Breast

Live SA-CME

Sunday, March 4, 2018
8:00 a.m. – 9:30 a.m.
Faculty Disclosures

Faculty and Committee disclosures are also on the 2018 ASTRO Annual Refresher Course website.

<table>
<thead>
<tr>
<th>Name</th>
<th>Employment</th>
<th>Funding Sources</th>
<th>Ownership or Investments</th>
<th>Leadership</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shannon MacDonald, MD</td>
<td>Massachusetts General Hospital, Boston</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
</tbody>
</table>
Disclosures

• No disclosures

• Other than, ..... my SAMS may not be in order but I promise you will notice them
Overview

• Basics of Breast Cancer
  – Work up/Staging
• Early Stage Breast Cancer – DCIS and Node negative IDC
  – BCT/Hypo-fractionation/Omission/Technique/Partial Breast Irradiation
• Locally Advanced Breast Cancer
  – PMRT/Surgical & Radiation Management of Axilla & RNI/Neoadjuvant Chemo/Atlas/Contouring/IMRT/Proton Therapy

Goal- Provide Practical Information, Summarize Studies to assist in Patient Management & Board Preparation
BASICS
Evaluation of the Patient

- H & P
  - Palpable mass, size, onset, change, redness, skin change, nipple discharge, axillary abnormality, pain
  - Family history of breast and ovarian cancer
  - Gynecological history (menarche, menopause, GP, age at first birth, hormonal treatments, any possibility of pregnancy)
  - Prior RT history
  - Breast exam in sitting and supine position, lymph node examination (axilla, SCV, cervical)
- Mammogram (MLO/CC views); consider DBT if available; US; consider MRI (usually after breast cancer is proven)
- Core biopsy if feasible (excisional only if core is not feasible; FNA does not give enough information)
- Determine if patient is appropriate for BCT or Mastectomy or other (multi-centric, prior RT, Pregnancy contraindications)
Mammogram

Annual screening MLO, CC
Diagnostic if something on screening US
Compression for density;
Magnification for calcifications

Pec muscle to mid-breast to ensure max breast tissue
Digital Breast Tomosynthesis

- Increases detection rates of small invasive cancers
- Decreases false positive callback rates
- Improves margin analysis & lesion conspicuity by decreasing effect of overlying breast tissue
- Improves localization of “one view only” lesions
- Helps distinguish skin lesions from breast lesions

Images look similar to a CT scan – you can scroll through images of the breast
2D Mammography

X-rays pass through breast tissue to the detector.

Masses can be obscured by overlapping tissue.

DBT

Multiple low-dose full field projection images are obtained from multiple angles in an arc.

Projection images are used to reconstruct 3D images of the breast.

Courtesy of Helen D’Allesandro
62 yo with DBT-only architectural distortion
Specimen Radiograph after lumpectomy to confirm clip and radiographic lesion or calcifications
Rare to obtain post-lumpectomy mammogram
MRI Breast

- Used for selected patients & no clear consensus on how to select patients
  - Difficult to detect lesions on mammo or tomo (extremely dense breast tissue, ILC, biopsy not corresponding well to area of abnormality, assess for feasibility of breast conservation); Young age: high risk for another primary

- Performed prone, difficult for claustrophobic patients, false +, some degree of timing required for premenopausal women, anxiety; delay to definitive treatment and possible additional work up; increase mastectomy rate; cost
Pathology

- Size
- Grade
- LVI
- Margins
- Association of DCIS (EIC)
- Lymph nodes (ECE); SLNB or ALND
- Receptors
  - ER
  - PR
  - Her-2-neu (immunohistochemistry and FISH amplification)
- Consider Oncotype Dx
Margins—what has changed

• In past, we favored margins of approximately ≥ 2mm
• Large met-analysis for early invasive cancer and BCT performed
• Negative margin optimizes local control (+ margin 2.4 X increase in LR)
• HOWEVER, NO BENEFIT to wider margin

After years of arguing with our surgeons for re-excision, we now just look for no tumor on ink for IDC

Houssami, N Ann Surg Oncol 2014; 21: 717
Morrow M, NEJM 2012, 367: 79
JCO 2014 volume 32; 14
What is an adequate margin for invasive ductal carcinoma for lumpectomy/breast conserving therapy?

- NO TUMOR ON INK

- We do not recommend re-excision if negative margins are obtained as there is not benefit to patient (may be detrimental – anxiety, cosmesis, cost, time etc..)

- DOES NOT APPLY- APBI, DCIS, patients treated with neoadjuvant chemotherapy
Metastatic Work up

- CBC
- CMP (include LFT’s and alkaline phosphatase)
- CT chest/abdomen/pelvis & bone scan
- Or PET/CT

Whether or not to obtain metastatic work up varies by provider and is usually decided by medical oncologist.

My preference is to discuss for any N+ patient especially since many N+ patients are now not getting ALND (hard to know true # LN).

If chest CT, MRI, or PET/CT obtained be sure to review for nodal, especially IMN involvement prior to RT to ensure any suspicious nodes are covered.
Criteria for Genetic Testing / BRCA 1/2

- Ovarian cancer
- Breast cancer < 50 years
- Triple negative breast cancer < 60 years
- Two breast cancer primaries in single individual
- Breast cancer and:
  - >1 blood relative w/ breast cancer <50
  - >1 blood relative w/ovarian cancer
  - >2 relative with breast, prostate, or pancreatic cancer
- Pancreatic cancer
- Increased risk population
- Blood relative: 1\textsuperscript{st} 2\textsuperscript{nd} or 3\textsuperscript{rd} degree relative
- Ashkenazi Jewish descent

Also seeing more frequent testing for p53 and for ATM and other mutations
Pregnancy / Fertility

- Discuss future plans for fertility for women of childbearing age & refer if appropriate to reproductive endocrinology
  - Egg preservation, embryo, other

- Always assure that patient is not pregnant at time of treatment
Tumor Stage

T4b - satellite skin nodules, edema (peau d’orange), ulceration T4c – both a and b, T4d-inflammation

Direct extension to chest wall not including pectoralis muscle.
pN2b is clinically + IMN with – axilla

pN3b is clinically + IMN with + axilla
### Stage Grouping

**AJCC 7th Edition**

* 8th Edition out; Anatomic Stage Grouping the Same but added Prognostic Stage

<table>
<thead>
<tr>
<th>Stage</th>
<th>Anatomic Stage</th>
<th>Prognostic Stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 0</td>
<td>Tis</td>
<td>N0</td>
</tr>
<tr>
<td>Stage IA</td>
<td>T1*</td>
<td>N0</td>
</tr>
<tr>
<td>Stage IB</td>
<td>T0</td>
<td>N1mi</td>
</tr>
<tr>
<td></td>
<td>T1*</td>
<td>N1mi</td>
</tr>
<tr>
<td>Stage IIA</td>
<td>T0</td>
<td>N1**</td>
</tr>
<tr>
<td></td>
<td>T1*</td>
<td>N1**</td>
</tr>
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<td></td>
<td>T2</td>
<td>N0</td>
</tr>
<tr>
<td>Stage IIB</td>
<td>T2</td>
<td>N1</td>
</tr>
<tr>
<td></td>
<td>T3</td>
<td>N0</td>
</tr>
<tr>
<td>Stage II A</td>
<td>T0</td>
<td>N2</td>
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<tr>
<td></td>
<td>T1*</td>
<td>N2</td>
</tr>
<tr>
<td></td>
<td>T2</td>
<td>N2</td>
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<tr>
<td></td>
<td>T3</td>
<td>N1</td>
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<td></td>
<td>T3</td>
<td>N2</td>
</tr>
<tr>
<td>Stage IIIB</td>
<td>T4</td>
<td>N0</td>
</tr>
<tr>
<td></td>
<td>T4</td>
<td>N1</td>
</tr>
<tr>
<td></td>
<td>T4</td>
<td>N2</td>
</tr>
<tr>
<td>Stage IIIC</td>
<td>Any T</td>
<td>N3</td>
</tr>
<tr>
<td>Stage IV</td>
<td>Any T</td>
<td>Any N</td>
</tr>
</tbody>
</table>
AJCC 7th correlation with DSS

Anatomic Stage Grouping DOES correlate well with DSS

Yi M et al. J Clin Oncol 2011;29:4654-4661 Courtesy of Dr. Mittendorf
But…. What about Biology???

