Fifth Annual Breast Cancer Symposium

Innovations in Radiation Oncology

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Innovative Techniques & Paradigm Shift

• Accelerated Partial Breast Irradiation
• Accelerated Partial Breast Proton Therapy
• Prone Position Whole Breast Irradiation
• Deep Inhalation Breath Hold Whole Breast Irradiation
• Hypofractionated Whole Breast Irradiation
• Ductal Carcinoma in Situ

Accelerated Partial Breast Irradiation (APBI)

• Multiple RT techniques:
  Brachytherapy (intraop; balloon catheter; interstitial).
  External beam 3D or IMRT.
  Proton Beam
A significant percentage of in-breast failure occur at the primary site.

Better stringent criteria for appropriate patient selection (ASTRO; ESTRO).

Single institution trials (U Mich, Tuft, Baptist Hospital, NYU).

Randomized Controlled Trials: Canadian RAPID (preliminary), Florence, RTOG (ongoing).

**APBI: Concept and Practice**

**Factors:**
- Oncoplastic surgery & tissue displacement.
- Placement of surgical clips before tissue rotation.
- Detailed knowledge about primary surgical procedure & margin orientation.
- Pre-op tumor localization based on imaging.
- Post-op surgical cavity to pre-op imaging.
- Safety margins.

**APBI Technique: GEC ESTRO Working Group (2015)**

**APBI Target Definition: GEC ESTRO Working Group (2015)**

- Surgical Scar
- Image Tumor Volume
- Estimated Tumor Bed
- Clinical Target Volume
- Surgical Clips

Strnad V. Radiotherapy and Oncology, (http://dx.doi.org/10.1016/j.radonc.2015.06.010)

APBI: IMRT Technique

APBI: Single arm IMRT

- Baptist H (Lewin & Der Hagopian): 36 pts: 38 Gy (3.8 Gy bid X5), respiratory gated: 94-97% good cosmesis (Harvard scale pt & MD); 3% grade 3 toxicity.
RAPID TRIAL APBI vs WBRT

- APBI vs Standard WBRT (50 Gy/25Rxs or hypofractionated 42.4Gy/16Rxs [Olivetto IAICO31:4038-45, 2013]).
- Multicenter, high quality with triangulation of evidence from multiple sources.
- Cosmesis evaluated by trained R.N, self report by pts., blinded photographs reviewed by M.D.

RAPID RCT APBI vs WBRT

- Adverse cosmesis APBI vs WBRT: 29% vs 17%; P < .001, worsening result with time.
- No excessive adverse events.
- Conclusion: APBI only for clinical research.

U FLORENCE APBI (IMRT) RCT

  >40 yo w/ pT1-2 <2.5cm, pN0 or +.
  Median FU 5yrs.
- Ipsilat breast tumor recurrence (IBTR): 1.5 %, ABPI vs 1.4 %, WBI (p=0.86).

U Florence RCT APBI vs WBRT (cont’d)

- OS 99.4% APBI VS 96.6% WBI (p=0.057).
- APBI had less acute (p=0.0001), late (0.004) and adverse cosmetic (p=0.045) outcomes than WBI.
- Cosmesis judged by M.D. only.

APBI USING PROTON BEAM

<table>
<thead>
<tr>
<th></th>
<th>MGH (Galland-Girodet. IJROBP 90:493-500, 2014)</th>
<th>LOMA LINDA (Bush D IJROBP 90:501-505, 2014)</th>
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</thead>
<tbody>
<tr>
<td># pts.</td>
<td>98(19 PB; 79 3D RT Conformal/ 1 Field/d)</td>
<td>100 (100% daily PT to all fields; skin sparing)</td>
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<tr>
<td>Stage</td>
<td>100% stage I</td>
<td>pT1-2 (up to 3 cm)pN0</td>
</tr>
<tr>
<td>PB/RT dose</td>
<td>32Gy/8 bid Rxs</td>
<td>40Gy/10 bid Rxs</td>
</tr>
<tr>
<td>Median FU</td>
<td>83 mos.</td>
<td>60 mos.</td>
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<td>Cosmesis PT (vs 3D RT)</td>
<td>92% vs 96% (pt reported); MD: excessive skin toxicities(telangiectasia(54-69% vs 16-22%, P&lt;5%); PB vs 3RT)</td>
<td>No acute Grade 3 dermatitis and only 7% late grade 1 telangiectasia.</td>
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APBI (cont’d)

- RTOG 0413/NSABP B39 RCT ~5000 pts. results unavailable (uses triangulation of data).
- Not ready for prime time outside RCT [Jagsi R: JCO 33(27), Sept 2013].
- Technical, dosimetric aspects need fine tuning (GEC ESTRO Guidelines helpful).
- NCI CTCAE not sensitive to pick up adverse cosmesis.
Prone Position Whole Breast RT

• Rapid adaptation of this technique.
• Significant reduction in lung and cardiac exposure.
• Significant improvement in acute dermatitis and cosmesis in large breast patients.
**Prone Position**

(Fermantli S. JAMA Network. 7/17/2013)

- Prospective study of 400 pts stage 0-IIA w/ = or < 3 lymph nodes +.
- Left: 85% cardiac dose sparing in prone position vs supine; 15% paradoxical reverse effect.
- 86-90% lung sparing prone vs supine in right and left breasts.

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**Deep Breath Hold vs Free Breathing**

- Simple well tolerated technique in left breast ca pts. to spare heart and lung.
- Requires Motion Management System (external surrogate and/or spirometric guidance).
Hypofractionated Radiation Therapy

- Quality of life:
- Convenience.
- Improved cosmesis.
- Decreased societal healthcare cost
- Recommendation:
  - ASTRO (2011) for all patients >50 y.o. pT1-2N0.

