

# BrachyNext

Working Together to Shape the Future of  
**Brachytherapy**



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**State-of-the-Art:  
The Optimal Means of Delivering  
Accelerated Partial Breast Irradiation  
(APBI)**

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## Disclosures

- Non-salaried Consultant for Nucletron/Elekta
- Recipient of an Unrestricted Educational/Research Grant from Elekta to Conduct a 6-Institution Registry Trial of Interstitial Brachytherapy APBI
- Cianna Medical: minor stock options

## APBI: The Concept

- Accelerated partial breast irradiation (APBI) is a 5-day or less alternative to conventional 5-7 weeks of external beam whole breast irradiation (WBI)
- Substantial pathology and clinical data demonstrates that residual cancer cells after a lumpectomy with clear margins are within 1-2 cm of the surgical cavity edge
- Remote in-breast recurrence in the other quadrants is rare (3-5%), and may be excluded from high-quality breast imaging (e.g. MRI) before the treatment



## APBI: The Concept

- The extended time for WBI is difficult for many busy, modern women
- Patients and their doctors wish to minimize exposure of normal tissues (heart, lung, skin, chest wall, lymphatics, uninvolved breast)
- These issues inspired us 22 years ago to investigate a treatment that only covers the involved portion of the breast, lasts one week or less, with minimal collateral damage
- Our original hypothesis: “Brachytherapy is the ideal choice for such a treatment.”

## APBI Early Clinical Trials

- The initial New Orleans trial (Ochsner Clinic) and the Michigan trial (Wm Beaumont Hospital) have reported 7-10 year data supporting the hypothesis of brachytherapy APBI
- RTOG 95-17 phase II trial of interstitial brachytherapy, now out 12.5 years, has demonstrated a very low 4.2% isolated breast recurrence rate with broad selection criteria (e.g. node +)
- The Hungarian phase III trial is positive for brachytherapy, since tumor control was equivalent with better cosmesis in the brachy arm over WBI



## RTOG 95-17: Interstitial Brachy w/12.5 yrs FU



### Long-term outcome from RTOG 9517: A phase I/II study of accelerated partial breast irradiation (APBI) with multicatheter brachytherapy (MCT) following lumpectomy for early-stage breast cancer.

J. White, K. Winter, R. Kuske, J. Bolton, D. Arthur, T. Scroggins, R. Rabinovitch, T. Kelly, L. Toonkel, F. Vicini, B. McCormick.  
Ohio State University, Radiation Therapy Oncology Group, Aurora Breast Cancer Specialty, Oshtor Clinic, Michigan Commonwealth University, University of Colorado, Medical College of Wisconsin, Moffitt State Comprehensive Cancer Center, Bobrow Hospital, Memorial Sloan Kettering

The data presented here are from the RTOG 9517 and 9517-2007 papers. © 2010 American Society for Radiation Oncology. All rights reserved. No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, without the prior written permission of the publisher.

#### BACKGROUND

APBI is standard wide breast irradiation (WBI) alternative to breast conservation in young women. It is a more time and costly than traditional whole breast irradiation. APBI has increasing gained acceptance in clinical trials. APBI has increasing gained acceptance in clinical trials. APBI has increasing gained acceptance in clinical trials.

#### RTOG 95-17 STUDY DESIGN

Phase I/II study of accelerated partial breast irradiation (APBI) with multicatheter brachytherapy (MCT) following lumpectomy for early-stage breast cancer.

#### RTOG 95-17 Treatment

Target volume: Lumpectomy cavity + 2 cm field. Quality assurance: All cases underwent rapid planning review prior to initiation of treatment.

#### ELIGIBILITY (Breast)

Stage I-II breast cancer, non-invasive lobular carcinoma in situ, no ipsilateral axillary nodes without axillary dissection, no ipsilateral axillary nodes without axillary dissection, no ipsilateral axillary nodes without axillary dissection.

#### OBJECTIVES

To determine whether radiation therapy delivered with therapy alone is technically feasible and non-toxic with acceptable toxicity in a multicatheter MCT. To evaluate toxicity, ipsilateral recurrence, and to results after MCT brachytherapy as the sole irradiation.

#### PATIENTS

Total patients entered: 180  
Analyzed: 86  
Median Follow-up: 12.1 years

#### Table I. Patient Population

Age (yr)	Median	80
Stage (%)		
T1N0	62	
T1N1	41	
T2N0	19	
T2N1	18	
T3N0	15	
T3N1	15	
T4N0	15	
T4N1	15	
T4N2	15	
T4N3	15	

#### Table II. Pathology

T-stage (%)		
T1	67.8	
T2	32.2	
T3	18.9	
T4	19.1	
T5	2.0	
T6	0.0	
T7	0.0	
T8	0.0	
T9	0.0	
T10	0.0	
T11	0.0	
T12	0.0	
T13	0.0	
T14	0.0	
T15	0.0	
T16	0.0	
T17	0.0	
T18	0.0	
T19	0.0	
T20	0.0	

#### RESULTS

#### EFFICACY

Table III. Local and Regional Cancer Event  
5 and 10 year Estimates of Ipsilateral In-breast Recurrence, Regional Nodal Recurrence and Contralateral Breast Cancer

Year	5	10
Rate (%)		
Ipsilateral In-breast Recurrence	3.1	4.2
Regional Nodal Recurrence	1.0	2.1
Contralateral Breast Cancer	3.1	3.1

#### Table IV. Causes of Death

Year	5	10
Rate (%)		
Deaths from any cause	30.00	39.70
Deaths from breast cancer	8.93	12.02
Deaths from other causes	21.07	27.68

#### CONCLUSIONS

This multicatheter phase I/II study of MCT-APBI continues to report durable regional cancer control rates with long follow-up.

