BrachyNext
Working Together to Shape the Future of
Brachytherapy

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Brachytherapy

Why Choose Brachytherapy and Not External Beam RT or IORT?

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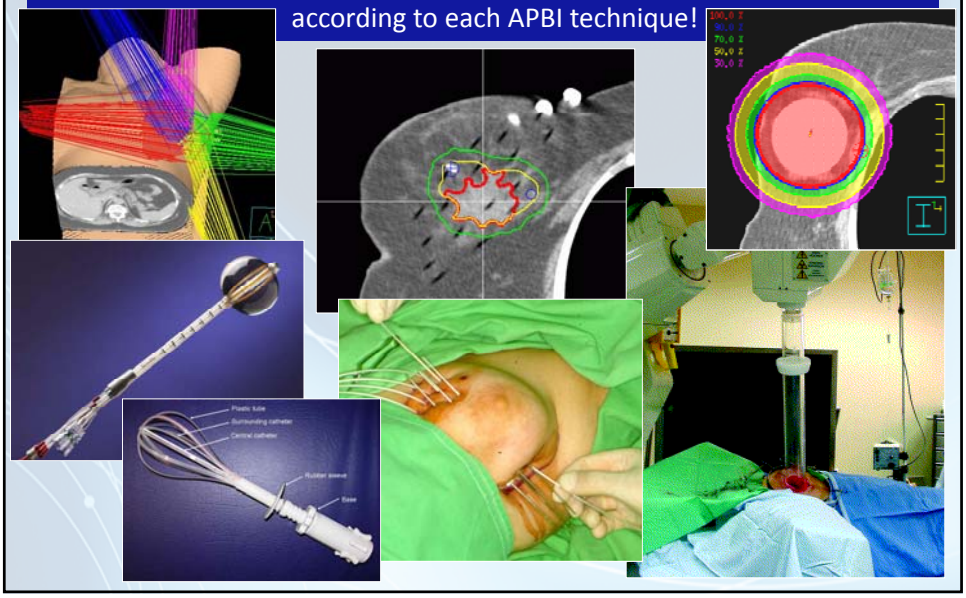
Disclosure

- Csaba Polgár, MD, PhD, MSc, does not have any financial relationships or products or devices with any commercial interest related to the content of this activity of any amount during the past 12 months.

Outline of the Presentation

- Why to Choose Brachytherapy? – Overview of clinical results with:
  - Multicatheter BT
  - Balloon-based BT
- Why Not to Choose External Beam RT? – Critical review of clinical results
- Why Not to Choose IORT? – Critical review of clinical results
  - ELIOT Trial
  - TARGIT Trial

- Motto: Before implementation of APBI into routine clinical practice, in addition to non-inferior local control and survival results in comparison with WBI, at least a comparable toxicity profile should be documented according to each APBI technique!



Accelerated partial breast irradiation (APBI)trials with ≥ 4 years FUP

- Early APBI series (80's-early 90's) - 7 trials:
  - 2D teletherapy – 2 trials
  - LDR, MDR & HDR brachytherapy – 5 trials

- Contemporary APBI series – 25 trials:
  - Multicatheter brachytherapy – 12 trials
  - MammoSite brachytherapy – 4 trials
  - 3D-CRT & IMRT – 6 trials
  - IORT – 3 trials

- Phase III APBI clinical studies – 8 trials

Results of Early APBI studies

Institute	Study period	APBI technique	Patient No.	Median FUP (y)	Crude LR%	Annual LR%
Christie Hospital*	1982-87	ELE	353	8	20	2.5
Guy's Hospital I.	1987-88	LDR BT – ^{192}Ir	27	6	37	6.2
Cookridge Hospital*	1986-90	EBI	84	8	12	1.5
Guy's Hospital II.	1990-92	MDR BT – ^{137}Cs	49	6.3	18	2.9
Uzsoki Hospital	1987-92	MDR BT – ^{60}Co	70	12	24	2.0
University Florence	1989-93	LDR BT – ^{192}Ir	115	4.2	6	1.4
London Reg. Cancer Center	1992-96	HDR BT	39	7.6	15	2.0
All pts.	**1982-93**		**698**	**4.2-12**	**6-37**	**1.4-6.2**

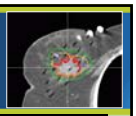
* Phase III trial

Patient "Selection" and Results of Early APBI Studies

Criteria	Christie Hosp.	Guy's Hosp. I.	Cookridge Hosp.	Guy's Hosp. II.	Uzsoki Hosp.	Univ. Florence	London Reg. Ca. C.
T-size	≤ 4 cm	≤ 5 cm	≤ 4.5 cm	≤ 4 cm	≤ 5 cm	≤ 5 cm	≤ 4.5 cm
Margins	10% pos. 90% UK	56% pos. 7% UK	100% UK	43% pos.	100% UK	8% pos. 7% UK	neg., 31% close
EIC	yes	41%	yes	yes	yes	yes	8%
Nodes	100% pNx	44% N+	41% N+	44% N+	4% N+ 80% pNx	38% N+	15% N+ 5% pNx
Age	Any	Any	Any	> 40 year	Any	Any	Any
LR rate	20%	37%	12%	18%	24%	6%	15%
Annual LR	2.5%	6.2%	1.5%	2.9%	2%	1.4%	2.0%

APBI with outdated techniques for unselected pts. ➡ Annual LR: 1.4-6.2%

Results of Contemporary APBI Studies (Median FUP ≥ 4 y) – Multicatheter Brachytherapy Series



Institute	Study period	APBI technique	Patient No.	Median FUP (ys)	Crude LR%	Annual LR%
Interstitial brachytherapy series						
Oschner Clinic	1992-93	LDR/HDR BT	51	6.25	2	0.32
W. Beaumont Hospital	l992-2001	LDR/HDR BT	199	10.7	5	0.47
Örebro Medical Center	1993-2003	PDR BT	51	7.2	5.9	0.82
Budapest	1996-98	HDR BT	45	13.8	11.1	0.80
RTOG 95-17	1997-2000	LDR/HDR BT	99	7	6.1	0.87
Tufts University	1997-2001	HDR BT	33	5.9	9.1	1.54
Harvard, Boston	1997-2001	LDR BT	50	11.2	12	1.07
Budapest Phase III	1998-2004	HDR BT/ELE	128	10.2	5.5	0.53
Ninewells Hospital	-1999	LDR BT	11	5.6	0	0
German-Austrian	2000-05	PDR/HDR BT	274	5.2	2.9	0.56
University Navarra	2000-07	HDR BT	26	4.4	3.8	0.86
Washington University	2002-07	HDR BT	202	>5	2.5	0.50
All patients	**1992-2007**		**1169**	**4.4-13.8**	**0-11.1**	**0-1.54**

