Updates from San Antonio Breast Cancer Symposium: Accelerated Partial Breast Irradiation
Full disclosure

- I am not a statistician
- I am a brachytherapist
The Results

The highlights from SABCS stated the following:
- APBI was not equivalent to WBI
- APBI had higher rate of recurrence
- APBI is an alternative option to WBI

But to understand these results better we can look at the studies in more detail.
The Studies

NSABP B-39 / RTOG 0431

• A Randomized Phase III Study of Conventional Whole Breast Irradiation (WBI) versus Partial Breast Irradiation (PBI) for Women with Stage 0, I, or II Breast Cancer

RAPID (Ontario Clinical Oncology Group)

• A randomized trial of accelerated partial breast irradiation using 3-dimensional conformal radiotherapy (3D-CRT)
APBI

- Accelerated Partial Breast Irradiation
  - Why use it?
  - What is it?
The Rationale – Why APBI?

• To understand why the studies were performed, a quick background on the treatment of breast cancer, particularly early stage breast cancer (primarily stage I)

• Breast Conservation Therapy (BCT) trials demonstrated equal survival in women who underwent breast conserving surgery (BCS) with radiation
  • Lpectomy, quadrantectomy, partial mastectomy
  • Radiation therapy was once daily typically for 5-7 weeks (25-33 treatments)
Early Stage Breast Cancer: BCT = M

Adding Radiation to BCS decreased chance of cancer returning, and improved survival

Outcomes of BCT were essentially the same to BCT in the early studies
Early Stage Breast Cancer: Avoid RT?

Radiation improved outcomes in all women regardless of age, stage, etc.
Side Effects of Whole Breast RT

• Skin reaction
  • Redness, sore and ‘bumps’
  • May look like a rash, sunburn
  • May progress week by week and can develop into a “burn”, where the skin may peel or blister

• Fatigue
  • Tiredness during the day
  • May progress over the weeks

• Swelling of the arm or breast
  • Usually arm swelling with lymph node involvement

• Rare long term effects
  • Pain in chest
  • Rib fractures (very rare nowadays)
  • Lung inflammation or scar tissue
    • Rare to cause symptoms
  • Heart injury
  • Radiation may cause future cancer (very rare)
Alternative to RT as part of BCS

- Mastectomy
- No RT
  - Select group of patients who can safely undergo observation
- APBI
  - Accelerated = delivered over a short time frame
  - Partial Breast = treatment to only the area around the tumor
- Hypofractionation
  - 3-4 weeks of RT
  - Was not standard of care in mid 2000s
The Rationale – APBI as an alternative

• To understand why the studies were performed, a quick background on the treatment of breast cancer, particularly early stage breast cancer (primarily stage I)

• Breast Conservation Therapy (BCT) trials demonstrated equal survival in women who underwent breast conserving surgery (BCS) with radiation
  • Lumpetomy, quadrantectomy, partial mastectomy
  • Radiation therapy was once daily typically for 5-7 weeks (25-33 treatments)

• Most women recommended RT for BCT

• Long time course – some women may not get RT (time/distance)
APBI – What is it

Radiation dose is delivered to the area that is at HIGHEST risk of developing recurrent cancer.

Treatment course is typically 10 treatments, treated twice daily over 1 week.
APBI

- Partial breast radiation can spare radiation to a lot of the normal breast, and other organs (lung, heart)

- Treatment is only 10 treatments TWICE a day for a total of 5 days
APBI Techniques

- Intracavitary
- Interstitial
- 3D Conformal external beam radiation therapy

More on these in upcoming slides
APBI: Potential Advantages

• Shorter time course
• Less treatment overall
• More convenient
• Less breast tissue treated

• Is it equivalent?

• The following trials attempted to ask that question...
A Randomized Phase III Study of Conventional Whole Breast Irradiation (WBI) versus Partial Breast Irradiation (PBI) for Women with Stage 0, I, or II Breast Cancer
NSABP B39/RTOG 0413: Background

WBI as part of BCT was equivalent to Mastectomy

Accelerated PBI appeared effective in reducing ipsilateral breast tumor recurrence (IBRT)
  • Risk of recurrence was 3-8%

The majority of IBRT occur at or in close vicinity to the tumor bed

Hypothesis is that PBI would be as effective as WBI in controlling IBTR

Equivalency study
  • Based on a 50% margin of increase in HR (HR=1.5)
  • Primary endpoint: IBTR
  • Secondary endpoints: OS, RFI, DDFI and toxicity
Equivalence Trial

