THE EMERGING ROLE OF IMAGE-GUIDANCE FOR BREAST RADIOTHERAPY

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***No disclosures***

Learning Objectives

- Review the clinical targets for breast RT as a function of cancer stage
- Learn about innovative uses of advanced radiotherapy techniques for breast treatment
- Highlight the emerging role of IGRT to guide planning and treatment
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Breast Anatomy

Chestwall draining lymphatics

- Lymph nodes
- Nipple
- Areola

Supraventricular
- High axillary, spical, level II
- Mid-axillary, level II
- Axillary vein, low axillary, level I

Internal mammary

Pectoralis minor muscle

pN0(i+)
- ≤0.2 mm or clus of fewer than 200 cells

pN1a
- >0.2-2 mm or more than 200 cells
- 1-3 nodes (at least one tumor deposit >2.0 mm)

pN1b
- 4-9 nodes (at least one tumor deposit >2.0 mm)

Financial support for AJCC 7th Edition Staging Poster provided by the American Cancer Society
Breast Cancer Staging

<table>
<thead>
<tr>
<th>ANATOMIC STAGE/PROGNOSTIC GROUPS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I 0</td>
</tr>
<tr>
<td>Tis N0 M0</td>
</tr>
<tr>
<td>Stage IA T1 N0 M0</td>
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<tr>
<td>Stage IB T0 N1 T1 N1 M0</td>
</tr>
<tr>
<td>Stage IIA T0 N1 M0</td>
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<tr>
<td>Stage IIB T2 N1 M0</td>
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<tr>
<td>Stage IIIA T0 N2 M0</td>
</tr>
<tr>
<td>Stage IIIB T4 N0 M0</td>
</tr>
<tr>
<td>Stage IIC Any T3 M0</td>
</tr>
<tr>
<td>Stage IV Any T Any N M M1</td>
</tr>
</tbody>
</table>

**Early stage non-invasive cancer:**
DCIS

**Early stage invasive cancer:**
Small tumor and/or 0-3 positive nodes

**Locally advanced/inflammatory cancer:**
Large tumor and/or ≥ 4 positive nodes

**Metastatic cancer**

Breast Cancer Survival

Survival rates for all women diagnosed with breast cancer are:
- 89% at 5 years
- 82% at 10 years
- 77% at 15 years
Radiotherapy for Breast Cancer

- Radiotherapy is a locoregional treatment that is always combined with surgery & often with chemotherapy
- Goals of treating with RT:
  - To reduce local-regional recurrence
  - To improve disease-free survival
  - To improve overall survival?
  - To palliate

"Modeling of the data showed that the avoidance of 4 local recurrences by year 5 was associated with the avoidance of 1 breast cancer death by year 15…"

- '4-to-1’ relationship was also seen for trials randomizing patients with positive nodes to receive postmastectomy radiation therapy or not…
- Benefits of adding RT occur earlier for local control than for breast cancer mortality…
- Radiation was associated with a very small risk in complications…largely caused by excess cardiac disease.”
**RT for Stage 0**

- **Surgery**
- **Mastectomy**
- **Lumpectomy**

**Stage 0:** DCIS

**Stage 1/IIA:** small tumor, 1-3 nodes

**Stage IIB/III:** Large tumor and/or ≥ 4 nodes

CAVEAT: Highly simplified!

**Treatment Complete**

**Breast RT**

---

**RT for Stage I/IIA**

- **Surgery**
- **Mastectomy**
- **Lumpectomy**

**Stage 0:** DCIS

**Stage 1/IIA:** small tumor, 1-3 nodes

**Stage IIB/III:** Large tumor and/or ≥ 4 nodes

CAVEAT: Highly simplified!

**+-Chemotherapy**

**Treatment Complete**

**+-Chemotherapy**

**Breast RT**
Stage 0: DCIS
Stage I/IIA: small tumor, 1-3 nodes
Stage IIB/III: Large tumor and/or ≥ 4 nodes

CAVEAT: Highly simplified!