Patient Selection and Results in Contemporary APBI Studies

Criteria	Beaumont Hospital	Örebro	Budapest Phase III	German-Austrian Phase II
T-size	≤ 3 cm	≤ 4.2 cm	≤ 2 cm	≤ 3 cm
Margins	≥ 2 mm	clear	clear (≥ 2 mm; 1999-)	≥ 2 mm
Unifocal	+	+	+	+
EIC	-	-	-	-
DCIS	-	-	-	-
Nodes	< 4 pos. (ECE neg.)	< 4 pos.	N0-N1mi (micromet.)	N0-N1mi (micromet.)
Age	≥ 40 y	≥ 40 y	≥ 40 y (2001-)	> 35 y
Actuarial LR rate	5% (12-year)	4% (7-year)	5.9% (10-year)	5% (8-year)
Annual LR	0.42%	0.57%	0.59%	0.63%

APBI for selected pts. → Annual LR ~ 0.5%

Twelve-year clinical outcomes and patterns of failure with accelerated partial breast irradiation versus whole-breast irradiation: Results of a matched-pair analysis

IJROBP 2011;100:210-214

Chirag Shah, John Vito Antonucci, John Ben Wilkinson, Michelle Wallace, Mihai Ghilezan, Peter Chen, Kenneth Lewis, Christina Mitchell, Frank Vicini *

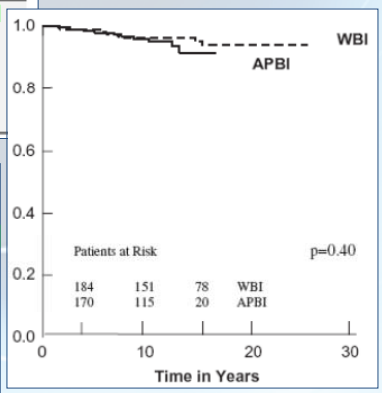
Department of Radiation Oncology, William Beaumont Hospital, MI, USA

Twelve-year outcomes between WBI and APBI patients.

12-year actuarial	WBI (%)	Interstitial APBI (%)	p-Value
LR	3.8	5.0	0.40
RR	0	1.1	0.15
DFS	87	91	0.30
DM	10.1	4.5	0.05*
CSS	93	95	0.28
OS	78	71	0.06

Univariate analysis of factors potentially associated local recurrence.

Characteristic	All patients	APBI	WBI
Age	0.02*	0.66	0.003*
ER status	0.07	0.09	0.42
PR status	0.39	0.12	0.73
Her-2 status	–	0.31	–
Tumor size	0.74	0.53	0.92
Hormonal therapy	0.42	0.03*	0.16
Chemotherapy	0.96	0.96	0.97
Margins	0.64	0.96	0.98
Nodal status	0.73	0.85	0.74
ASTRO consensus group	–	0.88	–



Pulsed dose rate brachytherapy as the sole adjuvant radiotherapy after breast-conserving surgery of T1–T2 breast cancer: First long time results from a clinical study

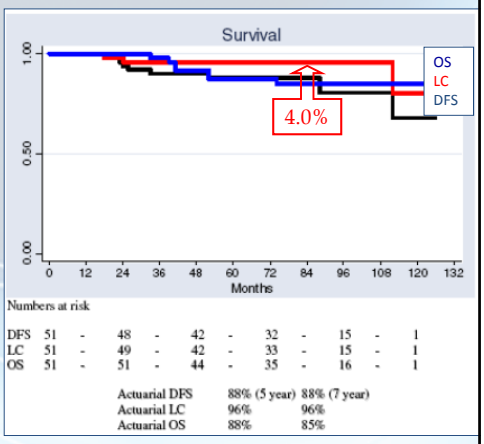
Radiother Oncol 2009;90:30-35.

Bengt Johansson [a,*], Leif Karlsson [b], Göran Liljegren [c], Lennart Hardell [a], Jan Persliden [b]

[a] *Department of Oncology, Örebro University Hospital and Örebro University, Sweden*

- 50 patients
  - 50 Gy PDR BT
- Median FUP: 7.2 years
- 7-y actuarial LR rate: 4%
- G3 fibrosis: 8%
- Telangiectasia: 22%
- Fat necrosis: 20%
- Excellent/good cosmesis: 56%

PTV = tumor bed + 3 cm margin

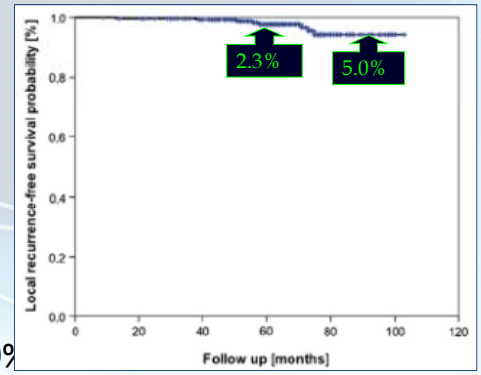


ACCELERATED PARTIAL BREAST IRRADIATION: 5-YEAR RESULTS OF THE GERMAN-AUSTRIAN MULTICENTER PHASE II TRIAL USING INTERSTITIAL MULTICATHETER BRACHYTHERAPY ALONE AFTER BREAST-CONSERVING SURGERY

IJROBP 2011;80:17-24

Vratislav Strnad, M.D.,* Guido Hildebrandt, M.D.,†‡ Richard Pötter, M.D.,§ Josef Hammer, M.D.,¶ Marion Hindemith, M.D.,† Alexandra Resch, M.D.,§ Kurt Spiegl, M.D.,¶ Michael Lotter, Ph.D.,* Wolfgang Uter, M.D.,‖ Mayada Bani,** Rolf-Dieter Kortmann, M.D.,† Matthias W. Beckmann, M.D.,** Rainer Fietkau, M.D.,* and Oliver J. Ott, M.D.*

- 274 patients
  - 50 Gy PDR or 8x4 Gy HDR BT
- 5-y actuarial LR rate: 2.3%
- 8-y actuarial LR rate: 5.0%
- G3 telangiectasia: 2.2%
- G3 fibrosis: 0.4%
- Fat necrosis: 5.1%
- Excellent/good cosmesis: 90%



ACCELERATED PARTIAL BREAST IRRADIATION WITH INTERSTITIAL IMPLANTS: RISK FACTORS ASSOCIATED WITH INCREASED LOCAL RECURRENCE

IJROBP 2011;80:1458-63

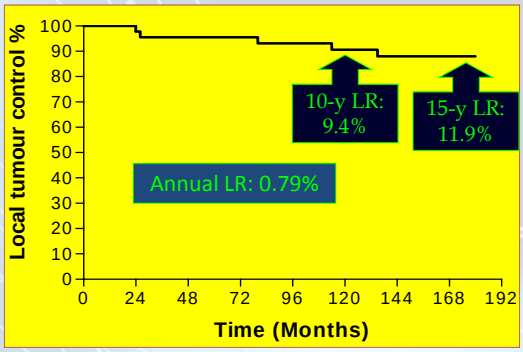
Oliver J. Ott, M.D.,* Guido Hildebrandt, M.D.,†‡ Richard Pötter, M.D.,§ Josef Hammer, M.D.,‖ Marion Hindemith, M.D.,† Alexandra Resch, M.D.,§ Kurt Spiegl, M.D.,‖ Michael Lotter, Ph.D.,* Wolfgang Uter, M.D.,¶ Rolf-Dieter Kortmann, M.D.,† Michael Schrauder, M.D.,# Matthias W. Beckmann, M.D.,# Rainer Fietkau, M.D.,* and Vratislav Strnad, M.D.*

Characteristic	5-y LR % (n)	p-value
Age		0.03
≥ 50 years	1.1% (4/225)	
< 50 years	7.5% (4/49)	
Hormonal therapy		0.0087
No	15.1% (4/24)	
Yes	1.0% (4/250)	

ER & PgR status, tumor size, histologic type, pN status, HG, and HER-2 status had no significant impact on LR rate!

