

ANCO's 2011 San Antonio Breast Cancer Symposium Highlights: Radiation Therapy

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Conflicts of Interest

- None

Selected Abstract Topics

- Controversy associated with accelerated partial breast radiation
- Which early stage breast patient can safely avoid radiation in the setting of breast conservation?
- Should patients with DCIS receive a boost?

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Study faults partial radiation for breast cancer

Women who had partial radiation were twice as likely to need their breasts removed later

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By **MARILYNN MARCHIONE**
AP Chief Medical Writer
AP Associated Press
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SAN ANTONIO — New research casts doubt on a popular treatment for breast cancer: A week of radiation to part of the breast instead of longer treatment to all of it.

[S2-1] Partial Breast Brachytherapy Is Associated with Inferior Effectiveness and Increased Toxicity Compared with Whole Breast Irradiation in Older Patients.

*Smith GL, Xu Y, Buchholz TA, Giordano SH, Smith BD.
University of Texas M.D. Anderson Cancer Center,*

Houston, TX

Session 2- oral

Background

- Accelerated partial breast brachytherapy (APBI-brachy) is an increasingly popular radiation treatment for older patients diagnosed with early stage breast cancer.
- Despite growing utilization, there is a lack of population-based cohort studies as well as randomized phase III data to compare its effectiveness and toxicity profile with standard whole breast irradiation (WBI).

Rationale

- The purpose of this study was to provide the first nationally comprehensive comparison of effectiveness and toxicity outcomes in older Medicare patients treated with APBI-brachy versus WBI.

Methods

- Medicare billing claims identified beneficiaries age>66 with incident invasive breast cancers diagnosed between 2000 and 2007 and treated with conservative surgery followed by APBI-brachy alone versus WBI.
- Cumulative incidence of subsequent mastectomy (a validated surrogate for local failure) was compared between the two treatment groups using the log-rank test.
- Adjusted risk of subsequent mastectomy was determined using a multivariate Cox proportional hazards model including demographic, socioeconomic, and clinical covariates.

Methods

- Risks of acute complications (hospitalization or infection within 120 days of radiation), were compared using the chi-square test.
- Adjusted odds of acute complications were determined using multivariate logistic models including covariates.
- Cumulative incidences of long-term toxicities (rib fracture, fat necrosis, breast pain, and pneumonitis) were compared using the log-rank test.

Results

- In 130,535 women, use of APBI-brachy increased over time from <1% of patients treated in 2000 to 13% of patients in 2007 ($P < 0.001$ for trend).
- Patients treated with APBI-brachy were less likely to have axillary lymph node involvement or to have received chemotherapy, and were more likely to be older, white, and have comorbid illness.
- At 5 years, the cumulative incidence of subsequent mastectomy was significantly higher in patients treated with APBI-brachy (4.0% in APBI-brachy vs. 2.2% in WBI, $P < 0.001$).

Results

- On multivariate analysis, there was a two-fold increased risk for subsequent mastectomy in patients treated with APBI-brachy (HR= 2.14; 95% CI 1.83-2.52, P<0.001).
- APBI-brachy was also associated with more acute complications, including a higher risk of hospitalization (9.6% vs. 5.7%; P<0.001) (Adjusted OR= 1.71; 1.58-1.86); and infection (8.1% vs. 4.5%; P<0.001) (Adjusted OR= 1.85; 1.69-2.02; P<0.001).

Results

- APBI-brachy was also associated with higher 5-year cumulative incidence
- Rib fracture 4.2% vs. 3.6% in WBI
- Fat necrosis 9.1% vs. 3.7%
- Breast pain 14.9% vs. 11.7%
- P<0.001 for all comparisons
- APBI lower incidence of pneumonitis 0.1% vs. 0.8%, P<0.001

Conclusion

- APBI-brachy was associated with inferior effectiveness.
- Increased acute and late toxicities compared with WBI in this cohort of older breast cancer patients.
- These data underscore the importance of awaiting mature results of randomized trials designed to prospectively compare these treatments before employing widespread adoption of APBI-brachy as an alternative to WBI in select patients.

