Indications for Radiation Therapy and Selection of Treatment Fields After Preoperative Therapy

Thomas A. Buchholz, M.D.
Radiation and Preoperative Chemotherapy

Radiation Overview

• Important role in breast conservation therapy
• New questions with preoperative chemotherapy
  – indications for postmastectomy radiation
  – indications for lymph node irradiation
  – should decisions be effected by response?
  – what is the efficacy of radiation treatment?
Known facts about postmastectomy radiation
- Some patients are at risk for local recurrence
- In such patients, radiation
  - reduces the risk of local-regional recurrence
  - decreases the risk of subsequent metastases
  - improves cause-specific and overall survival
  - adds to the benefits of systemic therapy
Oxford Overview: Mastectomy +/- Postmastectomy Radiation Trials

**Lymph Node-Positive Disease**

- **Local Recurrence**
  - 29% vs. 8%
  - 72% reduction

- **Breast Ca Survival**
  - none in LN-
None of These Trials Included Patients Treated With Preoperative Chemotherapy
Preoperative Chemotherapy Affects Radiation Decisions

Historical indications for postmastectomy radiation

- Pathology based
- Consensus statements
  - tumor size > 5 cm
  - >4 positive lymph nodes
- Stage II w/ 1-3 +LN – unclear
- Not indicated for lymph node-negative disease
Neoadjuvant Chemotherapy Changes Pathological Extent Of Disease In Most Patients
Local-Regional Recurrence and Pathological Extent of Disease

Correlated pathology and local-regional recurrence

150 patients: preoperative chemotherapy
Mastectomy
Chemotherapy
No Radiation

1,031 patients: postoperative chemotherapy

Buchholz et al., Int J Radiat Oncol Biol Phys, 2003
Pathological Size of the Primary Tumor

- Adjuvant Preop: 0% for 0-2.0 cm, 10% for 2.1-5.0 cm, 20% for >5.0 cm
- Preop: 18% for 0-2.0 cm, 36% for 2.1-5.0 cm, 28% for >5.0 cm

Significance:
- $p = 0.014$ for 0-2.0 cm
- $p = 0.0002$ for 2.1-5.0 cm
- $p = 0.028$ for >5.0 cm
Pathological Nodal Status

$p = 0.143$

$p = 0.087$

$p < 0.0001$

5-Year LRR

<table>
<thead>
<tr>
<th>5-Year LRR</th>
<th>Adjuvant</th>
<th>Preop</th>
<th>Adjuvant</th>
<th>Preop</th>
<th>Adjuvant</th>
<th>Preop</th>
</tr>
</thead>
<tbody>
<tr>
<td>0+LN</td>
<td>7%</td>
<td>12%</td>
<td>10%</td>
<td>18%</td>
<td>53%</td>
<td></td>
</tr>
<tr>
<td>1-3+LN</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥4+LN</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>23%</td>
</tr>
</tbody>
</table>
The Risk of Local-Regional Recurrence According to a Pathological Extent of Disease is Different in Patients Treated with Preoperative Chemotherapy Compared to the Risk in Patients Treated with Initial Surgery
150 patients, 1974-1998 at MDACC

- treated on prospective clinical trials
- preoperative chemotherapy
- modified radical mastectomy
- no radiation therapy

Buchholz et al., JCO, 2002
Factors Associated with Local-Regional Recurrence

<table>
<thead>
<tr>
<th>Pretreatment Factors</th>
<th>Postoperative Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>• clinical stage</td>
<td>• number of positive lymph nodes</td>
</tr>
<tr>
<td>• clinical T stage</td>
<td>• primary tumor size</td>
</tr>
<tr>
<td>• clinical N stage</td>
<td>• tamoxifen use</td>
</tr>
</tbody>
</table>
Multivariate Analysis: Both Pre- and Post-Chemotherapy Factors are Important

<table>
<thead>
<tr>
<th>Factors</th>
<th>$p$ value</th>
<th>hazard ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>pretreatment stage III</td>
<td>$&lt;0.001$</td>
<td>4.5</td>
</tr>
<tr>
<td>$\geq 4$ positive lymph nodes</td>
<td>0.008</td>
<td>2.7</td>
</tr>
<tr>
<td>no tamoxifen use</td>
<td>0.027</td>
<td>3.9</td>
</tr>
</tbody>
</table>
Take Home Message

Risk for local-regional recurrence depends in part on the pretreatment stage of disease

- Stage III has relevant risk
- What about stage II?
Recurrences in Clinical Stage I/II

Garg et al., Int J Radiat Oncol Biol Phys, 2004
Recurrences in Stage II

- $n = 6$ (LRR 67%)
- $n = 84$ (LRR 6%)
- $n = 42$ (LRR 8%)

$P = < 0.0001$
NSABP B-18 (Mamounas, SABCS, 2003)

B-18 Study

- Mastectomy patients did not receive radiation
- 87% of pts in the trial had T1, T2 tumors
- 239 patients were treated with preoperative chemotherapy + mastectomy
Local-Regional Recurrence According to Response

10-yr LRR by Pathological Response

- breast pCR w/ LN- or LN+ (n=13) 0%
- residual disease w/ LN- 10.5%
- residual disease w/ LN+ 20.3%

Patients with 1-3+LN had similar risk as those with ≥4 +LN
Is Postmastectomy Radiation Therapy Effective?

