New Modalities for Breast Cancer

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Disclosures

• Accuray Talk at ASTRO 10/2015.
• Xoft provided slides for the partial breast radiation equipment.
Outline

• Early Stage:
  • Deep Inspiratory Breath Hold (DIBH)
  • TomoDirect
  • Hypofractionated, faster treatment
  • Partial breast radiation

• Locally Advanced:
  • Axillary radiation versus axillary surgery for locally advanced breast
  • Re-emergence of treatment of IMLN

• Stage IV:
  • Oligometastatic breast cancer radiation: palliative versus more definitive SBRT
Early Stage Breast
Early stage Breast: Standard

- Breast conserving surgery (i.e. lumpectomy, partial mastectomy)
- Postop whole breast radiation
- 25 days to whole breast
- 5-8 days to tumor bed boost depending on surgery margin status
- 5 days boost most common for negative surgical margins
Early stage Breast standard tangents

• Insert picture of standard tangents
Breast Standard Tangents

• Standard tangents had hotspots at periphery of breast and at nipple areolar complex
• Optimized breast tangents use a technique “field in field” so that radiation dose is evenly spread throughout breast and hotspots are minimized
Early breast standard tangents

• With and without field in field show 2 pictures side by side
Different Techniques of Whole Breast Coverage

• City of Hope: use of Tomotherapy Machine versus standard linear accelerator for whole breast radiation tangents
• Tomotherapy Direct versus Standard breast tangents
• Goal: can improve dose delivery to breast
• Spare normal organs lung, heart
Notice:
Angle 226.0 passes through couch before reaching the target.

Display Options:
- Lines and Wash
- Lines Only
- Wash Only
- View Entire Treatment

Targets:
- Display: On
- Color: Red
- Name: CTV
- Use: On
- Angle: 33.0
- Angle: 226.0

Regions at Risk:
- Display: On
- Color: Red
- Name: CTV
- Name: Lung-RI
- Name: Border-Inferior
- Name: Border-Medial
- Name: Scar
Right breast contour: more conformal dose with TomoDirect
Lung optimized to be ~equivalent (V5, V20)
Same patient showing heart DVH
CTV = tumor bed boost: more conformal with TomoDirect
This patient initial plan using the breast contour PTV – breast PTV better coverage on TomoDirect but lung worse (standard 3DCRT breast plan generated respecting treating less than 1.5cm-2cm lung)
Same patient now optimized (medial 239 degree to 242 degree)
Equivalent right ipsilateral lung dose
Still better breast coverage with TomoDirect over Tangents
Techniques for whole breast radiation

- Deep Inspiratory Breath Hold (DIBH)
- Left sided breast tumors
- Decrease heart dose
- Future: right sided and decrease unnecessary liver dose!
DIBH technique
DIBH Technique
DIBH = Decrease Heart XRT
Early stage Breast and Radiation: Treat faster, higher dose per day.

• Whole breast radiation
• Standard radiation is 5-6 weeks.
• Hypofractionated radiation is 3-4 weeks.
• Boost standard ~1 week duration after whole breast radiation.

• With Faster radiation our main concerns are:
  • 1. protecting normal tissue as we go faster with more radiation per day
  • Cosmesis and keeping breast dose homogeneous
  • 3 Techniques I just discussed can help with these concerns (DIBH or tomotherapy or optimizing breast tangents)
Hypofractionated Breast Regimen: faster whole breast radiation

- Whelan NEJM 2010
  - One of the early papers
  - Phase III 16 days versus 25 days breast radiation 16 days (2 weeks faster!)

- Results (10+ year followup):
  - Local Control in breast similar
  - Cosmesis of breast similar

- **Caveats:**
  - trend for worse local control if grade 3 (but other papers have debated this)
  - Women with larger breasts excluded from trial (i.e. separation >25cm)
  - Systemic chemotherapy may be worse cosmesis (but other papers have debated this)
  - No boost radiation in this paper (subsequent papers have used boost with the faster radiation regimen)
Whelan NEJM 2010
Figure 2. Hazard Ratios for Ipsilateral Recurrence of Breast Cancer in Subgroups of Patients.
RTOG 1005 – now closed. Finish radiation even faster?