- Trial is designed to show that the difference between two treatments is not significant.
- The difference between results will be between two pre-defined limits (Lower limit $\Delta_L$, and Upper limit $\Delta_U$)
- The 90% confidence intervals must be between the limits to consider the trial ‘equivalent’

- Failure to do so only states that the results ‘may not be considered equivalent’ and does not mean a difference absolutely exists.
NSABP B39/RTOG 0413: Methods

Women who had undergone BCS (lumpectomy)

Negative margins (≥ 2 mm)

Stage 0, I or II

All ages (> 18)

Stratified by

- Stage (DCIS, invasive pN0, invasive pN1 with 1-3 LN pos)
- Hormone receptor status (ER+, ER-)
- Age (<49, >50)
- Intent to receive chemotherapy
**NSABP B39/RTOG 0413: Methods**

- 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
    - 34 Gy in 3.4 Gy bid x 5-7 days Mammosite Balloon Catheter
    - 38.5 Gy in 3.85 Gy bid x 5-6 days 3D Conformal External Beam
NSABP B39/RTOG 0413: Methods

- Techniques
  - Whole breast irradiation covering the entire breast
  - 50 Gy in 25 fractions to the whole breast
  - Partial breast irradiation – all options
NSABP B39/RTOG 0413: Methods

- Techniques
  - Whole breast irradiation covering the entire breast
  - Partial breast irradiation
    - Intracavitary (ie, “balloon brachytherapy” using Mammosite or equivalent)
**NSABP B39/RTOG 0413: Methods**

- **Intracavitary**
  - A balloon and catheter are placed into the lumpectomy site
  - Placed typically by the surgeon after surgery
  - A radioactive source travels to the center of the balloon and delivers a prescribed amount of radiation to 1 cm from the surface of the balloon
  - Typically 5-10 minutes per treatment session
  - Given twice a day (at least 6 hours in between)
  - After the last treatment is completed, the balloon is deflated and the balloon and catheter is removed

- **Approximately 23% of patients received this treatment**
NSABP B39/RTOG 0413: Methods

- Techniques
  - Whole breast irradiation covering the entire breast
  - Partial breast irradiation
    - Intracavitary (ie, “balloon brachytherapy” using Mammosite or equivalent)
    - Interstitial
NSABP B39/RTOG 0413: Methods

- Interstitial
  - Multiple needle-catheters are placed into the breast around the lumpectomy site
  - Radioactive seeds are placed in the catheters
  - The seeds remain in the tubes for a prescribed period of time
  - After the last treatment is completed, the catheters are removed
- Less than 6% of patients received this treatment
NSABP B39/RTOG 0413: Methods

- Techniques
  - Whole breast irradiation covering the entire breast
  - Partial breast irradiation
    - Intracavitary (i.e., “balloon brachytherapy” using Mammosite or equivalent)
    - Interstitial
    - 3D Conformal partial breast irradiation – “Vicini technique”

PBI: 3D Conformal EBRT

Per RTOG 04-13:
Electrons not allowed
Beams may not be directed toward critical structures
NSABP B39/RTOG 0413: Methods

- 3D Conformal EBRT
  - Treatment uses a linear accelerator, the same machine that whole breast radiation therapy is delivered on
  - Using CT scan the lumpectomy cavity is defined and targeted
  - Multiple beams are used to deliver a higher dose to the lumpectomy cavity site and minimizing dose to the remaining breast, contralateral breast as well as heart and lung
  - Treatments are twice a day for 1 week
  - This did not require any special procedures or equipment
  - Potentially available at any radiation

- The majority, 71% patients received this treatment
Between 3/21/2005 and 4/16/2013, 4216 patients randomized

- 2107 PBI
- 2109 WBI

Characteristics

- 81% ER +
- 61% post-menopausal
- 25% DCIS (Stage 0)
- 65% Stage I
- 10% Stage II (pN1)

Follow Up: Half were followed up for at least 10 years
NSABP B39/RTOG 0413: Results

161 with ipsilateral breast cancer recurrence
- 90 in the APBI arm
- 71 in the WBI

IBTR free at 10 years
- 95.2% PBI
- 95.9% WBI
- 0.7% absolute difference (NS)