Budapest Phase II APBI Study – Updated 15-year Actuarial Results*

- 45 patients
  - 7 x 4.33 HDR BT (n = 8) or
  - 7 x 5.2 Gy HDR BT (n = 37)
- Median FUP = 13.8 years



Radiother Oncol 2010;94:274-9

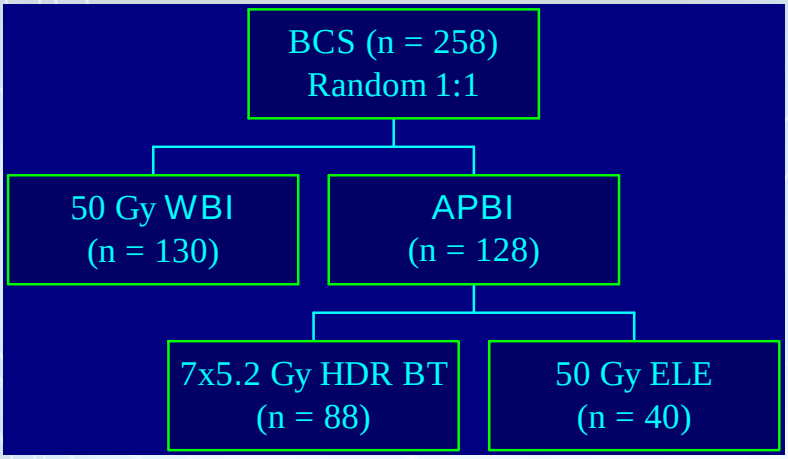
*Acta Medica Marisiensis 2011;57:717-720

Variable	N (%)	
Cosmetic results		
Excellent	12 (26.7%)	80%
Good	24 (53.3%)	
Fair	5 (11.1%)	
Poor	4 (8.9%)	
Skin side effects		
Grade 0	39 (86.7%)	
Grade 1	4 (8.9%)	
Grade 2	2 (4.4%)	
Grade 3	0 (0%)	
Fibrosis		
Grade 0	29 (64.4%)	
Grade 1	12 (26.7%)	
Grade 2	3 (6.7%)	
Grade 3	1 (2.2%)	
Fat necrosis		
Grade 0	26 (57.8%)	
Grade 1	9 (20.0%)	
Grade 2	9 (20.0%)	
Grade 3	0 (0%)	
Grade 4	1 (2.2%)	

Breast-conserving therapy with partial or whole breast irradiation: Ten-year results of the Budapest randomized trial

Radiother Oncol 2013;108:197-202

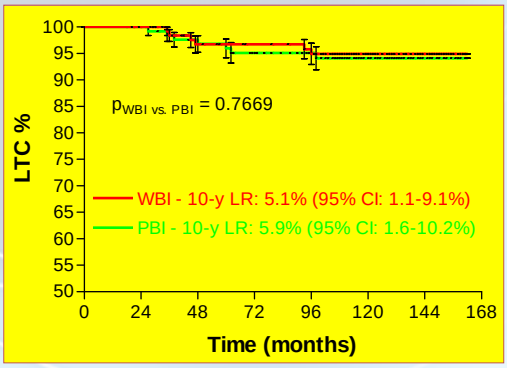
Csaba Polgár [a,*], János Fodor [a], Tibor Major [a], Zoltán Sulyok [b], Miklós Kásler [c]
[*] Center of Radiotherapy; [b] Center of Surgery; [c] National Institute of Oncology, Budapest, Hungary



Budapest Phase III APBI Study - 10-year Actuarial Results

Median FUP: 10.2 years

	WBI	APBI	p-value
LR	5.1%	5.9%	0.77
CLBC	6.4%	8.3%	0.56
RR	1.7%	2.4%	0.65
DM	11.5%	7.3%	0.61
DFS	84%	85%	0.97
OS	82%	80%	0.73
CSS	92%	94%	0.34



Annual LR rate:
APBI: 0.59%
WBI: 0.51%

Radiother Oncol 2013;108:197-202

Budapest Phase III Trial – Univariate Analysis of Prognostic Factors for LR

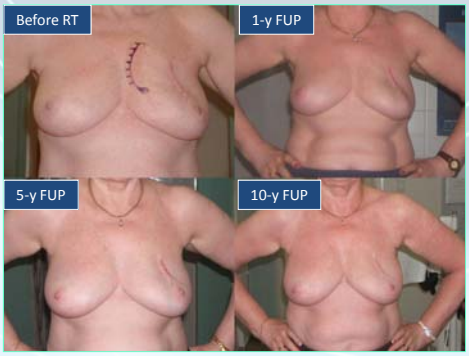
Menopausal status, ER & PgR status, tumor size, HG, NG and MAI had no significant impact on LR rate!

Characteristic	10-y LR % (n)	p-value	Hazard Ratio
Age		0.032	
> 40 years	4.8% (11/249)		1
≤ 40 years	22.2% (2/9)		5.20
Systemic therapy*		0.053	
No	10.1% (7/75)		1
Yes	3.6% (6/183)		0.58

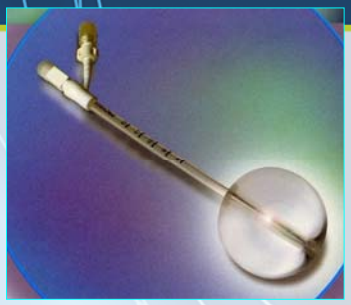
* Chemo and/or hormonal therapy

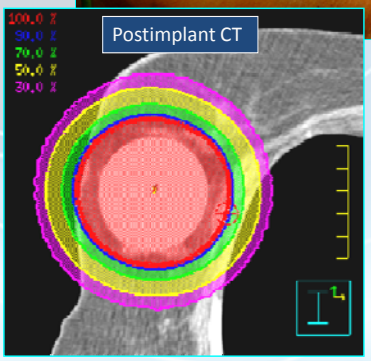
Budapest Phase III APBI Study – 10-year Cosmetic Results & Side-effects

	APBI - HDR BT	APBI - ELE	WBI	p-value
G 3 telangiectasia	0%	8%	3%	HDR BT vs. ELE = 0.0135
G 3 fibrosis	2%	0%	1%	NS
Exc./good cosmesis	85%	75%	62%	HDR BT vs. WBI = 0.003

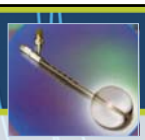


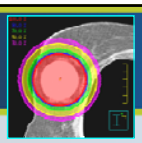
APBI - Intracavitary Balloon Brachytherapy



