

Innovations in Radiation Oncology: Clinical Trials and Future Directions

ASBD Symposium

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Las Vegas

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Agenda

✓ Whole breast irradiation (WBI)

- › Update clinical trials
- › Early Breast Cancer Trialists' Collaborative Group: local control and survival
- › WBI: Room for improvement
- › Trends in radiation delivery

✓ Partial breast irradiation (PBI)

- › Update clinical trials
- › 3 Methods: genesis and supporting literature
- › Status of randomized trials

Breast Radiation Following Lumpectomy

Goals

- Minimize local or in-breast cancer recurrence
- Preserve cosmetic appearance of the breast
- Maintain mastectomy-free survival

Radiation Therapy for Early Stage Breast Cancer Following Lumpectomy

Whole Breast Irradiation

- Rationale: Addition of whole breast irradiation following lumpectomy yields local control rates comparable to mastectomy
- Treatment: Whole breast irradiation
 - 45-50 Gy to the entire breast
 - 60 Gy to the lumpectomy cavity + margin
 - 1.8 – 2 Gy fraction given 5 days/ week
 - 5 – 7 week total treatment duration

Trends in Breast Cancer Management

- › Smaller tumors diagnosed as the result of screening mammography
- › Emergence of endocrine receptors and anti-endocrine therapy into clinical practice
- › Impact of anti-endocrine therapy on in-breast recurrence rates after lumpectomy in receptor positive tumor
- › Less utilization of breast conservation therapy than anticipated

Is the breast radiation necessary
after lumpectomy?

Randomized Trials Comparing Lumpectomy Alone vs. Lumpectomy and Breast Radiation

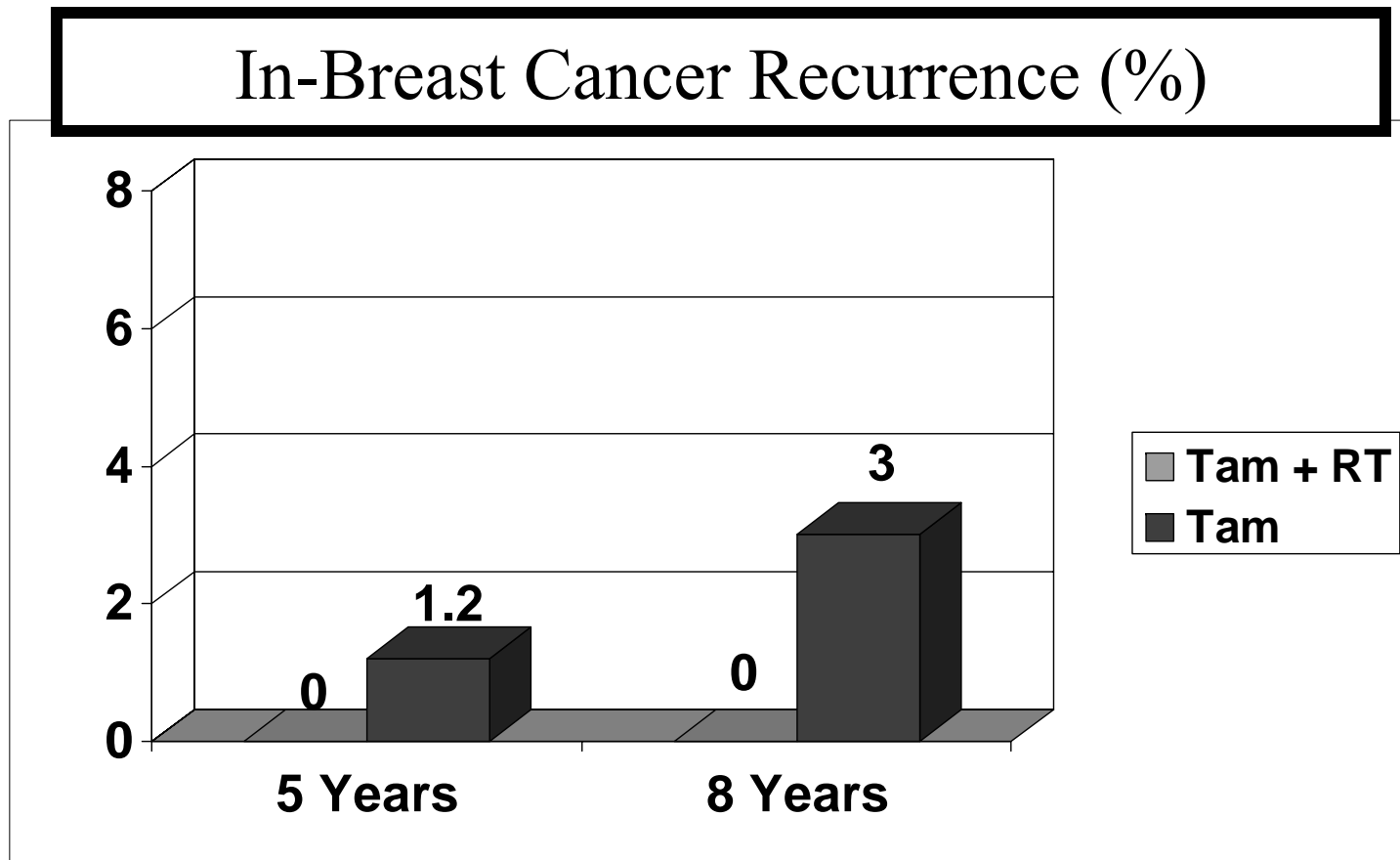
<i>Trial</i>	<i>No</i>	<i>Yrs. F/U</i>	<i>Max Tumor Size (cm)</i>	<i>Surgery</i>	<i>% Local Recurrence</i>	
					<i>Surgery</i>	<i>Surgery +RT</i>
Uppsala-Orebro	381	10	2	Q*	24	8.5
Milan III	579	10	2.5	Q	23.5	5.8
NSABP B-06	1262	20	4	L•	39	14
Ontario Clinical Oncology Group	837	7.6	3	L	35	11
Scottish Cancer Trials Breast Group	585	7.7	4	L	24.5	5
NSABP B-21	1009	8	1	L	16.5 ¹	9.3 2.8 ¹
Princess Margaret Hospital ¹	769	5.6	2	L	7.7	0.6
CALGB C 9343 ^{1,2}	629	5	2	L	4	1
BASO II ³	1172	4.5	2	L	3.7	1.4

* Quadrantectomy, • Lumpectomy, ¹ All patients received tamoxifen, ² All patients ≥ 70 years, ³ All Grade I, pN-0

Randomized Trials Comparing Lumpectomy + Tamoxifen vs. Same + Breast Radiation

Study	N	F/U yrs.	Age yrs.	% post-men	T-size cm	% Pos. receptors	In- breast failure		
							Tam	Tam + RT	RT
NSAB P B-21	1000	8	50% > 60	76	1	57 (unk. 30%)	16.5	2.8	9.3
PMH	769	5.6	68	95	2	81	7.7	0.6	-
CALG B 9343	636	5	≥ 70	100	2	97	5	0.6	-

PMH: Low Risk Subgroup (n=193)



Receptor Positive, > 60 , ≤ 1 cm

Low risk for in-breast failure after lumpectomy

- ≥ 70 age, receptor positive, ≤ 2 cm
- ≥ 60 , Grade I, receptor positive, 1 cm (?)

