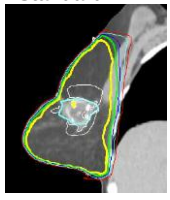
Primary results of NSABP B-39/ RTOG 0413 (NRG Oncology): A randomized phase III study of conventional whole breast irradiation (WBI) versus partial breast irradiation (PBI) for women with stage 0, I, or II breast cancer

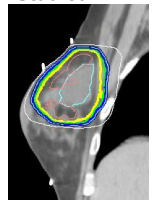
Background

- **Standard: WBI**



5-6 weeks

- **Studied: PBI**



5-10 days

NSABP B-39/RTOG 0413 Schema

STRATIFICATION

- **Disease Stage (DCIS; Invasive N0; Invasive N1)**
- **Menopausal Status (pre- and post-)**
- **Hormone Receptor Status (ER and/or PR+; ER and PR-)**
- **Intention to Receive Chemotherapy**

RANDOMIZED

Whole Breast Irradiation after Adjuvant Chemotherapy

50 Gy (2.0 Gy/fraction) or
50.4 Gy (1.8 Gy/fraction) to whole breast, followed by optional boost to ≥ 60 Gy

Partial Breast Irradiation prior to Adjuvant Chemotherapy

For a total of 10 treatments given on 5 days over 5 to 10 days:

34 Gy in 3.4 Gy fractions Interstitial Brachytherapy
or Mammosite Balloon Catheter
or 38.5 Gy in 3.85 Gy fractions
3D Conformal External Beam

NSABP B-39/RTOG 0413
Selected Eligibility Criteria

- Lumpectomy
- Stage 0, I, II
- Tumor size ≤3.0 cm
- Negative margins (No ink on tumor)
- N0, N1 ≤3 positive nodes
- Age >18

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NSABP B-39/RTOG 0413
Study Population

- Opened: March 21, 2005
- Closed: April 16, 2013
- Accrual: 4,216 pts (2,109 WBI and 2,107 PBI)
- Participating Sites:
  - 78 – NSABP
  - 142 – RTOG/CTSU
- Median follow-up time: 10.2 yrs

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Patient Characteristics

- 4,216 pts (2,109 WBI and 2,107 PBI)
- Median age: 54 yrs
- 61% postmenopausal
- 81% hormone receptor-positive
- 29% intended to receive chemotherapy
- Adjuvant hormonal therapy (reported among ER + and/or PR+)
  - 81.5% WBI
  - 85.3% PBI
- Intended PBI Method (ARM 2)
  - 71.0%: 3D Conformal
  - 23.3%: Balloon/Single-entry device
  - 5.7%: Multi-catheter Interstitial

- 24% DCIS
- 65% Invasive pN_0
- 10% Invasive pN_1
- 27% received chemotherapy

- WBI (ARM 1)
  - 80% Boosted

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Endpoints

- **Primary:**
  - Ipsilateral breast tumor recurrence (IBTR), both invasive and DCIS, as a first recurrence
- **Secondary:**
  - Distant disease-free interval (DDFI)
  - Recurrence-free interval (RFI)
  - Overall survival (OS)

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Analysis Plan

- Primary analysis was in the form of an equivalence test
- Margin of a 50% increase in the hazard ratio (HR) was chosen as the acceptable margin for this test
- Definitive analysis planned to occur after 175 IBTRs had been reported, or when the median follow-up was 10 yrs, whichever occurred first
  - Median follow-up: 10.2 yrs as of July 31, 2018, thus initiating the final analysis
- For all secondary endpoints, distributions of time to event were estimated by the Kaplan-Meier method and compared between treatments by stratified log-rank tests

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Ipsilateral Breast Tumor Recurrence (IBTR)

- Per protocol-defined margin, to declare PBI and WBI equivalent regarding IBTR risk, the 90%CI for the observed HR had to lie entirely between 0.667 and 1.5
- We observed 161 IBTRs as first events
  - 90 PBI *v* 71 WBI (HR 1.22; 90%CI 0.94-1.58)
- PBI did not meet the criteria for equivalence to WBI in controlling IBTR based on the upper limit of the HR CI
- Absolute difference in 10-yr cumulative incidence of IBTR between PBI and WBI was only 0.7% (4.6% *v* 3.9%)

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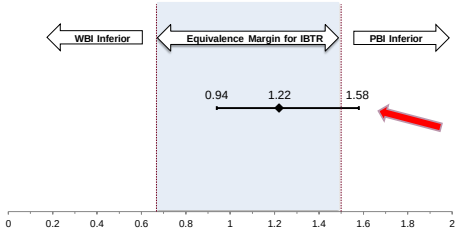
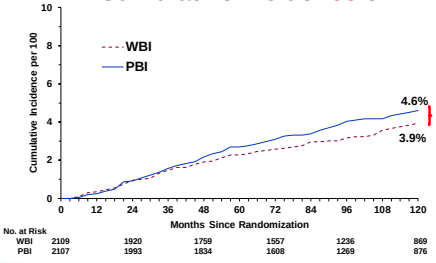
Ipsilateral Breast Tumor Recurrence (IBTR)