Statistical Outcome
- HR 1.22, 90%CI 0.94-1.58
- To meet “equivalence” 90% CI had to be between 0.67-1.50
NSABP B39/RTOG 0413: Results

10 year Recurrence free interval (RFI)
- PBI 91.9% vs 93.4% WBI (1.5% difference)
- HR 1.32; 95%CI 1.04-1.68; \( p=0.02 \)
- Not statistically equivalent

Distant Disease Failure Interval (~3%)
- HR 1.31; 95%CI 0.91-1.91; \( p=0.15 \)
- Not statistically different

Overall Survival
- HR 1.10; 95%CI 0.90-1.35; \( p=0.35 \)
- Not statistically different

Diseases Free Survival
- HR 1.12; 95%CI 0.98-1.29; \( p=0.11 \)
NSABP B39/RTOG 0413: Toxicity

Grade 3
- 9.6% PBI
- 7.1% WBI

Grade 4-5
- 0.5% PBI
- 0.3% WBI

Slightly higher toxicity in the PBI arm
**Conclusions**

PBI did not meet the criteria for equivalence to WBI for IBTR

- The upper limit of the HR confidence interval cross 1.5
- The absolute difference was <1%: 4.8% PBI vs 4.1% WBI

RFI was statistically significantly higher for PBI

- The absolute differences was also small at 1.5%

DDFI, OS and DFS were not different

Grade 3-5 toxicities were more common for PBI
RAPID Trial

A randomized trial of accelerated partial breast irradiation using 3-dimensional conformal radiotherapy (3D-CRT)
RAPID Trial: Background

Whole breast irradiation (WBI) was given over 3-6 weeks

Accelerated partial breast irradiation (APBI) could be delivered over a week to the surgical cavity with a margin of normal tissue

Same arguments – less time, and less tissue being treated

All patients had 3D EBRT as the method of delivery
RAPID: Treatment

- 3D Conformal EBRT
  - Treatment uses a linear accelerator, the same machine that whole breast radiation therapy is delivered on
  - Using CT scan the lumpectomy cavity is defined and targeted
  - Multiple beams are used to deliver a higher dose to the lumpectomy cavity site and minimizing dose to the remaining breast, contralateral breast as well as heart and lung
  - Treatments are twice a day for 1 week
  - This did not require any special procedures or equipment
  - Potentially available at any radiation

- All patients received this treatment 100%
RAPID Trial: Methods

- Women over the age of 40
- All had Stage 0 DCIS or Stage I invasive ductal carcinoma (IDC)
- No lymph node positive patients were eligible (all pN0)
- All tumors were 3 cm or smaller with negative margins
RAPID Trial: Methods

Patients were stratified by:

- Age (<50 vs ≥50 years old)
- Histology (DCIS vs IDC)
- Tumor size (< or ≥ 1.5 cm)
- ER status (+/-)
- Treatment center
RAPID Trial: Methods

All patients were randomized to one of two arms

Arm 1: WBI
- Treatment to the whole breast
- 50 Gy in 25 fractions (standard fractionation)
- 42.5 Gy in 16 fractions (hypofractionation)
- A lumpectomy boost was permitted (as discretion of treating physician)

Arm 2: ABPI
- 38.5 Gy in 10 fractions
- Twice daily
RAPID Trial: Methods

Primary Outcome
- Ipsilateral breast tumor recurrence (IBTR)

Secondary Outcomes
- Radiation toxicity
- Nurse reported adverse cosmesis

Non-inferiority Trial
- The trial was designed to show that the 5 year IBTR rate in the APBI arm was not inferior to the WBI by more than $1.5\%$ (HR < 2.02)
RAPID Trial: Results

Between 2/2006 and 7/2011: 2135 patients enrolled

Canada, Australia and New Zealand

1070 to APBI and 1065 to WBI

Median follow up was 8.6 years

Mean age was 61 years old
RAPID Trial: Results

- 82% had invasive cancer (Stage I IDC)
- 18% DCIS (Stage 0)
  
  **For Invasive Cancer**
  - 60% were < 1.5 cm
  - 90% were ER positive
  
  **For DCIS**
  - 68% were < 1.5 cm
RAPID Trial: Results

65 IBTRs were observed

5 year IBTR
- APBI 2.3%
- WBI 1.7%

8 year IBTR
- APBI 3.0%
- WBI 2.8%

The HR for APBI vs WBI was 1.27 (90% CI 0.84 – 1.91)

