Role and Techniques of Accelerated Partial Breast Irradiation

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Changing paradigms of Radiotherapy in EBC

Radical mastectomy

(Halsteadian paradigm)

↓

Breast Conserving Therapy

(Whole Breast RT compensated for less extensive surgery)

↓

Accelerated Partial Breast Irradiation

(Irradiation of the tumour bed with 1-2 cm margins using a regime of accelerated RT)

↓

Omission of radiotherapy

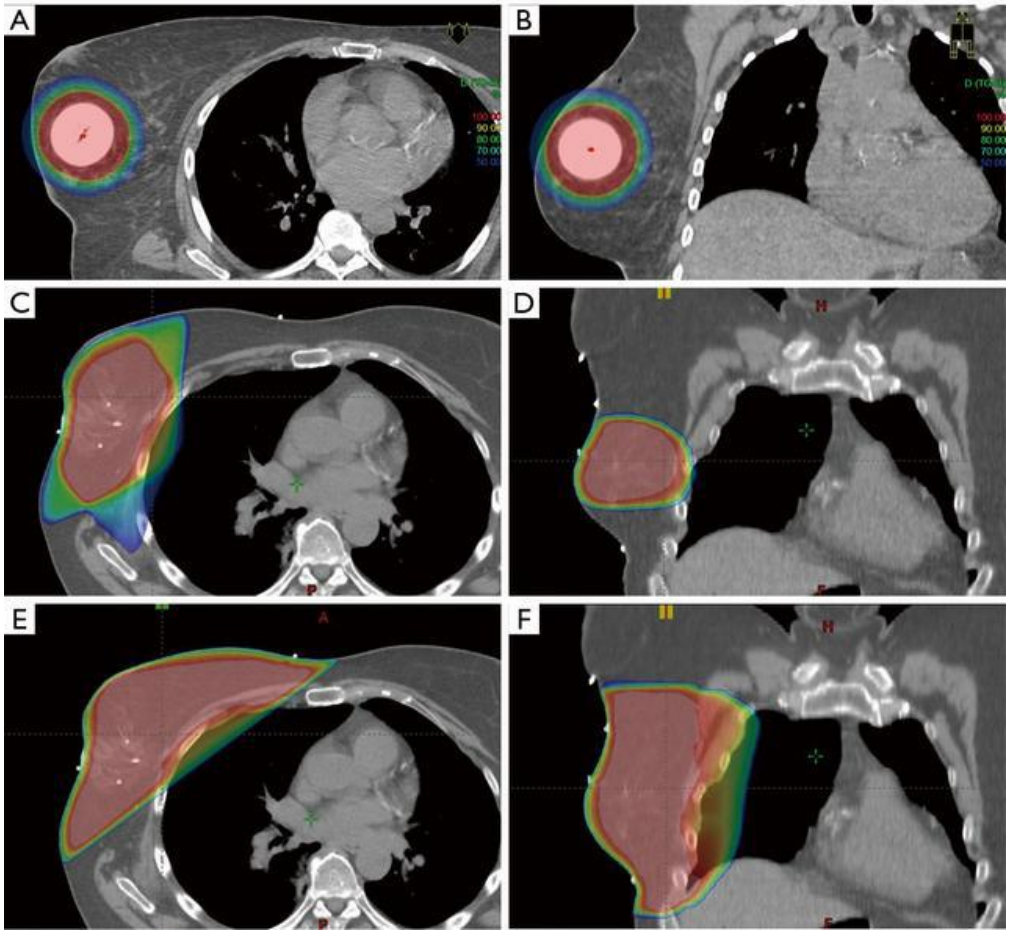
(No adjuvant RT after BCS for elderly women with low risk of local recurrence)

Flow of presentation

- Definition
- Rationale
- Case selection
- Methods
- Clinical outcome
- Future directions

Definition

- Acceleration: 1 day to 1 week (single # and up to 10 fractions)
- Partial breast: Target volume is the tumor bed alone with margins



Why APBI?