## RTOG 95-17 Tumor Control at 5 & 10 years

### 5 and 10 year Estimates of Ipsilateral In-breast Recurrence, Regional Nodal Recurrence and Contralateral Breast Cancer

	5 year			10 year		
	#	(%)	# at risk	(%)	# at risk	
<b>ISOLATED</b> in-breast recurrence	4	3.1	84	4.2	68	
In field	3	2.1	85	3.1	69	
Out of field	1	1.0	85	1.0	69	
<b>In-breast &amp; Regional recurrence</b>	2	1.0	84	2.1	68	
<b>ALL In-breast recurrences</b>	6	4.1	86	6.2	69	
<b>ISOLATED</b> Regional recurrence	3	3.1	84	3.1	68	



## APBI Later Clinical Trials

- Large phase III trials from North America (NSABP B39/RTOG 0413 with 4214 patients) and GEC-ESTRO are maturing after closure and should be published in 2-3 years
- IORT phase III trials (TARGiT-UK, ELIOT-Milan)
- Overall, > 12 phase III APBI clinical trials
- More patients in one trial (NSABP/RTOG) than all randomized clinical trials that took us from mastectomy to breast conservation with WBI

## APBI: Successors to Interstitial Brachy

- Simplifying APBI with **single-entry** balloon catheters or a strut-based device has been reported in large registry trials
- Disappointing pre-treatment path review, dosimetry, quality assurance, and clinical outcomes has plagued **intraoperative radiotherapy** with Intrabeam or electron beam



## Milan IORT Randomized Phase III Trial

### Articles

#### Intraoperative radiotherapy versus external radiotherapy for early breast cancer (ELIOT): a randomised controlled equivalence trial



Umberto Veronesi, Roberto Orecchia, Patrick Maisonneuve, Giuseppe Viale, Nicole Rotmensz, Claudia Sangalli, Alberto Luini, Paolo Veronesi, Viviana Gallimberti, Stefano Zurrida, Maria Cristina Leonardi, Roberta Lazzari, Federica Cattani, Oreste Gentilini, Mattia Intra, Pietro Caldarella, Betelina Balaurdini

##### Summary

**Background** Intraoperative radiotherapy with electrons allows the substitution of conventional postoperative whole breast irradiation with one session of radiotherapy with the same equivalent dose during surgery. However, its ability to control for recurrence of local disease required confirmation in a randomised controlled trial.

**Methods** This study was done at the European Institute of Oncology (Milan, Italy). Women aged 48–75 years with early breast cancer, a maximum tumour diameter of up to 2.5 cm, and suitable for breast-conserving surgery were randomly assigned in a 1:1 ratio (using a random permuted block design, stratified for clinical tumour size [ $<1.0$  cm vs  $1.0$ – $1.4$  cm vs  $\geq 1.5$  cm]) to receive either whole-breast external radiotherapy or intraoperative radiotherapy with electrons. Study coordinators, clinicians, and patients were aware of the assignment. Patients in the intraoperative radiotherapy group received one dose of 21 Gy to the tumour bed during surgery. Those in the external radiotherapy group received 50 Gy in 25 fractions of 2 Gy, followed by a boost of 10 Gy in five fractions. This was an equivalence

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See Online/Comment  
Lancet 2013; published online  
November 11.  
[http://dx.doi.org/10.1016/S0140-6736\(13\)62304-1](http://dx.doi.org/10.1016/S0140-6736(13)62304-1)

Scientific Directorate  
(Prof U Veronesi MD), Division  
of Radiation Oncology  
(Prof R Orecchia MD).

## Milan IORT Conclusions

- “The rate of IBTR was significantly higher with electron IORT over WBI, although the Survival rates did not differ.”
- Better selection criteria for IORT may improve these results



## TARGIT-A Trial: Soft x-ray IORT vs. WBI

### Risk-adapted targeted intraoperative radiotherapy versus whole-breast radiotherapy for breast cancer: 5-year results for local control and overall survival from the TARGIT-A randomised trial

Jayant S Vaidya, Frederik Wenz, Max Bulsara, Jeffrey S Tobias, David J Joseph, Mohammed Keshtgar, Henrik L Flyger, Samuele Massarut, Michael Alvarado, Christobel Saunders, Wolfgang Eiermann, Marinos Metaxas, Elena Sperk, Marc Sütterlin, Douglas Brown, Laura Esserman, Mario Roncadin, Alastair Thompson, John A Dewar, Helle M R Holtveg, Steffi Pigorsch, Mary Falzon, Eleanor Harris, April Matthews, Chris Brew-Graves, Ingrid Potyka, Tammy Corica, Norman R Williams, Michael Baum, on behalf of the TARGIT trialists' group

#### Summary

**Background** The TARGIT-A trial compared risk-adapted radiotherapy using single-dose targeted intraoperative radiotherapy (TARGIT) versus fractionated external beam radiotherapy (EBRT) for breast cancer. We report 5-year results for local recurrence and the first analysis of overall survival.