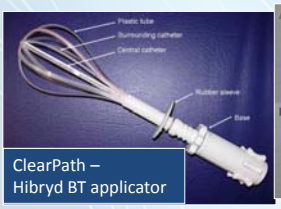


Results of APBI studies – MammoSite BT series

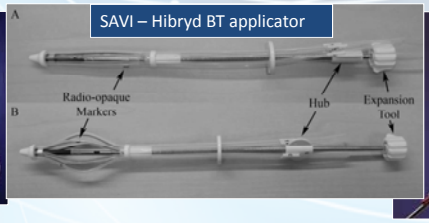




Institute	Patient No.	Median FUP (years)	Crude LR%	Telangiectasia %
FDA Trial	43	5.5	0	40%
Kiel/Budapest	11	5	0	64%
ASBS Registry Trial	1449	5.3	2.8%	NA
Univ. Pittsburgh	157	5.5	2.5%	27%
USA multicentric	483	2	1.3%	17%
Medicare	4617	1	NR	34%



ClearPath – Hibryd BT applicator



SAVI – Hibryd BT applicator

Contura – Hibryd BT applicator

Patterns of Use and Short-Term Complications of Breast Brachytherapy in the National Medicare Population From 2008-2009

* Presley et al.: JCO 2012;35:4302-4307.

Table 3. Estimated Adjusted 1-Year Complication Rates for Patients Receiving Brachytherapy and Whole-Breast Irradiation

Treatment	Any Complication		Wound and Skin Complications		Deep-Tissue and Bone Complications	
	% of Patients	95% CI	% of Patients	95% CI	% of Patients	95% CI
Brachytherapy	35.2	28.6 to 41.9	33.7	27.3 to 40.1	4.4	1.3 to 7.6
Whole-breast irradiation	18.4	15.5 to 21.3	16.8	14.0 to 19.5	2.5	1.1 to 3.9
Difference	16.8	9.6 to 24.1	16.9	10.0 to 23.9	1.9	−1.5 to 5.4

NOTE. Rates are adjusted for age at breast-conserving surgery, race, income, comorbidity, type of radiation facility, axillary node dissection, receipt of chemotherapy, prior hospital admission, prior screening mammogram, and prior visit to primary care physician.

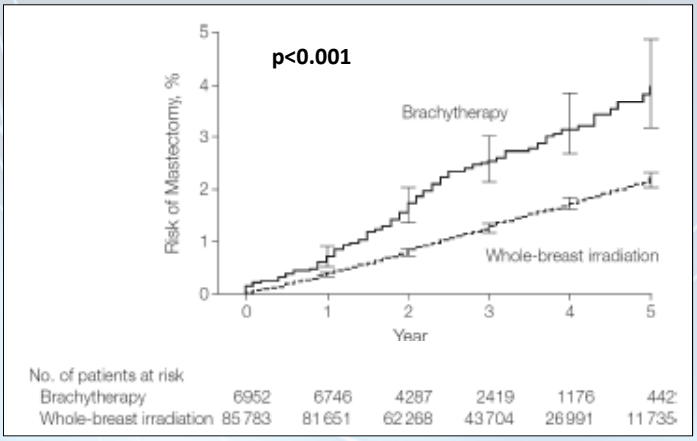
Increased Rates of Long-Term Complications after MammoSite Brachytherapy Compared with Whole Breast Radiation Therapy

* Rosenkranz et al.: J Am Coll Surg 2013;2013:217:497-502.

Table 2. Long-Term Complications

Complication	MammoSite APBI		WBRT		p Value
	n	%	n	%	
Patients developed a palpable mass	19/71	26.7	18/245	7.3	<0.001
Palpable masses biopsied	12/19	63	12/18	67	NS
Patients with palpable masses undergoing biopsy	12/71	16.9	12/245	4.9	0.02
Patients with local recurrence	2/71	2.8	4/245	1.6	NS
Patients with ipsilateral in-breast recurrence	3/71	4.2	5/245	2.0	NS
Patients developing telangectasia	17/71	24	10/245	4	<0.001

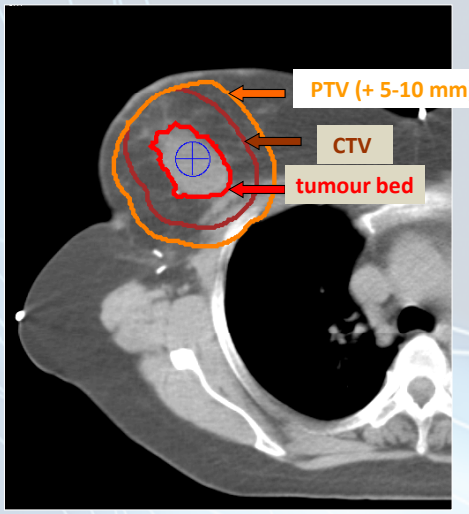
Association Between Treatment With Brachytherapy vs Whole-Breast Irradiation and Subsequent Mastectomy, Complications, and Survival Among Older Women With Invasive Breast Cancer

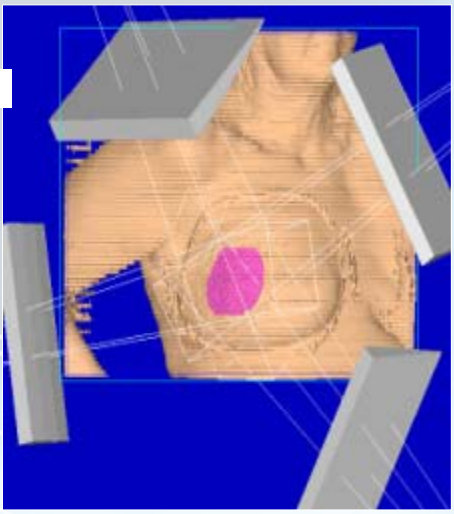


Mastectomy rate is significantly higher after balloon-based BT!

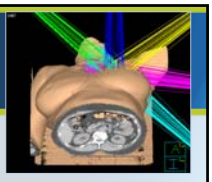
* Smith GL. et al: JAMA 2012;307:1827-1837

APBI: 3D-CRT





Results of APBI studies (median FUP ≥ 4 ys) – 3 D-CRT series



Institute	Study period	APBI technique	Patient No.	Median FUP (ys)	Crude LR%	Annual LR%
3D-CRT series						
New York University	2000-05	3D-CRT	98	5.3	1	0.19
W. Beaumont Hospital	2000-11	3D-CRT	192	4.8	1.6	0.33
RTOG 0319	2003-04	3D-CRT	52	4.5	5.8	1.29
Dana Farber/Harvard	2003-05	3D-CRT/ IMRT	98	5.9	5.1	0.86
Rocky Mountain Cancer Centers	2004-07	3D-CRT	136	4.4	0.7	0.16
Budapest	2006-11	3D-CRT	44	4.9	2.3	0.47
All patients:	**2000-11**		**620**	**4.4-5.9**	**0.7-5.8**	**0.16-1.29**

Interim Cosmetic and Toxicity Results From RAPID: A Randomized Trial of Accelerated Partial Breast Irradiation Using Three-Dimensional Conformal External Beam Radiation Therapy