RT for Stage IIB/III

Pre-operative Chemotherapy → Surgery → Mastectomy → Post-operative Chemotherapy → Chestwall & nodal RT

Pre-operative Chemotherapy → Surgery → Lumpectomy → Post-operative Chemotherapy → Breast, chestwall, & nodal RT

Treatment Complete

RT for ~80%* of Breast Cancer Patients

In situ cancer: RT to breast
Early stage invasive cancer: RT to breast
Locally advanced/inflammatory cancer: RT to breast and chestwall

Patients with node-positive or high-risk node-negative disease treated with BCT and adjuvant chemotherapy and/or endocrine therapy were randomized to WBI or WBI plus regional nodal irradiation (RNI) to the internal mammary, supraclavicular, and high axillary lymph nodes.

Adding RNI significantly improved:
- Local-regional disease-free survival (96.8% vs 94.5%)
- Distant disease-free survival (92.4% vs 87.0%).

There was a trend towards improvement in overall survival (92.3% vs 90.7%, p=0.07)

RNI lowered the absolute risk of a distant metastatic event within 5 years of diagnosis, from 13% down to 7.7%.

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**Personalized Radiotherapy**

- **Prognostic factors:**
  - Tumor size & location
  - Nodal status
  - Histologic subtype & grade
  - Multifocality/multicentricity
  - Patient age/menopausal status
  - Receptor status (ER, PR, HER2-neu)
  - Resection margin distance
  - Lymphovascular invasion
  - Extracapsular extension
  - Genetic marker status (BRCA1, BRACA2)

- **Adjuvant hormone therapy:**
  - Tamoxifen
  - Aromatase inhibitor
  - Herceptin
Learning Objectives

- Review the clinical targets for breast RT as a function of cancer stage
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Radiotherapy Techniques

- 2D planning
- 3D CT-based planning
- Field-in-field (FIF) segments to modulate intensity of tangent beams
- Inverse-planned IMRT:
  - Multiple static gantry angles (coplanar or not)
  - Intensity-modulated arc therapy (VMAT, RapidArc)
- Partial breast irradiation (PBI)
  - Usually delivered in hypofractionated regimen
2D vs 3D Radiotherapy Planning

- Accepted 2D planning criteria:
  - Central lung distance (CLD) ≤ 3cm
  - Mean heart distance (MHD) ≤ 1.5cm
- “The 3D tangential plan failed to reduce the volumetric dose of lung and heart from that of a 2D plan.”


3D Radiotherapy Planning

- For opposed beams, dose to critical organs is a function of beam angles.
- 3D CT data but no target volumes contoured?
- 3D CT data used to:
  - Determine tangent angles
  - Match beams for IMN, supraclavicular nodes
  - Shield critical organs from radiation (design blocks)
  - Delineate surgical cavity
  - Optimize dose homogeneity within tangents
**FIF Radiotherapy Planning**

- “Beaumont technique” used aperture-based optimization constrained to traditional tangent fields
- Compared to planning with wedges, IMRT:
  - Significantly reduced moist desquamation
  - Significantly reduced palpable induration
  - Significantly reduced rates of grade 2 or greater dermatitis, edema, and hyperpigmentation
- Hypofractionated IMRT provides comparable toxicity…except:
  - Excludes acute dermatitis
  - No boost was given

*Shah et al., Practical Radiation Oncology, in press, 2012.*

**3D Radiotherapy Planning**

- “As the radiotherapy community moves to more comprehensively treat the regional lymphatics for potential improvements in survival in breast cancer patients, it seems that the current techniques may not be capable of meeting this challenge without potentially increasing the probability of late-onset treatment-related morbidities.
- The (Beaumont) techniques we have embraced are the necessary ‘stepping-stones’ to these more complex applications.”

Increased degrees of freedom, due to increased number of beam angles and radiation intensity levels, enables precise placement of steep dose gradients within the patient.

The use of many different beam angles results in low doses being delivered to the entire heart and contralateral lung, organs not irradiated conventionally.

Conclusions: “IMRT significantly improved conformity and homogeneity for plans when the breast + IMNs were in the CTV. Heart and lung volume receiving high doses were decreased, but more healthy tissue received low doses.”