+

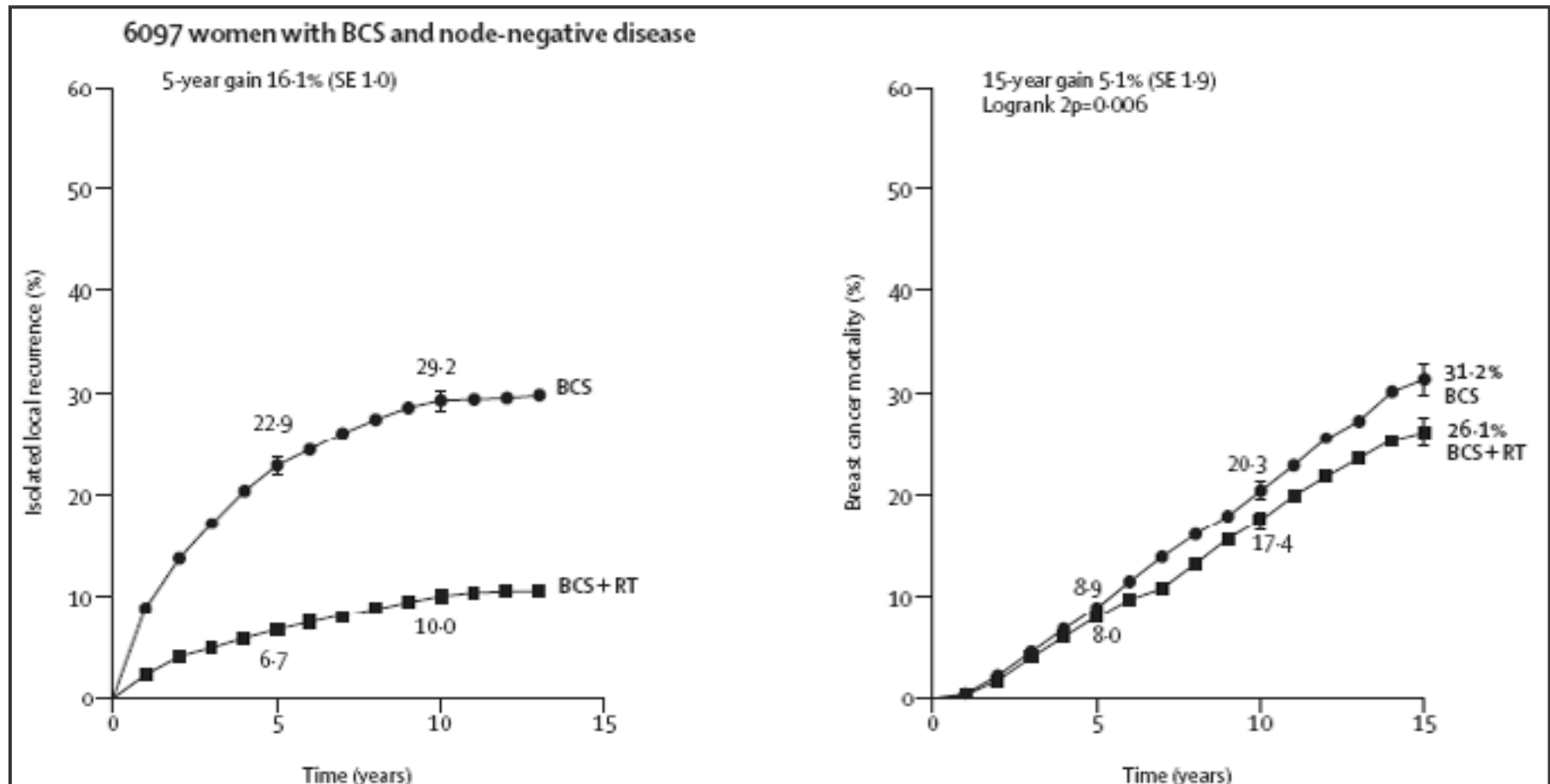
Anti-endocrine therapy

What is the meaning of local control after lumpectomy?

Early Breast Cancer Trialists' Collaborative Group

- Meta-analysis demonstrated cause specific survival advantage from radiation after BCS
- Reduction in Local Recurrence:
 - 7 % BCS + RT versus
 - 26 % BCS (p<0.00001)
- 15 yr. Breast Cancer Death Risk:
 - 30.5 % BCS + RT versus
 - 35.9 % BCS alone (p=0.0002)
- However, continued excess in non-breast cancer deaths after RT