15-30% drop out rate after BCT

- Lack of commitment to usual 3-4 weeks course of adjuvant RT
- Lack of access (distance, transport) (Athas et al: *JNCI* 92:269-271, 2000)
- Logistics (ambulatory status, social support, temporary loss of employment)
- Availability of expertise & facility
- **Prolonged waiting time**
- Cost saving
- **Patient age** (Ballard et al: *JNCI* 88:716-725, 1996)

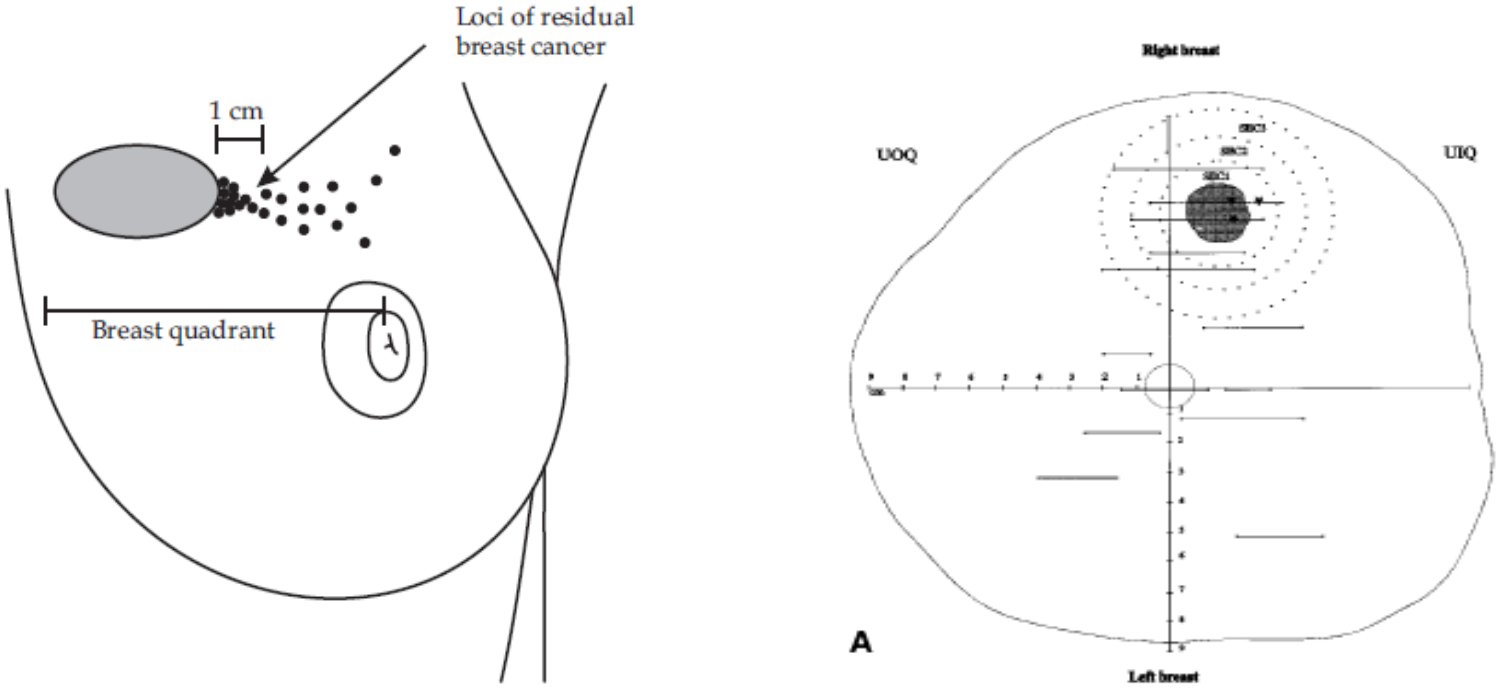
Women opt for mastectomy though eligible for BCS or never receive RT after BCS even in the west

Lazovich DA, JAMA, 1991

Advances in radiotherapy

- **Reduced toxicities** markedly secondary to treatment
- Made **hypo-fractioanted** regimens practical for delivery

Strong clinico-pathological rationale



- 69-90% recurrences occur at the immediate vicinity of the primary tumor
- Incidence of elsewhere failures 0.9-3.5%
- Several studies on mastectomy specimens suggest residual disease may extend ***1 to 2.5 cm*** margin around excision cavity