**RTOG 1005**

A Phase III Trial of Accelerated Whole Breast Irradiation with Hypofractionation plus Concurrent Boost versus Standard Whole Breast Irradiation Plus Sequential Boost for Early-Stage Breast Cancer

**SCHEMA (6/21/11)**

<table>
<thead>
<tr>
<th>S</th>
<th>T</th>
<th>R</th>
<th>A</th>
<th>T</th>
<th>I</th>
<th>F</th>
<th>Y</th>
<th>Histologic Grade</th>
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</thead>
<tbody>
<tr>
<td>Age</td>
<td>&lt; 50 vs. ≥ 50</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1, 2 vs. 3</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>Yes vs. No</td>
<td></td>
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</table>

**ARM 1:** Standard fractionation

Whole Breast 50.0 Gy/25 fractions/2.0 Gy daily

Optional fractionation of 42.7 Gy in 16 fractions permissible

Sequential Boost 12.6 Gy/6 fractions/2.0 Gy daily or 14.0 Gy/7 fractions/2 Gy daily

**ARM 2:** Hypofractionation (15 fractions total)

Whole Breast 40 Gy/15 fractions/2.67 Gy daily

Concurrent boost 48.0 Gy/3.2 Gy daily

**Whelan:** 16 days whole breast + 5 days boost = 21 days
Treat even faster: radiation in the OR suite during the breast cancer operation

- Select patients only
- ASTRO guidelines
<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Suitable</th>
<th>Cautionary</th>
<th>Unsuitable</th>
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<tbody>
<tr>
<td>Age</td>
<td>&gt;=60 yo</td>
<td>50-59 yo</td>
<td>&lt;50 yo</td>
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<tr>
<td>BRCA1, BRCA 2</td>
<td>No</td>
<td>If present</td>
<td></td>
</tr>
<tr>
<td>Tumor Size</td>
<td>&lt;=2cm</td>
<td>2.1-3cm</td>
<td>&gt;3cm</td>
</tr>
<tr>
<td>T stage</td>
<td>T1</td>
<td>T0 or T2</td>
<td>T3 or T4</td>
</tr>
<tr>
<td>Margins</td>
<td>Negative by &gt;=2mm</td>
<td>Close &lt;2mm</td>
<td>Positive margins</td>
</tr>
<tr>
<td>Grade</td>
<td>Any</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVS1</td>
<td>No</td>
<td>Limited/focal</td>
<td>extensive</td>
</tr>
<tr>
<td>ER status</td>
<td>Positive</td>
<td>Negative</td>
<td></td>
</tr>
<tr>
<td>Multicentric Tumor?</td>
<td>No unicentric only</td>
<td></td>
<td>Multicentric</td>
</tr>
<tr>
<td>Multifocal</td>
<td>Clinically unifocal</td>
<td>Microscopic multifocal allowed but total tumor &lt;3cm</td>
<td>multifocal</td>
</tr>
<tr>
<td>Histology</td>
<td>Invasive ductal</td>
<td>Invasive lobular</td>
<td></td>
</tr>
<tr>
<td>Pure DCIS</td>
<td>No</td>
<td>&lt;=3cm</td>
<td>&gt;3cm</td>
</tr>
<tr>
<td>EIC</td>
<td>No</td>
<td>&lt;=3cm</td>
<td>&gt;3cm</td>
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<tr>
<td>Associated LCIS</td>
<td>Okay</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N stage</td>
<td>pN0 (i-, i+)</td>
<td>pN1, pN2, pN3</td>
<td>None performed</td>
</tr>
<tr>
<td>Nodal surgery</td>
<td>SLN or ALND</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Intraoperative Radiation Therapy (IORT)

Radiation therapy at the time of lumpectomy
Breast Cancer: Evolution of Radiation Therapy

1950 - Present
6 - 7 weeks of treatment
WBRT

1992 - Present
5 days twice a day
APBI

2000 - Future
As little as 8 min. during surgery
IORT
Xoft Axxent Electronic Brachytherapy (eBx) System

A multi-platform system of care FDA cleared for use anywhere in the body.