5-yr BCSS According to Subtype

<table>
<thead>
<tr>
<th></th>
<th>HR+/HER2-</th>
<th>HR+/HER2+</th>
<th>HER2+/HR-</th>
<th>TNBC</th>
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</thead>
<tbody>
<tr>
<td>Stage T2N0</td>
<td>96%</td>
<td>94%</td>
<td>92%</td>
<td>88%</td>
</tr>
<tr>
<td>Stage IV</td>
<td>47%</td>
<td>39%</td>
<td>24%</td>
<td>17%</td>
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</table>

We know receptor status is also important for prognosis; not taken into account AJCC 7


Courtesy of Dr. Mittendorf
### Oncotype Dx

<table>
<thead>
<tr>
<th>Score</th>
<th>Formula</th>
</tr>
</thead>
<tbody>
<tr>
<td>HER2 Group Score</td>
<td>(0.9 × GRB7) + (0.1 × HER2) If HER2 Group Score is less than 8 then the HER2 Group Score is considered equal to 8</td>
</tr>
<tr>
<td>ER Group Score</td>
<td>([0.8 × ER] + [1.2 × PgR] + Bcl2 + SCUBE2]) / 4</td>
</tr>
<tr>
<td>Proliferation Group Score</td>
<td>(SURV + KI-67 + MYBL2 + Cyclin B1 + STK15) / 5</td>
</tr>
<tr>
<td>Invasion Group Score</td>
<td>(Cathepsin L2 + Stromelysin 3) / 2</td>
</tr>
</tbody>
</table>

- **PROLIFERATION**
  - Ki-67
  - STK15
  - Survivin
  - Cyclin B1
  - MYBL2

- **HER2**
  - GRB7
  - HER2

- **ESTROGEN**
  - ER
  - PGR
  - Bcl2
  - SCUBE2

- **INVASION**
  - Stromelysin 3
  - Cathepsin L2

- **REFERENCE**
  - Beta-actin
  - GAPDH
  - RPLPO
  - GUS
  - TFRC

- **What about multigene panels??**

- 21 gene panel with 16 genes taken into consideration and 5 controls
Oncotype DX

- **Low risk Group**
  - Score less than 18
  - Group Average 7%

- **Intermediate risk Group**
  - Score 18-31
  - Group Average 14%

- **High Risk Group**
  - Score > 31
  - Group average 31%

Distant recurrence at 10 years on Y-axis to be a continuous function of recurrence score on X-axis.
• Similar to other disease sites (CNS, pediatrics, GU, etc), it is being recognized that biology is extremely important for risk stratification

• Complex - made me feel happy 😊 that I do not need to recertify, feel empathy 😞 for my residents taking boards & very grateful that Dr. Elizabeth A. Mittendorf, MD, PhD was kind enough to share slides that help to explain the new system
AJCC 8th Edition – Prognostic Stage

- **Prognostic Stage Group**
  - Incorporates grade, ER, PR, HER2 status in addition to T,N,M
  - Inclusion of multigene panels as stage modifiers when available
  - Over 150 groupings
  - 6 pages of tables in AJCC chapter (It is a long chapter!!)
AJCC 8th Edition – Summary of Significant Changes

• Added clinical and pathologic prognostic stages
• Tumor grade defined by Nottingham histologic grade is required element for staging
• LCIS classified as a benign entity and removed from TNM staging
## AJCC 8th Edition Prognostic Stage

### Traditional TNM Factors + Expanded Non-Anatomic Factors

<table>
<thead>
<tr>
<th>Tumor Grade</th>
<th>HER2 Status</th>
<th>ER Status</th>
<th>PR Status</th>
<th>Prognostic Stage Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1</td>
<td>N0</td>
<td>M0</td>
<td>1</td>
<td>Positive</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Any</td>
<td>Any</td>
</tr>
<tr>
<td>T1</td>
<td>N0</td>
<td>M0</td>
<td>1</td>
<td>Negative</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Positive</td>
<td>Negative</td>
</tr>
<tr>
<td>T2</td>
<td>N0</td>
<td>M0</td>
<td>1,2</td>
<td>Negative</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Positive</td>
<td>Positive</td>
</tr>
<tr>
<td>T1</td>
<td>N0</td>
<td>M0</td>
<td>1-3</td>
<td>Negative</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>T2</td>
<td>N0</td>
<td>M0</td>
<td>3</td>
<td>Negative</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Positive</td>
<td>Positive</td>
</tr>
<tr>
<td>T3</td>
<td>N0</td>
<td>M0</td>
<td>1</td>
<td>Negative</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Positive</td>
<td>Negative</td>
</tr>
</tbody>
</table>

### 8th Edition Prognostic Stage Group

- **IA**: T1 N0 M0 1 Positive Any Any
- **IB**: T1 N0 M0 1 Negative Positive Negative
- **IB**: T1 N0 M0 1,2 Negative Positive Positive
- **IIA**: T1 N0 M0 1-3 Negative Negative Negative
- **IIA**: T2 N0 M0 3 Negative Positive Positive
- **IIIA**: T3 N0 M0 1 Negative Positive Negative

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**Hortobagyi G, et al. AJCC Manual 8th ed.**  
**Courtesy of Dr. Mittendorf**
Expert panel determined it was appropriate to incorporate multigene molecular profiling based on the data reported from Arm A of the TAILORx study.

<table>
<thead>
<tr>
<th>When T is...</th>
<th>When N is...</th>
<th>When M is...</th>
<th>And G is...</th>
<th>And HER2 Status is...</th>
<th>And ER Status is...</th>
<th>And PR Status is...</th>
<th>The Prognostic Stage Group is...</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1-T2</td>
<td>N0</td>
<td>M0</td>
<td>1-3</td>
<td>Negative</td>
<td>Positive</td>
<td>Any</td>
<td>IA</td>
</tr>
</tbody>
</table>

**MultiGene Panel** - Oncotype DX Recurrence Score Results Less Than 11

Courtesy of Dr. Mittendorf
AJCC 8th Edition

1977 - 2017

- Anatomic Stage
- Tumor Size
- Node Status
- Metastasis

2018+

- Tumor Size
- Node Status
- 8th Edition Prognostic Stage Group
- Tumor Grade
- Receptor Status (HER2/ER/PR)
- Recurrence Score Value (0 To 10)*
- Metastasis

Courtesy of Dr. Mittendorf
Impact of Including Oncotype DX

When Oncotype DX Breast Recurrence Score result is <11, all of these patients are classified as Stage IA

- Stage IB: T1 G1 PR-, T1 G3 PR+, T2 G1 PR+, T2 G2 PR+
- Stage IIA: T1 G3 PR-, T2 G1 PR-, T2 G3 PR+
- Stage IIB: T2 G2 PR-
- Stage IIIA: T2 G3 PR-
There’s an app for that....

Oncotype DX appears here as option if appropriate to use

Courtesy of Dr. Mittendorf
Early Breast Cancer

DCIS, Stage I or minimal nodal disease
Local Recurrence Lumpectomy Alone versus Lumpectomy and RT

<table>
<thead>
<tr>
<th></th>
<th>Lump</th>
<th>Lump RT</th>
<th>Reduction</th>
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<tbody>
<tr>
<td>NSABP Bo6</td>
<td>36</td>
<td>12</td>
<td>67</td>
</tr>
<tr>
<td>Uppsala-Orebro</td>
<td>24</td>
<td>9</td>
<td>63</td>
</tr>
<tr>
<td>Ontario</td>
<td>35</td>
<td>11</td>
<td>69</td>
</tr>
<tr>
<td>Milan</td>
<td>24</td>
<td>6</td>
<td>75</td>
</tr>
</tbody>
</table>

Trials also established BCT as an alternative option to MRM showing comparable LRC and equivalent OS.
Conclusions

• Multiple randomized trials demonstrated equivalence in overall survival and similar local recurrence for segmental excision and radiation and MRM

• Local recurrence was significantly increased when segmental excision was performed without radiation

• Established lumpectomy and RT as an alternative option to mastectomy
Metanalysis of the aforementioned trials demonstrated that lumpectomy + radiation therapy decreases the risk of any recurrence (LR or DM with greater impact on LR) and impacts breast cancer survival.

Older studies benefit from long-term follow up but LRR rates are now lower likely as a result of improvements in surgery, pathological examination, radiation techniques and systemic therapy.

Whole Breast Hypofractionation

- “Standard Fractionation” for decades has been 5 weeks of whole breast irradiation (+/- “boost” to the seroma of approximately 10 Gy)
  - Very effective but time consuming and resource consuming for society and patients
- “Financial Toxicity” for cancer patients has received great interest in recent years
- Now Level 1 evidence /multiple randomized trials that show equivalence of hypofractionated whole breast RT and standard RT for early invasive breast cancer
  - Ontario, Canada Study/UK Start B Study

Great interest in minimizing burden of treatment for patients and decreasing healthcare costs

Whelan T et al, NEJM: 362; 513, 2010
Canadian Study

- 1234 patients randomized to 42.5 Gy in 16 fractions versus 50 Gy in 25 fractions (no boost**)
- T1 or T2 primary tumors and Node negative
- Excluded very large breasted women (separation > 25 cm) but methods used to improve homogeneity not used
- Median follow up of 12 years, LR, DFS, OS no different
- Cosmetic outcomes no different
- Not intended for subset analysis, but subset analysis did show that grade 3 tumors may do better with standard treatment
- Only 11% of patients received chemotherapy
- No boost

Whelan T et al, NEJM: 362; 513, 2010
Hypo-frac Whole Breast

- Should be discussed as a standard of care option for patients receiving whole breast RT

- Though few patients on RTC received boost, we typically do offer a boost following treatments (i.e. 42.5 Gy/16 fx f/b 10 Gy boost in 4-5 fractions)

- Using 3D planning, field-in-field, and IMRT techniques we feel comfortable offering to women with large breasts/separation of > 25 cm

- Additional studies support hypofractionation for any grade (i.e. grade 3 and using boost)

- Additional studies support use in the setting of chemotherapy

- In US, the use of hypofractionation for RNI is being explored but not yet standard
What is the hypo-fractionation regimen used in the “Canadian” study published by Whelan et al?