Discussion: “Current practice is to use conformal IMRT if the plan results in an absolute reduction in heart V30 of 10% or greater compared to MWT or DIM technique.”

Role of IMRT for breast?

- “Requires complete development of MWT (≤3.5cm lung) or DIM plans to make the decision to use IMRT.
- Balancing the short- to medium-term benefits of reducing the volume of heart and left lung receiving a high dose of RT against the risk of later malignancy requires an individual assessment of the treatment volume goals and the patient's longevity prospects with and without RT.”


CTV Contouring for IMRT
7mm expansion to PTV

*Figure 1. Example of chestwall (green), AX (blue) SCV (cyan) nodes, IMNs (yellow), & expanded PTV (red colorwash) volumes.*
Are we treating more or less lung with PTV?

3D Plan

IMRT Plan

Are we treating more or less lung with PTV?

3D Plan

IMRT Plan
Are we treating more or less lung with PTV?

Solid Line = IMRT Plan, Dashed Line = 3D Plan
### IMRT vs. 3D to Right Breast/Cw, Nodes + Bilateral IMNs in 5 patients to 50.4Gy

<table>
<thead>
<tr>
<th></th>
<th>3D MEAN</th>
<th>STDEV</th>
<th>MIN</th>
<th>MAX</th>
<th>IMRT MEAN</th>
<th>STDEV</th>
<th>MIN</th>
<th>MAX</th>
<th>Significant at p &lt; 0.05</th>
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<tr>
<td><strong>Contralateral Breast</strong></td>
<td></td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>Mean Dose (cGy)</td>
<td>454</td>
<td>265</td>
<td>153</td>
<td>654</td>
<td>785</td>
<td>354</td>
<td>519</td>
<td>1170</td>
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<tr>
<td>V30Gy (%)</td>
<td>16.8</td>
<td>13.1</td>
<td>15.9</td>
<td>18.3</td>
<td>4.9</td>
<td>1.8</td>
<td>4.0</td>
<td>7.6</td>
<td>*</td>
</tr>
<tr>
<td>V20Gy (%)</td>
<td>25.6</td>
<td>11.7</td>
<td>22.7</td>
<td>30.3</td>
<td>12.5</td>
<td>9.3</td>
<td>13.1</td>
<td>16.5</td>
<td>*</td>
</tr>
<tr>
<td>V5Gy (%)</td>
<td>50.9</td>
<td>29.8</td>
<td>30.7</td>
<td>47.6</td>
<td>43.3</td>
<td>84.8</td>
<td>11.7</td>
<td>69.1</td>
<td>98.1</td>
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<tr>
<td>Mean Dose (cGy)</td>
<td>1408</td>
<td>1227</td>
<td>1269</td>
<td>1738</td>
<td>1209</td>
<td>1044</td>
<td>1085</td>
<td>1540</td>
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<tr>
<td><strong>Ipsilateral Lung</strong></td>
<td></td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>Mean Dose (cGy)</td>
<td>50.6</td>
<td>4.9</td>
<td>44.4</td>
<td>56.3</td>
<td>62.9</td>
<td>10.0</td>
<td>55.6</td>
<td>82.0</td>
<td>82.6</td>
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<tr>
<td>V30Gy (%)</td>
<td>53.8</td>
<td>10.6</td>
<td>56.4</td>
<td>81.9</td>
<td>38.1</td>
<td>10.7</td>
<td>45.3</td>
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<td>V20Gy (%)</td>
<td>60.5</td>
<td>12.9</td>
<td>83.0</td>
<td>99.7</td>
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<td>10.0</td>
<td>55.6</td>
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<td>82.6</td>
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<td>Mean Dose (cGy)</td>
<td>31.1</td>
<td>269.2</td>
<td>218</td>
<td>340</td>
<td>2319</td>
<td>364.1</td>
<td>1875</td>
<td>2723</td>
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<tr>
<td><strong>Whole Lung</strong></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean Dose (cGy)</td>
<td>20.9</td>
<td>240</td>
<td>1680</td>
<td>2252</td>
<td>1594</td>
<td>294</td>
<td>1245</td>
<td>1851</td>
<td>*</td>
</tr>
<tr>
<td>V20Gy (%)</td>
<td>18.2</td>
<td>6.4</td>
<td>10.1</td>
<td>24.4</td>
<td>14.7</td>
<td>3.9</td>
<td>12.0</td>
<td>20.5</td>
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<tr>
<td>Cord Max Dose (cGy)</td>
<td>1093</td>
<td>821</td>
<td>398</td>
<td>2254</td>
<td>1732</td>
<td>728.1</td>
<td>1085</td>
<td>2945</td>
<td>*</td>
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<tr>
<td>PTV</td>
<td>0.44</td>
<td>0.24</td>
<td>0.13</td>
<td>0.63</td>
<td>0.70</td>
<td>0.12</td>
<td>0.57</td>
<td>0.88</td>
<td>*</td>
</tr>
</tbody>
</table>