- IORT
  - BREAST
  - REST OF BODY

- APBI

- SKIN

- GYN
  - ENDOMETRIAL
  - CERVICAL

One System. Multiple Solutions.
Xoft Breast Intraoperative Radiation (IORT)

- Targeted radiation is delivered directly to the tumor bed at lumpectomy
- 50 kV low energy, high dose, isotope-free, stepping X-ray source is unique to Xoft
  - Allows for safe placement of source into surgical site without need for shielded bunker
- Mobile, multi-platform system offers significant patient and cost advantages
X-ray Source

- Miniaturized x-ray tube
- Operates at 50 kV and 300 microamps (15 Watts)
Axxent MPX Controller Components

- Display screen/touch screen control
- Computer screen
- Handheld barcode scanner
- Adjustable arm (in storage position)
- Wheel brakes
- Well chamber
MPX Controller Components

Source high voltage cable attachment

Source connected to source nest

Applicator hub attachment
Early T stage Breast Cancer with lymph node positivity

- Previous section was covering only early stage breast cancer and cN0 and pN0
  - Standard techniques: whole breast. Some cases partial breast.

- What radiation fields to use in the case of SLN positive?
- Historically full ALND was done, over 10 lymph nodes removed
- Total number of lymph nodes and other patient characteristics would determine radiation fields
  - i.e. treat chest wall where breast was versus chest wall and regional lymph nodes

- Recent Trials have led to less surgery and more axillary radiation:

- **Radiotherapy or surgery of the axilla after a positive sentinel node in breast cancer (EORTC 10981-22023 AMAROS):** a randomised, multicentre, open-label, phase 3 non-inferiority trial
AMAROS Trial – if less surgery more lymph node targeted radiation

• Traditional postmastectomy radiation fields:
• Treat chest wall and part of regional lymph nodes
• Not full coverage of lymph nodes because most patients traditionally got full axillary lymph node dissection
• Sentinel lymph node has led to less surgery
• We know if SLN positive, risk of further lymph nodes over 20%
• If no full axillary lymph node dissection after surgery, then current plan is for full axillary lymph node radiation
AMAROS

• Axillary lymph node dissection (ALND) versus
• Axillary lymph node radiation (AxRT) and only sentinel lymph biopsy (SLN)

• AxRT:
  • Cover axilla level I, II, III, medial supraclavicular LN (only 10% added internal mammary lymph nodes)

• Results:
  • AxRT noninferior to ALND (5yr DFS ~83%, 5yr OS ~93%)
  • Less clinical lymphedema in AxRT arm (11% vs 23% at 5yrs)
AMAROS and lymphedema

Table 2

<table>
<thead>
<tr>
<th>Clinical sign of lymphoedema in the ipsilateral arm</th>
<th>Axillary lymph node dissection</th>
<th>Axillary radiotherapy</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>3/655 (&lt;1%)</td>
<td>0/586 (0%)</td>
<td>0.25</td>
</tr>
<tr>
<td>1 year</td>
<td>114/410 (28%)</td>
<td>62/410 (15%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>3 years</td>
<td>84/373 (23%)</td>
<td>47/341 (14%)</td>
<td>0.003</td>
</tr>
<tr>
<td>5 years</td>
<td>76/328 (23%)</td>
<td>31/286 (11%)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Arm circumference increase &gt;10% of the ipsilateral upper or lower arm, or both</th>
<th>Axillary lymph node dissection</th>
<th>Axillary radiotherapy</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>33/655 (5%)</td>
<td>24/586 (4%)</td>
<td>0.497</td>
</tr>
<tr>
<td>1 year</td>
<td>32/410 (8%)</td>
<td>24/410 (6%)</td>
<td>0.352</td>
</tr>
<tr>
<td>3 years</td>
<td>38/373 (10%)</td>
<td>22/341 (6%)</td>
<td>0.080</td>
</tr>
<tr>
<td>5 years</td>
<td>43/328 (13%)</td>
<td>16/286 (5%)</td>
<td>0.0009</td>
</tr>
</tbody>
</table>

Data are n/N (%), unless otherwise specified.
Guidelines for lymph node irradiation
Radiation fields with AMAROS versus traditional

• Show three field including or not including full axilla
Internal Mammary Lymph nodes Techniques

• regional lymph node area
• Historically omitted. Low recurrence. More risk of lung and heart dose
• Recent papers (MA.20) have brought back consideration of IMLN to help improve locoregional control
• More treatment of internal mammary lymph nodes considered now
• -- lung and heart still issue
• -- deep inspiratory breath hold can help
• Balance of treating internal mammary lymph nodes versus damage to normal heart and lung
• -- unclear role in modern chemotherapy era with H2N targeted agents such as trastuzumab and pertuzumab which also have risk of damage to heart
Fields for IMLN

• Partial wide tangents, electron/photon match
Full Circle – treat vs. no treat regional lymph nodes?