- Dose of 2.66 Gy for 16 fractions to a total dose of 42.5 Gy to the breast without a boost.
Lumpectomy Cavity Boost

- EORTC randomized 5318 patients BCT with negative margins for IDC to 50 Gy in 25 fractions to breast f/b boost of 16 Gy in 8 fractions or NO additional boost
- Median follow up of 17 years LR as first event decreased by boost (16.4% versus 12.0%)
- No difference in DM, DFS, OS
- Fibrosis and severe fibrosis greater in boost group (severe 5.25 versus 1.8%)

Bartelink H, Lancet Oncology, 2015; 16(1)
Omission of Radiation CALGB9343

- CALGB randomized 636 women ≥ 70 with T1N0 clinical stage breast cancer any grade ER+ to Tamoxifen alone or Tamoxifen and RT
- SLNB not required (63% no axillary surgery)
- CALBG 9343 trial showed no advantage to RT for DFS or OS at 10 years with a median follow up of 12.6 years
- At 10 years, for TAM/RT LRC was 98% versus 92% for TAM alone
- No difference in time to mastectomy, time to DM, BCSS, OS
- Tamoxifen alone is a reasonable option for women ≥70

Hughes et al, vol 31, No 19 JCO 2013
What is an acceptable treatment for a 75 y/o F with an invasive ductal carcinoma measuring 1.5 cm, negative margins, negative sentinel lymph node, ER+, PR+, Her-2-neu-?

• Tamoxifen (or other anti-estrogen therapy) without RT
Summary

Early Invasive Breast Cancer

- RT improves outcomes for early stage breast cancer and has been a well established standard for decades
- Multiple RTC for standard whole breast irradiation delivered over 6-7 weeks and this treatment was the “most” standard for early stage breast cancer
- Modern trials report very low rates of in-breast recurrence with recent trials reporting 5 year recurrence rates as low as 1-3%
- Modern RTC trials now support Hypofractionated whole breast RT as a less expensive and more convenient standard for Early Stage Breast Cancer & we should be offering this option to most if not all patients as a whole breast regimen
- Women over the age of 70 should be offered no RT as an option if they agree to anti-estrogen therapy
DCIS
DCIS
NSABP-B17

- Prospective randomized trial of 818 pts w/DCIS
- Randomized

Lumpectomy (391 pts)
Lumpectomy + RT (50Gy) (399 pts)

Margins: inked margin negative for tumor

Fisher, NEJM 1993
NSABP B-17

- Median follow up of 17 years, lumpectomy alone 35% LR versus 20% lumpectomy and radiation
  - Invasive lumpectomy alone 20% versus invasive lumpectomy + RT 11%
  - DCIS lumpectomy alone 15% versus 9% lumpectomy and RT

- No difference in DFS, OS
DCIS
EORTC
10853

- 1010 women w/DCIS (≤ 5cm) randomized to lumpectomy alone or lumpectomy plus 50 Gy of irradiation to the breast (no boost)
- Negative surgical margins
- 71% tumors detected by mammo
- Median follow-up of 15 years, lumpectomy alone 30% versus 17% for lumpectomy and RT
  - For lumpectomy alone, 50/50 IDC/DCIS and similar for lumpectomy + RT (56% IDC versus 44% DCIS)
  - No difference in DFS, OS

Julien et al. Lancet 2000
EBCTG Metanalysis

- Lumpectomy without RT 28.1% risk of LR versus 12.9% for lumpectomy + RT

Correa, JNCI Mono 2010; 41
What about hypofractionation for DCIS?

• Mainly extrapolation from studies for invasive cancer but becoming widely accepted as a
• Small series have been published showing excellent local control for hypofractionation
• TROG has randomized trial for conventional fractionation versus hypofractionation and boost versus no boost for DCIS
**DCIS -trials of Omission**

- Recognized that DCIS is pre-invasive cancer and goal of therapy is prevention of an invasive cancer but we “over treat” a large number of women with this disease
- While some women benefit from RT, efforts to select patients who could avoid RT is ongoing
- RT does carry risks and patients with DCIS who do recur are likely to go on to mastectomy and reconstructive options may be compromised by deliver of RT for BCT
RTOG 9804

- 636 patients (of 1790 planned*** did not meet accrual goal) with grade 1 or 2 DCIS and margins $\geq$3mm randomized to lumpectomy plus RT versus lumpectomy alone

- Median follow up of 7 years, LR for lumpectomy alone 6.9% versus 0.9% significantly different (essentially 7 years follow up 7% v 1%)

- Small but significant benefit for RT

McCormick et al, JCO 2015; 33;709-715
ECOG 5194

- Prospective non-randomized single arm study for lumpectomy without RT for DCIS

- 2 cohorts
  - Cohort #1- DCIS Grade 1&2, ≤ 2.5 cm, margins ≥ 3 mm 561 patients
  - Cohort #2 DCIS Grade 3, ≤ 1 cm, margins ≥ 3mm, 104 patients

- At median follow up of 12.3 years,
  - Cohort #1/Grade 1&2 DCIS- LR 14.4% for IDC or DCIS and 7.5% for IDC
  - Cohort #2/Grade 3- LR 24.6% for IDC or DCIS and 13.4% for IDC

Solin, JCO 2015 Nov 20;33(33):3938-44
DCIS summary

- Adjuvant RT should be discussed with all patients considering or having undergone BCT for DCIS
- Still trying to find the right cohort for omission of RT and no clear consensus
- Discussion about trials of omission and consideration of all risks and benefits appropriate to help patients make informed decisions about treatment
TECHNIQUE EARLY STAGE BREAST CANCER
Supine Breast Treatment
Breath Hold

- Displaces heart inferior and posterior to improve therapeutic ratio for many patients
- Requires verification of position

Courtesy of Dr. Taghian
**Prone Breast Treatment**

- Displaces breast tissue anteriorly and can remove tumor bed or breast tissue away from chest wall.
- Great for pendulous breasts and tumor beds more anterior and in center of breast tissue.
- Improves homogeneity for the whole breast (decreases separation).
- Very low lung dose; often improved cardiac sparing.
- Great for pre-invasive/early disease when target is just breast tissue.
- Can be difficult position to tolerate (uncomfortable and sometimes causes more anxiety); good to ask patients that have had MRI how they tolerated it.
- Some large breasted women contralateral breast tissue gets in the way.
- Medial tumors may require treatment through board or be harder to reach.

Courtesy of Dr. Raymond Mailhot
Field-in-Field Technique

Hot spots of 112 and 108%

Alternative to IMRT to reduce hot spots and is not charged as IMRT
Field-in-Field Technique

MLCs to block out 112

Give small weight to subfield
Field-in-Field Technique
ACCELERATED PARTIAL BREAST IRRADIATION
Despite benefits of RT....

• Standard radiation is inconvenient and expensive
• Not all patients will receive for these reasons and “Financial Toxicity” to patients is becoming an increasing concern
• APBI offers a short treatment (1 day to 2 weeks) and may allow more patients to receive RT and some regimens are less expensive; patients at a distance need only a short hotel stay to receive treatment
Rationale

- Vast majority of recurrences (80-90%) occur in the tumor bed
- More convenient
- May allow more patients to undergo BCT
- Decreased exposure of normal tissues

Veronesi et al. 2002; Clark RM, et al.; Athos 2002
Rationale

• Whole breast volume was chosen in an era of aggressive surgical treatment and skepticism that BCT would prove a feasible option
• Improvements in imaging allow for better visualization of tumor bed
Arguments against PBI

- Why risk changing something that works?
  - No expectation that PBI will improve upon local control

- EBCTG meta-analysis demonstrated OS benefit for WBI
  - Could be more to lose than LC

- Shorter WBI courses are another alternative
  - With Phase III RTC and longer follow up

EBCTG 2005; Whelan et al. 2010; Dewer et al. 2007
Arguments against PBI

• Not all studies report low rate of recurrence outside of the tumor bed
• MRI has been shown to reveal multifocal or multicentric disease, but this imaging may not be available for all patients receiving PBI & MRI is costly
• Even with more extensive surgery, RT is of benefit (quadrantectomy)

Bartelink et al. 2001; Al-Hallaq, et al. 2006; Veronisi, 2002
Biological Considerations

- Does APBI deliver adequate dose?
- Variety of dose schedules
- BED models suggest WBI may be more biologically effective than APBI but BED is an estimate $\alpha/\beta$ of breast cancer unknown and could differ between subtypes
- Inhomogeneity of many techniques
- Dose falls off with distance from cavity
- Shorter time to RT
- Effects of immediate RT on proliferation