**Methods** TARGIT-A was a randomised, non-inferiority trial. Women aged 45 years and older with invasive ductal carcinoma were enrolled and randomly assigned in a 1:1 ratio to receive TARGIT or whole-breast EBRT, with blocks stratified by centre and by timing of delivery of targeted intraoperative radiotherapy: randomisation occurred either before lumpectomy (prepathology stratum, TARGIT concurrent with lumpectomy) or after

## TARGIT Outcomes Graphs

was larger than 2.5%: TARGIT 5.4% (95% CI 3.0–9.7) vs EBRT 1.7% (0.6–4.9;  $p=0.069$ ). Breast-cancer mortality was three patients for TARGIT versus one patient for EBRT (1.2%, 0.4–4.2 vs 0.5%, 0.1–3.5;  $p=0.35$ ), and non-breast-cancer mortality was five patients for TARGIT versus eight patients for EBRT (1.58%, 0.62–3.97 vs 1.76%, 0.7–4.4;  $p=0.32$ ). Thus, in absolute terms, there were eight additional local recurrences and one less death in the postpathology TARGIT stratum (figure 3).

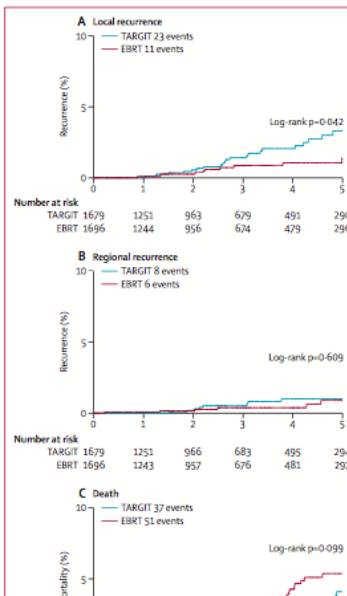
The results of a comparison<sup>16</sup> of cumulative incidence for local recurrence in the presence of competing risks (death and withdrawal from trial) were no different from Kaplan-Meier estimates, showing that these risks did not bias the main results (data not shown).

Analysis limited to the mature cohort, first reported in 2010 ( $n=2232$ , median follow-up now 3 years 7 months), in which most events had occurred (32 of 34 local recurrences and 85 of 88 deaths), yielded much the same results (data not shown).

Table 3 shows the Z score and  $p_{non-inferiority}$  for the primary outcome of local recurrence in the conserved breast, for the whole cohort, the mature cohort, and the earliest cohort. Non-inferiority is established for the whole cohort and for prepathology patients but not for post-pathology patients.

Figure 4 shows the primary (local recurrence in the conserved breast) and secondary outcomes (deaths) for the prepathology stratum. It shows the differences in 5-year estimates for these outcomes for the whole cohort,

	TARGIT	EBRT
Other cancers	8	16
Cardiovascular causes		





## APBI Options: IORT vs. Brachytherapy

- The data for brachytherapy is favorable with long-term follow-up, and more aggressive tumors are allowed (grade 3, endocrine receptor negative, Her-2 +, node +, etc.)
- The data for IORT seems to be deteriorating over time with less aggressive tumors (grade 1-2, ER +, Her-2 -, smaller node -)