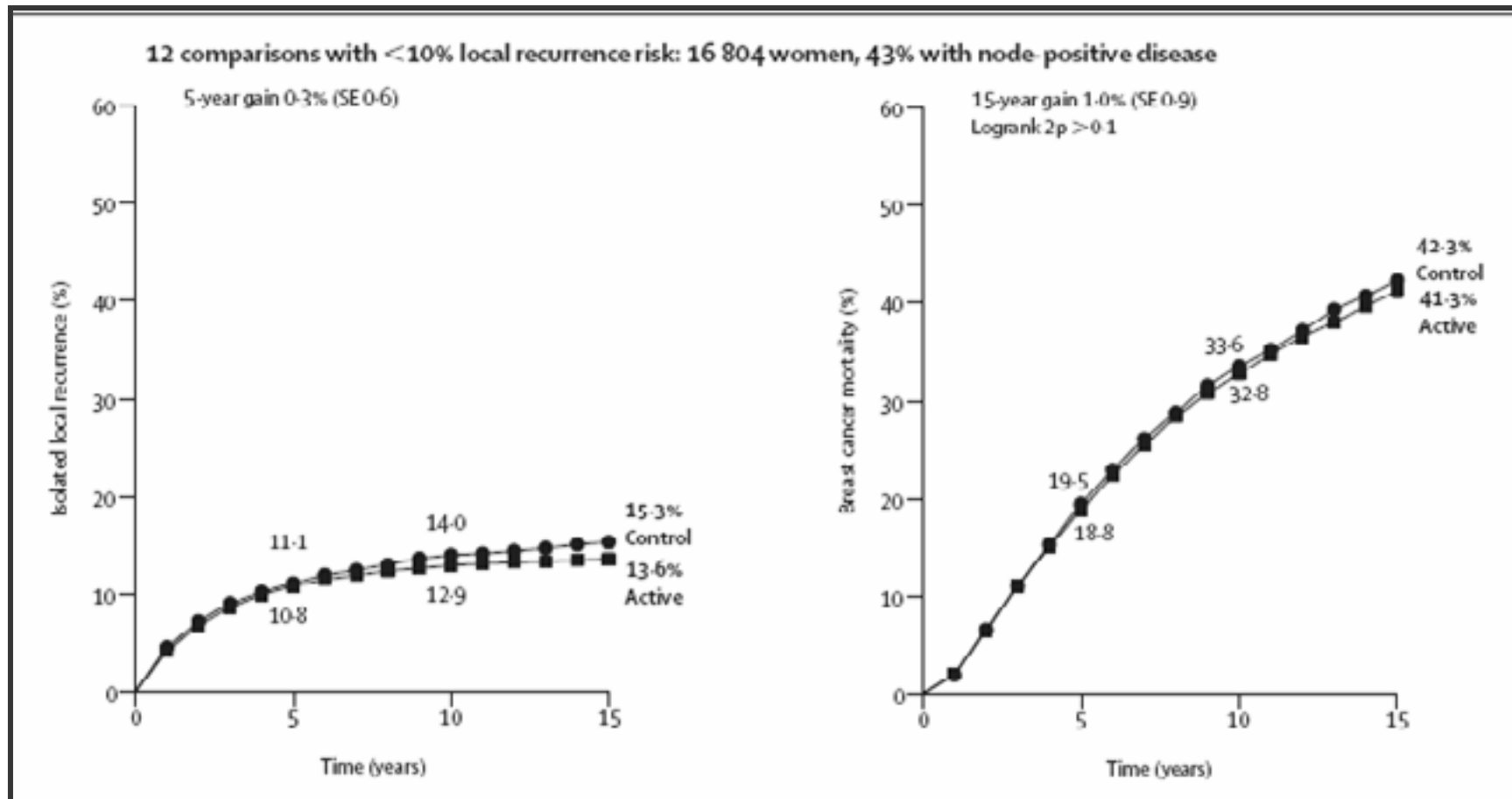
EBCTCG: Outcome By Nodal Status



EBCTCG: 5-year Local Recurrence Risk by Age

Age (years)	5-year local recurrence risk (%) in trials of:	
	(a) RT after BCS (node-negative)	
	RT versus control	Absolute reduction (SE)
<50	11 vs 33	22 (2)
50-59	7 vs 23	16 (2)
60-69	4 vs 16	12 (1)
≥70	3 vs 13	11 (2)

EBCTCG: Outcome By Initial Risk Of Local Recurrence



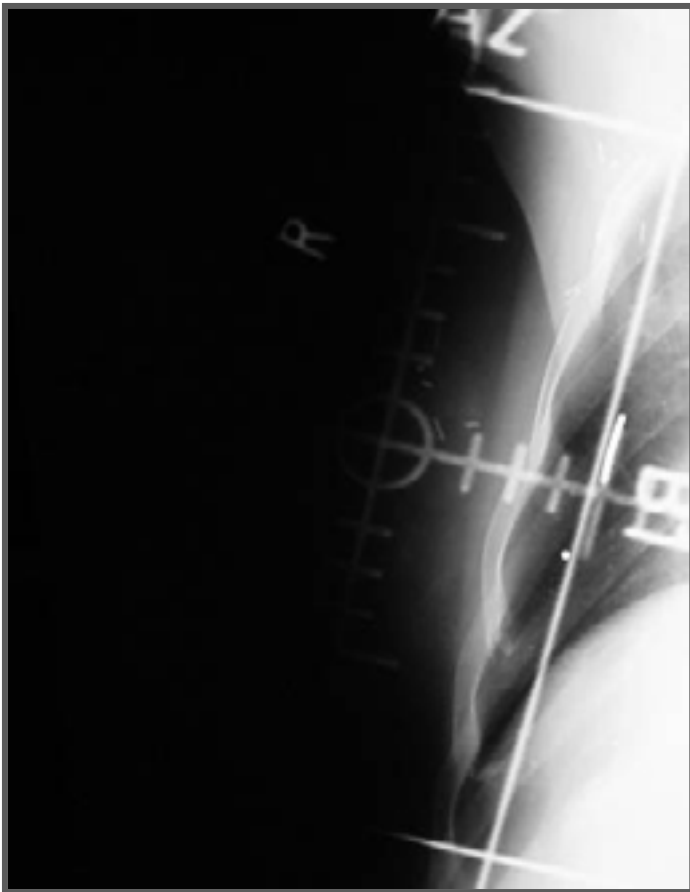
Local Control of Disease in the Breast

- Maintains intact sensate breast
 - Minimizes disfigurement
 - Facilitates adjustment to disease
- Modest impact on cancer specific survival at 10-15 years
- Diminished impact on cancer specific survival:
 - $< 10\%$ baseline risk of local recurrend after lumpectomy
 - Age > 60 yo