Rosenstein, et al. 2004
## Cost

<table>
<thead>
<tr>
<th>Cost</th>
<th>Whole breast</th>
<th></th>
<th>Partial breast</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>WBRT-B ($)</td>
<td>WBRT ($)</td>
<td>WBRT-AC ($)</td>
<td>WBRT-IMRT ($)</td>
</tr>
<tr>
<td>Payer’s</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Technical</td>
<td>7,500</td>
<td>5,800</td>
<td>4,100</td>
<td>15,600</td>
</tr>
<tr>
<td>Professional</td>
<td>2,000</td>
<td>1,600</td>
<td>1,300</td>
<td>2,300</td>
</tr>
<tr>
<td>Subtotal</td>
<td>9,500</td>
<td>7,400</td>
<td>5,400</td>
<td>17,900</td>
</tr>
<tr>
<td>Patient’s</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time</td>
<td>900</td>
<td>700</td>
<td>500</td>
<td>900</td>
</tr>
<tr>
<td>Transport</td>
<td>500</td>
<td>400</td>
<td>200</td>
<td>500</td>
</tr>
<tr>
<td>Subtotal</td>
<td>1,400</td>
<td>1,100</td>
<td>700</td>
<td>1,400</td>
</tr>
<tr>
<td>Society’s</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>10,900</td>
<td>8,500</td>
<td><strong>6,100</strong></td>
<td>19,300</td>
</tr>
</tbody>
</table>

*Least expensive hypo fractionated WBRT (42.5 Gy in 16 fractions)*

*Brachytherapy can be up to 1.7 times the cost of WBRT*

Suh, et al, 2005
Methods of Delivery

- Interstitial brachytherapy
- Intraoperative radiotherapy
- Intracavitary brachytherapy
- External beam radiation

Courtesy of Dr. Taghian
Interstitial Brachytherapy

• One of the first techniques utilized for the administration of APBI
• For delivery of this treatment, interstitial catheters are placed at the time of surgery or at a separate surgical procedure
• Advantage of placing catheters at the time of resection is sparing an additional surgical procedure but no final pathology evaluation prior to RT
• # of catheters and planes depends on the target volume
• Implants are planned to cover the tumor bed + 1-3 cm margin. Can be delivered with LDR or HDR.
**Interstitial Implants (HDR and LDR)**

<table>
<thead>
<tr>
<th><strong>Advantages</strong></th>
<th><strong>Disadvantages</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Experience and long follow up</td>
<td>- Invasive procedure</td>
</tr>
<tr>
<td>Conformal</td>
<td>- Infection, hematoma risks</td>
</tr>
<tr>
<td>4 - 5 days</td>
<td>- Formal training</td>
</tr>
<tr>
<td>Well-tolerated</td>
<td>- Operator dependent</td>
</tr>
<tr>
<td></td>
<td>- Requires hospital stay (LDR) or multiple visits with catheters in place (HDR)</td>
</tr>
</tbody>
</table>
# Published APBI Results

- Catheter Based Brachytherapy -

<table>
<thead>
<tr>
<th>Institution</th>
<th># Patients</th>
<th>Follow-Up (Months)</th>
<th>% Local Recurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td>NIO-Hungary (phase II)</td>
<td>45</td>
<td>136</td>
<td>9.3*</td>
</tr>
<tr>
<td>RTOG 95-17</td>
<td>99</td>
<td>146</td>
<td>6.2</td>
</tr>
<tr>
<td>Hungary Phase III</td>
<td>129</td>
<td>144</td>
<td>6</td>
</tr>
<tr>
<td>WBH</td>
<td>199</td>
<td>113</td>
<td>5*</td>
</tr>
<tr>
<td>Orebro University</td>
<td>50</td>
<td>86</td>
<td>4+</td>
</tr>
<tr>
<td>MGH</td>
<td>48</td>
<td>84</td>
<td>2</td>
</tr>
<tr>
<td>Tufts/Brown University</td>
<td>33</td>
<td>84</td>
<td>9</td>
</tr>
<tr>
<td>NIO-Hungary (phase III)</td>
<td>128</td>
<td>81</td>
<td>4.7</td>
</tr>
<tr>
<td>Oschner Clinic</td>
<td>51</td>
<td>75</td>
<td>2.0</td>
</tr>
<tr>
<td>RTOG 95-17</td>
<td>99</td>
<td>74</td>
<td>4.0</td>
</tr>
<tr>
<td>Joe Arrington Cancer Center</td>
<td>214</td>
<td>72</td>
<td>4.2</td>
</tr>
<tr>
<td>German-Austrian MC Trial</td>
<td>171</td>
<td>71</td>
<td>-</td>
</tr>
<tr>
<td>University of Wisconsin***</td>
<td>136</td>
<td>60</td>
<td>4.8</td>
</tr>
<tr>
<td>Tufts-Brown University</td>
<td>33</td>
<td>58</td>
<td>6</td>
</tr>
<tr>
<td>Washington University</td>
<td>192</td>
<td>55</td>
<td>2.1</td>
</tr>
<tr>
<td>VCU</td>
<td>59</td>
<td>50</td>
<td>5.1</td>
</tr>
<tr>
<td>University of Wisconsin</td>
<td>247</td>
<td>48</td>
<td>3**</td>
</tr>
<tr>
<td>Joe Arrington Cancer Center</td>
<td>136</td>
<td>48</td>
<td>3.7</td>
</tr>
<tr>
<td>German-Austrian MC Trial</td>
<td>274</td>
<td>38</td>
<td>0.4</td>
</tr>
<tr>
<td>University Kansas</td>
<td>24</td>
<td>37</td>
<td>0</td>
</tr>
<tr>
<td>University of Perugia, Italy</td>
<td>80</td>
<td>30</td>
<td>0</td>
</tr>
<tr>
<td>Florence Italy</td>
<td>90</td>
<td>27</td>
<td>4.4</td>
</tr>
<tr>
<td><strong>Totals</strong></td>
<td>2309</td>
<td>27-136</td>
<td>0-9%</td>
</tr>
</tbody>
</table>

*12-year rate, += 7-year rate
**High-risk patients, ***ASTRO Cautionary Group

Collectively, thousands of patients

![> 10 years]

Courtesy F. Vicini & A Taghian

---

> 10 years
Mammosite™ Balloon Catheter

- Mammosite Balloon catheter is a device designed to deliver brachytherapy in a less technically demanding fashion c/w catheter.
- The balloon is filled with saline and a HDR source inserted into the center of the balloon and dose is prescribed to a determined distance from the balloon surface (usually 1 cm).
- It is important that the balloon surface is flush against the tumor bed cavity and that an adequate distance (approx 7 mm) from the skin. Poor balloon conformance and inadequate skin-to-balloon distance are the major reasons for aborting a Mammosite procedure.
## Intracavitary Implants

<table>
<thead>
<tr>
<th><strong>Advantages</strong></th>
<th><strong>Disadvantages</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>- Experience and studies with long follow up</td>
<td>- Invasive procedure</td>
</tr>
<tr>
<td>- Conformal</td>
<td>- Infection, hematoma risks</td>
</tr>
<tr>
<td>- 4 - 5 days</td>
<td>- Formal training</td>
</tr>
<tr>
<td>- Well-tolerated</td>
<td>- Steep learning curve</td>
</tr>
<tr>
<td>- Relative ease of use</td>
<td>- Limitations if close to skin</td>
</tr>
<tr>
<td>(compared to interstitial brachytherapy)</td>
<td></td>
</tr>
</tbody>
</table>
### Published APBI Results - **MammoSite** -

Collectively, thousands of patients

<table>
<thead>
<tr>
<th>Institution</th>
<th># Cases</th>
<th>Follow-Up (Months)</th>
<th>% Local Recurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td>FDA Trial</td>
<td>43</td>
<td>66</td>
<td>0%</td>
</tr>
<tr>
<td>ASBS Registry</td>
<td>400</td>
<td>60</td>
<td>3.2%</td>
</tr>
<tr>
<td>NY Hospital/Cornell (DCIS)</td>
<td>48</td>
<td>60</td>
<td>6.3%</td>
</tr>
<tr>
<td>University of Wisconsin</td>
<td>26</td>
<td>48.5</td>
<td>3%*</td>
</tr>
<tr>
<td>ASBS Registry Trial</td>
<td>1449</td>
<td>51</td>
<td>2.6%</td>
</tr>
<tr>
<td>MUSC</td>
<td>99</td>
<td>46</td>
<td>3.1%</td>
</tr>
<tr>
<td>Texas Cancer Center</td>
<td>573</td>
<td>31</td>
<td>1.0%</td>
</tr>
<tr>
<td>Rush</td>
<td>70</td>
<td>26</td>
<td>6%</td>
</tr>
<tr>
<td>WBH</td>
<td>80</td>
<td>24</td>
<td>2.9%</td>
</tr>
<tr>
<td>VCU</td>
<td>483</td>
<td>24</td>
<td>1.2%</td>
</tr>
<tr>
<td>Tufts/VCU/NEMC</td>
<td>28</td>
<td>19</td>
<td>0%</td>
</tr>
<tr>
<td>Single Institution Experiences</td>
<td>1000</td>
<td>2-12</td>
<td>0-3%</td>
</tr>
<tr>
<td><strong>Totals</strong></td>
<td><strong>3899</strong></td>
<td><strong>2-66</strong></td>
<td><strong>0-6.3%</strong></td>
</tr>
</tbody>
</table>