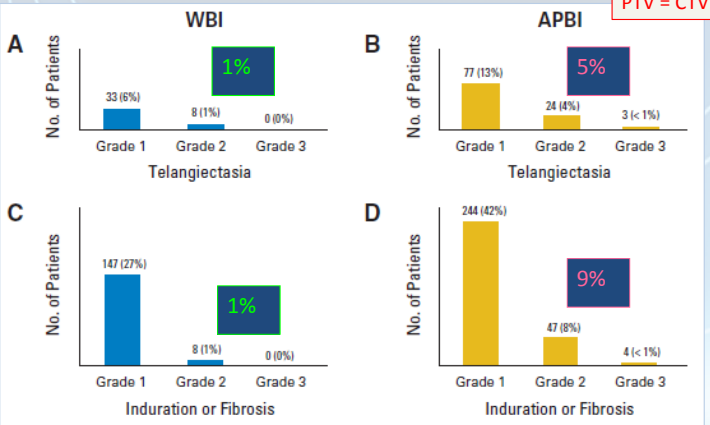
Published Ahead of Print on July 8, 2013 as 10.1200/JCO.2013.50.5511

Ivo A. Olivotto, Timothy J. Whelan, Sameer Parpia, Do-Hoon Kim, Tanya Berrang, Pauline T. Truong, Iwa Kong, Brandy Cochrane, Alan Nichol, Isabelle Roy, Isabelle Germain, Mohamed Akra, Melanie Reed, Anthony Fyles, Theresa Trotter, Francisco Perera, Wayne Beckham, Mark N. Levine, and Jim A. Julian

Median FUP = 36 months

Late toxicities

CTV = cavity + 1 cm
PTV = CTV + 1 cm



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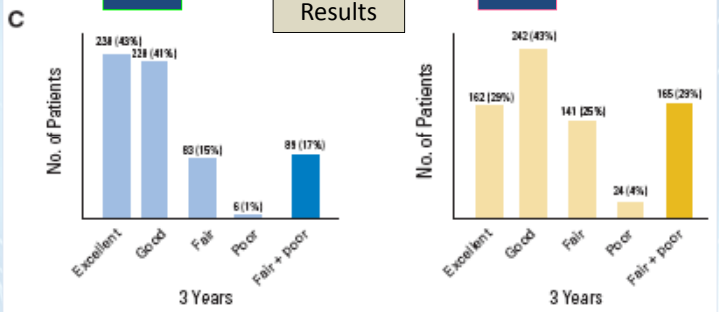
Exc./Good Cosmetic Results

84%

72%



CLINICAL INVESTIGATION **Breast**

TOXICITY OF THREE-DIMENSIONAL CONFORMAL RADIOTHERAPY FOR ACCELERATED PARTIAL BREAST IRRADIATION

IJROBP 2009;75:1290-96

JAROSLAW T. HEPEL, M.D.,*† MARI TOKITA, B.A.,† STEPHANIE G. MACAUSLAND, M.D.,† SUZANNE B. EVANS, M.D.,*† JESSICA R. HIATT, M.S.,† LORI LYN PRICE, M.S.,‡ THOMAS DIPETRILLO, M.D.,*† AND DAVID E. WAZER, M.D.*†

* Department of Radiation Oncology and † Biostatistics Research Center, Tufts University, Tufts Medical Center, Boston, MA; and † Department of Radiation Oncology, Brown University, Rhode Island Hospital, Providence, RI

- 10 x 3.85 Gy 3D-CRT (NSABP-B39)
- Median FUP: 15 months
- 22/60 pts. (37%) had G2-4 toxicities
- 19% fair-poor cosmesis

Table 2. 3D-CRT APBI late toxicity

Type	Grade 0-1	Grade 2	Grade 3	Grade 4
SQ fibrosis	45	10	4	1
Late skin	58	2	0	0
Fat necrosis	45	13	1	1
Other	0	0	1*	0
Total†	38	16	5	1

CLINICAL INVESTIGATION — Breast

UNACCEPTABLE COSMESIS IN A PROTOCOL INVESTIGATING INTENSITY-MODULATED RADIOTHERAPY WITH ACTIVE BREATHING CONTROL FOR ACCELERATED PARTIAL-BREAST IRRADIATION

IJROBP 2010;76:71-78

Reshma Jagsi, M.D., D.Phil.,* Merav A. Ben-David, M.D.,* Jean M. Moran, Ph.D.,* Robin B. Marsh, C.M.D.,* Kent A. Griffith, M.P.H., M.S.,† James A. Hayman, M.D., M.B.A.,* and Lori J. Pierce, M.D.*

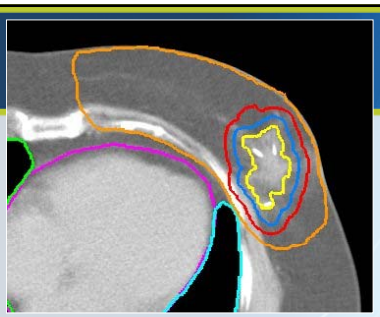
*Department of Radiation Oncology and †Biostatistics Unit, University of Michigan Comprehensive Cancer Center, University of Michigan, Ann Arbor, MI

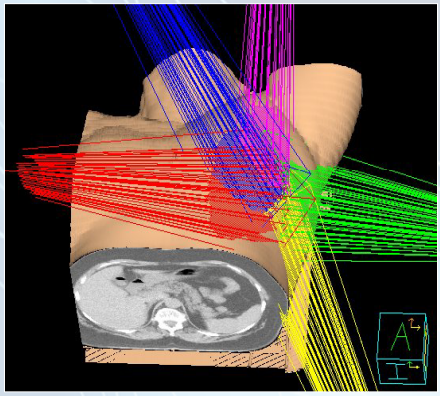
- 10 x 3.85 Gy IMRT + ABC
- Median FUP: 2.5 years
- 7/32 pts. (22%) had unacceptable cosmesis
- Premature study closure

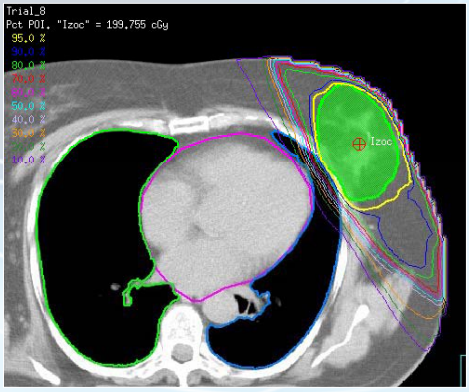
Excision cavity (GTV) (cm^3)	40.3 (10.1–102.3)
PTV (cm^3)	185.8 (59.8–382.0)
V100 to BRV (%)	17.5 (6.8–29.5)
V50 to BRV (%)	37.7 (16.6–64.5)
V100 to contoured breast (%)	27.2 (11.7–48.8)
V50 to contoured breast (%)	47.9 (22.7–79.1)

APBI: 3D-CRT – Budapest Phase II study

- 104 pts. (2006-2014)
  - 3D-CRT – 44 pts. (2006-2011)
  - IMRT + IGRT – 60 pts. (2011-2014)
- Dose: 36.9 Gy (9x4.1 Gy/5 days)
- CTV = cavity + 2 cm – free surgical margin
- PTV = CTV + 5 mm