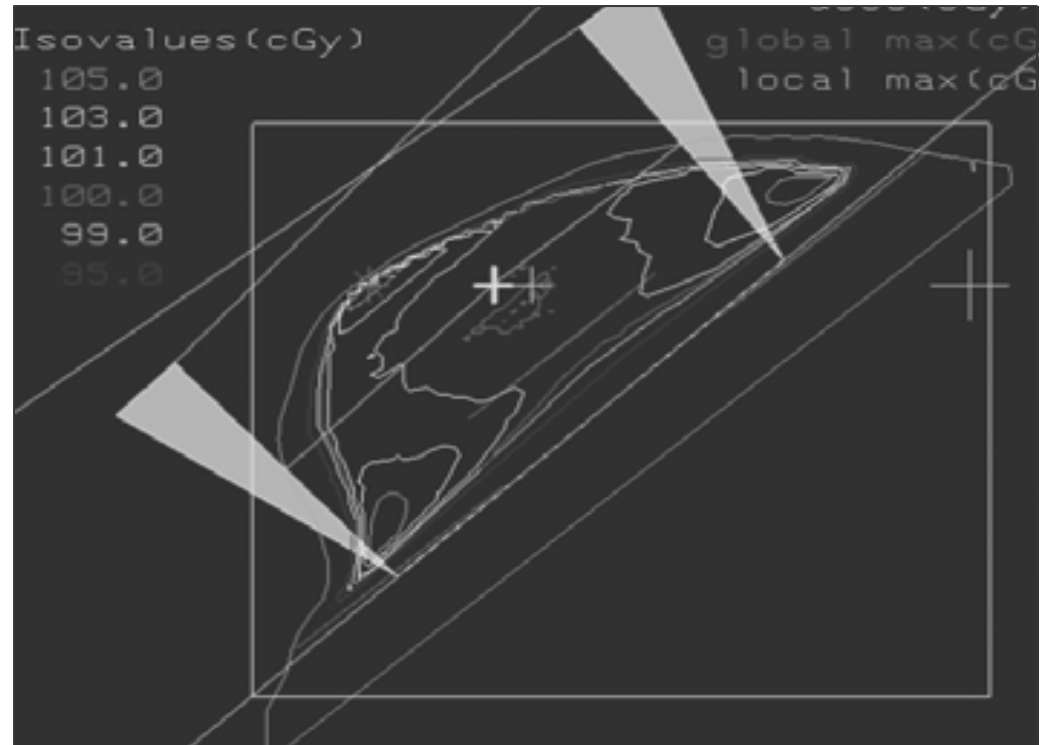
Can we improve the delivery of
WBI?

2-D Treatment planning for breast cancer

Fluoroscopic simulation



Central plane dosimetry



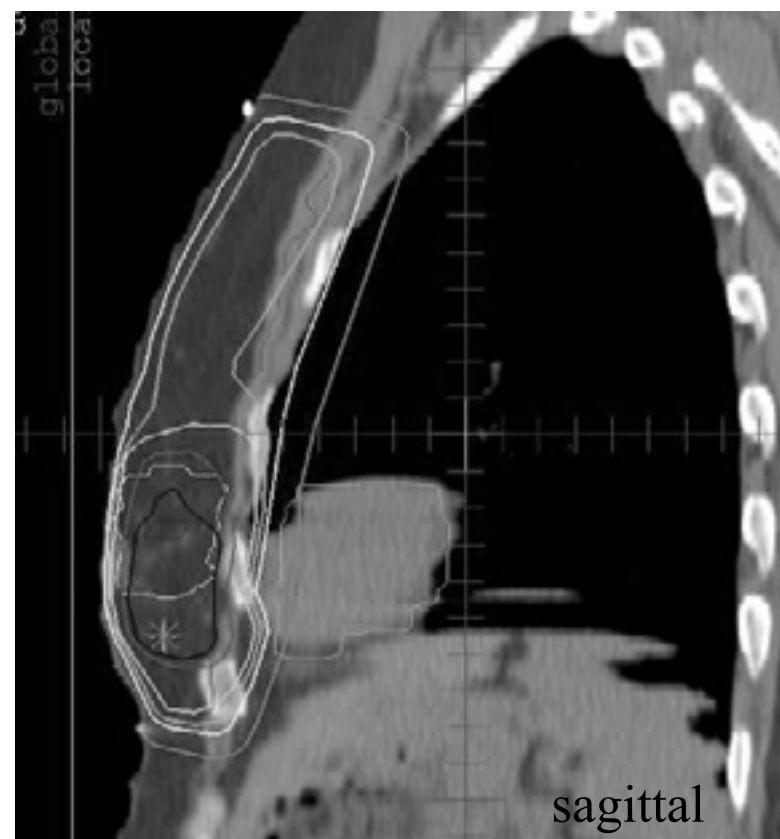
Toxicity from Breast Radiation

Acute		Late	
Common and Temporary		Uncommon and Permanent	
Skin Redness	90%	Fibrosis	15%
Dry desquamation	30-50%	Hyper pigmentation	10%
Moist desquamation	10%	Pneumonitis	< 0.5%
Pain – OTC analgesics	25%	Rib Fracture	< 0.1%
Pain – Narcotics	9%	Secondary Malignancy	0.01%
Fatigue	70%	Cardiac morbidity	0.1- 1%
		Cosmetic failure	15%

Radiation factors associated with late fibrosis and cosmetic failure

<i>Institution</i>	<i>N</i>	<i>F/U yrs</i>	<i>Excellent (%)</i>	<i>Good (%)</i>	<i>Fair (%)</i>	<i>Poor (%)</i>	<i>Radiation factors associated with poorer cosmesis</i>
Tufts U.	234	4.2	41	47	9	3	- Heterogeneous RT dose - Boost - Use of > 2 Fields
Harvard/ JCRT							
< 1981	504	8.9	58	28	10	4	- Breast dose > 50 Gy - Use of > 2 fields
1982-85	655	5.6	73	23	3.5	0.5	- Boost dose > 18 Gy - Implant boost
Washington U.	458	4.4	38	44	15	4	- Use of > 2 fields - Breast dose > 50 Gy - No compensator filters

Image-based Conformal Radiation Therapy: improve targeting and avoidance of normal tissues



Left Breast

3-DCRT for left prone breast radiation:

Improved targeting and avoidance of lung

Sagittal



Transaxial



Accelerated Whole Breast Irradiation: Reducing the burden of care

Canadian Phase III Randomized Trial:

42.5 Gy – 16 fractions – 22 days vs.

50 Gy – 25 fractions – 35 days

- 1,234 patients
- ER positive - 71%
- T1 – T2, N 0 (80% T1)
- Median F/U: 69 months

	In-Breast Recurrence (%)	Excellent/ good Cosmesis (%)
Accelerated WBI	2.8	76.8
Standard WBI	3.2	77.4

Accelerated Whole Breast Irradiation:

A Phase II clinical trial of a 4 week course of RT for breast cancer using hypo fractionated IMRT with a concomitant boost.

- 4 week course – 20 treatments
 - 45 Gy whole breast dose
 - 56 Gy boost dose
- Results:
 - 16 patients treated
 - Acute toxicity: Grade I 57%, Grade II 43%

Does the entire breast need to be irradiated to achieve comparable local control?