*High-risk patients

5-years

Courtesy F. Vicini & A Taghian
Intra-operative Radiation

Applicator sphere in tumour bed
# Intra-Operative RT

## Advantages
- Conformal
- One treatment
- Decreased interval from surgery to RT
- Phase I/II trials promising
- Phase III with early results

## Disadvantages
- Invasive procedure
- RT delivered at time of surgery for all patients before the availability of final path
- Late effect of a large single dose
- Dose distribution
- Biological impact
- Availability
External Beam Radiation
3-D Conformal External RT

<table>
<thead>
<tr>
<th><strong>Advantages</strong></th>
<th><strong>Disadvantages</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>- Non-invasive</td>
<td>- Optimal doses?</td>
</tr>
<tr>
<td>- Knowledge of final pathology</td>
<td>- Optimal fractionation?</td>
</tr>
<tr>
<td>- 4 - 5 days</td>
<td>- Patient set up</td>
</tr>
<tr>
<td>- Homogeneous dose distribution</td>
<td>- Tolerance of non-target tissues to RT</td>
</tr>
<tr>
<td>- Widely available</td>
<td>- Long term cosmesis</td>
</tr>
<tr>
<td>- Less costly</td>
<td>- Greater dose to uninvolved breast tissue</td>
</tr>
<tr>
<td>- Requires less specialized training</td>
<td>- Shorter follow up</td>
</tr>
</tbody>
</table>
3D conformal techniques

- Vicini technique
- William-Beaumont Hospital, MI
- Formenti technique
- New York University, NY
- MGH technique
- Boston, MA
- Others, IMRT, protons, etc
Vicini technique

Multiple photon fields
3.85 Gy X 10 fractions BID / 1 weeks
RTOG/NSABP fractionation scheme
Formenti/Prone technique

- Photon technique (usually 2 fields)
- 6.0 Gy X 5 fractions 2 weeks
**Taghian / MGH technique**

- 2 mini-tangents and en face electrons
- 4.0 Gy X 8-10 fractions BID / 4 days
Seroma should have 4-6 clips
Margins: 1.5 to 2 cm
Ratio PTV/breast volume <20%
Non-target breast volume receiving 50% of dose <50%
95% isodose line covers 95% of the PTV
Use IGRT (VisionRT) for accurate set-up
Lung volume:
  ILV-20Gy: <3%
  ILV-10Gy: <10%
  ILV-5Gy: <20%
### Published APBI Results
- **3D Conformal External Beam RT** -

<table>
<thead>
<tr>
<th>Institution</th>
<th># Patients</th>
<th>Follow-Up (Months)</th>
<th>% Local Recurrence</th>
<th>Grade III Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>NYU (prone)</td>
<td>98</td>
<td>60</td>
<td>1%</td>
<td>3%</td>
</tr>
<tr>
<td>WBH</td>
<td>96</td>
<td>47</td>
<td>1%</td>
<td>4%</td>
</tr>
<tr>
<td>RTOG 0319</td>
<td>52</td>
<td>42</td>
<td>6%</td>
<td>4%</td>
</tr>
<tr>
<td>Canadian Multi-Center</td>
<td>127</td>
<td>36</td>
<td>&lt;1%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Loma Linda (Protons)</td>
<td>50</td>
<td>36</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>NYU/Keck School Medicine</td>
<td>10</td>
<td>36</td>
<td>0%</td>
<td>--</td>
</tr>
<tr>
<td>MGH</td>
<td>99</td>
<td>36</td>
<td>2%</td>
<td>--</td>
</tr>
<tr>
<td>Rocky Mountain Cancer Center</td>
<td>105</td>
<td>36</td>
<td>0%</td>
<td>--</td>
</tr>
<tr>
<td>NIO-Hungary</td>
<td>40</td>
<td>34</td>
<td>2%</td>
<td>--</td>
</tr>
<tr>
<td>NSABP B39/RTOG 0413</td>
<td>338</td>
<td>32</td>
<td>--</td>
<td>&lt;2%</td>
</tr>
<tr>
<td>Stanford</td>
<td>62</td>
<td>29</td>
<td>0%</td>
<td>1.6%</td>
</tr>
<tr>
<td>NYU</td>
<td>78</td>
<td>28</td>
<td>0%</td>
<td>--</td>
</tr>
<tr>
<td>University of Michigan</td>
<td>34</td>
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<tr>
<td>California Pacific Med Center</td>
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<td>22</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Virginia Commonwealth Univ</td>
<td>61</td>
<td>18</td>
<td>0%</td>
<td>7%</td>
</tr>
<tr>
<td>Tufts</td>
<td>64</td>
<td>15</td>
<td>--</td>
<td>8.3%</td>
</tr>
<tr>
<td>Baptist</td>
<td>24</td>
<td>13</td>
<td>0%</td>
<td>--</td>
</tr>
<tr>
<td><strong>Totals</strong></td>
<td><strong>1289</strong></td>
<td><strong>13-47</strong></td>
<td><strong>0-6%</strong></td>
<td><strong>1-8%</strong></td>
</tr>
</tbody>
</table>

Collectively, over a thousand patients

Courtesy F. Vicini
**Target definition**

- Surgical clips useful for tumor bed definition
KV Films for set up

Clips are also useful for set up
Surface Imaging System
## Phase III Trials

<table>
<thead>
<tr>
<th>Institution/Trial</th>
<th># Cases</th>
<th>Control Arm</th>
<th>Experimental Arm</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSABP B 39/RTOG 0413</td>
<td>4300</td>
<td>50-50.4 Gy WB +/- 10-16 Gy Boost</td>
<td>(1) Interstitial Brachytx, or (2) MammoSite™, or (3) 3D Conformal EBRT</td>
</tr>
<tr>
<td>National Institute of Oncology Budapest, Hungary</td>
<td>258</td>
<td>50 Gy WB</td>
<td>(1) Interstitial Brachytx (5.2 Gy X 7) or (2) Electrons (50 Gy)</td>
</tr>
<tr>
<td>European Brachytherapy Breast Cancer GEC-ESTRO Working Group</td>
<td>1170</td>
<td>50-50.4 Gy WB +/- 10 Gy Boost</td>
<td>Brachytherapy Only 32.0 Gy 8 fractions HDR 30.3 Gy 7 fractions HDR 50 Gy PDR</td>
</tr>
<tr>
<td>European Institute of Oncology ELIOT</td>
<td>1200</td>
<td>50 Gy WB +/- 10 Gy Boost</td>
<td>Intra-operative Single fraction EBRT 21 Gy x 1</td>
</tr>
<tr>
<td>Canadian Trial RAPID</td>
<td>2128</td>
<td>WB 42.5 Gy in 16 or 50 Gy in 25 +/- 10 Gy boost</td>
<td>3D CRT only 38.5 Gy in 10</td>
</tr>
<tr>
<td>Medical Research Council – UK IMPORT LOW</td>
<td>1935</td>
<td>WB 2.67 Gy X 15</td>
<td>(1) WB 2.4 Gy X 15 PB 2.67 Gy X 15 (2) PB only 2.67 Gy X 15</td>
</tr>
</tbody>
</table>

Courtesy of Dr. Taghian
NSABP-39 (RTOG 04-15)

Eligible patient treated with lumpectomy
Post-Lumpectomy CT evaluation

Stratification
Disease stage – DCIS, invasive N0, invasive N1 (1-3)
Age - ≤49, ≥50
Hormone receptor status (ER-, ER+)

WBI after adjuvant chemotherapy
50 Gy (2.0 Gy/fx) or
50.4 Gy (1.8 Gy/fx) - whole breast
optional boost to 60-66.4 Gy

APBI
Prior to adjuvant chemotherapy
34 Gy in 3.4 Gy bid x 5-7 days Interstitial Brachytherapy
or
34 Gy in 3.4 Gy bid x 5-7 days Mammosite Balloon Catheter
or
38.5 Gy in 3.85 Gy bid x 5-6 days
3D Conformal External Beam
Marked decline in accrual when trial closed to stage I ER+ tumors; rapid accrual before this time.
NSABP B-39/RTOG 0413

- Open: March 21, 2005
- Accrual:
  - June 14, 2013: 4217 (4300 total) 98%
- Closed (completed)
- Participating Sites:
  - 78 – NSABP
  - 142 – RTOG/CTSU
  - PBI Technique
    - 71.0%: 3D Conformal
    - 23.3%: MammoSite
    - 5.7%: Interstitial