Patient numbers APBI

Treatment technique	Total patients	Total follow-up (patient-years)	Average follow-up (y)
Interstitial	1,321	7,133	5.4
MammoSite	1,787	4,110	2.3
Intraoperative	681	1,430	2.1
External beam			
3D-CRT/IMRT	319	335	1.0
Protons	40	20	0.5

Outcomes

- Effectiveness of WBI/APBI
- NSABP data IBRT 6-9% at 10 years
- ABPI data IBRT 1-7%, usually reported at 5 years
- Toxicity
- Fibrosis/Cosmesis

ASTRO 2011

Early Toxicity Results with 3-D Conformal External Beam Therapy (CEBT) from the NSABP B-39/RTOG 0413 Accelerated Partial Breast Irradiation (APBI) Trial

- 3,877 pts enrolled (90%)
- Toxicity for 3DCRT APBI reviewed
- Deep tissue toxicity, cosmesis
- Late toxicity: grade 2<12%, grade 3<3%, grade 4=0%
- Acceptable toxicity

*ASTRO 2011**Updated Toxicity Results of Three-dimensional Conformal Accelerated Partial Breast Irradiation**K. L. Leonard et al.*

- 80 pts treated from 2003-2010
- Grade 2 fibrosis: 31%, grade 3: 7%
- Cosmetic outcome: fair poor 19%
- Fat necrosis: 11%
- Grade 2 toxicity remains high
- Correlation with dosimetric parameters

Different forms of APBI

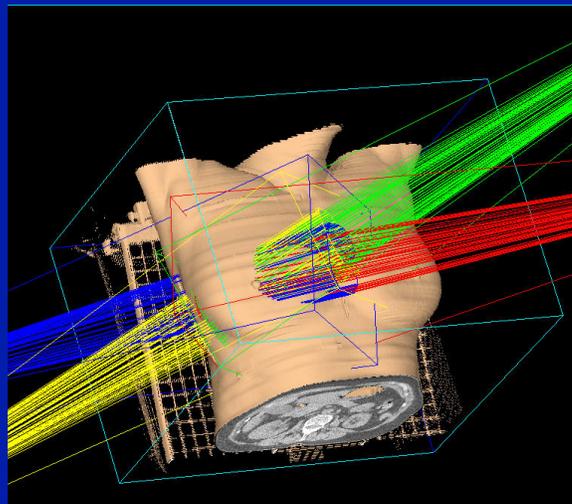
- Interstitial breast brachytherapy
- Catheter based brachytherapy
- 3D conformal brachytherapy
- Different target volumes and expansions
- PTV for 3DCRT 2.5cm expansion on the cavity vs. brachytherapy 1-1.5cm

Dose constraints APBI

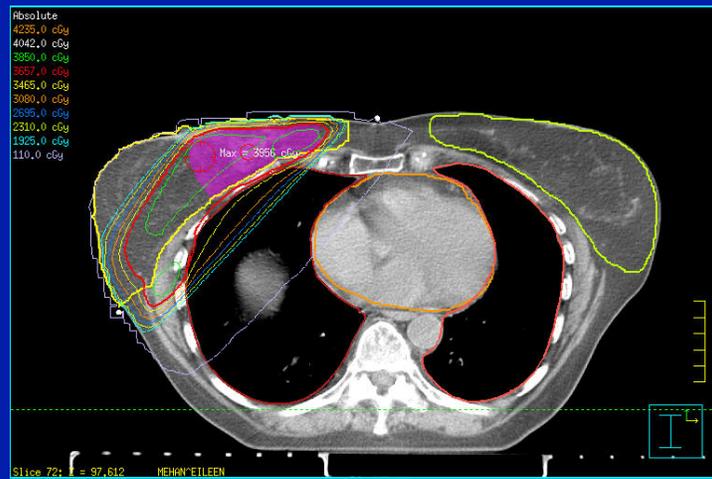
- Selective candidates for APBI
- Ongoing B39 trial, breast to cavity ratios
- Uninvolved ipsilateral breast, <60% whole breast volume receives >50% Rx, <35% breast receive Rx

3D APBI Treatment Plan

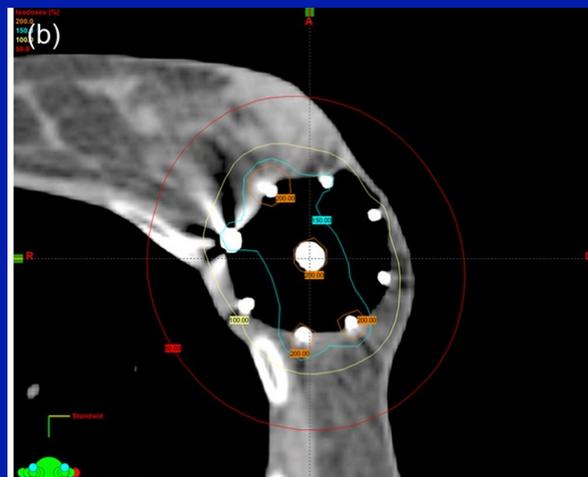
- Suggested beam arrangements:
 - 3-5 noncoplanar fields
 - Isocenter placed in center of PTV
 - Approximate breast tangents
 - 3 anterior fields
 - 1 posterior fields