## Secrets?

**Who keeps secrets!**



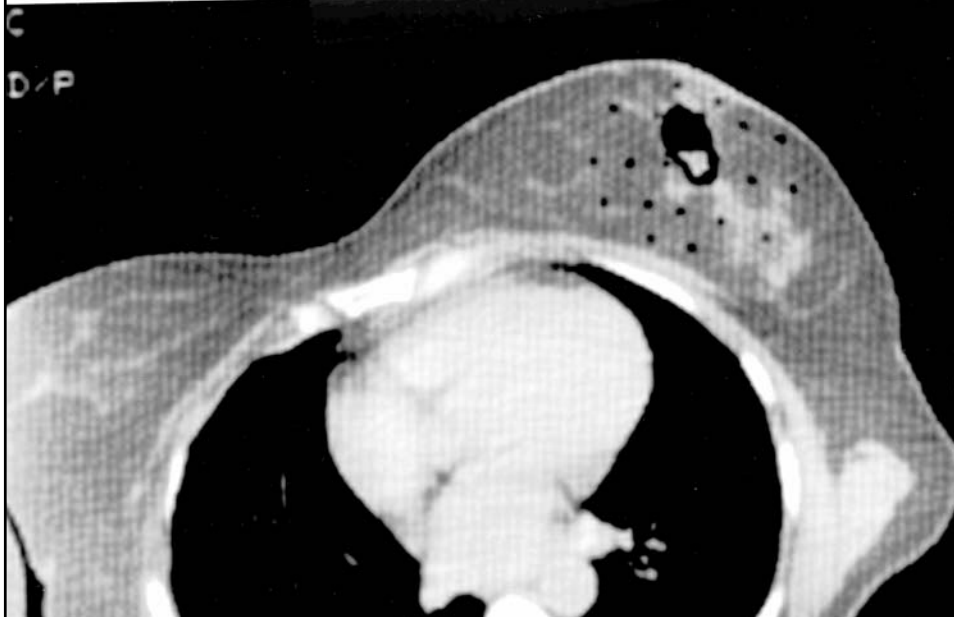


## Secrets?

*Who keeps secrets!*



## The Secret to High Quality Breast Brachytherapy



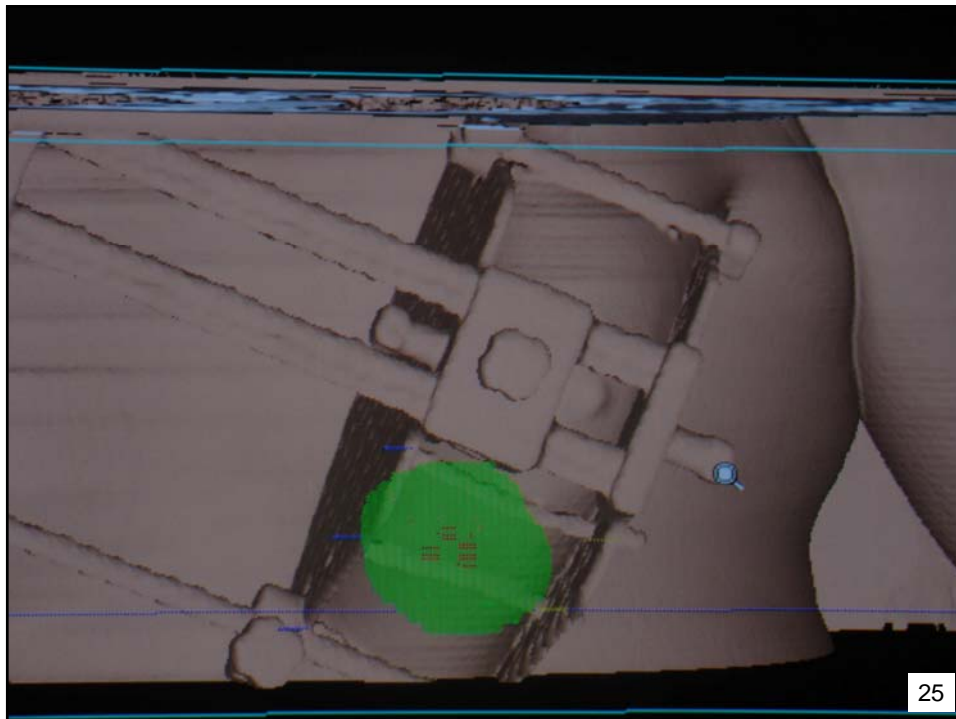


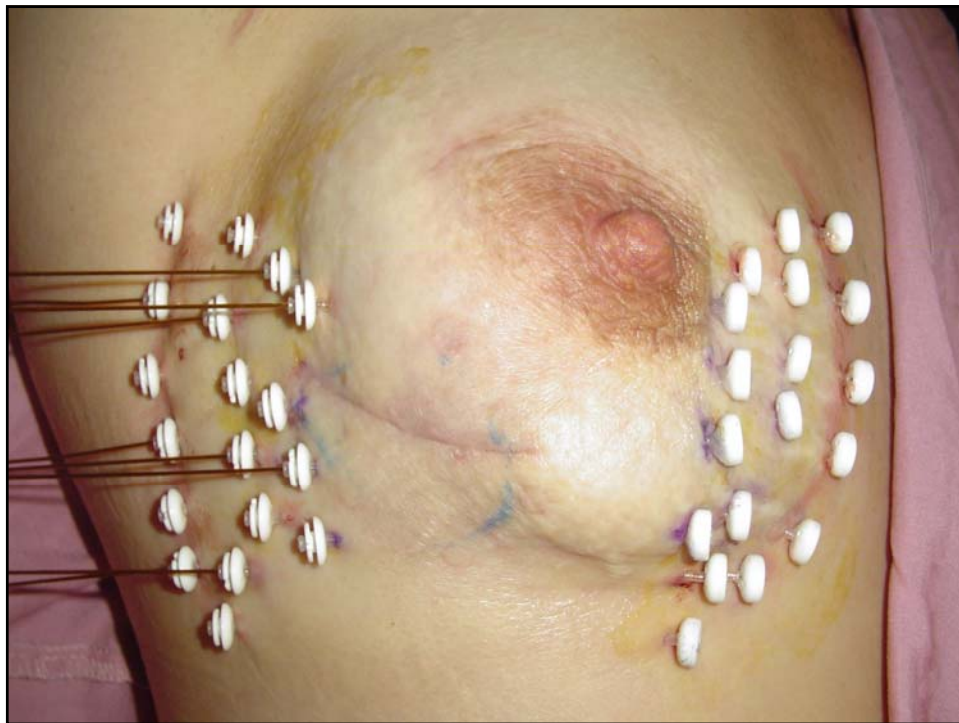
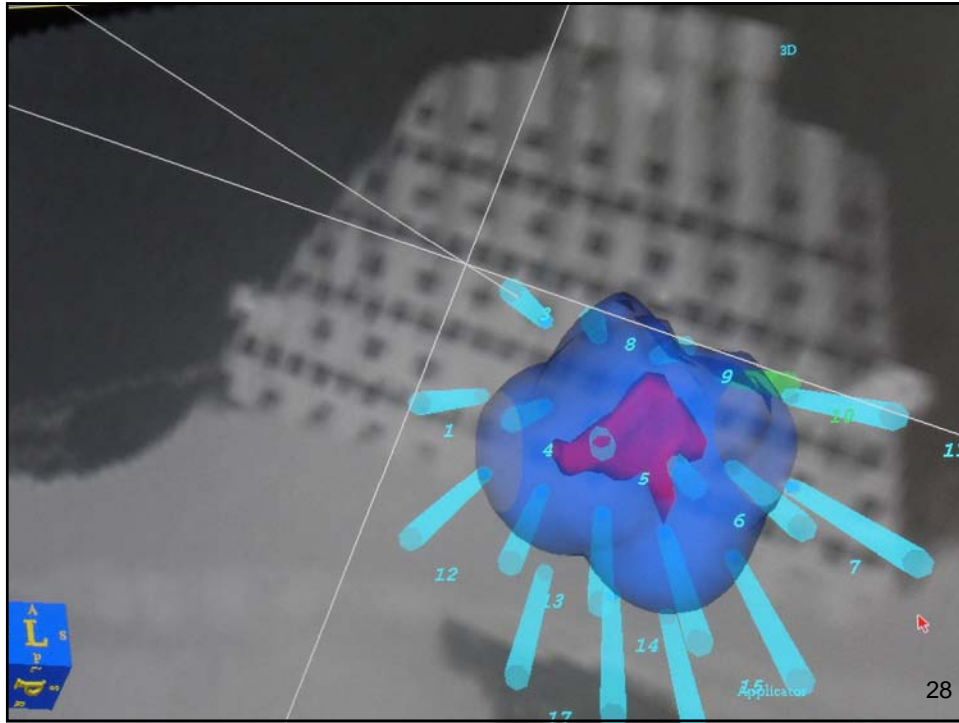
### The Secret to High Quality Breast Brachytherapy