### Partial Breast Irradiation

- **Rationale:**
  - Ipsilateral recurrences primarily occur near tumor bed
  - “Elsewhere” tumor rate comparable to that in contralateral breast (<15% at 13 years)
- **Target volumes (per NSABP B-39/RTOG 0413):**
  - GTV = Surgical cavity (delineated by clips)
  - CTV = GTV + 1.5cm **Quadrentectomy**
  - PTV = CTV + 1cm
- **Delivered in hypofractionated regimen**

Recent Radiotherapy Trends

- More frequent regional nodal irradiation
- More frequent tumor bed or chestwall boost
- Partial breast irradiation for select patients
- Hypofractionated regimens (WBI & PBI)
- Contouring targets (per RTOG breast atlas)

Learning Objectives

- Review the clinical targets for breast RT as a function of cancer stage
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IGRT Goals

- To deliver higher tumor dose while sparing nearby critical organs
- To improve setup accuracy by accounting for:
  - Geometric uncertainties
  - Organ motion
- Serve as a QA and safety tool to verify treatment accuracy
- “IGRT provides the means to measure geometrical offsets and develop more accurate PTV margins.”
  (Bujold et al., Semin Radiat Oncol 22:50-61, 2012)
- Instead of relying on surrogates for positioning (i.e., bony landmarks), use tumor itself if visible or has implanted fiducials

IGRT to Optimize PTV Margins

- 14 patients receiving inverse-planned, multi-beam IMRT to cw + regional nodes (+ IMNs)
- Daily kV positioning for 450 treatment fractions
- Only translational shifts following correction for patient rotation were included
- Systematic and random components of error were computed following the methodology of van Herk

\[ PTV_{margin} = 2.5 \cdot \Sigma + 0.7 \cdot \sigma \]

Results to be presented at ASTRO 2012.
While a uniform 7mm PTV margin would account for setup errors in more than 90% of treatment sessions, approximately 1/3 of the treatment sessions would be implemented without correction for rotations by forgoing daily image-guidance.

Results to be presented at ASTRO 2012.
Surgical Clip Locations
Surgical Clip Locations

Clip Location Comparison

Free-Breathing Scan
Clip Location Comparison

Gated Scan

3D Euclidian Distance = 1.6mm

Clip Location Comparison

CBCT Scan

3D Euclidian Distance = 7.0mm
Rotational/Translational Error Misinterpretation

“Error can be introduced by a rotational shift….Point A, the measured isocenter, is offset by the translational error from Point O, the true origin. An increase in the degree of rotation results in a corresponding increase in the calculation error.”


Rotational/Translational Error Misinterpretation

- Error misinterpretation is exacerbated for large targets:
  - Chestwall + RN PTV average volume: 1404 ± 479 cc
  - Right lung average volume: 1442 ± 379 cc
  - Left lung average volume: 1228 ± 335 cc
- Average 3D displacement of 20 clips in CBCT (3.2mm) compared to gated scan (1.6mm)
- Deformation (e.g., shoulder joint) can affect translational misinterpretation
Can PTV Margin Be Reduced?