Dose Distribution



Dose Distribution Catheter



**ACCELERATED PARTIAL BREAST IRRADIATION CONSENSUS STATEMENT FROM
THE AMERICAN SOCIETY FOR RADIATION ONCOLOGY (ASTRO)**

BENJAMIN D. SMITH, M.D.,*† DOUGLAS W. ARTHUR, M.D.,‡ THOMAS A. BUCHHOLZ, M.D.,†

Table 2. Patients "suitable" for APBI if all criteria are present

Factor	Criterion
Patient factors	
Age	≥60 y
<i>BRCA1/2</i> mutation	Not present
Pathologic factors	
Tumor size	≤2 cm*
T stage	T1
Margins	Negative by at least 2 mm
Grade	Any
LVI ¹	No ¹
ER status	Positive
Multicentricity	Unicentric only
Multifocality	Clinically unifocal with total size ≤2.0 cm [†]
Histology	Invasive ductal or other favorable subtypes ³
Pure DCIS	Not allowed
EIC	Not allowed
Associated LCIS	Allowed
Nodal factors	
N stage	pN0 (i [†] , i [†])
Nodal surgery	SN Bx or ALND
Treatment factors	
Neoadjuvant therapy	Not allowed

Controversy with suitability

- Several single institution reported outcomes of those in the unsuitable category
- Consideration of revamp of the categories as an update
- Late toxicity benefit on lung and heart?
- Await the ongoing B39 trial

S2-2. Luminal A subtype predicts radiation response in patients with T1N0 breast cancer enrolled in a randomized trial of Tamoxifen with or without breast radiation

Fyles A, McCreedy D, Pintilie M, Shi W, Done S, Miller N, Olivotto I, Weir L, Liu F-F. Princess Margaret Hospital, Toronto, Canada; British Columbia Cancer Agency, Vancouver, Canada.
Session 2- Oral

Objective

- To determine the predictive effect of molecular subtyping using the six biomarker immunohistochemical panel in predicting ipsilateral breast relapse (IBR)
- Age 50 and older with T1 and T2 node negative breast cancer in a randomized trial of tamoxifen (Tam) +/- whole breast radiation (WBRT).

Methods

- December 1992- June 2000
- 769 women were randomized to WBRT and Tamoxifen (Tam, n=386) 20 mg daily for 5 years or Tam alone (n=383)
- Median age was 68 years
- 639 (83%) had pT1 tumors
- Median follow-up was 10 years

Methods

- Intrinsic molecular subtype was determined using semi-quantitative analysis of ER, PR, Ki-67, HER2, EGFR and cytokeratin (CK) 5/6 on tissue microarrays constructed from tumor blocks from 172 of 345 available tumors
- Patients were classified into the following categories: luminal A, luminal B, luminal-HER2, HER2 enriched, basal-like, or triple-negative phenotype-nonbasal

Results

- IBR at 10 years was 13.8% with Tam compared to 5.0% with Tam/WBRT ($p < 0.0001$).
- Tumor size (HR 1.54, $p = 0.001$), ER positive (HR 0.35, $p = 0.006$), age (HR 0.96, $p = 0.014$), and treatment with Tam/WBRT (HR 0.28, $p < 0.0001$) were significant factors for IBR.
- Luminal A tumors (ER or PR positive, HER2 negative, Ki-67 < 14%, $n = 95$) had the lowest rate of IBR, 6.9% at 10 years with Tam alone and 4.5% with Tam/WBRT, $p = 0.4$).

Results IBRT

Subtype	N	Tam	Tam/RT	p
A	74	5.4%	6%	.8
B	53	23.8%	0%	.012
Her2	10	“highest risk”		Not given
Her2 enr	14			

Conclusions

- Six marker IHC subtype appears to be predictive for radiation response in women over 50 with T1/2 node-negative breast cancer
- Luminal A subtype demonstrated a low risk of breast relapse with Tam alone, particularly in women age 60 and older

Conclusions

- Require validation in additional specimens and clinical trials
- Luminal A significant proportion of women (74/172 or 43%)
- RT for higher risk subtypes (Luminal B, HER2 enriched, basal)
- Limitations of this analysis include the relatively small numbers of patients and the low event rate in smaller subgroups.