Still awaiting Final results/publication

Courtesy of Dr. Taghian
### Off Protocol Guidelines

#### ASTRO-suitable

2016 Guidelines Update

**Age:** >50 years

**Stage:** Tis / T1

**DCIS:** <2.5 cm grade I-II, 3 mm margins

#### GEC-ESTRO-low-risk

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>A/low-risk group – good candidates for APBI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient age</td>
<td>&gt;50 years</td>
</tr>
<tr>
<td>Histology</td>
<td>IDC, mucinous, tubular, medullary, and colloid cc.</td>
</tr>
<tr>
<td>ILC</td>
<td>Not allowed</td>
</tr>
<tr>
<td>Associated LCIS</td>
<td>Allowed</td>
</tr>
<tr>
<td>DCIS</td>
<td>Not allowed</td>
</tr>
<tr>
<td>HG</td>
<td>Any</td>
</tr>
<tr>
<td>Tumour size</td>
<td>pT1 – 2 (≤30 mm)</td>
</tr>
<tr>
<td>Surgical margins</td>
<td>Negative (≥ 2 mm)</td>
</tr>
<tr>
<td>Multicentricity</td>
<td>Unicentric</td>
</tr>
<tr>
<td>Multifocality</td>
<td>Unifocal</td>
</tr>
<tr>
<td>EIC</td>
<td>Not allowed</td>
</tr>
<tr>
<td>LVI</td>
<td>Not allowed</td>
</tr>
<tr>
<td>ER, PR status</td>
<td>Any</td>
</tr>
<tr>
<td>Nodal status</td>
<td>pN0 (by SLNB or ALND*)</td>
</tr>
<tr>
<td>Neoadjuvant chemotherapy</td>
<td>Not allowed</td>
</tr>
</tbody>
</table>

*Courtesy of Dr. Taghian*

---

Smith et al., 2009 IJROBP
Polgar et al., 2010 Radiat Onc
Off Protocol Guidelines

ASTRO – cautionary
2016 Guidelines Update

Age: 40 – 49 years if all criteria of suitable
50 + if at least one path criteria
DCIS: <3 cm if all other criteria of suitable

<table>
<thead>
<tr>
<th>Table 3. “Cautionary” group: Any of these criteria should invoke caution and concern when considering APBI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Factor</strong></td>
</tr>
<tr>
<td>Patient factors</td>
</tr>
<tr>
<td>Age</td>
</tr>
<tr>
<td>Pathologic factors</td>
</tr>
<tr>
<td>Tumor size</td>
</tr>
<tr>
<td>T stage</td>
</tr>
<tr>
<td>Margins</td>
</tr>
<tr>
<td>LVSI</td>
</tr>
<tr>
<td>ER status</td>
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<tr>
<td>Multifocality</td>
</tr>
<tr>
<td>Histology</td>
</tr>
<tr>
<td>Pure DCIS</td>
</tr>
<tr>
<td>EIC</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>GEC-ESTRO-intermediate-risk</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Characteristic</strong></td>
</tr>
<tr>
<td>Patient age</td>
</tr>
<tr>
<td>Histology</td>
</tr>
<tr>
<td>ILC</td>
</tr>
<tr>
<td>Associated LCIS</td>
</tr>
<tr>
<td>DCIS</td>
</tr>
<tr>
<td>HG</td>
</tr>
<tr>
<td>Tumour size</td>
</tr>
<tr>
<td>Surgical margins</td>
</tr>
<tr>
<td>Multicentricity</td>
</tr>
<tr>
<td>Multifocality</td>
</tr>
<tr>
<td>EIC</td>
</tr>
<tr>
<td>LVI</td>
</tr>
<tr>
<td>ER, PR status</td>
</tr>
<tr>
<td>Nodal status</td>
</tr>
<tr>
<td>Neoadjuvant chemotherapy</td>
</tr>
</tbody>
</table>

Smith et al., 2009 IJROBP
Polgar et al., 2010 Radiat Onc
Off Protocol Guidelines

ASTRO-unsuitable

Table 4. Patients “unsuitable” for APBI outside of a clinical trial if any of these criteria are present

<table>
<thead>
<tr>
<th>Factor</th>
<th>Criterion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient factors</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>&lt;50 y</td>
</tr>
<tr>
<td>BRCA1/2 mutation</td>
<td>Present</td>
</tr>
<tr>
<td>Pathologic factors</td>
<td></td>
</tr>
<tr>
<td>Tumor size*</td>
<td>&gt;3 cm</td>
</tr>
<tr>
<td>T stage</td>
<td>T3-4</td>
</tr>
<tr>
<td>Margins</td>
<td>Positive</td>
</tr>
<tr>
<td>LVI</td>
<td>Extensive</td>
</tr>
<tr>
<td>Multicentricity</td>
<td>Present</td>
</tr>
<tr>
<td>Multifocality</td>
<td>If microscopically multifocal &gt;3 cm in total size or if clinically multifocal</td>
</tr>
<tr>
<td>Pure DCIS</td>
<td>If &gt;3 cm in size</td>
</tr>
<tr>
<td>EIC</td>
<td>If &gt;3 cm in size</td>
</tr>
<tr>
<td>Nodal factors</td>
<td></td>
</tr>
<tr>
<td>N stage</td>
<td>pN1, pN2, pN3</td>
</tr>
<tr>
<td>Nodal surgery</td>
<td>None performed</td>
</tr>
<tr>
<td>Treatment factors</td>
<td></td>
</tr>
<tr>
<td>Neoadjuvant therapy</td>
<td></td>
</tr>
<tr>
<td></td>
<td>If used</td>
</tr>
</tbody>
</table>

GEC-ESTRO-contraindication

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>C/high-risk group – contraindication for APBI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient age</td>
<td>≤40 years</td>
</tr>
<tr>
<td>Histology</td>
<td>–</td>
</tr>
<tr>
<td>ILC</td>
<td>–</td>
</tr>
<tr>
<td>Associated LCIS</td>
<td>–</td>
</tr>
<tr>
<td>DCIS</td>
<td>–</td>
</tr>
<tr>
<td>HG</td>
<td>–</td>
</tr>
<tr>
<td>Tumour size</td>
<td>pT2 (&gt;30 mm), pT3, pT4</td>
</tr>
<tr>
<td>Surgical margins</td>
<td>Positive</td>
</tr>
<tr>
<td>Multicentricity</td>
<td>Multicentric</td>
</tr>
<tr>
<td>Multifocality</td>
<td>Multifocal (&gt;2 cm from the index lesion)</td>
</tr>
<tr>
<td>EIC</td>
<td>Present</td>
</tr>
<tr>
<td>LVI</td>
<td>Present</td>
</tr>
<tr>
<td>ER, PR status</td>
<td>–</td>
</tr>
<tr>
<td>Nodal status</td>
<td>pN0X ≥ pN2a (4 or more positive nodes)</td>
</tr>
<tr>
<td>Neoadjuvant chemotherapy</td>
<td>if used</td>
</tr>
</tbody>
</table>

ASTRO –unsuitable 2016 Guidelines Update

Age: <40 years

Courtesy of Dr. Taghian
PBI for re-irradiation

RTOG 1014

A Phase II study of Repeat Breast Preserving Surgery and 3D-Conformal Partial Breast Re-Irradiation (PBRI) for Local Recurrence of Breast Carcinoma

SCHEMA

| REGISTER | Partial Breast Re-Irradiation (PBRI) 3D-Conformal External Beam 1.5 Gy x 15 (BID) to 45 Gy Total |

Patient Population: (See Section 3.0 for Eligibility)
- Histopathologic confirmation via lumpectomy of local in-breast ipsilateral recurrence
- Final breast surgery (lumpectomy and/or final re-excision) within 42 days prior to study entry;
- Initial lumpectomy followed by whole breast radiation >1 year prior to study entry;
- Bilateral breast mammogram and bilateral breast MRI within 120 days prior to study entry;
- Negative histologic margins of resection, no tumor on ink, following breast-preserving surgery of local recurrence.