Hypofractionated Whole Breast Irradiation

- Mature randomized controlled trials(pT1-2N0) (Canadian Alliance[Whelan T:NEJM362:513-20,2010] & British START A & B) confirm equivalency in intra breast event (IBE) and enhanced cosmesis.
- Reduces treatment time from six weeks to three weeks.
- Adaptation at Baptist Hospital is close to 100% for eligible pts, pT1-2N0.

Hypofractionated Breast: Current Issues

- Age <50 vs >50yo: No significant difference (4 % vs 7%) IBE Canadian Alliance trial(stratified) without RT boost.
- British START B(1,389 pts.): No significant difference in IBE age <50 vs >50 yo. but used RT boost.
- Data supports use of hypoFx RT in pts. <50(ASTRO guideline (2011) predated START B publication) with consideration of RT boost.
Hypofractionated RT: High grade histology

- Canadian Alliance post hoc 10 yr analysis G3 vs G1-2 shows IBE 15.6% vs 4.7%(p=.01), resp.
- START trials (with RT boost common) showed no significant difference 10 yr analysis.
- Conclusion: RT boost highly recommended (Cancer Network Oncology Journal 2014).

Hypofractionated RT: Node + requiring regional RT

- Pts. treated with regional RT: Canadian Alliance (0%), British START A & B (14% & 7%).
- Concern about RT induced brachial plexopathy (RIBP) raised (449 pts 45 Gy/15 Gy/Rx, 3 Gy/Rx vs 54 Gy/30Rx/1.8 Gy/Rx: 6% vs 1% (Powell S. Radiother Oncol.v18, pp 213-20, 1990).
- Only one of 750 pts HypoFx (0.1%) START A had RIBP with mean FU 9.3 yr; 0% in Canadian Alliance, mean FU 12 yr).
- My take: No enthusiasm among rad onc's for hypoFx regional RT until safe guidelines established.

Hypofractionated RT: Large Breast

- Greater RT dose heterogeneity associated with enhanced acute dermatitis, fibrosis and adverse cosmesis.
- Canadian Alliance excluded large breast patients (separation >24 cm central axis) and START trials had underrepresented large breast pts (14.3% & 17.2%).
- Both trials used 2D RT planning (not current standard).
- Modern 3D or forward IMRT planning decrease RT dose heterogeneity in unfavorable anatomy pts and can meet ASTRO guideline +/-7% maximum intrabreast guideline.
- Additionally, deep inhalation breath hold & prone position significantly reduce lung/heart exposure and acute dermatitis/ altered cosmesis in unfavorable anatomy pts.
- My take: Unfavorable anatomy is not a contraindication to hypoFx RT.
Ductal Carcinoma in Situ (DCIS)

- “Heterogeneous disease with large variation in clinical behavior”: (Cutuli B. Radiotherapy & Oncology 112:1-8, 2014)
- Treatment de-intensification advisable?
- Is DCIS indolent or life threatening disease?
- Do we understand the biology of DCIS?
- Newer concepts of tailored treatment modalities.

ECOG E5194 non-randomized trial of lumpectomy only: Identification of Local Recurrence Risk

- Low risk: cohort 1: G1-2, <2.5 cm unifocal; cohort 2: G3, <1 cm unifocal. (Solin L. JCO v33: eVersion, 2015)
- Excision with minimal negative margin 3 mm width (median size 6 mm & 7 mm for cohorts 1&2)
- 561 entered (mean FU time 12.3 yr): 99 (18%) Intra-breast event [IBE] (52% invasive) without plateau.
- Tumor size and study cohort predicts IBE. Overall survival not reported.

Population Based Breast Cancer Specific Mortality (BCSM) of DCIS

- SEER Analysis 108K shows 20 yr BCSM: overall 3.3%; <35 yo, 7.8%, Afro-Americans 7%(p=.001 both) (Narod S. JAMA Oncology, published online Aug. 2015).
- Risk of BCSM increased after ipsilateral invasive recurrence(p=.001).
- 517 pts died of breast cancer without local recurrence.
- RT reduced breast recurrence (2.5 vs 4.9%) but not BCSM (0.8 vs 0.9%), p=.001 & .22, resp.)
20 yr DCIS SEER Breast Cancer Mortality based on Race/Ethnicity

- SEER analysis of 108K pts shows 2 population at high risk of breast cancer mortality:
  - Patients <35 yo and Afro-Americans have 20 yr breast cancer mortality of 7%.
  - Local Intra-breast failure predicts distant failure (DF).
  - Paradox of reduced IBF does not protect from DF.

DCIS: Identifying Pts. at Greater Risk of Mortality

- 327 pts. from ECOG ES194 had adequate tissue.
- 10 yr IBE based on predetermined score: non-invasive: 10.6%, 26.7% and 25.9%; invasive: 3.7%, 12.3% and 19%, p=.006.
- Conclusion: Oncotype DCIS useful tool for individualized treatment.
Ontario Validation of DCIS Oncotype Score

- 718 case cohort population based with similar ECOG 5194 criteria treated with lumpectomy with margins neg (1-3mm, 45%), median 61 yo, FU 9.6 yrs. (Rakovitch E. Breast Cancer Res Treatment 152:389-398, 2015).
- 10 yr IBE 19.2% (100; 44 DCIS; 57 inv.).
- Risk of IBE was 12.7%, 33% and 27.8% for the low, intermediate and high DCIS scores, resp (p<.001).
- DCIS Oncotype Score is validated for determining IBE.