Discussion

- Avoidance of radiation in the elderly
- SEER incidence of breast cancer close to 50% pts 65yrs and older
- Age 70 years, life expectancy is 15.5 years

Further analysis

The **NEW ENGLAND**
JOURNAL of MEDICINE

ESTABLISHED IN 1812 SEPTEMBER 2, 2004 VOL. 351 NO. 10

Tamoxifen with or without Breast Irradiation in Women
50 Years of Age or Older with Early Breast Cancer

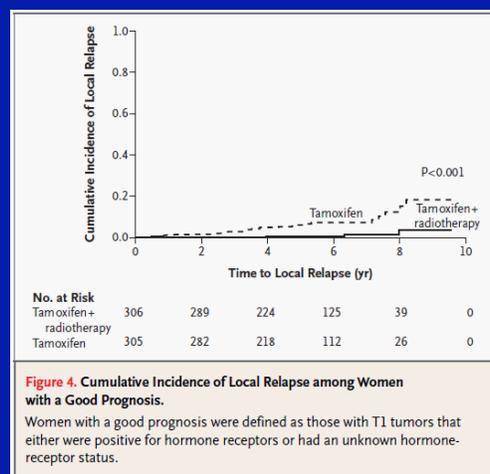
Anthony W. Fyles, M.D., David R. McCreedy, M.D., Lee A. Manchul, M.D., Maureen E. Trudeau, M.D.,
Patricia Merante, R.N., Melania Pintilie, M.Sc., Lorna M. Weir, M.D., and Ivo A. Olivotto, M.D.

Results

- Median 5 years
- IBRT 7% tam vs. 0.6% tam/RT (sig P)
- DFS: 84% vs 91%
- RT improved DFS, IBRT, axillary recurrences

Fyles et al. NEJM 2004; 351:10

Results



Fyles et al. NEJM 2004; 351:10

ASCO 2010 update

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Lumpectomy plus Tamoxifen with or without Irradiation in Women 70 Years of Age or Older with Early Breast Cancer

Kevin S. Hughes, M.D., Lauren A. Schnaper, M.D., Donald Berry, Ph.D.,

ASCO 2010

- Women 70 years of age or older with early breast cancer undergoing lumpectomy
- Randomized 636 pts to Tam vs. Tam/RT
- F/U 10 years
- Clinical stage I, estrogen receptor + (ER+)

Hughes et al. ASCO 2010

Results

- IBRT : 8% vs. 2%
- No difference in mastectomy free survival, breast cancer specific survival
- Absolute reduction with RT but no difference in various endpoints

Hughes et al. ASCO 2010

Avoidance of RT

- Patient specific features
- Pathologic features
- Caution for the non luminal A patients
- Growing elderly population, comparative effectiveness research

Boost Radiation Therapy Not of Value in Reducing IBTR of Invasive or Noninvasive Breast Cancers for Patients with DCIS: Results from the NSABP B-24 Trial

Julian TB, Vicini FA, Costantino JP, Arthur DW et al.

Session 3- Poster

Objectives

- Whole breast irradiation therapy following lumpectomy for invasive breast cancer (IBC) or noninvasive breast cancer (DCIS) significantly reduces the risk of local recurrence.
- Boost radiation therapy to the tumor bed has been proven to additionally lower the risk of recurrence for IBC.
- The benefit of boost therapy in patients with DCIS is less certain. We carried out a review of the NSABP B-24 trial to assess the benefit of boost therapy.

Methods

- After lumpectomy and radiation therapy, 1804 women with DCIS were randomly assigned to placebo (902) or tamoxifen (902).
- Whole breast irradiation therapy (50 Gy) was mandatory.
- Boost radiation therapy was optional, and boost status was known for 1,569 patients.
- 613 received boost therapy ranging from 1 Gy -20 Gy, with 81.5% receiving 10 Gy.
- Mean time of follow-up was 13yrs

Results

- Patients who received boost radiation therapy were more likely to be younger ($p=0.04$), have positive margins ($p=0.007$), and be more likely to have comedo necrosis ($p=0.03$).
- Multivariate analysis identified only treatment (tamoxifen vs placebo) age (≥ 50 verses < 50) and margin status (positive vs negative) as significant predictors for ipsilateral breast tumor recurrence (IBTR).
- Boost had no significant effect on IBTR (HR=0.87, 95% CI=0.66-1.15, $p=0.33$).
- The lack of boost effect applied to both invasive (HR=0.86, 95% CI=0.58-1.27, $p=0.44$) and noninvasive IBTR (HR=0.89, 95% CI=0.60-1.33, $p=0.56$).

