Dr. Woodward has no relevant financial relationships with commercial interests to disclose

Radiotherapy 2018: Balancing Benefit and Risk

Wendy A. Woodward, MD. PhD
Professor and Chief of Breast Radiation Oncology
The University of Texas MD Anderson Cancer Center
@ibcradiation; wwoodward@mdanderson.org

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SAN ANTONIO BREAST CANCER SYMPOSIUM®

Outline

- Context
- **Accelerated partial breast irradiation (APBI) 1 week, BID** – Validated standard or more toxic and possibly inferior?
- **Simultaneous integrated boost (SIB)** – Safe, but more data pending.
- **Regional nodal irradiation (RNI)**–systemic benefits, lymph node preserving?
- Tomorrow – what's changed?

A few facts about breast radiotherapy

1. SAVES LIVES/SPARES ORGANS
   Radiotherapy is allows breast and lymph node preservation
2. NOT INVASIVE
   Radiotherapy is NOT INVASIVE – many patients go to work and carry on with day-to-day life
3. IMPROVES QUALITY OF LIFE
   Radiotherapy alleviates cancer symptoms such as pain and improves quality of life

- In the last decade the length of breast radiotherapy has been cut in half
- Advances in radiotherapy technology have markedly reduced toxicities secondary to radiotherapy
- These improvements markedly increase the accessibility and feasibility of radiotherapy for women with breast cancer

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Accelerated Partial Breast Irradiation (APBI)

One week, twice daily regimen (BID)

Main Trial Differences

RAPID (N = 2,135, 18% DCIS)

- APBI 90% 3D conformal photons; 10% IMRT
- WBI predominantly 16 fraction regimen, 20% Boost
- 100% node negative
- Median age 61 years old

NRG B39/0413 (N = 4,216, 24% DCIS)

- APBI 71% 3D conformal photons; 29% brachytherapy
- WBI 25-28 fraction regimens, 80% boost
- 10% node positive
- Median age 54 years old

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Main Trial Difference Summary -

- RAPID vs. NRG B39/0413
  - The Rapid trial enrolled an older, lower risk population treated all with external beam APBI (90% 3DCRT) vs. a shorter, lower dose WBI regimen than used in the B39/0413 WBI arm.

APBI (1 week, BID) Main Findings

RAPID (N = 2,135)

- 8-yr IBTR WBI 2.8% vs APBI 3%, P= NS
- Non-inferiority endpoint met

NRG B39/0413 (N = 4,216)

- 10-yr IBTR WBI 4.1% vs APBI 4.8%, P = NS
- Non-inferiority endpoint not met
- Recurrence Free Interval 1.6% worse with ABPI, P = 0.02

IBTR by PBI Method – exploratory analysis

Treatment Group	# of Pts	# of Events	Hazard Ratio (HR)	HR 95% Confidential Interval	10-yr Cum Incidence
WBI	2,011	67	REF		3.8%
PBI					
Multi-catheter brachytherapy	130	9	2.21	1.10 – 4.46	7.7%
Single-entry brachytherapy device	358	24	2.15	1.34 – 3.44	7.8%
3DCRT (external beam)	1,535	55	1.04	0.73 – 1.49	3.7%

- Hypothesis generated: 3DCRT APBI is non-inferior to WBI.
- Rapid trial tested and validates this hypothesis

APBI (1 week, BID) Main Findings

- RAPID (N = 2,135)
  - 3-yr Grade 3 Toxicity WBI 1% vs APBI 4.5%, P < 0.001
  - 7-yr fair/poor cosmesis more common in the APBI arm
- NRG B39/0413 (N = 4,216)
  - 10-yr Grade 3 Toxicity WBI 7.1% vs. APBI 9.6%, P = NS