Clinically T1–3, N1 Breast Cancer
Documented Positive Axillary Nodes by FNA or by Core Needle Biopsy

Minimum of 12 Weeks of Standard Neoadjuvant Chemotherapy
Plus Anti-HER2 Therapy for Patients with HER2-Positive Tumors

Definitive Surgery with Histologic Documentation of Negative Axillary Nodes
(Either by Axillary Dissection or by Sentinel Node Biopsy = Axillary Dissection)

STRATIFICATION
- Type of surgery (mastectomy, lumpectomy)
- Hormone receptor status (ER-positive and/or PgR-positive: ER- and PgR-negative)
- HER2 status (negative, positive)
- Adjuvant chemotherapy (yes, no)
- pCR in breast (yes, no)

RANDOMIZATION

Arm 1
(Groups 1A and 1B)*, **
No Regional Nodal XRT
- Group 1A Lumpectomy: No regional nodal XRT with WBI
- Group 1B Mastectomy: No regional nodal XRT and no chestwall XRT

Arm 2
(Groups 2A and 2B)*, **
Regional Nodal XRT
- Group 2A Lumpectomy: Regional nodal XRT with WBI
- Group 2B Mastectomy: Regional nodal XRT and chestwall XRT

NSABP B51
Stage IV Breast Cancer

- Traditionally palliative radiation given to sites of pain, low dose radiation
- Push for more aggressive treatment when stage IV oligometastatic (i.e. less than 5 metastatic sites)
  - → stereotactic body radiation treatment (SBRT)
- NRG has two national trials using SBRT for stage IV breast cancer
NRG trials for SBRT and stage IV breast cancer

• Very select group of stage IV breast cancer patients
• Excludes breast cancer patients with brain metastases

• NRG BR001: A Phase 1 Study of Stereotactic Body Radiotherapy (SBRT) for the Treatment of Multiple Metastases (breast, lung, prostate). <= 4 metastases
• NRG BR002: A Phase IIR/III Trial of Standard of Care Therapy with or without Stereotactic Body Radiotherapy (SBRT) and/or Surgical Ablation for Newly Oligometastatic Breast Cancer <=4 metastases. If <=2 metastases one metastases must be single liver, lung, or abdominal, cervical lymph node
Stage IV Breast Cancer and SBRT

- Treatment in 1, 3 or 5 days
- Much shorter treatment
- Dose is much higher than traditional palliative radiation for pain, prevent bone fracture, etc.
SBRT -- slide courtesy of S. Chmura, MD

1) Multiple Treatment Sites
2) Varying dose/fraction

<table>
<thead>
<tr>
<th>Metastatic Locations</th>
<th>Initial Starting Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung—Peripheral</td>
<td>45 Gy (3 fractions)</td>
</tr>
<tr>
<td>Lung—Central</td>
<td>50 Gy (5 fractions)</td>
</tr>
<tr>
<td>Mediastinal/Cervical Lymph Node</td>
<td>50 Gy (5 fractions)</td>
</tr>
<tr>
<td>Liver</td>
<td>45 Gy (3 fractions)</td>
</tr>
<tr>
<td>Spinal/Paraspinal</td>
<td>30 Gy (3 fractions)</td>
</tr>
<tr>
<td>Osseous</td>
<td>30 Gy (3 fractions)</td>
</tr>
<tr>
<td>Abdominal-pelvic metastases (lymph node/adrenal gland)</td>
<td>45 Gy (3 fractions)</td>
</tr>
</tbody>
</table>
Address questions in talk?
Acknowledgements

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  - Jeffrey Wong, MD
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  - An Liu, PhD

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  - Robert Martin
  - Thomas Joseph
  - Peter Tsai