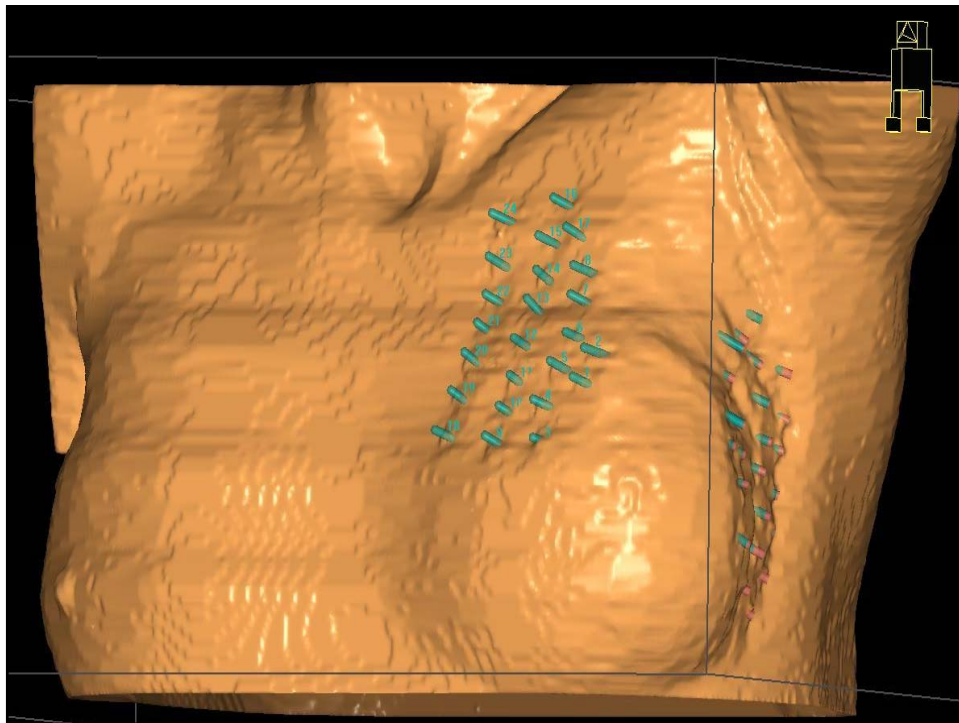
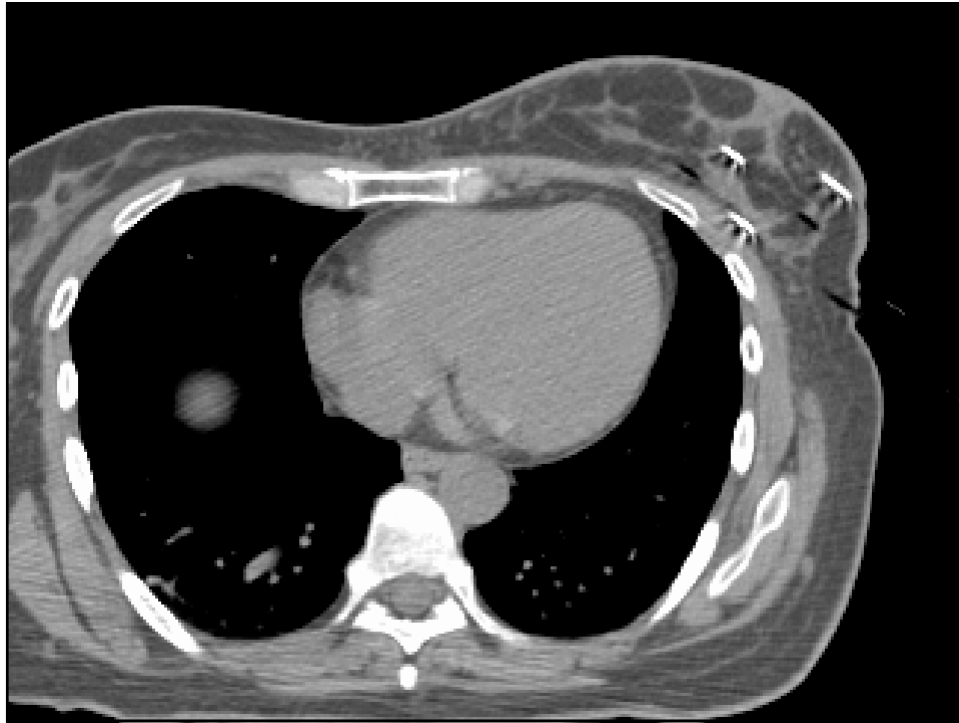
- Is image-guidance