Similar results to RTOG/NSABP trial
RAPID Trial: Results

Acute radiation toxicity (within 3 months of start of treatment)

- Examples – radiation dermatitis and breast swelling
- Less common in APBI compared with WBI
- Grade 2: 28% APBI versus 45% WBI

Late radiation toxicity (those occurring beyond 3 months)

- Examples – breast induration, telangiectasia
- More common in APBI patients
- Grade 2: 32% APBI versus 13% WBI
- Grade 3: 4.5% APBI versus 1.0% WBI
RAPID Trial: Results

Adverse cosmesis was worse in APBI:
- 3 years poor cosmesis
  - APBI 29%
  - WBI 17%
- 5 years poor cosmesis
  - APBI 32%
  - WBI 16%

Still about 70% with good cosmesis in APBI, c/w 85% in WBI.
RAPID Trial: Conclusions

APBI regimen was non-inferior to WBI in preventing local recurrences.

It was associated with less acute toxicity, but more late toxicity and worse cosmesis.
Summary of Trials

- **NSABP/RTOG**
  - Not equivalent
  - Worse acute and late side effects

- **RAPID**
  - Not inferior
  - Better acute, worse late side effects

What does this all mean?
### Comparison of Trials

<table>
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<th>Nodal status</th>
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<td>All invasive and DCIS</td>
<td>pN1 allowed (10%)</td>
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<td>RAPID</td>
<td>40 yo and older</td>
<td>IDC and DCIS</td>
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## Comparison of Trials

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Another Phase III trial: GEC ESTRO

- Randomized, Phase 3 non-inferiority trial using interstitial brachytherapy

- Eligibility
  - Women ≥ 40 with stage 0, I, IIA breast cancer
  - Tis, T1, T2a (≤ 3cm), and pN0/pNmi
  - Margins at least 2 mm for IDC (5mm for DCIS or ILC)
  - No LVSI

- Whole breast RT
  - 50-50.4 Gy in 25-28 fx with boost

- APBI – all interstitial
  - 4.0 Gy x 8 or 4.3 Gy x 7, all twice daily
GEC ESTRO Results

• 1328 Patients Enrolled
  • Of which 1188 eligible
  • 575 WBI vs 613 APBI
  • Treated as per protocol: 528 WBI and 613 APBI

• Patient profile
  • Median age 62
  • 5% DCIS, 11% T2a, and remaining 84% T1
  • Only 1% pN1mi
  • 81% ER/PR positive, 11% ER positive/PR negative
• 5 year IBTR
  • APBI 1.44%
  • WBI 0.92%
    • Difference 0.52%
    • 95% CI: -0.72 – 1.75
    • Not inferior

• Late toxicities, grade 2-3
  • Skin
    • APBI 3.2%
    • WBI 5.7%
  • Subcutaneous tissue
    • APBI 7.6%
    • WBI 6.3%
Comparison of Trials – All 3 studies

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## Comparison of Trials – All 3 studies

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<td>12%</td>
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<td>0.2% - 0.7% diff</td>
<td>-2% - 3% diff</td>
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Final Summary

- Three trials – TWO from SABCS
  - One negative for equivalence (NSABP/RTOG)
    - Statistical design flaw?
    - Most heterogenous group
  - Two non-inferior (RAPID)
    - Both with pN0 patients, and lowest risk group population
  - Difference is about 0.5-1% in IBRT from APBI to WBI
    - Small difference but consistent
    - Are we missing breast cancer is other quadrants of breast
  - Toxicity is higher in RAPID
    - Possibly due to all patients being treated with 3DCRT
    - Brachytherapy may reduce late toxicities? (GEC ESTRO)
  - Patient selection may be key
    - Await manuscript details of the studies
How to Interpret

- APBI is still an alternative to WBI
- Careful patient selection
  - ASTRO consensus guidelines
- I personally believe that technique matters
  - Brachytherapy vs EBRT
- Will need full results to interpret subgroups
  - Does age matter (GEC ESTRO says no)
  - Size, grade, ER status, etc.
- Some women may accept a <1% risk in LF to receive appropriate treatment
  - APBI is clearly better than NO radiation
Low Risk group patients
Similar to what was seen in RAPID and GEC ESTRO:
• 50 and older
• DCIS or T1, pN0
• Negative margins (typically by 2 mm)
I am more likely to offer to **ER positive** (80-90% of patients on trial)
Thank you for your time

Any questions?
Comments?