenton-Kerimian
Martin Donach

The NYU therapists

our patients