Required Sample Size: 61
PBI for repeat RT/RTOG 1014

- Phase II study for repeat BCT with 3D-CRT PBI
- 1.5 Gy x 15 (BID) to 45 Gy
- Last BCT must be > 1 yr prior
- Mammogram and MRI required
- Must have negative margins (no tumor on ink)

Awaiting results
Conclusions

• Whole breast Irradiation should remain standard until more results from well-designed randomized trials of APBI become available

• APBI an option off study if patients understand data available and meet suitable criteria

• For patients with favorable breast cancer that are unable to undergo 3-6 weeks of RT, APBI is a reasonable alternative to no RT
LOCALLY ADVANCED OR NODE + BREAST CANCER
Overview

- Indications for PMRT
- Supporting Data
  - Classic Studies supporting PMRT (Danish, BC, EBCTCG)
  - PMRT LN negative patients (retrospective data)
- Modern era decision making for axillary management and regional nodal RT (ACOSOG Z-11, NCIC MA 20, EORTC 29922, AMAROS)
- Neoadjuvant chemotherapy
- Treatment planning/CT based contours
Indications for PMRT/RNI

- T₃/T₄, ≥ 4 positive ALN
  - T₃N₀- some exceptions
- SCV or IMN involvement
- Strong consideration for PMRT/RNI in patients with 1-3 nodes
- For T₁/₂N₀ patients, PMRT is generally avoided but retrospective data indicates some of these patients have higher risk of LRR
LABC

- Multiple clinical presentations:
  - T3 tumor (>5cm) in setting of + LN
  - Extensive regional lymphatic involvement (ie. N2, N3)
  - Direct involvement of skin (T4b) or chest wall (T4a)
  - Inflammatory breast cancer (T4d)
  - Unresectable non-metastatic disease

- Stage groups:
  - IIIA (T0 N2; T1-2 N2; T3 N1-2)
  - IIIB (T4 N0-2) including inflammatory
  - IIIC (Tany N3)
Considerations for N+ Disease

• Over past decade, more data to support PMRT and RNI in patients not considered to have LABC

• In addition, due to changes in axillary management we more often now have only SLNB for patients with + LN and we no longer obtain the classic or true pathological N stage as we do not know how many LN in axilla are truly involved
**Randomized PMRT Trials- Danish 82b**

- 1708 pre-menopausal women
- Stage II-III breast cancer
- Modified radical mastectomy
- 8 cycles CMF
- PMRT (chest wall + regional nodes incl IMNs) vs observation

Overall Survival Benefit: 10% at 10 years

**PMRT decreased LRR:**
32% → 9%
(Median FU 114 months)

Overgaard, NEJM 1997
Randomized PMRT Trials-Danish 82c

- 1708 post-menopausal women
- Stage II-III breast cancer
- Modified radical mastectomy
- Tamoxifen
- PMRT (chest wall + regional nodes incl IMNs) vs observation

PMRT decreased LRR: 35% → 8%

Overall Survival Benefit: 10% at 10 years

Overgaard, Lancet 1999)
Randomized PMRT Trials British Columbia

- 318 pre-menopausal women
- ≥1 positive nodes
  - Modified radical mastectomy
  - Median 11 nodes removed
  - CMF
  - PMRT (chest wall + regional nodes incl IMNs) vs observation

PMRT decreased LRR: 26% → 10%

Ragaz, JNCI 2005
Overall survival benefit was seen in both the 1-3 and ≥4 LNs

Ragaz, JNCI 2005
Criticisms of Original Danish & British Columbia Studies

- Local failure rate of 26-35% in these trials considered high
- Mean number of nodes (7) in the Danish studies again indicated poor quality surgery
- Outdated chemotherapy
- Modern surgery and pathological evaluation improved
EBCTCG showed benefit in both 1-3 and >4+

Isolated local recurrence:

1-3 nodes:

>4 nodes:

Disease specific mortality:

No benefit for PMRT for No patients

8135 women in 22 randomised trials

Lancet 366:2087, 2005
EBCTCG 2014 Update: Trials of Mastectomy & RT in pN1-3

Lancet March 19, 2014
For patients with 1-3 + lymph nodes after mastectomy, radiation

- Reduces local recurrence and breast cancer mortality
Criticisms of Oxford Overview

- Largely driven by Danish studies (with relatively high LF rates without RT)
- Patients with 1-3+ LN these days have lower risk of LRR than this review suggests
- Systemic therapy not used or outdated
- Little information on additional factors (LVI, etc)
T1/2 N0 – retrospective only

- 1505 women with pT1-2 pN0; from 1989-1999
- Median f/u 7 years
- LRR rate overall low -- 7.8%
- Factors affecting LRR:
  - Histologic grade
  - LVI
  - T stage
  - Systemic chemotherapy
T1/2 N0 – retrospective only

- **Highest risk:** T2 gr3 LVI- (LRR = 13.4%) → w/o systemic tx (LRR = 23.2%)

Truong et al. IJROBP, 2005.
T1/2N0–retrospective only

- MGH experience of 877 N0 patients s/p MRM
- Median follow-up 100 months
- Overall 10yr LRR was 6%.
- Analyzed for independent prognostic risk factors:
  - Size >2cm, margin <2mm, premenopausal, LVI+
  - Risk groups by 10-year LRR:
    - 0 factors 1.2%
    - 1 factor 10.0%
    - 2 factors 17.9%
    - 3 factors 40.6%
Risk factors to consider for PMRT in N0 pts

• Higher risk LRF
  – Young age / premenopausal
  – T stage
  – LVI
  – Grade 3
  – No systemic therapy**
  – Close or positive margins

** many received no chemotherapy

All data retrospective– be cautious with recommendations for this group
Modern era decision making for axillary management and regional nodal RT

• “The variety of options now available for managing the axilla is really confusing”

Morrow, Monica JAMA Oncology 2017
Evolution

• For years, ALND upfront was standard treatment

• In past decade, SLNB alone, SLNB + RT, neoadjuvant therapy have made it more difficult for radiation oncologists to make decisions regarding management of the axilla
Clinically Node Positive Disease

• These patients should undergo biopsy of positive LN to confirm cancer involvement

• The only way to avoid ALND is with the use of neoadjuvant chemotherapy
Clinically Negative Lymph Nodes

• SLNB and what to do if the SLN is positive
  – In past, + SLN meant ALND but now there are other options for most patients
  – For patients with 2 or fewer SLN+, studies exit for RNI or whole breast RT alone (Z-11) or RNI (AMAROS)
  – Studies supporting RNI (MA20, EORTC 22922) shortly after Z-11 made RT decisions difficult
Z-11 (ACOSOG Z0011) examined axillary dissection vs no axillary dissection in women with invasive breast cancer and sentinel node metastasis.

- Patients randomized after a positive sentinel lymph node biopsy to ALND or no further axillary surgery.
- All patients were then to go on to receive whole breast radiation. Only patients who underwent ALND and had 3 or more positive lymph nodes were not eligible to go on to randomization.
Z-11 (ACOSOG Z0011) was a trial that examined axillary dissection vs no axillary dissection in women with invasive breast cancer and sentinel node metastasis in a randomized trial.

Outcomes – No difference

- Median follow-up = 6.3 years
- Regional recurrence seen in only 0.7% of the entire population
- ALND
  - LRR 4.1%/Local 3.6%/Regional 0.5%
  - DFS 91.8%
  - OS 83.9%
- SLNB only
  - LRR 2.8%/Local 1.8%/Regional 0.9%
  - DFS 92.5%
  - OS 82.2%

Supports use of SLNB only for N+ patients undergoing BCT and receiving whole breast RT
Caveats

- 46% of + SN were micromets
- Only 27% of patients undergoing ALND had additional LN
- Radiation fields were not centrally reviewed
  - 28.5% had evaluable RT records
  - Many patients may have received “high tangents” (50%) and 19% had separate nodal field
- Remember this is for BCT patients only

Confusing as this study comes out at the same time others studies supporting regional nodal radiation & EBCTG supporting PMRT for 1-3 + LN’s

Jagsi et al. 2014, JCO
Radiotherapy or surgery of the axilla after a positive sentinel lymph node in breast cancer (EORTC 10981-22023 AMAROS).
AMAROS

• RT can be used in lieu of ALND with lower rates of lymphedema
AMAROS”: After mapping axillary radiation or surgery was a trial that examined

• Radiotherapy or surgery after a positive sentinel lymph node with radiotherapy on this trial including the regional lymphatics (at least axillary)
NCIC MA 20

- High Risk BCT patients only (N+ or high risk No- > 5 cm or > 2 cm and <10 LN removed and grade 3 or LVI or ER-)
- RTC to whole breast v whole breast and regional LN RT (level 1, 2, 3, SCV & IMN)
- LRR 5.5% WB v 3.2% RNI (p=0.02)
- DFS 84% WB v 89.7% RNI (p=0.003)
- OS 90.7% WB v 92.3% RNI (p=0.07)

Whelan, T MA20 RNI in early stage breast cancer, NEJM 2015;373(4):307-316
NCIC MA 20

- RNI improves outcomes
• Irradiation of the internal mammary and medial supraclavicular (IM-MS) lymph node chain irradiation in stage I-III breast cancer
• Final analysis of all 4004 patients
• Median follow up 10.9 years
• BCT and mastectomy

Poortmans P, NEJM 2015;373(4):317-327
EORTC phase III trial 22922/10925

- pN+ axillary nodes
- or
- pN- central or medial tumors

Randomize:
- NO IM-MS Irradiation
- IIM-MS Irradiation 50 Gy

Poortmans P, NEJM 2015;373(4):317-327
EORTC 22922

- DMFS 75% no nodal RT v 78% nodal RT (p=0.02)
- DFS 69.1% no nodal RT v 72.1% nodal RT (p=0.04)
- OS 80.7% no nodal RT v 82.3% nodal RT (p=0.056)

- Comprehensive nodal RT improves outcomes
Recent data supports RNI for high risk patients with small benefits in outcomes

MA 20 and EORTC included SCV and IMN indicating that inclusion of these nodes should be considered

AMAROS indicates RT can be used in place of ALND with less lymphedema

Z-11 reported good outcomes for N+ patients undergoing BCT with WB RT which includes some level 1/2 lymph nodes but not SCV or IMN. For this study, a somewhat more favorable cohort & appropriate for more favorable patients
PMRT after Neoadjuvant Chemotherapy

***Tough cases for many Radiation Oncologists
Neoadjuvant Chemotherapy

- Our recommendations are based on RCT based on pathological information and absence of similar evidence for these patients makes RT controversial.
- Recent marked increased use of neoadjuvant chemotherapy for patients with advanced disease, especially for Her-2-neu + disease and Triple negative disease.
- For radiation oncologists, this means loss of upfront pathological evaluation to assist in determining the need for PMRT or RNI.
Neoadjuvant Chemotherapy

- For surgeons- axillary management? Is SLN after chemo enough? For clinical No pre-chemo? For clinical N+pre-chemo?
- For radiation oncologists? Should we recommend PMRT for SLN – after neoadjuvant chemo? For clinical No pre-chemo? For clinical N+ pre-chemo?