Budapest 3D-CRT APBI Phase II study

Accelerated partial breast irradiation with external beam three-dimensional conformal radiotherapy

Five-year results of a prospective phase II clinical study

Strahlenther Onkol 2014;75:1290-96

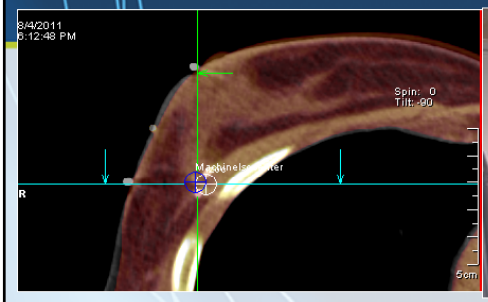
Mean FUP: 58.2 months

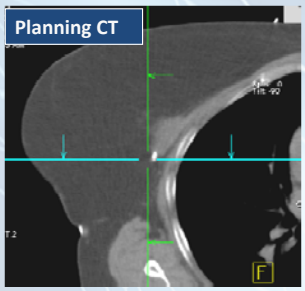
5-y LR rate: 3.7%
Exc./Good Cosmesis: 84%

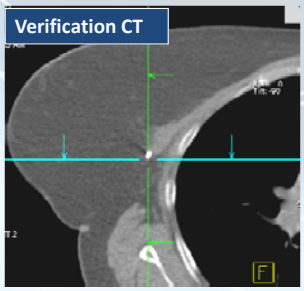
Table 4 Early and late radiation side effects and cosmetic results

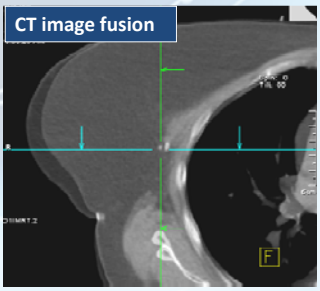
	Grade 0	Grade 1	Grade 2	Grade 3–4
Early side effect				
Skin	11 (25%)	33 (75%)	0 (0%)	0 (0%)
Breast parenchyma	24 (54.5%)	20 (45.5%)	0 (0%)	0 (0%)
Pain	24 (54.5%)	20 (45.5%)	0 (0%)	0 (0%)
Late side effect[a]				
Skin	38 (88.4%)	5 (11.6%)	0 (0%)	0 (0%)
Fibrosis	20 (46.5%)	19 (44.2%)	3 (7%)	1 (2.3%)
Fat necrosis	37 (86%)	6 (14%)	0 (0%)	0 (0%)
Pain	42 (97.7%)	1 (2.3%)	0 (0%)	0 (0%)
Cosmetic result[a] (rated by physicians)	**Excellent**	**Good**	**Fair**	**Poor**
	13 (30.2%)	23 (53.5%)	7 (16.3%)	0 (0%)
Cosmetic result[a] (rated by patients)				
	14 (32.6%)	23 (53.5%)	6 (13.9%)	0 (0%)

APERT: IGRT + IMRT

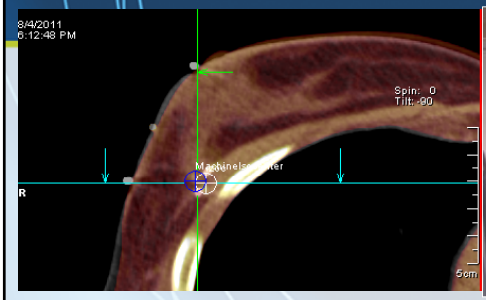








APBI: IMRT + IGRT – matching to bony anatomy



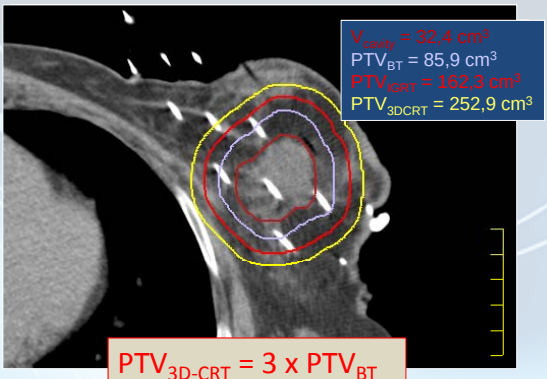
PTV to CTV margin needed using daily set-up correction with kV CT image guidance

	LAT	LONG	VERT	SD LAT	SD LONG	SD VERT
Mean (range)	1.4 (0.4-2.8)	0.1 (0.2-2.8)	0.1 (0.1-2.8)	1.5 (0.4-2.5)	2.0 (0.5-2.6)	1.5 (0.7-2.2)
Systematic error	1.6	1.5	2.0			
Random error				1.5	2.1	1.5
PTV margin	**5.1 mm**	**5.0 mm**	**6.1 mm**			