APBI (1 week, BID) Main Findings

- RAPID (N = 2,135)
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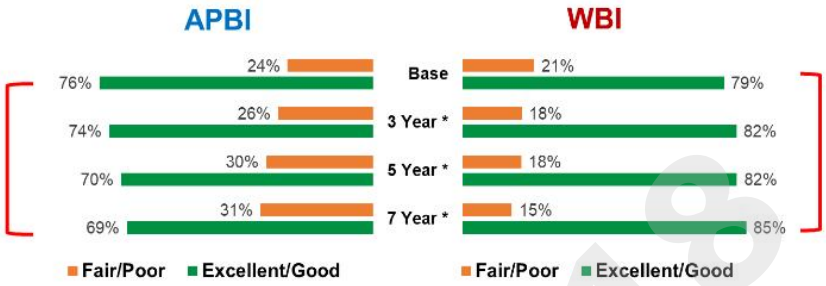

APBI Conclusions

- 1 week, BID APBI delivered with 3DCRT is not inferior to WBI for IBTR for those well-represented among RAPID patients
  - Small, node negative, invasive or non-invasive tumors in women > 50.
- IBTR rates for 3DCRT APBI and WBI are very low and similar in both trials
- APBI using the brachytherapy techniques represented on B39/0413 and in patients not eligible for the Rapid trial could be inferior to WBI.

APBI Conclusions

- Toxicity and cosmetic risks are higher with APBI 3DCRT than WBI on the RAPID trial but not on NRG B39/0413.
- Offering patients a 1 week, BID 3DCRT APBI regimen must include discussing a higher risk of a fair/poor cosmetic outcome due largely to induration, fibrosis, and skin telangiectasia.
  - Approximately 16% of APBI patients had a potentially avoidable patient assessed fair/poor cosmetic outcome

APBI Conclusions

- Toxicity and cosmetic risks are higher with APBI 3DCRT than WBI on the RAPID trial but not on NRG B39/0413.
- Offering patients a 1 week, BID 3DCRT APBI regimen must include discussing a higher risk of a fair/poor cosmetic outcome due largely to induration, fibrosis, and skin telangiectasia.
  - Important to discuss that the current standard WBI regimen for these patients is now three weeks.

APBI Future

- Consideration of alternate APBI schedules and techniques to further improve the therapeutic ratio is warranted.
- Updates of consensus guidelines for APBI and further integration of these results with published randomized trials using alternate techniques and regimens without significant toxicity are warranted.

Simultaneous Integrated Boost (SIB) –

Safety Data on Import High

IMPORT HIGH – Patients who require a tumor bed boost

		40Gy/15F + 16Gy/8F N=871	48Gy/15F (3.2Gy/F) N=874	53Gy/15F (3.5Gy/F) N=872
		%	%	%
Age (years)	Median (range)	49 (45-56)	49 (45-55)	49 (44-57)
Tumour size (cm)	Median (range)	2.0 (1.5-2.7)	1.9 (1.4-2.6)	2.0 (1.5-2.6)
Grade	1	10	8	8
	2	40	36	38
	3	50	55	54
Pathological node status	Positive	30	31	29
	Negative	70	69	71
ER poor & HER2 poor		18	21	19
ER poor & HER2 positive		4	4	6
ER positive & HER2 poor		64	63	62
ER positive & HER2 positive		14	12	13