Conclusions

- In NSABP B-24, the addition of boost radiation therapy was not found to be of value in reducing IBTR of invasive or noninvasive breast cancers for patients with DCIS.

Discussion

- Previous data to support a boost in retrospective form
- Numbers too small to show a difference
- Only 34% patients received a boost
- No standard on who was selected for a boost

Discussion

- No published prospective randomized data on the role of a boost in DCIS nor boost to the chest wall in the PMRT setting
- Practice pattern variation
- Trials in invasive cancer did not use a boost

Role of a boost

➤  **Boost radiotherapy in young women with ductal carcinoma in situ: a multicentre, retrospective study of the Rare Cancer Network**

Aurelius Omlin, Maurizio Amichetti, David Azria, Bernard F Cole, Philippe Fournier, Philip Poortmans, Diana Naehrig, Robert C Miller, Marco Krengli, Cristina Gutierrez Miguez, David Morgan, Hadassah Goldberg, Luciano Scandolaro, Pauline Gastelblum, Mahmut Ozsahin, Dagmar Dohr, David Christie, Ulrich Oppitz, Ufuk Abacioglu, Guenther Gruber

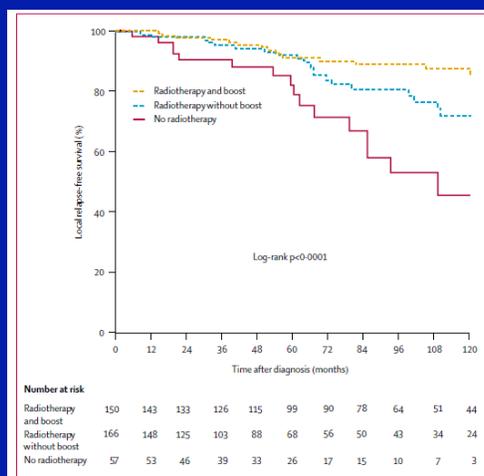
Lancet Oncology 2006; 7: 652-656

Role of boost in DCIS

- Retrospective review of 373 women
- Age 45 yrs or younger
- 45% given boost RT (50Gy +10Gy)
- Primary outcome local relapse free survival

Lancet Oncology 2006; 7: 652-656

Results



LRFS at 10 yrs: 46% no RT, 72% RT, 86% RT +boost

Role of RT boost

- Conclusion of the *Omlin et al.* that in the absence of prospective data, a boost should be strongly considered
- But, will all patients benefit?

Boost in Invasive Cancer

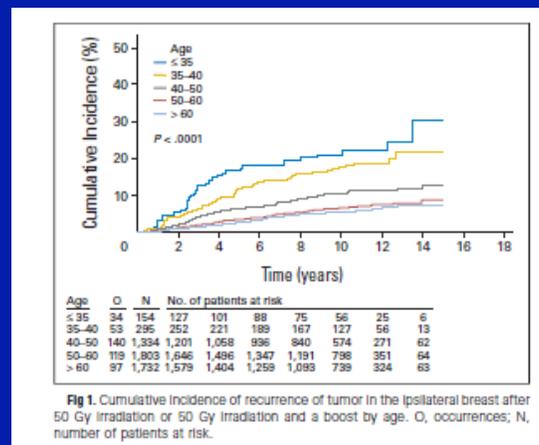


Fig 1. Cumulative incidence of recurrence of tumor in the ipsilateral breast after 50 Gy irradiation or 50 Gy irradiation and a boost by age. O, occurrences; N, number of patients at risk.

Bartelink et al. JCO, vol 25, number 22, Aug 2007

Selectivity

- Selecting those that will benefit
- Radiation dose adequate for preinvasive cancer
- Boost dose increases side effect profile

Ongoing trials

- A Phase III Randomized Multicentric French Study To Evaluate the Impact of a Localized 16-Gy Boost after Conservative Surgery and a 50-Gy Whole-Breast Irradiation in Breast Ductal Carcinoma In Situ (The BONBIS Trial)