San Antonio Breast Cancer Symposium
-Radiation Therapy Updates-

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Radiotherapy Abstracts
Impact of radiotherapy on complications and patient-reported satisfaction with breast reconstruction: Findings from the prospective multicenter MROC study

*Oral Presentation*

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University of Michigan, Ann Arbor, MI; Memorial Sloan Kettering Cancer Center, New York, NY

Impact of RT on Reconstruction Outcomes

- Prospective, multicenter cohort study (Mastectomy Reconstruction Outcomes Consortium, MROC, funded by NCI)
- 11 institutions, 2012-15
- Responses from 553 radiated and 1461 non-radiated pts who received different approaches to reconstruction

- Primary variables of interest were
  - development of any breast complications (e.g. hematoma, wound infection) by one year post-reconstruction
  - satisfaction measured with the validated BREAST-Q instrument.
Impact of RT on Reconstruction Outcomes

• Mixed-effects regression models assessed impact of reconstruction type and RT on the outcomes of interest

• Covariate adjustment included:
  • reconstruction timing
  • age
  • extent of disease
  • bilateral vs unilateral treatment
  • chemotherapy receipt
  • nodal management
  • BMI
  • smoking
  • diabetes
  • race
  • ethnicity
  • education
  • employment
  • income
  • marital status
  • hospital site

Impact of RT on Reconstruction Outcomes: Results

• Median age: 49

• Bilateral mastectomy received by 45.6% of radiated and 53.3% of non-radiated pts (p=0.002)

• Autologous reconstruction more commonly received by radiated pts (38.3% vs 25.1%, p=0.001)

• Immediate reconstruction was less common in radiated pts (82.6% vs 95.6%, p<0.001)

• By one year, at least one complication occurred in
  — 28.8% of radiated pts (30.8% of implant pts and 25.5% of autologous pts)
  — 22.3% of non-radiated pts (20.4% of implant pts and 28.1% of autologous pts)

• At 2 yrs, a complication had occurred in 34.1% of 331 radiated pts vs 22.5% of 946 non-radiated pts
Impact of RT on Reconstruction Outcomes: Results

• On multivariable analysis, predictors of complications at 1 year:
  – immediate reconstruction
  – bilateral treatment
  – higher BMI

• RT effect differed by reconstruction type
  – RT was associated with 2.1 (95% CI = 1.45, 3.10) times higher odds of complication in implant pts
  – No difference in autologous pts (OR=1.3, 95% CI = 0.76, 2.09)

Impact of RT on Reconstruction Outcomes: Results

• RT effect on patient outcomes also differed by reconstruction types

• In implant pts, adjusted mean BREAST-Q satisfaction with breast scores were significantly lower in radiated pts than in non-radiated pts (51.5 vs. 58.0 at 1 year, p<.001; 48.9 vs. 59.8 at 2 years, p<.001)

• While satisfaction in autologous pts did not differ by radiation (61.3 in radiated vs. 63.5 in non-radiated at 1 year; 62.8 vs. 65.8 at 2 years)
Impact of RT on Reconstruction Outcomes

- **Conclusions:**
  - In the largest prospective multicenter study of outcomes of breast reconstruction to date, autologous reconstruction appears to yield superior patient-reported outcomes and lower risk of complications than implant-based approaches among patients receiving PMRT.

- Validates common perception that patient satisfaction is improved with autologous vs implant-based reconstruction.

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Are there patients with T1-T2, node-negative breast cancer who are at high risk for locoregional recurrence?

*Mamtani A, Patil S, Stempel M, Morrow M*

*Breast Service, Memorial Sloan Kettering Cancer Center, New York, NY*
T1-T2 N0 patients at high risk for locoregional recurrence?

- Indications for post-mastectomy radiotherapy (PMRT) in T1-T2, node negative (N0) breast cancer pts with “high-risk” features are controversial based on lack of consensus as to what constitutes “high-risk”, and variable results of small retrospective studies

- EORTC 22922 and MA20 trials reported improved 10-year disease-free survival with nodal irradiation included high-risk N0 patients but these patients were not analyzed separately and did not receive modern systemic therapy

- Question: What is the long-term locoregional control in T1-T2N0 patients with high-risk features undergoing mastectomy in the contemporary era?