Skowronek J, JCB 2012, Faverly DR Cancer 2001

APPROPRIATE SELECTION OF TECHNIQUE AND CASE: **CRITICAL**

Table 4 Clinical outcome of PBI with suboptimal patient selection or techniques.[a]

Institution APBI technique	Number of patients [median follow up (years)]	Criticism of selection or technique	Breast recurrence	Cosmesis and complications
Christie Hospital RCT[31] External electrons 40Gy/8#/10days	353 [8]	Lobular cancer ~15% Margins unknown or +ve in 19%. Inadequate target coverage and fractionation	25% (8 year actuarial). Excess recurrences in lobular cancer	Marked telangiectasia in 33% and marked fibrosis in 14%. Cosmesis NA
Guys Hospital[45] LDR 55 Gy over 5 days	27 [6]	Positive margins in 55% and EIC in 40% cases	37% (crude)	Cosmesis good to excellent in 83%. Telangiectasia in 4%
Uzsoki Hospital, Budapest[40] LDR 50 Gy in 10–22 hours	70 [12]	Cut margins not known; lobular component in 10%. Single plane implant with unacceptable dose rate	24% (crude) (7% outside tumour bed)	Poor cosmesis in 50%. Grade 3 or 4 radiation sequelae in 59%
London Regional Cancer Centre, Ontario[39]	39 [7.5]	Average implant volume only 30 cc. Single plane in 11. Cut margins <2 mm in 12 and EIC in 3 patients	16% (10% outside tumor bed)	Cosmesis—median score 90. Fat necrosis in 13%
Tufts New England[46]	33 [5]	HDR technique optimal but 55% had EIC	6%	Cosmesis good to excellent in 87%. Fat necrosis in 24%
University of Kansas[47] LDR 20–25Gy	25 [4]	Inadequate LDR dose	0	Cosmesis good to excellent in 100%; no late complication

[a]Not conforming to the ABS guideline.[4] #, Number of fractions.

R SARIN, NATURE CLINICAL PRACTICE ONCOLOGY, 2005

Partial-breast treatment for early breast cancer: emergence of a new paradigm

Rajiv Sarin

Table 3 Five-year results of APBI using quality assured LDR or HDR interstitial implants in optimally selected patients.[a]

Institution	Number of patients	Median follow up (years)	5-year actuarial ipsilateral breast recurrence rates		Contralateral breast cancer incidence
			Anywhere in breast	Outside the tumor bed	
[b]Ochsner Clinic[11,37]	160	7	2.5% (crude)	1.2% (crude)	NA
[b]NIO, Budapest, phase I/II[16]	45	6.7	4.4%	4.4%	0
[b]William Beaumont[11,24]	199	5.4	1.2%	0.6%	1%
Virginia Commonwealth University[11,38]	59	4.2	5.1%	2.6%	0
Orebro[25]	49	4.6	4% (crude)	2% (crude)	NA
RTOG 9517 phase II[17]	99	3.7	3% (4 year)	NA	3%
All mature series	611	4–7	1–5%	0.6–4.4%	0–3%

[a]Patient selection and treatment quality assurance generally conforming to the American Brachytherapy Society (ABS) guidelines.[4] None of these series have reported an unacceptable incidence of adverse cosmetic outcome or symptomatic late sequelae.
[b]Present or earlier reports from the Ochsner clinic, William Beaumont and the Budapest phase I/II studies show APBI results comparable to matched controls treated with whole-breast irradiation.

Older recommendations

CRITERIA	ABS	ASBS
AGE	>/= 45 years	>/= 50 years
TUMOR SIZE	Up to 3 cm	Up to 2 cm
NODE	Negative	Negative
HISTOLOGY	IDC	IDC OR DCIS
MARGINS	Microscopically negative	2 mm

ASTRO GUIDELINES 2009

Prognostic Factor	Suitable	Cautionary	Unsuitable
Age	≥ 60 years	50-59 years	< 50 years
BRCA mutation	Not present	-	Present
Tsize	≤ 2 cm	2.1-3.0 cm	> 3 cm
Tstage			
Margins			
Grade			
LVSI			
ER status			
Multicentrici			
Multifocality			Micro
Histology			
Pure DCIS			
EIC	Not allowed	≤ 3 cm	> 3 cm
Associated LCIS	Allowed	-	
Nstage	pN_0	-	pN_1-pN_3
Nsurgery	SLN Bx or ALND	-	None performed
Neoadjuvant therapy	Not allowed	-	If used

