Radiotherapy Pearls
at SABCS 2019

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University of Wisconsin
Radiotherapy Pearls at SABCS 2019

• Accelerated partial breast or whole breast irradiation after breast conservation surgery for patients with early breast cancer: 10-year follow up results of the APBI IMRT Florence randomized phase 3 trial (Meattini et al)

• Adverse effects of breast radiation (Karen Hoffman)
  • Identifying patients at higher risk of acute toxicity after breast radiotherapy: analysis of patient reported outcomes in the Michigan Radiation Oncology Quality Consortium cohort (Jagsi et al)
  • Risk of radiation induced secondary malignancies in BRCA carriers following breast cancer radiotherapy (Schlosser et al)

• Plenary session: The Role of Radiotherapy Combined with Immunotherapy in Oligometastatic Cancer (Ralph Weichselbaum)
**APBI IMRT Florence**

**Phase III trial (n=520 patients)**
- Breast conserving surgery
- pT <25 mm
- Final surgical margins ≥5 mm
- Age >40 years

**APBI using IMRT**
- 30 Gy in 5# non-consecutive

**CF-WBI**
- 50 Gy in 25# + 10 Gy in 5# boost

**Primary endpoint**
- IBTR

**Secondary endpoints**
- Overall (OS) and breast cancer specific-survival (BCSS)
- Contralateral breast cancer (CBC)
- Early and late toxicity
- Physician-rated cosmesis

**Follow Up**

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Ipsilateral Breast Tumour Recurrence

**HR (APBI) 1.57**
[95% CI 0.56-4.41], p = 0.39

<table>
<thead>
<tr>
<th></th>
<th>APBI</th>
<th>WBI</th>
</tr>
</thead>
<tbody>
<tr>
<td>10-yr IBTR, n</td>
<td>9</td>
<td>6</td>
</tr>
<tr>
<td>10-yr IBTR, %</td>
<td>3.9</td>
<td>2.6</td>
</tr>
</tbody>
</table>

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5- and 10-year event rate according to allocated group (ITT population)

<table>
<thead>
<tr>
<th>Event</th>
<th>Total°</th>
<th>5-year</th>
<th>10-year</th>
<th>P-value</th>
<th>5-year</th>
<th>10-year</th>
<th>P-value</th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>APBI</td>
<td>WBI</td>
<td></td>
<td>APBI</td>
<td>WBI</td>
<td></td>
</tr>
<tr>
<td>Ipsilateral breast tumour recurrence</td>
<td>17</td>
<td>6 2.4</td>
<td>3 1.2</td>
<td>0.31</td>
<td>9 3.3</td>
<td>6 2.6</td>
<td>0.39</td>
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<tr>
<td>Local relapse</td>
<td>10</td>
<td>3 1.2</td>
<td>3 1.2</td>
<td>0.99</td>
<td>5 2.2</td>
<td>4 1.8</td>
<td>0.69</td>
</tr>
<tr>
<td>New ipsilateral breast cancer</td>
<td>7</td>
<td>3 1.2</td>
<td>0 -</td>
<td>0.08</td>
<td>4 1.7</td>
<td>2 0.8</td>
<td>0.39</td>
</tr>
<tr>
<td>Locoregional tumour recurrence</td>
<td>19</td>
<td>6 2.4</td>
<td>4 1.6</td>
<td>0.52</td>
<td>9 3.9</td>
<td>7 3.0</td>
<td>0.56</td>
</tr>
<tr>
<td>Contralateral breast tumour</td>
<td>10</td>
<td>1 0.4</td>
<td>4 1.6</td>
<td>0.18</td>
<td>2 0.9</td>
<td>8 3.5</td>
<td>0.07</td>
</tr>
<tr>
<td>Distant metastasis</td>
<td>16</td>
<td>4 1.6</td>
<td>5 2.0</td>
<td>0.74</td>
<td>7 3.1</td>
<td>7 3.1</td>
<td>0.95</td>
</tr>
<tr>
<td>Deaths</td>
<td>40</td>
<td>5 2.0</td>
<td>8 3.1</td>
<td>0.41</td>
<td>15 7.3</td>
<td>16 6.7</td>
<td>0.97</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>13</td>
<td>2 0.8</td>
<td>3 1.2</td>
<td>0.66</td>
<td>5 2.4</td>
<td>6 2.5</td>
<td>0.82</td>
</tr>
<tr>
<td>Other cause</td>
<td>27</td>
<td>3 1.2</td>
<td>5 1.9</td>
<td>0.48</td>
<td>10 4.3</td>
<td>10 5.0</td>
<td>0.90</td>
</tr>
<tr>
<td>Other primary tumour</td>
<td>13</td>
<td>4 2.5</td>
<td>3 1.8</td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

° at time of analysis

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# Physician-rated Cosmesis

Harvard Breast Cosmesis Scale

<table>
<thead>
<tr>
<th>Cosmesis</th>
<th>APBI (n=246)</th>
<th>WBI (n=274)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Excellent</td>
<td>235 95.5%</td>
<td>182 70.0%</td>
<td>0.0001</td>
</tr>
<tr>
<td>Good</td>
<td>11 4.5%</td>
<td>71 27.3%</td>
<td></td>
</tr>
<tr>
<td>Fair</td>
<td>-</td>
<td>7 2.7%</td>
<td></td>
</tr>
<tr>
<td>Poor</td>
<td>-</td>
<td>-</td>
<td></td>
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</tbody>
</table>

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2018 SABCS: NSABP B39

- N = 2089 (2005-2013)
- Lumpectomy for stage 0 cancer or stage I or II (tumor size ≤3 cm) invasive
- Primary endpoint IBTR (invasive and non-invasive) did not meet criteria for equivalence
Conclusions:
APBI in 2020 and beyond

• Thousands of women in multiple PRTs of partial vs whole breast irradiation, all with IBTR within ~1%
  • Except Intrabeam IORT

• Follow consensus guidelines to select patients
  • NOT for node positive, margin positive, tumors >3 cm, age <40, age <50 with additional risk factors (i.e. LVSI, margins <2 mm, ER-).