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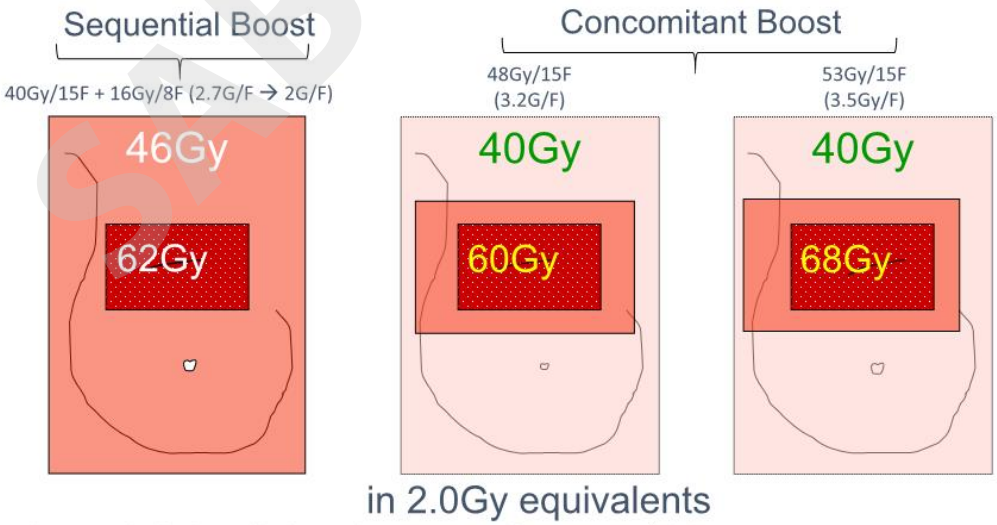
Total Doses Assuming α/β = 3.0Gy



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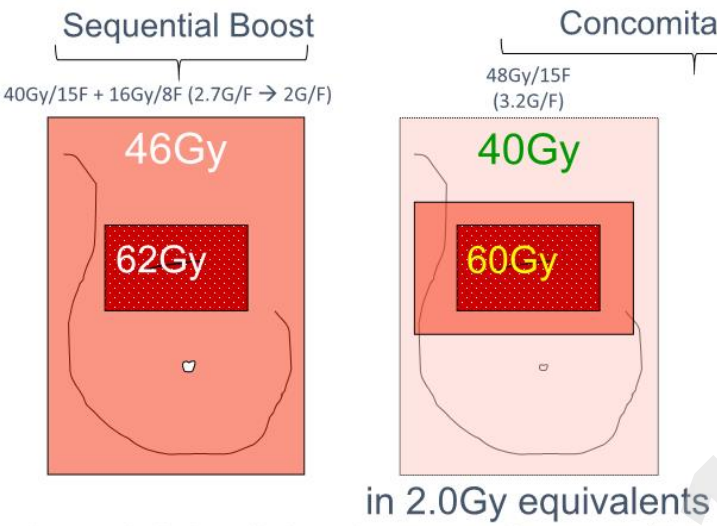

Increased CRO Breast Induration

HR = 1.35 (85%CI 1.03-1.77); p = 0.029

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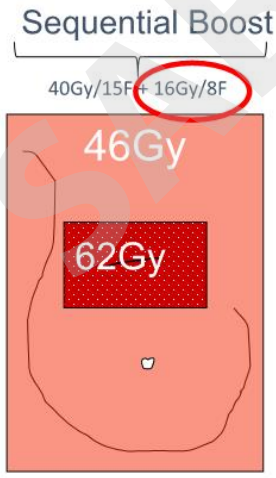

- 16Gy/8F may have a higher baseline toxicity than commonly used 10 Gy/5F
- NRG 1005 expected 2019
  - WBI + 12-14Gy vs. WBI + 48/15 SIB
- Local control data pending

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Benefits of Regional Nodal Irradiation (RNI)

When is more, more?

MA-20/EORTC 22922 RNI vs. No RNI

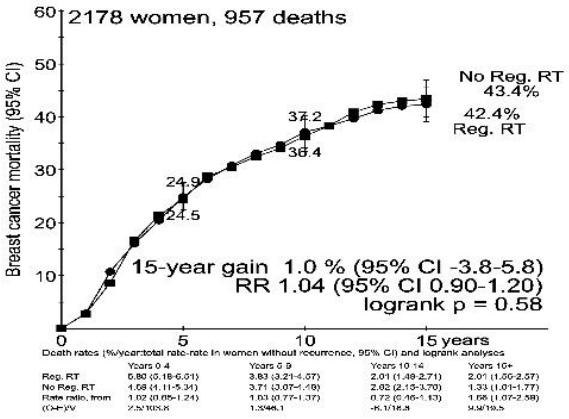
- Two large well-conducted randomized phase III trials (1,2)
- Early stage breast cancer including N0 patients
- Demonstrated improved DFS with RNI *independent* of a reduction in local control
- Highlighted a systemic effect of RNI

Should early stage patients get RNI?