**And**

- Exquisite ability  
to shape the radiation dose cloud

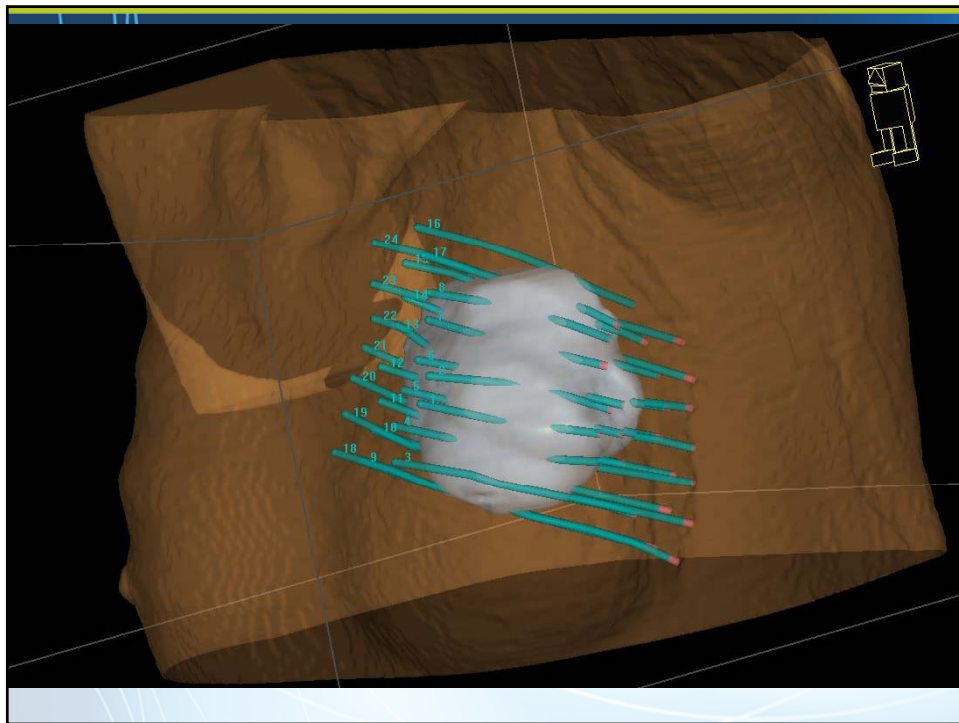
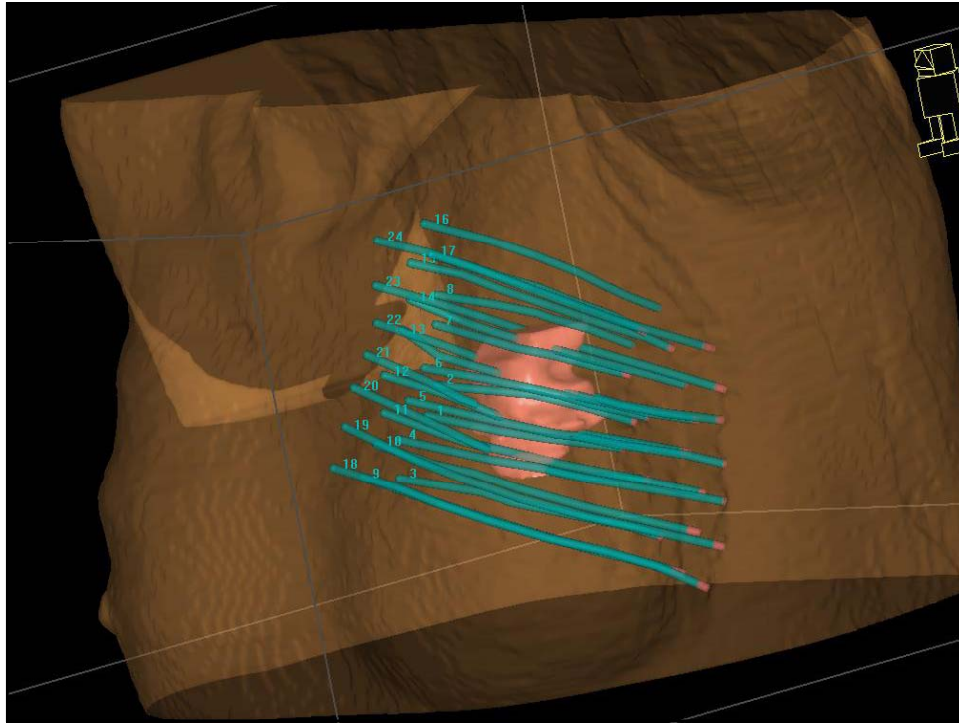