**Methods**: Retrospectively reviewed pts with T1-T2N0 breast cancer with ≥1 high-risk feature treated with mastectomy from 2006-2011

- High-risk features were defined as
  - age <40 years
  - multifocal/multicentric disease
  - lymphovascular invasion (LVI)
  - medial or central tumor location

- Primary outcome of interest was LRR
T1-T2 N0 patients at high risk for locoregional recurrence?

- 672 pts
  - 187 (28%) had 1 risk factor: 15 (2%) pts were excluded (PMRT was received by 15 (2%) pts)
  - 21 (3%) were age <40 years
  - 132 (20%) were multifocal/multicentric
  - 34 (5%) had LVI
  - 449 (67%) patients had ≥2 high-risk features

<table>
<thead>
<tr>
<th>Table 1: Clinicopathologic characteristics, n = 672</th>
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<tbody>
<tr>
<td>Age, years:</td>
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<tr>
<td>67 (24-98)</td>
</tr>
<tr>
<td>Tumor size, cm:</td>
</tr>
<tr>
<td>3.4 (1.0-15.3)</td>
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<tr>
<td>Ductal histology:</td>
</tr>
<tr>
<td>30% (58%)</td>
</tr>
<tr>
<td>High nuclear grade**:</td>
</tr>
<tr>
<td>20% (41%)</td>
</tr>
<tr>
<td>LV:</td>
</tr>
<tr>
<td>25% (35%)</td>
</tr>
<tr>
<td>Multifocal/multicentric:</td>
</tr>
<tr>
<td>54% (25%)</td>
</tr>
<tr>
<td>Medial/central tumor:</td>
</tr>
<tr>
<td>22% (34%)</td>
</tr>
<tr>
<td>Receptor status**:</td>
</tr>
<tr>
<td>ER+ (61%)</td>
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<tr>
<td>HER2+</td>
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<tr>
<td>ER-/HER2-</td>
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</tbody>
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- SLNbx alone in 98% pts
- Median 4 LNs retrieved (range 1-15).
- Adjuvant systemic therapy received by 86% pts
- Median f/u 5.6 years
  - LRR rate was 4.7% (n = 31)
  - Majority (55%) of events involving the chest wall
  - Increasing tumor size was associated with LRR (HR 1.70, 95% CI 1.26-2.29, p = 0.006)
  - Age, histology, grade, subtype, LVI, multifocality/multicentricity, and tumor location were not (all p > 0.05)

<table>
<thead>
<tr>
<th># of risk factors*</th>
<th>n (%)</th>
<th>Rate of LRR</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>183 (28%)</td>
<td>3.8%</td>
</tr>
<tr>
<td>2</td>
<td>265 (40%)</td>
<td>5.3%</td>
</tr>
<tr>
<td>3</td>
<td>143 (22%)</td>
<td>6.9%</td>
</tr>
<tr>
<td>4 or 5</td>
<td>31 (5%)</td>
<td>9.4%</td>
</tr>
</tbody>
</table>

- Although LRR increased from 3.8% to 9.4% with 1 vs. ≥4 high-risk features, a comparison of 1 vs. 2 vs. 3 vs. ≥4 risk factors was not significant by Kaplan-Meier estimation (p = 0.54).
T1-T2 N0 patients at high risk for locoregional recurrence?

**Conclusions:**

- A low LRR rate of 4.7% was seen in this large unselected cohort of T1-T2N0 cancers with "high-risk" features treated by mastectomy and systemic therapy without PMRT.

- While increasing tumor size was predictive, other features did not confer a higher risk of LRR either independently or together, and do not by themselves mandate the use of PMRT in this population.

Hypofractionated nodal radiotherapy (RT) did not increase arm morbidity compared to conventional fractionated nodal RT

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Hypofractionated RNI

- Regional nodal irradiation can contribute to adverse arm symptoms and lymphedema

- Hypofractionation (HF), defined as >2 Gy/fraction, improves convenience but whether it increases arm morbidity is unclear

- Canadian study evaluates patient-reported arm symptoms in women treated with HF compared to conventional fractionation (CF) RT (defined as ≤2Gy/fraction)

Hypofractionated RNI

- Pts who received 3DCT nodal RT for pT1-3 pN0-2 M0 breast cancer from 2007-2009 in British Columbia and 2008 – 2010 in Alberta, Canada