1. Whelan et al NEJM, 2015
2. Pootmans et al NEJM, 2015

Breast Cancer Mortality

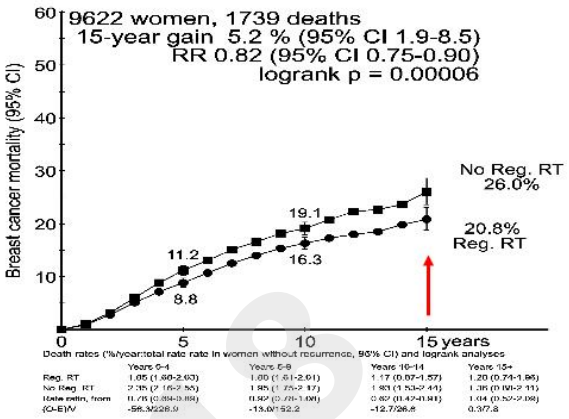
Older



Death rates (%/year:total rate-rate in women without recurrence, 95% CI) and logrank analyses

	Years 0-4	Years 5-9	Years 10-14	Years 15+
Reg. RT	5.80 (5.18-6.51)	3.83 (3.21-4.57)	2.01 (1.49-2.71)	2.01 (1.60-2.57)
No Reg. RT	4.68 (4.11-5.34)	3.71 (3.07-4.49)	2.02 (1.53-2.70)	1.33 (1.01-1.77)
Rate ratio, from	1.02 (0.85-1.21)	1.03 (0.77-1.37)	0.72 (0.46-1.13)	1.56 (1.07-2.58)
(O-E)/V	2.5/10.6	1.3/4.1	-5.1/16.8	9.4/19.5

1989+ trials

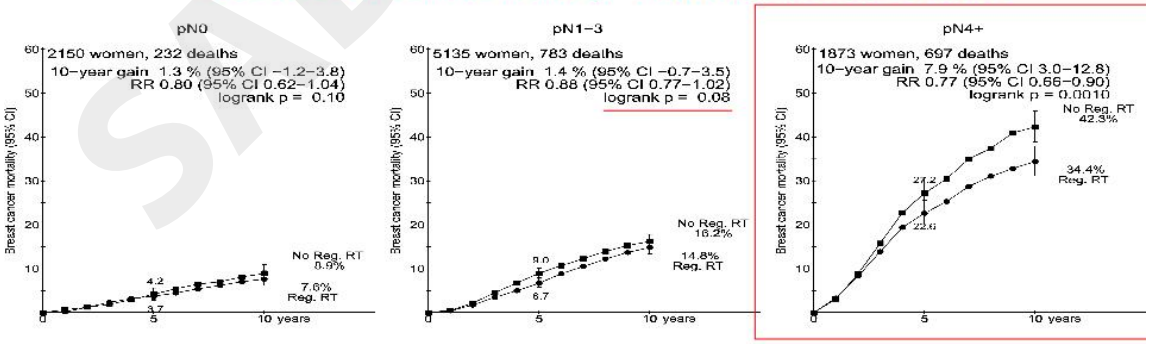


Death rates (%/year:total rate-rate in women without recurrence, 95% CI) and logrank analyses

	Years 0-4	Years 5-9	Years 10-14	Years 15+
Reg. RT	1.65 (1.50-2.63)	1.00 (1.61-2.61)	1.17 (0.87-1.57)	1.20 (0.74-1.95)
No Reg. RT	2.35 (2.16-2.55)	1.85 (1.75-2.17)	1.83 (1.53-2.44)	1.36 (0.90-2.11)
Rate ratio, from	0.70 (0.64-0.89)	0.54 (0.76-1.00)	0.64 (0.42-0.91)	1.04 (0.52-2.08)
(O-E)/V	-56.3/226.9	-13.0/152.2	-12.7/26.6	0.3/7.8