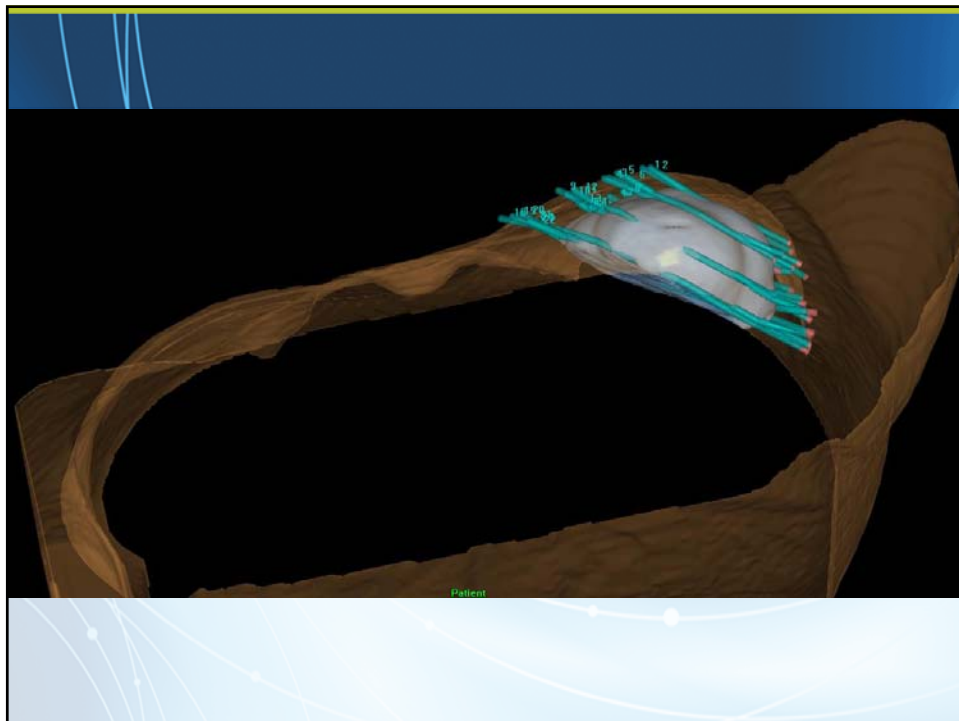
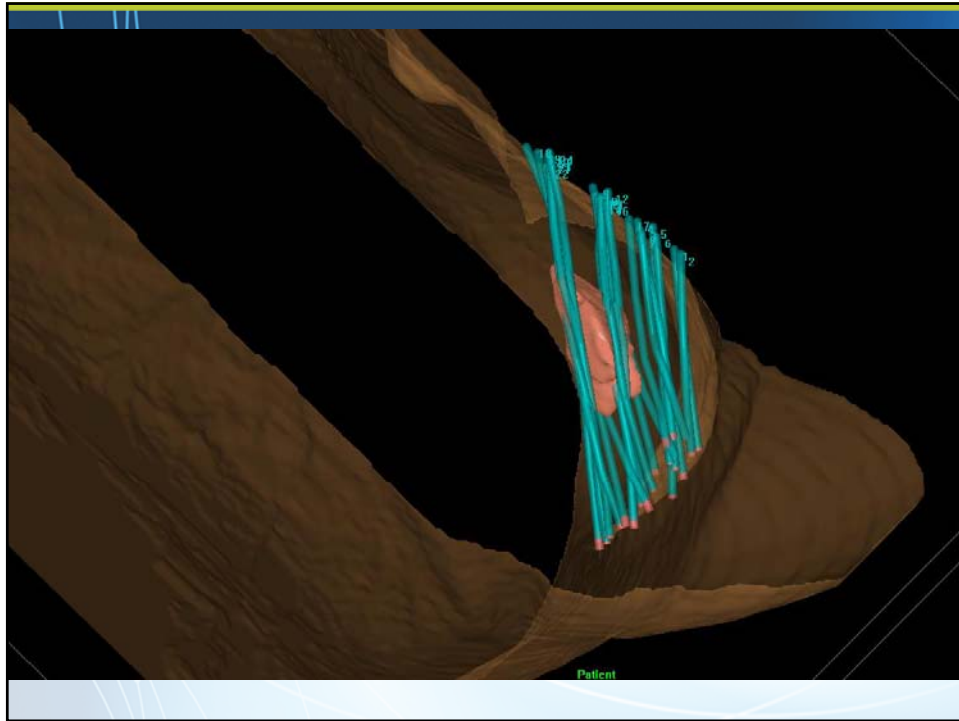
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## Interstitial Brachytherapy Registry Study

### Interstitial Multi-catheter Brachytherapy for Breast Cancer: a Multi-institutional Study

Mitchell Kamrava, MD, Robert R. Kuske, MD, FAACE, Peter Chen, MD, John Hayes, MD, Bethany Anderson, MD, Coral Quiet, MD, Pin-Chieh Wang, PhD, Darlene Veruttipong, BS, Margaret Snyder, RN and D. Jeffrey Demanes, MD.