(In the Setting of Neoadjuvant Chemotherapy)
Limited Available Data

713 patients
Neoadjuvant Doxorubicin → Mastectomy

136 patients
No XRT

579 patients
+ XRT

XRT: Non-randomized
6 consecutive prospective MDACC trials
1974-1998

Huang et al., JCO, 2005
Comparisons Between Groups

Irradiated patients had significantly worse:

- Clinical T3-4: RT 85%, No RT 56%
- Clinical N2-3: RT 44%, No RT 20%
- Minimal response: RT 24%, No RT 11%
- 4 or more pos. nodes: RT 39%, No RT 22%
- Close/pos. margins: RT 12%, No RT 3%

\[ P < .01 \text{ for all factors} \]
Local-Regional Recurrence

Rate of LRR

\[ P < .0001 \]

No Radiation

Radiation

22%

12%
Local-Regional Recurrence
By Extent of Disease

<table>
<thead>
<tr>
<th>Table 3. Ten-Year Actuarial Rates of LRR According to Clinical and Pathological Disease Status</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Factor</strong></td>
</tr>
<tr>
<td>-------------</td>
</tr>
<tr>
<td><strong>Clinical T-stage</strong></td>
</tr>
<tr>
<td>T1</td>
</tr>
<tr>
<td>T2</td>
</tr>
<tr>
<td><strong>T3</strong></td>
</tr>
<tr>
<td>T4</td>
</tr>
<tr>
<td><strong>Clinical N-stage</strong></td>
</tr>
<tr>
<td>N0</td>
</tr>
<tr>
<td>N1</td>
</tr>
<tr>
<td><strong>N2-3</strong></td>
</tr>
<tr>
<td><strong>Pathological tumor size, cm</strong></td>
</tr>
<tr>
<td>0-2</td>
</tr>
<tr>
<td><strong>2.1-5.0</strong></td>
</tr>
<tr>
<td>≥ 5.1</td>
</tr>
<tr>
<td><strong>No. of positive nodes</strong></td>
</tr>
<tr>
<td>0</td>
</tr>
<tr>
<td>1-3</td>
</tr>
<tr>
<td>≥ 4</td>
</tr>
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Abbreviation: LRR, local regional recurrence.
Local-Regional Recurrence

Clinical Stage I-II

Rate of LRR

Years

P = 0.82

Clinical Stage III

Rate of LRR

Years

P = 0.009

20% (no RT)

9% (RT)

Good pathologic response to chemotherapy

(0-5cm tumor, 0-3 nodes)
### Local-Regional Recurrence

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<th>Multivariate analysis</th>
<th>Hazard</th>
<th><em>P</em>-value</th>
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<tbody>
<tr>
<td>No radiation</td>
<td>4.1</td>
<td>.0001</td>
</tr>
<tr>
<td>≥20% pos. nodes</td>
<td>2.9</td>
<td>.0001</td>
</tr>
<tr>
<td>Stage ≥ IIIB</td>
<td>2.3</td>
<td>.001</td>
</tr>
<tr>
<td>Nodes sampled &lt; 10</td>
<td>2.0</td>
<td>.005</td>
</tr>
<tr>
<td>No tamoxifen</td>
<td>1.9</td>
<td>.034</td>
</tr>
<tr>
<td>ER negative</td>
<td>1.8</td>
<td>.014</td>
</tr>
<tr>
<td>Path size &gt;2cm</td>
<td>1.7</td>
<td>.026</td>
</tr>
</tbody>
</table>
Cause-Specific Survival

Univariate subset analysis  P-value
• clinical stage IIIB/C  0.002
• clinical T4 tumors  0.015
• 4 or more positive nodes  0.011

Radiation improved CSS ~ 20%
Cause-Specific Survival

Univariate Subset Analyses

Radiation improved CSS ~ 20%

Clinical T4

44% (RT) 24% (no RT)

P=.015

≥ 4 nodes

39% (RT) 18% (no RT)

P=.011

Stage IIIB/C

44% (RT) 22% (no RT)

P=.002
# Cause-Specific Survival

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<td>.0001</td>
</tr>
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<td>Path. tumor size &gt;0 cm</td>
<td>2.3</td>
<td>.001</td>
</tr>
<tr>
<td>≥4 positive nodes</td>
<td>2.1</td>
<td>.0001</td>
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<td>.004</td>
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<td>1.5</td>
<td>.003</td>
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Local-Regional Recurrences in Patients with a pCR

Clinical Stage II Disease
- no radiation: 0/20
- radiation: 0/10
- no LRR events

Clinical Stage III Disease
- n=62, 93%
- n=12, 67%

McGuire et al., Int J Radiat Oncol Biol Phys, in press
Patients with Stage III Disease and a pCR

**Freedom From Distant Metastases**
- +XRT: 88%
- -XRT: 41%

**Overall Survival**
- +XRT: 77%
- -XRT: 33%

p = .0006

P = 0.0016
Selecting Radiation Treatment Fields

(There is no data to guide clinicians in patients treated with neoadjuvant chemotherapy)
Postmastectomy Radiation and Treatment Field Selection

Postmastectomy Radiation and Lymphatic Radiation

- preoperative stage III disease - yes
- higher risk preoperative stage II disease – yes
  
  cofactors to consider: >2 cm residual primary, LVSI, extracapsular extension, close margins, >20% + LN

- lower risk preoperative stage II – risks/benefits
- stage II with pCR – most likely no
Possible Clinical Trial

Eligibility
Pretreatment Stage II/III Postoperative
• >4 cm primary
• -LN

Postmastectomy Radiation

Observation
Conclusions

After preoperative chemo and mastectomy:

• reduces local-regional recurrence
• deaths from breast cancer for selected patients

Radiation is indicated for:

• pretreatment stage III or clinical T3 tumor
• ≥4 positive nodes before or after chemotherapy
• selected patients with pretreatment stage II disease