- Patients mailed an explanation letter and an externally validated, Self-reported Arm Symptom Scale (SASS) survey

- The SASS included 8 questions about arm symptoms, with responses on a 5-point Likert scale regarding arm/hand problems (numbness, pain, stiffness, immobility and swelling), and 5 questions related to activities of daily living (ADL)

- Clinicopathologic characteristics and SASS scores were compared between HF vs. CF nodal RT cohorts
Hypofractionated RNI

- 708 pts (non-metastatic, non-recurrent)
- 406 (57%) patients received HF RT - 40 Gy/15 fx and 45 Gy/20 fx
- 302 (43%) received CF RT - 45 Gy/25 fx, 48-50 Gy/25 fx, and 50.4 Gy/28 fx
- Boost delivered in 22% of subjects in both groups
- Median time interval since RT completion: 5.67 years
- Mean age at diagnosis: 59.0 in HF vs 53.8 years in CF cohorts (p<0.001)
- Mean # positive (n=3) and excised (n=12) LNs similar between cohorts (p=0.44)
- Primary tumor size was marginally larger in the CF group (2.8 vs. 2.7 cm, p=0.03)
- 42.9% of patients were treated with partial mastectomy with no significant difference in fractionation (p=0.54)
- Overall, 602 (75.3%) patients received chemotherapy
- A trend toward increased use of CF after chemotherapy was observed (78.8% vs. 72.7%, p=0.07)

Leong et al SABCS 2016

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Hypofractionated RNI

**Results:**
- CF group had a higher prevalence of self-reported symptoms, including shoulder stiffness (p=0.04), trouble moving the arm (p=0.02), and ability to reach overhead (p<0.01)
- No difference in self-reported arm swelling between the two groups (p=0.57)

**Conclusions:**
- Hypofractionated nodal RT was not associated with an increase in patient-reported arm symptoms or disability compared to conventional fractionated nodal RT.
- Subjects treated with CF RT reported more disability in certain aspects of arm and shoulder function
- These data support the use of shorter fractionation when the regional lymph nodes are part of the therapeutic target
The use of hypofractionated radiotherapy for the treatment of women with early breast cancer in the Brazilian public health system may increase access to treatment: Cost effectiveness and budget impact analyses

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Cost effectiveness of hypofractionated RT in Brazil

- **OBJECTIVES:**
  - To evaluate the cost effectiveness and economic impact of increasing the use of hypofractionated RT for the treatment of women older than 50 years, with early breast cancer (stages I and II) within the Brazilian National Health System (SUS)

- **METHODS:**
  - Authors built a ‘cost-effectiveness’ Markov model in Excel which quantifies the cost and the amount of photon beams linear accelerator time used for the treatment of patients using hypofractionated (2.67 Gy/fraction) or conventional (2 Gy/fraction) over 5 yr period
  - Effectiveness measured as # hours saved using hypofractionated vs conventional RT
  - Costs considered included RT planning, physics QA, and the use of linear accelerator
  - Authors determined the # of women > 50 yo with Stage 1-2 breast CA treated with adjuvant RT in 2013 and 2014, and then projected these populations to 2016 to 2020.
  - Authors considered a yearly increase of 20% in the adoption of hypofractionated RT for the years 2016 to 2019 (2016 20%; 2017 40%; 2018 60%; 2019 80% and 2020 90%)
  - The treatment fraction time was set as 15 minutes
Cost effectiveness of hypofractionated RT in Brazil

• RESULTS:
  – Use of hypofractionated RT at 5 years was able to decrease the number of hours of treatment (-21,835 hours) and the total cost of treatment (-$11,790,229.64)

  • Annual incremental impact would be of -$243,202.65, -$490,294.13, -$741,085.61, -$995,388.73 and -$1,127,712.81 providing 3,378, 6,810, 10,294, 13,826 and 15,664 free hours of the linear accelerator for the years 2016, 2017, 2018, 2019 and 2020, respectively

  • The “linac-free” hours may allow 613, 1,380, 2,306, 3,392 and 4,010 additional patients to have access to breast CA treatment during 2016 to 2020 respectively.

CONCLUSIONS:

• Considering the conditions proposed in this model, increasing use of hypofractionation to treat women older than 50 years is expected to increase the system efficiency, save money and improve access to treatment for more patients.