- **Objective:** To report outcomes for breast cancer treated with breast-conserving therapy using accelerated partial breast irradiation (APBI) with interstitial multi-catheter brachytherapy by a cooperative group of institutions.

## Interstitial Brachytherapy Registry Study: Results

- 849 pts in the first ABS report (>1500 in the final analysis)
- Median follow-up of 4.3 years (range 0.003-20.9)
- The 5 year actuarial risk of an ipsilateral breast tumor recurrence was 3% for all patients (3.8% for DCIS, 3% for IDC, 0% for ILC, and 3.8% for other)
- 34/849 (4.0%) Crude rate of local recurrence
- Elsewhere failures in 26/34 (76%) cases, marginal misses in 5/34 (15%) cases, and true recurrences in 3/34 (9%) cases.

{Study supported by an unrestricted  
educational/research grant from Elekta}



## Interstitial Brachytherapy Registry Study

### Interstitial Multi-Catheter Brachytherapy for Select DCIS with 5 Year Follow-up: A Multi-Institutional Study PROMIS: Pooled Registry of Multicatheter Interstitial Sites

R. Kuske, MD<sup>1</sup>, M. Kamrava, MD<sup>2</sup>, P. Chen, MD<sup>3</sup>, J. Hayes, MD<sup>4</sup>, B. Anderson, MD<sup>5</sup>, C. Quiet, MD<sup>6</sup>, P.C. Wang, PhD<sup>7</sup>, D. Veruttipong, BS<sup>8</sup>, M. Snyder, RN<sup>9</sup> & J. Demanes, MD<sup>10</sup>  
<sup>1</sup>Arizona Breast Cancer Specialists, Scottsdale, AZ; <sup>2</sup>William Beaumont Hospital, Royal Oak, MI; <sup>3</sup>Gamma West, Salt Lake City, UT; <sup>4</sup>UCLA Medical Center, Los Angeles, CA; <sup>5</sup>UW Cancer Center, Madison, WI

Interstitial multi-catheter brachytherapy (BCT) using accelerated partial breast irradiation (APBI) with interstitial multi-catheter brachytherapy by a group of institutions with single-entry brachytherapy devices have been reported. This is the first report with patients treated by interstitial brachytherapy.

#### Methods

Patients from five institutions with extensive experience in breast cancer with interstitial brachytherapy from 1997 to August 2013, 240 patients with Stage 0 breast cancer treated with breast conserving surgery and adjuvant interstitial multi-catheter brachytherapy. An analysis of patients with at least 1 year follow up is presented herein with a median follow-up of 36.3 months.

Mean DCIS size was 0.94 +/- 0.66 cm. Surgical margins were positive in 3 patients (1.5%), < 2 mm in 38 (19.0%) and ≥ 2 mm in 77 (38.5%) of patients, negative but size of margin not specified in 66 (33%) and not known in 16 (8%). ER/PR was 61.5% / 55.5% positive and 23% were sentinel node negative. DCIS was Grade 1 in 19.0% and 2 in 40.5% and 3 in 38.5% and not reported in 2% of patients. 41.5% of patients received endocrine therapy.

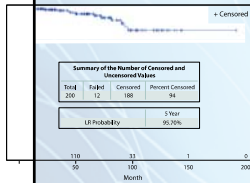
#### Results

With a median follow up of 60 months the overall and cause-specific survival rates were 99% and 100%, respectively. The 5-year actuarial risk of an ipsilateral breast tumor recurrence was 4%. The recurrences included 12 ipsilateral breast (7 elsewhere, 5 marginal miss/true recurrence) (5 IDC, 7 DCIS).

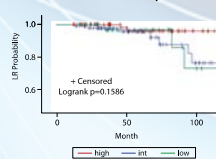
#### Conclusions

This pooled multi-institutional study is the largest published report of the outcomes of patients with DCIS treated by interstitial brachytherapy. Brachytherapy to complete BCT for pure DCIS was associated with excellent local control (96%) and survival rates at 5 years median follow-up. Young age, ER negativity, grade, margins or endocrine therapy did not predict for recurrence. APBI is an acceptable option for select women with DCIS. Survival rates are equivalent to published outcomes of mastectomy or BCT, and recurrence rates compare favorably to 6-7 week whole breast irradiation.

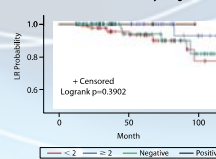
Local Recurrence



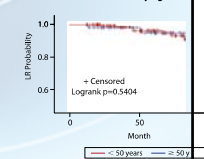
Local Recurrence by Grade



Local Recurrence by Margin



Local Recurrence by Age at 5



## NSABP B39/RTOG 0413: 6 weeks vs. 5 days

- While the first publication is not expected for 2-3 years (data ripening on the vine), the statisticians have not noted a difference between the arms sufficient to release the outcomes early {early stopping rules}
- 70% 3dCRT, 25% single entry, 5% interstitial
- 4214 patients entered exceeds the total number in 7 randomized trials of BCT vs MRM





## APBI: Current Arizona Selection Criteria

- APBI appears to be an acceptable option for treatment of select tumors < 3 cm
- Excised with clear margins
- With 0-3 + nodes without extracapsular extension