- These remain challenging cases and at present off study best to base on perceived stage at time of diagnosis using all available information (CT chest, MRI, PET/CT, US)
Evaluation of Axilla Prior to Chemotherapy

- In past, we would obtain SLN prior to neoadjuvant chemotherapy
- At present, for clinically LN – patients we require thorough clinical evaluation but do not require SLN upfront for majority of patients & there is no consistency in the use of pre-neoadjuvant chemo use of axillary US
NSABP B18 and B27

- This combined analysis looked at prognostic factors for LRR
- Preop AC from B18 and preop AC+/-T B27
- SLNB after chemotherapy
- pCR associated with lower rates of LRR
- Age, tumor size, clinical node status and conversion to pathological CR in nodes

Mamounas, EP, JCO 2012 30:3960
Current Trials

- NSABP B51/RTOG 1304
  - Phase III designed to answer whether RT improves breast cancer recurrence free interval in women who present with clinical N1 axillary disease before neoadjuvant chemotherapy and become N0 after (N2 and N3 disease not eligible)

- Alliance 011202
  - Phase III trial designed to answer whether axillary node dissection improves rate of breast cancer recurrence over SLN alone when RT is delivered for clinically T1-3N1 tumors
Hypofractionation trials for RNI

• Alliance A221505 after mastectomy randomized to 50 Gy/25 fractions versus 42.5 Gy/16 fractions to chest wall and RNI

• FABREC after mastectomy randomized to 50-50.4/25-28 fractions versus 42.5/16 fractions
PMRT/LABC Planning
Breast atlas/3D Planning

- CT based imaging gives us the ability to define regions at risk of harboring disease and organs we wish to avoid based on 3D anatomy
- Contours required for some modalities (IMRT, Protons)

Always look at diagnostic CT chest for patients with involved nodes to help you learn nodal locations
LN location

- malignant
- benign

Always review pre-chemotherapy/pre-surgery CT chest and MRI when contouring

Low/deep SCV LN (beneath clavicle)
Draw Level 1, 2, 3 and SCV
Looking back

• What Does Coverage Look Like When We Use Old Planning Techniques?
RTOG Volume Coverage

- With use of standard fields
  - For prescription of 50 Gy, 45 Gy covered
  - 74% of chest wall
  - 84% of Level 1 LN
  - 88% of Level 2 LN
  - 93% of Level 3 LN
  - 84% of SCV LN
  - 80% of IMN

Important to remember that outcomes have been very good with this coverage, but perhaps we can do better with defined contours while keeping in mind normal tissue toxicity

Fontanilla, et al Practical Radiation Oncology 2012
Level 1 & 2 Coverage

"High Tangent"

Dose-Volume Analysis
45 Gy Axilla: 78% Lev-1, 21% Lev-2
V-20 Left Lung 9.75%

"Customized Tangent"

Dose-Volume Analysis
45 Gy Axilla: 100% Lev-1, 95% Lev-2
V-20 Left Lung 13.2%
3 Field Single Isocenter Technique

- 1 isocenter is used for both tangents and supraclavicular fields
- Tangents are ½ beam blocked superiorly, sclav is ½ beam blocked inferiorly to avoid overlap of fields
- Collimator for tangent fields typically set to 0, MLC leaves are drawn in to block lung

Courtesy of Liam Vanbentuysem
Single Iso (continued)

Supraclavicular Field

Single Iso 3D View

Courtesy of Liam Vanbentuysem
3 Field Double Isocenter Technique

- 1 iso for breast tangents, separate iso for supraclavicular field (needed for tall patients or patients that need high SCV field)
- In order to match superior border of tangents to inferior border of s’clav, couch kicks are needed for tangents to account for beam divergence
- Tangent collimator is rotated to match slope of chest wall
- MLC leaves are used in tangent fields to form match line
- Sclav field is ½ beam blocked inferiorly
Double Iso (continued)

Double Iso 3D

Courtesy of Liam Vanbentuysem
Breast Double Iso – couch kick away from gantry

(CSI kick couch towards gantry- keep your kids close)
SCV/PAB
SCV with 10 MV photons
VMAT for Breast Treatment

- Useful for high risk patients, better target coverage
- Multifield and higher mean heart dose, lung $V_5$
- Lower lung $V_{20}$
- Large arcs, avoid entering through contralateral breast
- Daily CBCT
- IMRT can be used without multiple arcs to provide some benefit without low dose spread
Protons Therapy

Improve coverage of difficult to treat nodal areas

Photons

Protons
Protons may be useful for:

- Advanced disease
- IMN involvement (R or L sided)
- Cardiotoxic chemo
- Young age
- Permanent implants
- Poor cardiac anatomy
- Left medial tumors
- Pre-existing cardiac disease
- Decreased arm mobility
- Predisposition for additional cancers (P53 mutations)

At present most costly and less widely available
AVOIDANCE
ORGANS
Cardiac Toxicity

- Myocardial infarction
- Coronary revascularization tx
- Death from ischemic heart disease

7.4% increase MCE for each increase of 1 Gy in mean radiation dose to the heart without a threshold

Darby et al. NEJM 2013
LAD and Major Vessels

Left sided breast RT – mid and distal LAD
Right sided breast RT with IMN - RCA

Nilsson et al JCO 2011
Consider RCA for right sided breast cancer when treating IMN
Left Ventricle and LAD

Cardiac Atlas is available

LAD may be hard to spare

For a tangent field to cover IMN Left, LAD & portion RV & LV would receive full dose.

For a tangent field to cover IMN right, RCA would receive high dose.
Coronary Angiography

LAD branching into distal LAD and 2nd Diagonal

Left main coronary artery

Diagonal D1

Distal LAD

2nd Diagonal

Courtesy of Dr. Marcio Fagundes
Thyroid Gland & Esophagus

SCV volume is in very close proximity to the esophagus and thyroid.
Study Overview

“A Study at the Heart of Breast Cancer Treatment”

Pragmatic Randomized Trial of Proton vs. Photon Therapy for Patients with Non-Metastatic Breast Cancer Receiving Comprehensive Nodal Radiation

RADCOMP Consortium
Schema

**Age**
(<65 vs ≥65)

**Cardiovascular risk**
(0-2 vs > 2 risk factors)

**Surgery**
(mastectomy vs lumpectomy)

**Laterality**
(right versus left)

Both arms: Breast/chest wall and nodal radiation with internal mammary node treatment

- **Arm 1:** Photon Therapy*
- **Arm 2:** Proton Therapy*

*Pragmatic dose specification: 45.0 Gy(RBE) to 50.4 Gy(RBE) in 1.8 to 2.0 Gy(RBE) fractions with or without a tumor bed boost
Primary Objective

- To assess the effectiveness of proton vs. photon therapy in reducing major cardiovascular events (MCE)
- Primary hypothesis: For patients with locally advanced breast cancer, proton therapy will reduce the 10-year MCE rate after radiation from 6.3% to 3.8%
- Sample size: 1,716 patients
Secondary Objectives

- To assess the non-inferiority of proton vs. photon therapy in reducing ipsilateral breast cancer local-regional recurrence and in reducing any recurrence.

- To assess the effectiveness of proton vs. photon therapy in improving patient-reported body image and function, fatigue and other measures of health-related quality of life (HRQOL) and adverse events.

- To develop predictive models to examine the association of radiation dose distribution to heart and MCE and HRQOL outcomes.
Key Inclusion Criteria

- Invasive mammary carcinoma (ductal, lobular or other) of the breast
- Non-metastastic or locally recurrent
- Mastectomy or lumpectomy with any type of axillary surgery or axillary sampling
- Left or right sided
- Proceeding with comprehensive nodal radiation with inclusion of internal mammary nodes
Key Exclusion Criteria

- Prior radiotherapy to ipsilateral breast or chest wall
  - prior contralateral radiotherapy eligible
- Scleroderma
Current Status

- 61 accruing sites in 21 proton networks
- Enrolled: 335 patients as of 03/01/2018
- 18-20 patients per month
Thank you!