Many health care systems interested in these analyses to encourage policy change
NRG oncology/NSABP B-51/RTOG 1304: A phase III superiority clinical trial designed to determine if chest wall and regional nodal radiotherapy (CWRNRT) post mastectomy (Mx) or the addition of RNRT to breast RT post breast-conserving surgery (BCS) will reduce invasive cancer events in patients (pts) with positive axillary (Ax) nodes and convert to ypN0 after neoadjuvant chemotherapy (NC)

Mamounas EP, Bandos H, White JR, Julian TB, Khan AJ, Stahelmes SF, Torres MA, Vicki FA, Gane PA, McCloskey SA, Pahk S, Gupta N, U XA, DiCostanzo DJ, Curran, Jr WE, Wolmark N (NRG Oncology/NSABP (NSABP Legacy Trials Are Now Part of the NRG Oncology Portfolio), Pittsburgh, PA; UF Health Cancer Center at Orlando Health, Orlando, FL; University of Pittsburgh, Pittsburgh, PA; NRG Oncology/RTOG, Philadelphia, PA; Ohio State University, Columbus, OH; Allegheny Health Network Cancer Institute, Pittsburgh, PA; Rutgers Cancer Institute of New Jersey, New Brunswick, NJ; University of Texas MD Anderson Cancer Center, Houston, TX; Winship Cancer Institute Emory University, Atlanta, GA; St. Joseph Mercy Oakland, Pontiac, MI; University of California at Los Angeles, Los Angeles, CA; Severance Biomedical Sci Inst and Yonsei Univ College of Medicine, Seoul, Korea; Medical College of Wisconsin, Milwaukee, WI; The Ohio State University Wexner Medical Center, Columbus, OH)
Decisions on the use of RNI are generally based on the pathological nodal status at the time of surgical staging.

Neoadjuvant chemo has been shown to down-size large primary tumors and down-stage involved axillary nodes.

Several randomized and non-randomized studies have shown that achieving a path CR in the breast and LNs leads to improved local regional control.

Phase III randomized post-neoadjuvant chemotherapy trial evaluates if CWRNRT post Mx or whole breast irradiation (WBI) with RNRT after BCS significantly reduces the invasive breast cancer recurrence-free interval (IBC-RFI) rate in pts presenting with positive Ax nodes that are pathologically negative after NC.

Secondary aims are OS, LRRFI, DRFI, and second primary cancer, as well as comparing RT effect on cosmesis in reconstructed Mx pts.

Correlative science studies examine RT effect by tumor subtype, molecular outcome predictors for residual disease pts, and predictors for the degree of reduction in loco-regional recurrence.
NSABP 51

- 1636 pts to be enrolled over 5 yrs with definitive analysis at 7.5 yr
- Accrual as of 6/13/16 is 356

A randomized trial of 15 fraction vs 25 fraction pencil beam scanning proton radiotherapy after mastectomy in patients requiring regional nodal irradiation

Mutter RW, Park SS, Hieken TJ, Vargas CE, Mei-Yin PC, Kathryn RJ, Hector VR, Kimberly CS, Elizabeth YS, Daniel VW Mayo Clinic, Rochester, MN
**Hypofractionated Proton PMRT**

**Background:**
- Pencil beam scanning proton therapy is attractive due to potential to reduce the dose to the heart and lungs compared with traditional photon techniques while improving conformality and limiting skin dose compared with passively scanned proton therapy

- The optimal dose and fractionation for pencil-beam scanning proton therapy remains unknown

**Trial Design:**
- Multi-center open label phase II randomized controlled trial to determine the safety of 15 fraction vs 25 fraction pencil beam scanning proton radiotherapy after mastectomy in patients requiring RNI

- Patients ≥ 18 years with primary, non-inflammatory invasive breast cancer who have undergone mastectomy with or without immediate reconstruction and chest wall and regional nodal irradiation planned
Hypofractionated Proton PMRT

• Aims:
  – Determine whether the 24 month complication rate (defined as grade 3 or greater late adverse events, and unplanned surgical intervention in patients who undergo mastectomy with reconstruction) of 15 fraction chest wall and regional node pencil beam scanning proton radiotherapy is acceptable relative to a 25 fraction regimen

• Statistical methods: The study is designed as a non-inferiority/superiority design

• Accrual: The study opened in June 2016. Five of a planned eighty-two patients have been accrued to date

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Thank you!