Hazard Ratio and 90%CI for IBTR

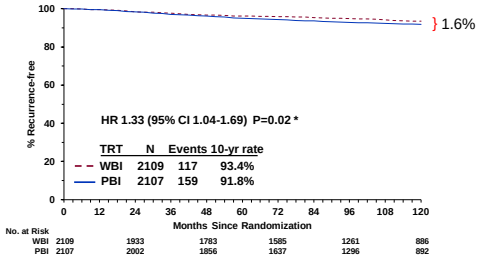
Cumulative Incidence of IBTR



IBTR by Location in the Breast

	# of Pts		# of Events		Hazard Ratio (HR)	HR 95% Confidential Interval	10-yr Cum Incidence	
Location of IBTR	WBI	PBI	WBI	PBI			WBI	PBI
At site of primary tumor	2109	2107	46	39	0.81	0.53 - 1.24	2.4%	1.9%
Elsewhere in the breast	2109	2107	25	51	1.99	1.23 - 3.23	1.5%	2.7%

Recurrence-free Interval



*Based on Cox proportional hazards models stratified on disease stage, menopausal status, hormone receptor status, and intention to receive chemotherapy.

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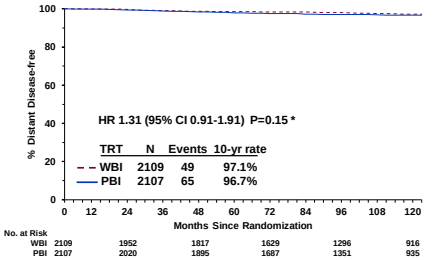
Distant Disease-free Interval



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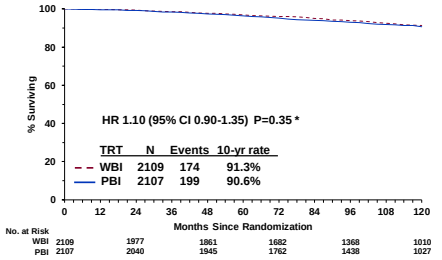
Overall Survival



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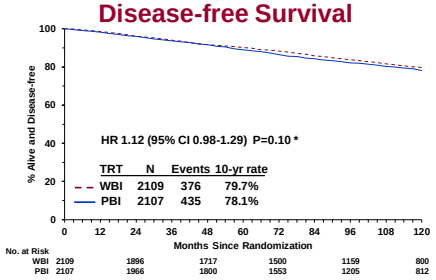
Disease-free Survival



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Adverse Events

Toxicity:

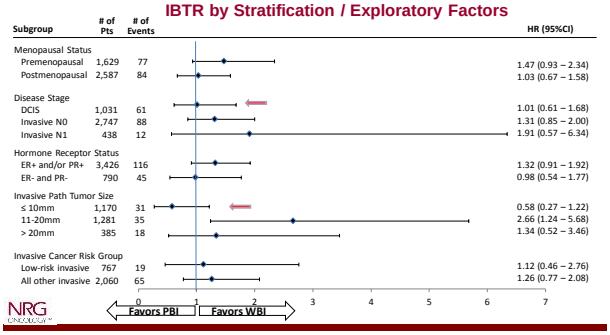
- **Grade 3 toxicity was 9.6% PBI *v* 7.1% WBI - NS**
- **Grade 4-5 toxicity was 0.5% PBI *v* 0.3% WBI - NS**

Second Cancers:

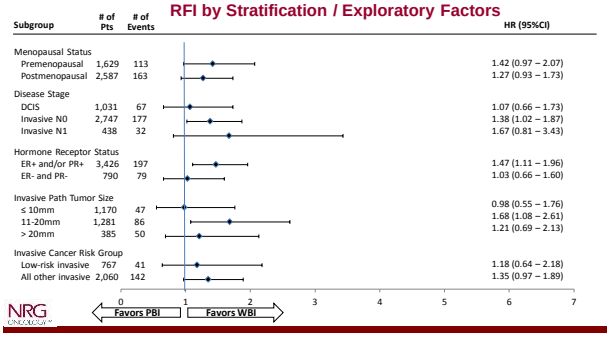
First Site of Second Primary Cancer	WBI	PBI	Total
Contralateral breast	72	63	135
All other sites	128	129	257
Total	200	192	392

No statistically significant differences

IBTR by Stratification / Exploratory Factors



RFI by Stratification / Exploratory Factors



IBTR by PBI Method

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%

This analysis used a per-protocol population, which excluded those who did not receive their randomly assigned treatment

Conclusions

- **Intent-to-treat and as-treated analyses could not refute the hypothesis that PBI is inferior and cannot declare that WBI and PBI are equivalent in controlling local in-breast tumor recurrence. However, the absolute difference in the 10-yr cumulative incidence of IBTR was only 0.7%.**
- **Risk of an RFI event was statistically significantly higher for PBI *v* WBI, but again, the absolute difference in 10-yr RFI cumulative incidence was also small (1.6%)**
- **Breast cancer event rates at a median follow-up of 10.2 yrs in this population were overall low: IBTR rate: ~4.5%, DM rate: ~3%, and breast cancer death rate: ~2%**

Conclusions

- **DDFI, OS, and DFS were not statistically different for PBI *v* WBI**
- **Grade 3-5 toxicities were low. Additional analyses are underway to evaluate secondary endpoints of QOL and cosmesis**
- **Because the differences relative to both IBTR (0.7%) and RFI (1.6%) were small, PBI may be an acceptable alternative to WBI for a proportion of women who undergo breast-conserving surgery**

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