Accelerated Partial Breast Irradiation (PBI): *Definition*

- Delivery of larger doses/fraction of radiation therapy (RT) to the lumpectomy cavity (plus 1-2 cm margin) after breast conserving surgery using brachytherapy or external beam irradiation techniques
- Complete RT in < 5-8 days after lumpectomy instead of 6-7 weeks

In-Breast cancer recurrences after breast conserving therapy: Majority occur around lumpectomy site

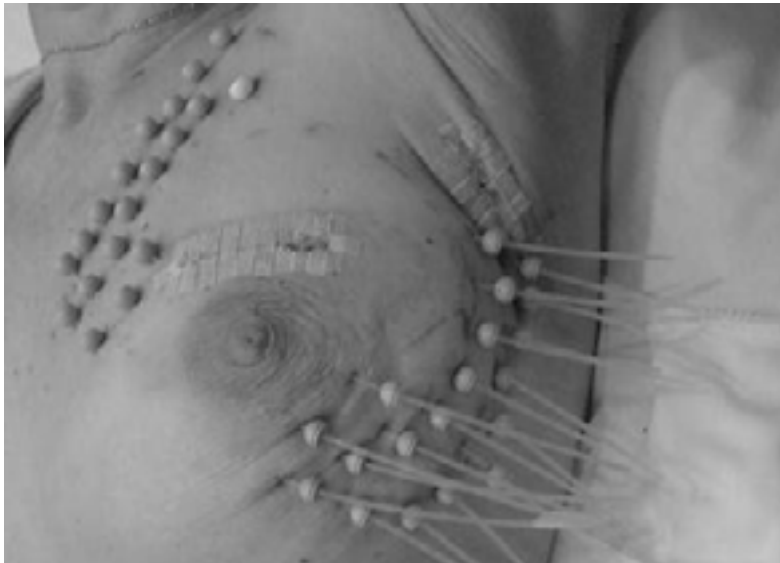
“Elsewhere” In-Breast Cancer Recurrences

<i>Randomized Trials (BCS vs. BCS+RT)</i>	<i># Cases</i>	<i>Follow-up (mos)</i>	<i>Failure Outside Lumpectomy Region</i>			
			<i><u>No XRT</u></i>		<i><u>XRT</u></i>	
			<i>Crude</i>	<i>%</i>	<i>Crude</i>	<i>%</i>
Ontario	837	43	15/421	3.5	4/416	0.9
Milan III	579	109	8/280	2.8	2/299	0.6
NSABP B06	1265	144	17/636	2.7	24/629	3.8
Uppsala-Orebro	381	33	3/194	1.5	1/187	0.5

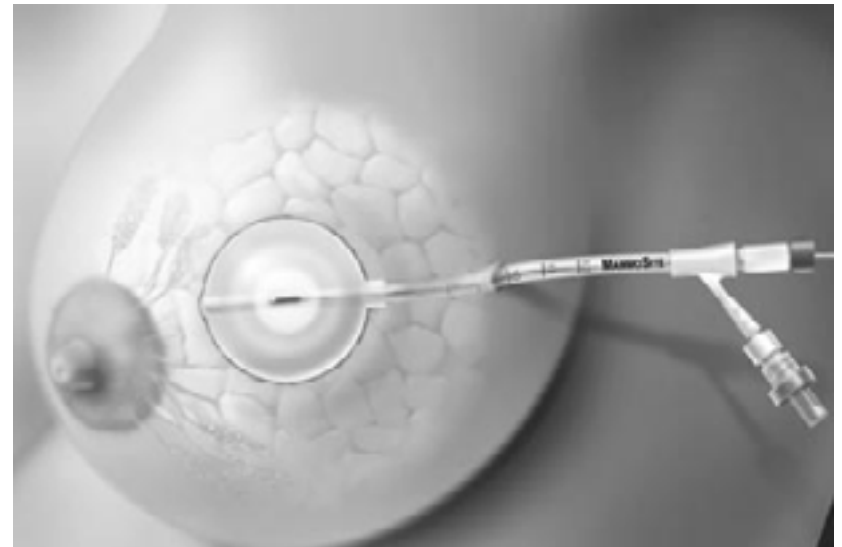
Potential Benefits of Partial Breast Irradiation

- Reduce time and inconvenience of BCT
- Improve documented underutilization of breast conserving therapy (BCT)?
- Potentially reduce acute and chronic toxicity
- Reduce burden of care for patients
- Eliminate scheduling problems with chemotherapy

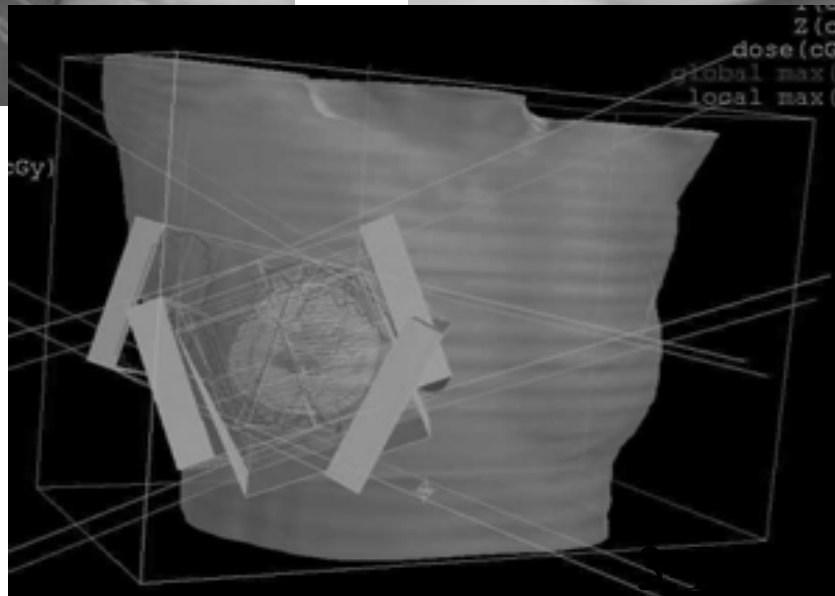
Three Established Methods For PBI



Multi Catheter



Mammosite®



formal

RTOG 95-17: A phase I/II trial to evaluate multi-catheter brachytherapy as the sole method of radiation therapy for stage I - II Breast Cancer

- 99 patients accrued between 1997- 2000
 - › 66 HDR 3.4 Gy x 10 BID over 5 days
 - › 33 LDR 45 Gy over 4.5 days
- 10 institutions
- Adequate coverage of target volume 97%
- Implants: 2 planes -74, > 2 planes - 24,
1 plane - 1

RTOG 95-17: Multi-catheter PBI

- Results updated at ASCO '04, Submitted ASTRO '06
- Median f/u 3.7 yrs (range 0.6-5.7)
- Patients:
 - Age: 78% > 50 yo
 - T-1: 88%
 - N-1: 21%
- Actuarial 4-yr breast and nodal recurrence rate of 3%
 - Local failure 3 pts
 - Nodal failure 2 pts
- Contralateral failure = 3 pts