<table>
<thead>
<tr>
<th></th>
<th>AP (cm)</th>
<th>SI (cm)</th>
<th>LR (cm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Absolute shifts (± SD)</td>
<td>0.18 (±0.24)</td>
<td>0.25 (±0.25)</td>
<td>0.23 (±0.24)</td>
</tr>
<tr>
<td>% shifts within 5 mm</td>
<td>90.89</td>
<td>79.78</td>
<td>64.44</td>
</tr>
<tr>
<td>% shifts within 7 mm</td>
<td>97.33</td>
<td>92.89</td>
<td>94.22</td>
</tr>
<tr>
<td>% shifts within 10 mm</td>
<td>99.11</td>
<td>98.44</td>
<td>98.44</td>
</tr>
<tr>
<td>Total setup error (M) cm</td>
<td>-0.006</td>
<td>-0.012</td>
<td>-0.060</td>
</tr>
<tr>
<td>SD of systematic error (E)</td>
<td>0.058</td>
<td>0.16</td>
<td>0.17</td>
</tr>
<tr>
<td>SD of random error (σ)</td>
<td>0.30</td>
<td>0.34</td>
<td>0.30</td>
</tr>
<tr>
<td>PTV expansion (cm)</td>
<td>0.35</td>
<td>0.63</td>
<td>0.63</td>
</tr>
</tbody>
</table>

Table 1: Setup errors and PTV expansions for 14 patients with clips.

Reduction of PTV Expansion from 7mm to 0mm

0 mm margin

7 mm margin
Reduction of PTV Expansion from 7mm to 0mm

Lung $V_{30} \downarrow 9\%$

Reduction of PTV Expansion from 7mm to 0mm

Lung $V_{20} \downarrow 8\%$
Surface Imaging as a Surrogate for kV?

- Post-mastectomy chestwall targets expected to be less affected by deformation than breast
- We investigated the accuracy of 3D surface matching using AlignRT (v4.5) compared to positioning with daily orthogonal kV imaging
- 130 surfaces from 10 patients:
  - Immobilized with upper/lower custom alphacradles
  - Treated *without* respiratory management
  - Treated with inverse-planned IMRT to cw + nodes
  - Setup with skin marks/kV imaging only

Surface Imaging

3D surface image and ROIs selected for registration.

Results presented in Poster SU-E-J-70
Results presented in Poster SU-E-J-70

Discrepancy between surface imaging & kV was > 0.5cm in 28% of surfaces.

Slope = 0.91
R = 0.64

Discrepancy between surface imaging & kV was > 0.5cm in 2.5% of surfaces.

Slope = 0.91
R = 0.86
Registration of ‘cw’ ROI

Registration of ‘All’ yielded rotation of 0.47°.

‘All’: 0.27° ± 0.18°
‘Cw’: 0.62° ± 0.58°

Surface registration depends upon the ROI

A smaller ROI (‘cw’) showed:
- Higher correlation with kV shifts
- Less stability when calculating table rotations

Before clinical implementation:
- Investigate the sources of error that prevent a direct one-to-one correlation between AlignRT and kV 3D shifts (e.g., respiratory motion, misinterpretation errors due to kV imaging)
- Reconcile frequent mismatch (> 25%) between kV & AlignRT shifts > 0.5cm

Surface Imaging: Conclusions
IGRT Limitations

- “Variability in repositioning is dominated by the ability of therapists to make small, controlled changes in the position of the patient.”
  (Milliken et al., Int J Rad Onc Biol Phys, 38(4):855-866, 1997)

- IGRT does not preclude need for:
  - Good immobilization
  - Adequate PTV margins
  - Common sense!

Conclusions

- Breast RT undergoing significant clinical changes with advent of new technology:
  - Larger target including nodes (MA.20 trial)
  - Smaller target (PBI trials)

- To make impact on survival, planning techniques need to harness the power of IGRT:
  - Improve dosimetric conformity
  - Reduce PTV margins in order to spare critical organs
  - Improve positioning accuracy for large target by detecting/correcting deformations
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Carla Rash, B.A.

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