• Individualize patient recommendations
  • Careful attention to the volume of breast tissue being treated with accelerated schedules (brachytherapy to reduce volume, also consider 3-week IMPORT LOW schedule)

• Growing interest in pre-op APBI
Michigan Radiation Oncology Quality Consortium (MROQC) prospectively collects clinical, sociodemographic, treatment, dosimetric, and outcomes data for patients receiving adjuvant RT after lumpectomy at 18 centers. Funded by BCBS, but collects data on all patients, regardless of insurance type.
MROQC: Patient-reported outcomes

Cohort: 7,698 women receiving whole breast irradiation.

• Within 7 days of completing RT:
  • 37% moderate to severe breast pain
  • 13% breast bother (itching, burning, stinging, hurting)
  • 23% fatigue all or most of the time

• Factors associated with increased toxicity:
  • Conventional fractionation
  • Tumor bed boost (pain & bother)
  • Younger age
  • Black race (pain & bother)
  • Higher BMI
  • Smoking
  • Diabetes (pain & fatigue)

Jagsi et al, PD6-06 SABCS 2019
Radiation-induced cancer in BRCA carriers

- Since BRCA is an important component of DNA repair, it has been hypothesized that germline BRCA carriers may be more susceptible to radiation-induced cancers.
- Occur at least 5 years after radiation exposure
- Occur within or at the edge of prior radiation fields
  - Sarcoma, lung, contralateral breast
- Rare; relatively more common in young patients
  - i.e. mantle radiation for Hodgkin lymphoma in very young adults
- Dose-response relationship
  - Can occur with low doses (i.e. diagnostic radiology)
  - Increased risk with larger fields and higher dose
BRCA+ women treated with RT >5 years ago

Key message

gBRCA carriers treated with radiotherapy have low risk for radiation induced secondary malignancies

Schlosser et al, PD6-04
SABCS 2019
Conclusions: Radiation Toxicities

• Whole breast irradiation causes side effects that can temporarily impair quality of life, esp. breast pain and fatigue.
• Acute side effects more common in certain patient populations: younger, black, high BMI, smoking, diabetes
• Carefully consider the need to deliver radiation, treat the whole breast, use conventional fractionation, add a boost.
• Adjuvant radiation is safe in BRCA carriers.
The Role of Radiotherapy Combined with Immunotherapy in Oligometastatic Cancer

Ralph R. Weichselbaum, MD
Department of Radiation and Cellular Oncology
Ludwig Center for Metastasis Research
University of Chicago Medicine

A tale of oligometastases...
Surgeons have been resecting metastases for a long time, and there seems to be a tail on the survival curve.
Advances in technology have enabled radiation oncologists to safely deliver ablative local therapy (SBRT).
The first study of SBRT for extracranial oligometastases was done at the University of Chicago, again showing some patients alive 15 years later.
Searched human tumor samples for micro-RNAs (negative regulators of genes) for promising targets
The most promising miRNA that they identified was a known tumor suppressor gene, yet when they transfected melanoma cells and injected them back into mice, they made MORE metastases.

...so in the context of a cancer that had already metastasized, expressing this tumor suppressor mRNA was a bad thing!
In a group of patients treated with systemic therapy and resection of 1-5 pulmonary metastases, survival was correlated with miRNA expression.
Another study was done in colorectal cancer patients with oligometastatic disease (liver). All patients were MSI negative, so would not be predicted to respond to immunotherapy. All patients were treated with peri-op chemo, definitive treatment of the primary cancer, and resection of their liver metastases.
Combining patients’ molecular subtypes (integrated mRNA-miRNA analysis) with clinical risk factors yielded 3 groups that strongly correlated with overall survival.
These were all patients who would not have been expected to respond to immunotherapy (MSI negative), yet the “immune” gene signature group did well with chemotherapy + surgery.

“There’s more to be discovered here!”
ASTRO 2019: Randomized phase II trials of +/-SBRT

• SABR-COMET (Palma et al, Lancet 2019)
  • 99 patients (18% breast) had median PFS 6 vs. 12 months, median overall survival 28 vs. 41 months

Progression-free survival

Overall survival
ASTRO 2019: Randomized phase II trials of +/-SBRT

• Oligometastatic NSCLC (Gomez et al, JCO 2019)
  • 49 patients (trial closed early due to PFS benefit) treated +/- SBRT or surgery
    had median overall survival 9.4 vs 37.6 months, median PFS 4.4 vs 14.2 months
More studies for oligometastatic patients are underway...

**NRG BR002**

- Phase IIR/III trial of oligometastatic breast cancer patients with \( \leq 3 \) metastatic sites \( \leq 5 \) cm each, locoregional disease controlled, received \( < 4 \) months of systemic therapy without progression
- +/- SBRT or resection to all sites
- Hypothesis: local therapy for oligometastases will improve 5YS
- Phase IIR component accrued; phase III portion will open if there’s enough PFS benefit seen
Conclusions

• Some patients have oligometastatic disease and can be cured with ablative therapy

• These patients can likely be identified through clinical features and molecular parameters

• Some patients with oligo-progressive disease may be cured
Thank you!