1989+ trials

Breast Cancer Mortality - Axillary Nodal Status



<u>Any Recurrence</u>:

10-year gain 2.3%, P = .15

10-year gain 2.9%, p = 0.03

10-year gain 4.6% p = 0.03

EBCTCG Meta-analysis RNI vs. No RNI

- Contemporary radiotherapy improves risk benefit ratio
- RNI improves breast cancer mortality using contemporary radiotherapy
- RNI reduced any recurrence but did not improve breast cancer mortality in low nodal burden patients

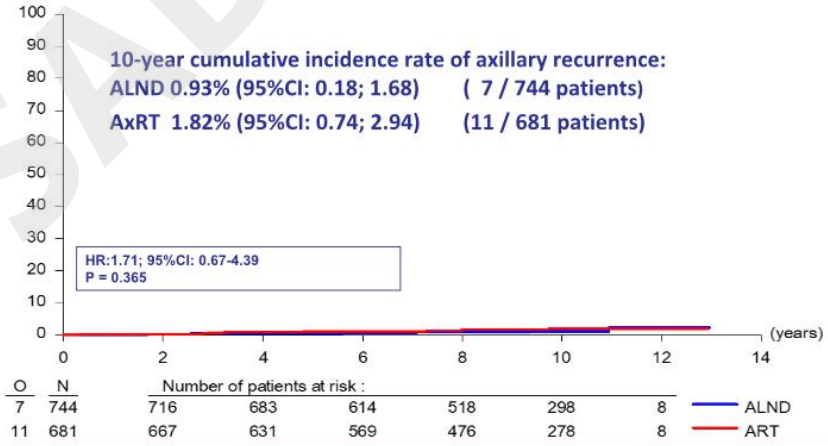
Should early stage patients get RNI?

- N0, N1mic in a SLN - uncommon, case by case basis for high risk features
- N1-3 - contemporary risk stratification including biology should be used to aid in selecting and counseling higher risk patients
- RNI may facilitate surgical de-escalation - omitting axillary node dissection

Is this benefit sufficient to warrant RNI or axillary RT alone in otherwise low risk SLN+ patients?

Axillary RT = Axillary LND

AxSN+ ITT population



Cumulative incidence analysis considers death as a competing risks. HR and Wald p-value based on Fine & Gray model

Axillary RT Toxicity

- Lymphedema at 5 years after SLN Biopsy: LND vs RT
  - Clinical Observation and/or Treatment 29.4% vs 14.6%, P < 0.0001
  - Clinical Observation 24.5% vs. 11.9%, P < 0.0001
  - Treatment 18.2% vs. 6.6%, P < 0.0001
- Shoulder Function 5 years after SLN Biopsy:
  - No difference

AMAROS Conclusion

- Both provide excellent axillary tumor control
- Lymph node preservation reduces lymphedema
- Increase in contralateral breast cancer unlikely due to radiation given the contralateral breast is remote from the axillary RT field

Tomorrow -

- Offer 1 week BID 3DCRT APBI with appropriate counseling to eligible low risk patients for whom reducing treatment time from 3 weeks to 1 week is a priority over cosmetic risk.
- Await local control data to fully evaluate a shortened 3 week radiation course that includes a simultaneous boost
- Consider Axillary RT an option in eligible cT1-2N0 patients preferring to avoid axillary LND
- Offer RNI to high risk pN1-3 and all pN4+ patients. Pragmatically, well vetted risk factors - age, LVSI, tumor and nodal burden, grade, subtype approximation, and genomic score when available may all aid in risk stratifying patients.
- Cardiac avoidance is critical to maximize risk benefit ratio.

CONGRATULATIONS!