Dose Distribution of MultiCatheter PBI



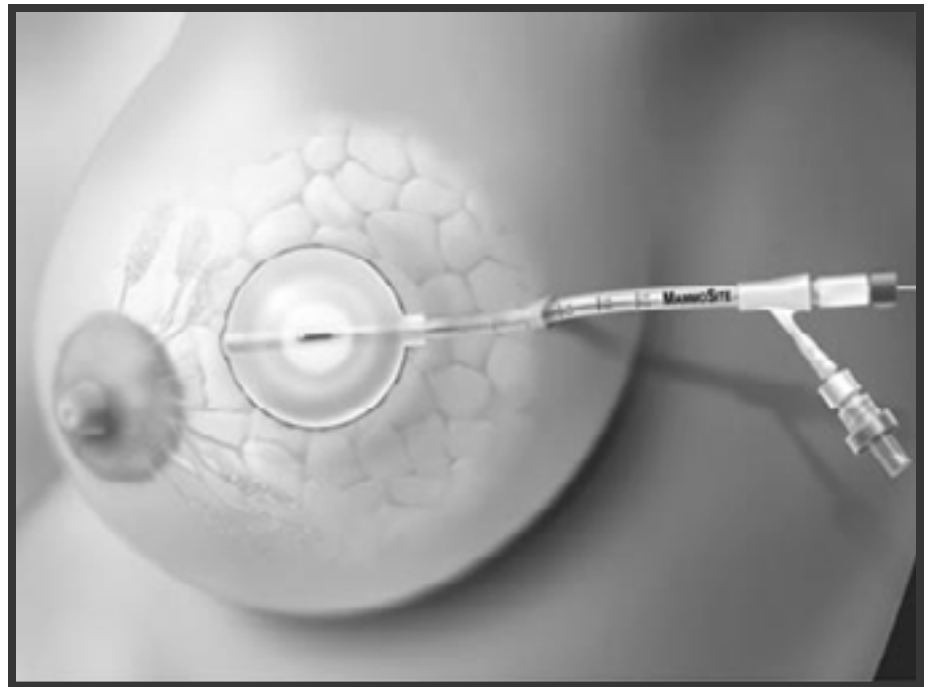
MultiCatheter PBI: HDR/ LDR Summary

<i>Institution</i>	<i>Pt. No.</i>	<i>Median age</i>	<i>F/U mo.</i>	<i>T size (cm) median</i>	<i>N+ %</i>	<i>ER+ %</i>	<i>Tam %</i>	<i>LR %</i>	<i>Exc/ good Cosmesis %</i>
Oschner	51	63	75	1.4	18	-	-	2	-
Beaumont	199	65	65	1.1	12	-	57	1.2	99
Tufts-NEMC	32	63	33	1.3	9	79	61	3	88
VCU	44	62	42	1.2	18	-	66	0	80
Nat. Inst. Onc. Budapest	45	56	81	1.2	2	82	16	6.7	97
Guys Cs 137	49	58	75	2.5	46	-	-	18	81
Average:		61 yo	61 mo.	1.4 cm	17.5%			5%	89%

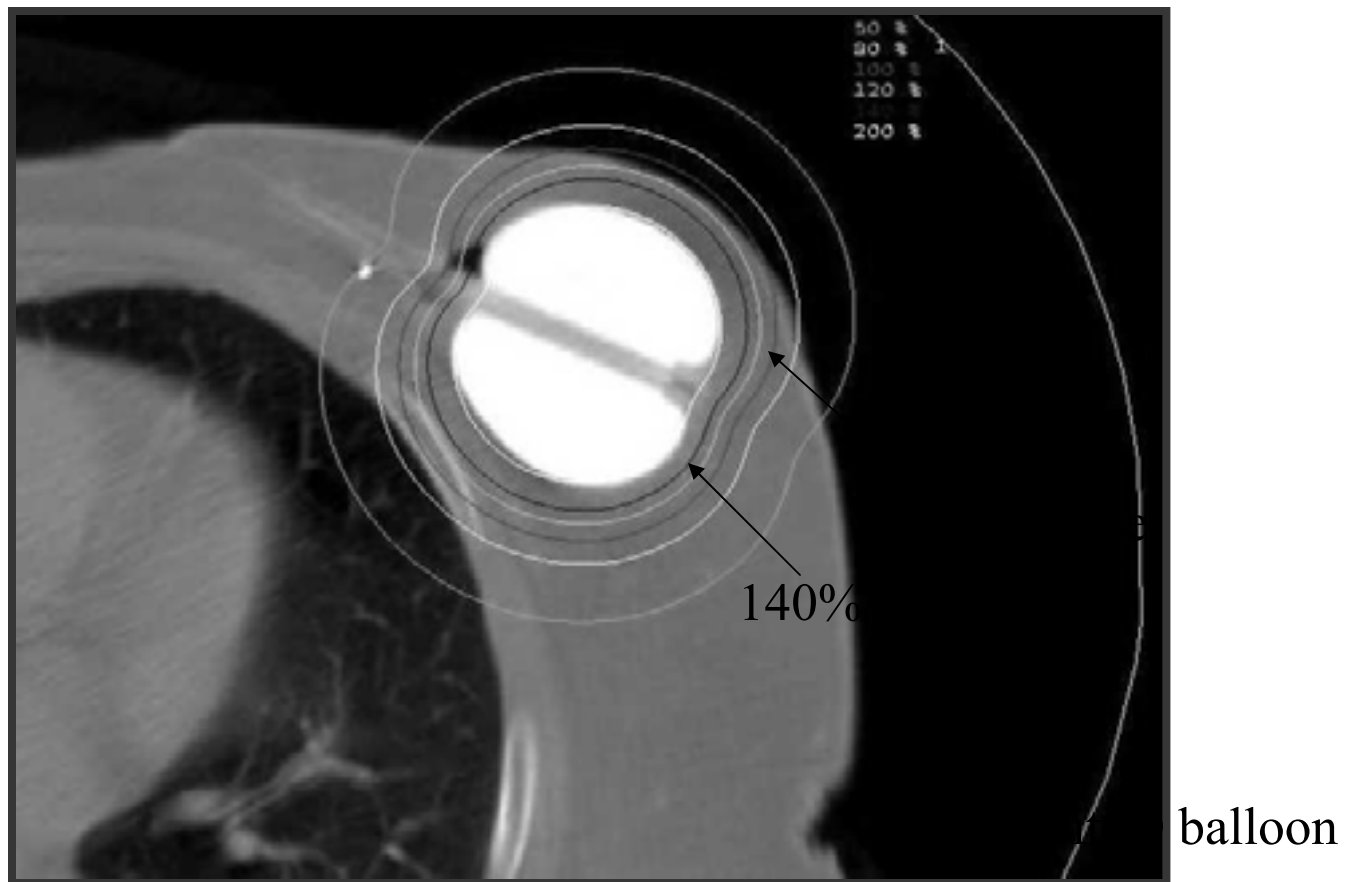
MammoSite PBI

Mammosite[®] Breast Brachytherapy Applicator

- Simplified brachytherapy method for PBI
- Dual lumen single catheter with expandable balloon at end
- Balloon expands to fill the lumpectomy cavity
- Radiation dose prescribed to 1 cm beyond balloon surface
- FDA approval May 2002
- > 15,000 used