Brachytherapy ➡ PTV = CTV

3D-CRT ➡ PTV = CTV + 1 cm

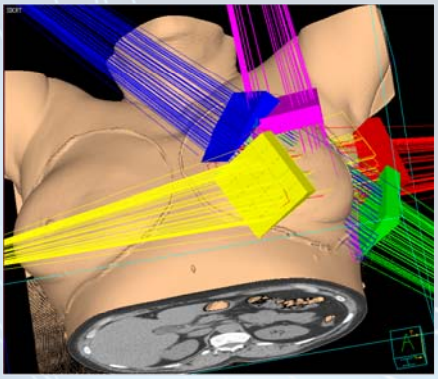
IGRT ➡ PTV = CTV + 0.5 cm

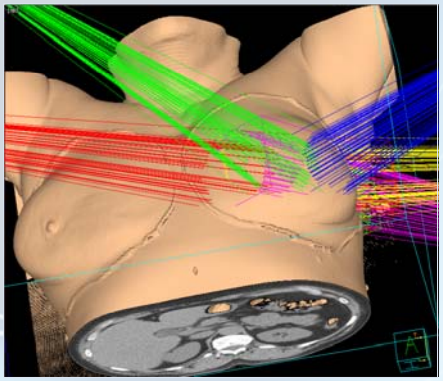


$PTV_{3D\text{-}CRT} = 3 \times PTV_{BT}$

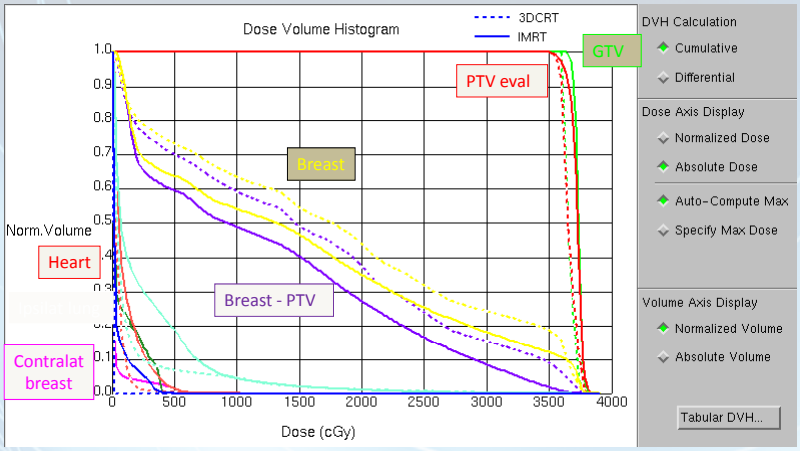
$PTV_{IGRT} = 2 \times PTV_{BT}$

APBI: 3D-CRT versus IMRT



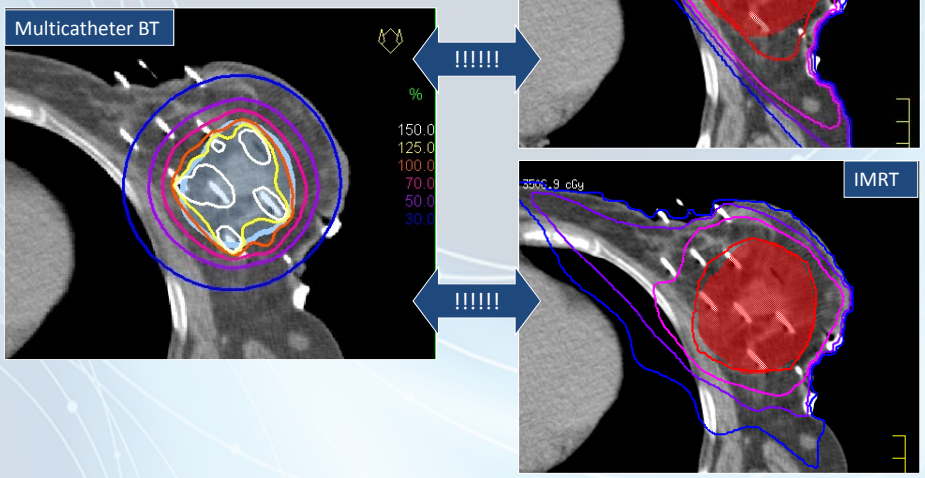


APBI: 3D-CRT versus IMRT



Ipsilateral non-target breast is better spared with IMRT!

Dose distribution by APBI technique



Results of APBI studies – IORT series

Institute	Study period	APBI technique	Patient No.	Median FUP (ys)	LR %	Annual LR%
IORT series						
ELIOT*	2000-07	ELE	651	5.8	5.4	0.93
TARGIT*	2000-09	50 KV photons	1679	2.4	1.4	0.58
Montpellier	2004-07	ELE	42	6	9.5	1.58
All patients:	**2000-09**		**2372**	**2.4-6**	**1.4-9.5**	**0.58-1.58**

* Phase III trial

ELIOT Phase III APBI clinical trial*

Nov/2000 – Dec/2007 (n=1305 pts.)

Median FUP: 5.8 years

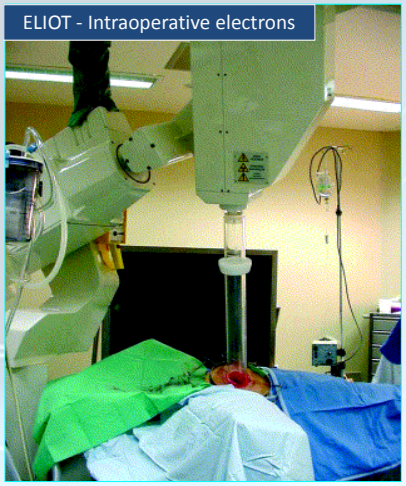
T <2.5 cm, cN0
AGE > 48 ys

654
BCS + WBI
(50 + 10 Gy boost)

R

651
BCS + ELIOT
(21 Gy)

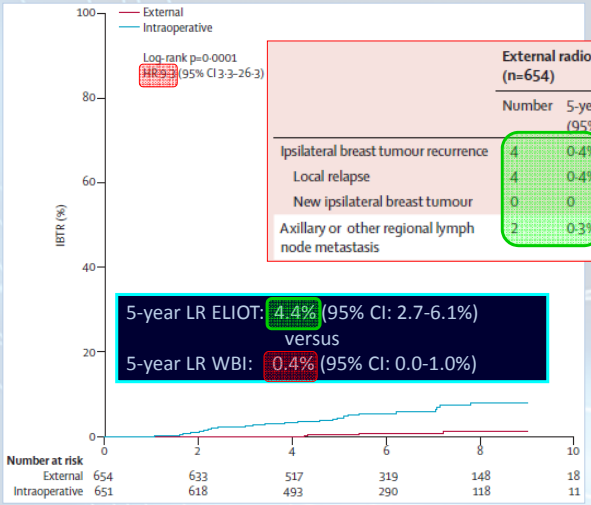
ELIOT - Intraoperative electrons



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

www.thelancet.com/oncology **Published online November 11, 2013**

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



	External radiotherapy (n=654)		Intraoperative radiotherapy with electrons (n=651)		Log-rank p value
	Number	5-year event rate (95% CI)	Number	5-year event rate (95% CI)	
Ipsilateral breast tumour recurrence	4	0·4% (0·0–1·0)	35	4·4% (2·7–6·1)	<0·0001
Local relapse	4	0·4% (0·0–1·0)	21	2·5% (1·2–3·8)	0·0003
New ipsilateral breast tumour	0	0	14	1·9% (0·8–3·1)	0·0001
Axillary or other regional lymph node metastasis	2	0·3% (0·0–0·8)	9	1·0% (0·2–1·9)	0·03

5-year LR ELIOT: 4.4% (95% CI: 2.7-6.1%)
versus
5-year LR WBI: 0.4% (95% CI: 0.0-1.0%)

ELIOT trial – Prognostic factors for LR

www.thelancet.com/oncology **Published online November 11, 2013**

	Patients (n/N)	IBTR 5-year event rate (95% CI)	Log-rank p value*
Total	35/651	4·4% (2·7–6·1)	--
Age			
48–49 years	0/44	0	--
50–59 years	21/286	5·6% (2·7–8·5)	--
60–69 years	10/259	3·1% (0·8–5·4)	--
≥70 years	4/62	7·2% (0·4–14·1)	0·11
Histology			
Ductal	28/524	4·5% (2·6–6·5)	--
Lobular	3/53	4·6% (0·0–10·8)	--
Ductal and lobular	2/17	6·3% (0·0–18·1)	--
Other	2/53	2·1% (0·0–6·1)	0·69
Pathological size			
<1 cm	5/199	1·9% (0·0–4·0)	--
1–1·5 cm	13/243	4·2% (1·5–6·9)	--
1·5–2·0 cm	7/120	4·7% (0·7–8·8)	--
>2·0 cm	10/83	10·9% (3·7–18·1)	0·006
Number of positive nodes			
None	21/478	3·5% (1·7–5·3)	--
1–3	10/138	5·3% (1·5–9·2)	--
≥4	4/31	15·0% (1·4–28·7)	0·06
Overall p value	--	--	
Tumour grade			
G1	5/196	1·1% (0·0–2·7)	--
G2	15/305	3·8% (1·5–6·1)	--
G3	15/129	11·9% (5·7–18·2)	0·0003
Oestrogen receptor			
Absent	8/63	14·9% (5·2–24·5)	--
Present	21/583	3·3% (1·8–4·9)	0·0004
Overall p value	--	--	
Progesterone receptor			
Absent	12/158	7·4% (2·9–11·8)	--
Present	23/487	3·5% (1·7–5·2)	0·17
Proliferative index (KI-67)			
<14%	8/263	1·8% (0·0–3·5)	--
14–20%	5/138	1·5% (0·0–3·6)	--
>20%	22/244	9·1% (5·1–13·1)	0·002
Molecular subtype			
Luminal A	7/256	1·4% (0·0–3·0)	--
Luminal B	20/327	4·9% (2·4–7·4)	--
HER2-positive (non-luminal)	1/20	5·9% (0·0–17·1)	--
Triple negative	7/43	18·9% (6·1–31·7)	0·001
Characteristics suggesting subsequent whole breast irradiation			
No	14/452	1·5% (0·3–2·7)	--
Yes†	21/199	11·3% (6·4–16·1)	<0·0001