Dose Distribution for Mammosite PBI



MammoSite[®] Phase II Study- 4 year Results

Keisch, et al

Overview:

43 patients enrolled 5/2000- 10/2001
34 Gy in 10 fractions over 5 days
dose 1 cm from applicator surface

Results:

Median follow-up 48 months

No local recurrences

80% good/ excellent cosmesis

Cosmesis correlates with skin spacing < 7 mm

98 % patient satisfaction

ASTRO 2005

MammoSite PBI: summary

<i>Institution</i>	<i>PL No.</i>	<i>Median age</i>	<i>F/U mo.</i>	<i>T size (cm) median</i>	<i>N+ %</i>	<i>ER+ %</i>	<i>Local relapse %</i>	<i>Excel/good Cosmesis %</i>
Initial Multi-Institutional	43	69	48	1.0	0	-	0	80
Rush Univ.	112	64	-	88% Tis-T-1	7	-	0	80
Tufts-NEMC/ VCU	28	62	19	1.1	0	100	0	86
St. Vincent Hospital	32	62	11	97% T-1	9	94	-	86
Average:		64 y	26 mo	1 cm	4%		0%	83%

ASBS MammoSite[®] Registry Trial

- 5/4/2002 – 7/30/2004
- 1270 patients evaluated, 87 facilities, 227 investigators
- Median F/U: 5 months
- 95% excellent/ good cosmesis

Patient Population

- median age: 65
- median T-size: 1 cm
- 3.1% node positive

Technique:

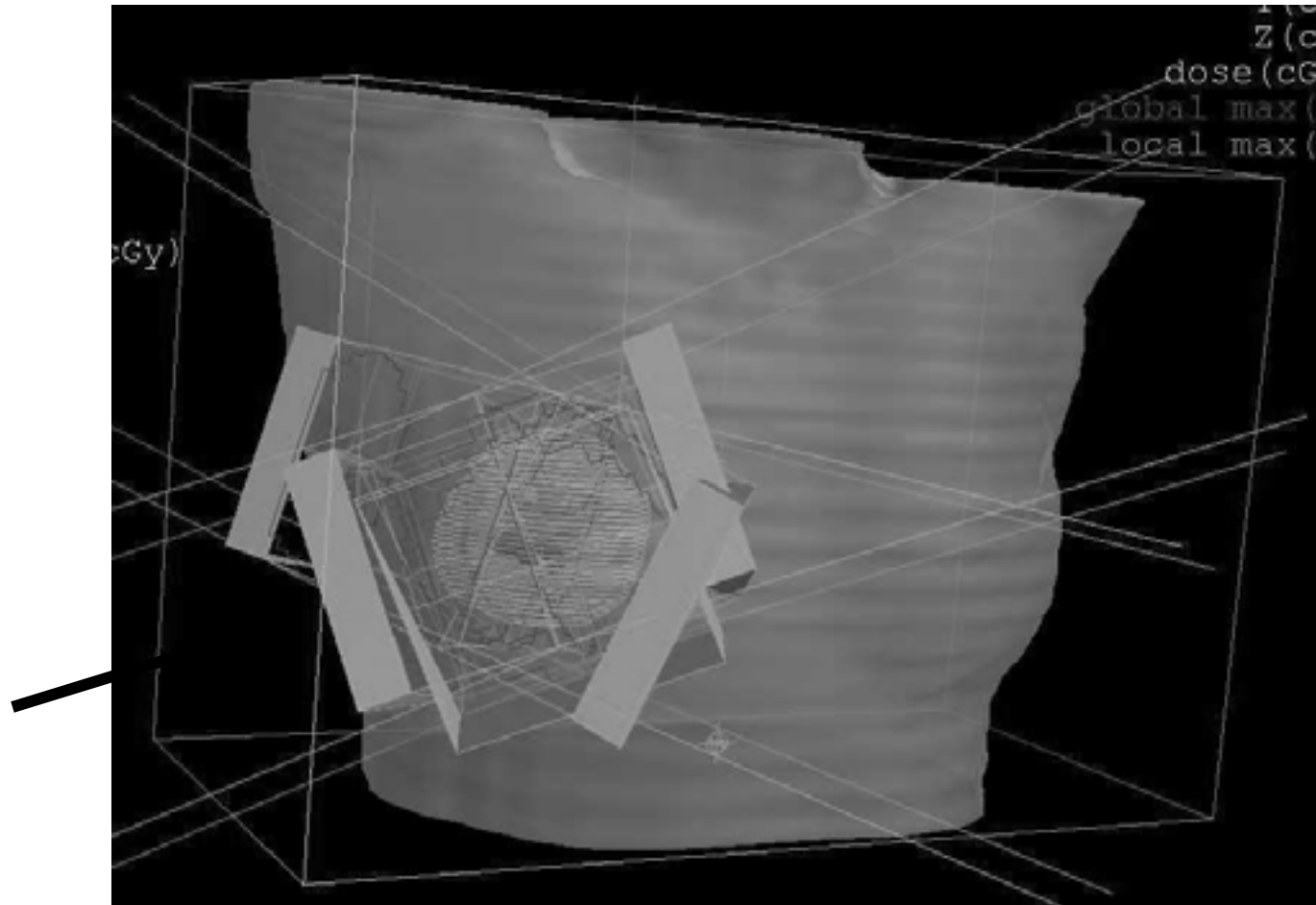
- Open cavity 45%
Closed cavity 55%
- 89% 7 mm minimum skin spacing
- 95% 34Gy/10 fractions

3-DCRT PBI

RTOG 0319: A Phase I/II trial to Evaluate 3D-CRT PBI for Stage I and II Breast Carcinoma

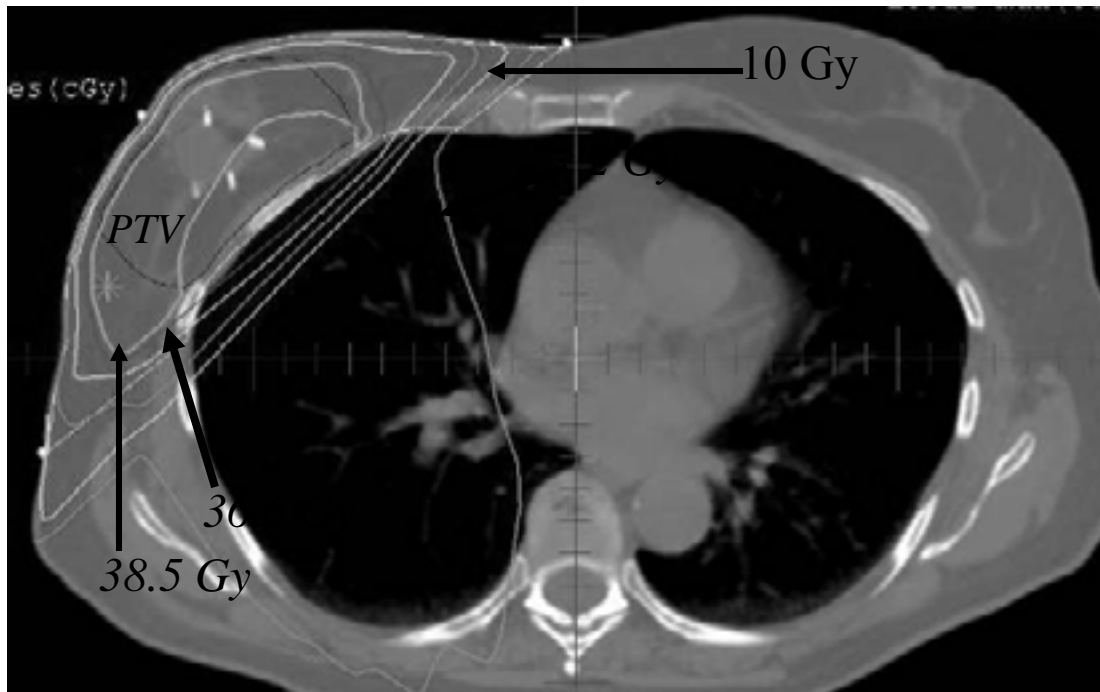
- 8/15/03 – 4/13/04
- 58 pts. enrolled, 42 evaluated, 19 institutions
- Q/A: 100% acceptable PTV coverage
90% acceptable dose constraints
- Median age: 61 years (31-83)
- Median T size: 0.85 cm (0.1 – 2.6 cm)
- Stage I 86%
- Toxicity: Grade I 42%, Grade II 21%

PBI: 3D-CRT Beam Arrangement



3.85 Gy BID x 10 fractions

3D-CRT PBI Isodose Distribution



3-DCRT PBI: Summary

<i>Institution</i>	<i>Pt. No.</i>	<i>Median age</i>	<i>F/U mo.</i>	<i>T-size (cm) median</i>	<i>N+ %</i>	<i>ER+ %</i>	<i>Local relapse %</i>
Beaumont	31	61	10	0.9	0	-	0
NYU	47	67	18	0.9	0	97.9	0
RTOG 0319	42	61	-	0.9	-	-	0
Average:		63 y	14 mo.	0.9 cm	0 %		0 %

NSABP B-39/RTOG 0413 Trial

Phase III

Stage 0, I-II breast cancer treated by lumpectomy

Randomization

WBI

- 50-50.4 Gy (1.8-2.0 Gy)
Fractions to the whole breast
followed by boost to ≥ 60 Gy

PBI

- 34 Gy in 3.4 Gy fxs bid
Mammosite® or
interstitial brachytherapy
OR
• 38.5 Gy in 3.85 Gy fxs
3D-CRT

NSABP B39/ RTOG 0413

Phase III Trial

- Sample size - 3000 patients
- Projected accrual 2.5 years
- Randomization stratified by
 - Stage (DCIS, node neg, node pos)
 - Age (less than 50, 50+)
 - ER-negative, ER-positive
 - Chemotherapy intention
- Rigorous Q/A for PBI methods: rapid review for first case, timely review for next 4.

Endpoints

- Primary endpoint: in-breast tumor recurrence
- Secondary:
 - Distant disease-free survival
 - Overall survival
 - QOL: Cosmesis, fatigue, symptoms, burden of care

NSABP/RTOG Phase III Trial

Eligibility (selected)

- Stage 0, I, II breast cancer
- DCS or invasive adenocarcinoma
- Tumor size ≤ 3 cm (unifocal)
- N-0, N-1 (≤ 3 positive nodes)
- Negative margins (NSABP)
- Life expectancy of at least 10 years
- MUST be randomized within *42 days* of last breast/axillary surgery
- Lumpectomy/whole breast ratio on CT $\leq 30\%$

NSABP 39 / RTOG 0413

- March 21, 2005 – open for accrual
- April 2006
 - ▶ 250 institutions credentialed for accrual
 - ▶ 1100 patients accrued
 - ▶ PBI methods: 74% 3-DCRT, 16% MammoSite, and 10% MultiCatheter

Other Randomized trials:

- GEC-ESTRO Breast Cancer Working Group
 - Phase III trial
 - Accrual goal: 1170
 - WBI: 50-50.4 Gy WB + 10 Gy boost
 - PBI: Brachytherapy only (HDR/PDR)
 - Open May 2004

Intra-operative PBI: ELIOT

- Intraoperative electrons at time of resection:
- Phase I-II: Dose escalation trial
 - 58 cases
 - Max. tolerated dose: 21 Gy
 - 3-12 MeV electrons, dose rate 15-20 cGy/min.
 - 4 year F/u: 3 in-breast failures
- Phase III: ELIOT 21Gy vs. 50 Gy WBI + Boost
 - Opened 2000
 - 824 patients to be accrued

Intra-operative PBI: TARGIT

- Intraoperative radiation with 50 kV
 - 5 Gy at 1 cm, 10 Gy at 0.5 cm, 20 Gy at surface
 - 25-30 minute treatment time
- Pilot study:
 - 227 patients “boost” + WBI
 - 22 patients sole modality PBI
 - Median F/U 22 months: 2 in-breast failures
- Phase III trial
 - Opened 2000
 - Accrual goal 2, 232

Conclusions

- Breast radiation following lumpectomy necessary in most early stage breast cancer patients to preserve mastectomy-free survival and impact long term cancer specific survival
- The optimal delivery of radiation to this cohort of breast conservation patients is evolving (e.g. IMRT Accelerated WBI, PBI) and requires prospective clinical studies to verify equivalent efficacy
- Low risk breast conservation patients may be able to maintain mastectomy free and cancer specific survival with omission of RT following lumpectomy