IBTR=ipsilateral breast tumour recurrence. *Overall p value. †Tumour larger than 2·0 cm, or four or more positive nodes, grade 3, or triple negative.

Table 3: **Factors associated with IBTR among patients randomised to receive intraoperative radiotherapy with electrons**

TARGIT phase III trial

March/2000 – Nov/2009

Median FUP: 2.4 years

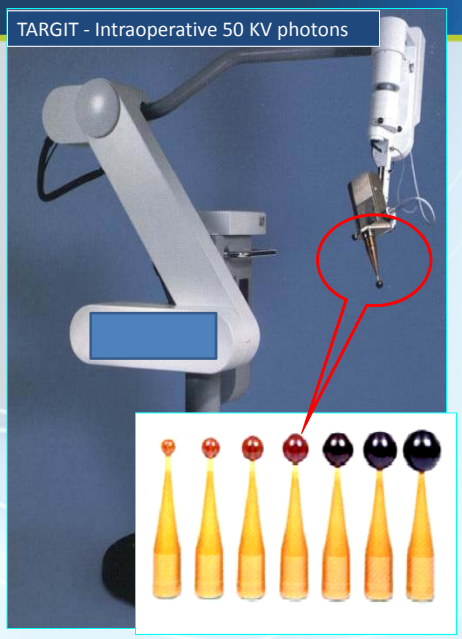
3451 pts.

R

BCS + WBI

BCS + TARGIT (20 Gy)

TARGIT - Intraoperative 50 KV photons

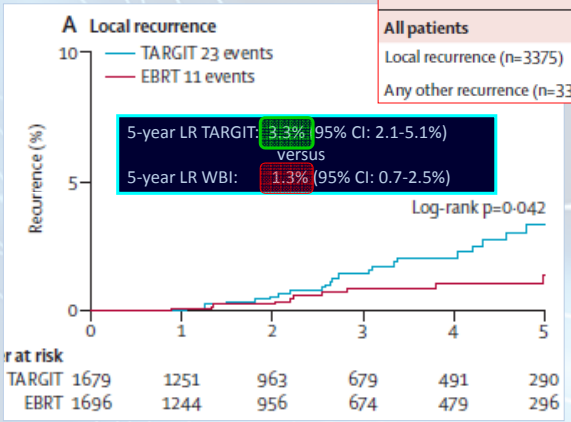


Risk-adapted targeted intraoperative radiotherapy versus whole-breast radiotherapy for breast cancer: 5-year results for local control and overall survival from the TARGIT-A randomised trial

www.thelancet.com Vol 382 Published online November 11, 2013

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,

	Events; 5-year cumulative risk (95%CI)	
	TARGIT	EBRT
All patients		
Local recurrence (n=3375)	23; 3·3% (2·1–5·1)	11; 1·3% (0·7–2·5)
Any other recurrence (n=3375)	46; 4·9% (3·5–6·9)	37; 4·4% (3·0–6·4)



APBI – Randomized clinical trials

Trial	Participants	APBI technique	Patient No.	Study period
Budapest	NIO, Budapest, HU	HDR BT	258	1998-2004
ELIOT	EIO, Milan; IT	IORT – electrons	1305	2000-2007
TARGIT	UK/AUS multicentric	IORT – 50 kV photons	2232	2000-2009
GEC-ESTRO	European multicentric	HDR/PDR BT	1193	2004-2009
RAPID	Canadian multicentric	3D-CRT	2128	2006-2011
NSABP-B39/ RTOG-0413	USA multicentric	HDR BT/ MammoSite/ 3D-CRT	4300	2005-2013
Florence	Univ. Florence, IT	IMRT	520	2005-2013
IMPORT-LOW	MRC, UK multicentric	IMRT	1935	2006-

≈ 14 000 pts.

GEC-ESTRO Phase III Trial*
May 2004 – July 2009

1192 pts.

LOW-RISK BREAST CC.

568
BCS + WBI
(50 + 10 Gy boost)

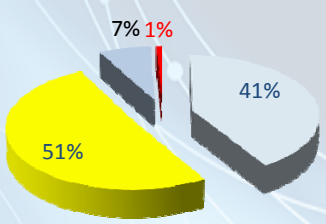
R

624
BCS + HDR/PDR BT

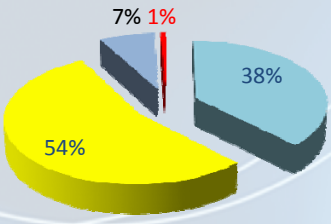
GEC-ESTRO APBI Trial –
Cosmetic results at 1 year

Doctors' view

Brachytherapy



EBRT

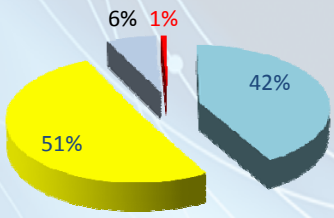


Excellent + good cosmesis: 92% after APBI vs 92% after WBI

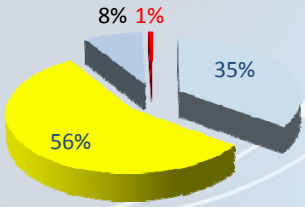
GEC-ESTRO APBI Trial – Cosmetic results at 1 year

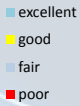
Patients' view

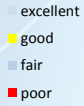
Brachytherapy



EBRT







Excellent + good cosmesis: 93% after APBI vs 91% after WBI

Conclusions based on clinical evidences

- Long-term results of contemporary APBI series confirmed that quality assured multicatheter BT is a safe alternative of conventional WBI for low-risk breast cancer patients.

- Skin toxicity is high after intracavitary (MammoSite) BT in case of close balloon to skin distance.

- Phase III IORT APBI trials trials (ELIOT & TARGIT) failed to demonstrate non-inferiority of IORT.

- One randomized trial (RAPID) suggested that 3D-CRT APBI increased the rates of adverse cosmesis and late radiation toxicity compared to WBI.

- Long-term results of the NSABP/RTOG and GEC-ESTRO Phase III APBI trials are eagerly awaited and will hopefully clarify the value of different APBI techniques.

In the Meantime Choose Multicatheter Brachytherapy!

Thank you for your kind attention!