UPDATED ASTRO GUIDELINES (2016)

- Suitable age goup **≥ 50 yrs**
- Patients who are aged **40-49 yrs** and who meet all other elements of suitability are considered cautionary
- Patients with low-risk DCIS, as per RTOG 9804 criteria, were categorized in the "suitable" group
- Patients with age less than 40 years or those who are 40 – 49 years without meeting other elements of suitable to be retained in the "unsuitable" group

Smith et al J. Radiation oncology 2009

GEC-ESTRO GUIDELINES 2010

Characteristic	A/low risk- Good candidates	B/ intermediate risk- possible candidates	C/high risk- contraindications
Age	>50 years	>40–50 years	≤40 years
Histology	IDC, mucinous, tubular, medullary, and colloid cc.	ILC, IDC, mucinous, tubular, medullary, and colloid cc.	-
ILC	Not allowed	Allowed	-
Associated LCIS	Allowed	Allowed	-
DCIS	Not allowed	Allowed	-
Grade	Any	Any	-
Size	pT1–2 (≤30 mm)	pT1–2 (≤30 mm)	pT2 (>30 mm), pT3, pT4
Margins	Negative (≥2 mm)	Negative, but close (<2)	Positive
Multi-centricity	Uni-centric	Uni-centric	Multic-entric
Multi-focality	Uni-focal	Multi (<2 cm from index)	Multi (<2 cm from index)
EIC	Absent	Absent	Present
LVI	Absent	Absent	Present
ER/PR status	Any	Any	-
Nodes	pN0	pN1mi or pN1a	4 or more
NACT	Not allowed	Not allowed	If used

Polgar et al Radiation onclogy 2010

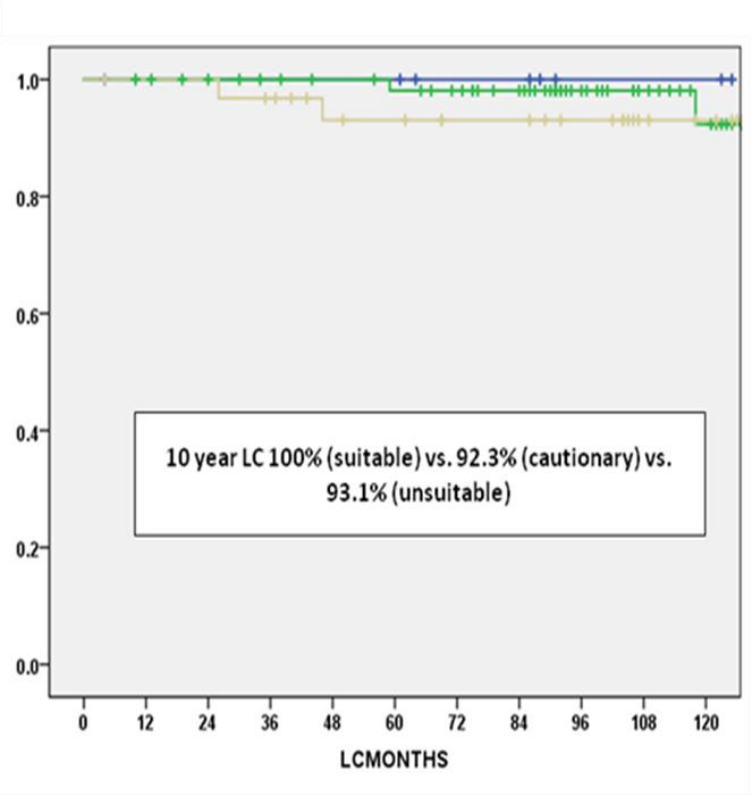
Variable recommendations

- Hormone receptor status (ASTRO)
- Histology (?all lobulars)
- Node positivity (NSABP, unsuitable, higher risk)
- Lymphatic invasion (ASTRO, ESTRO, ?extent)
- Width of negative margins (minimum 2 mm)
- Tumor size
- Age (NSABP >18 years)

- Disregards:
  - Her2neu status
  - Grade

Ten year outcome of patients treated with Accelerated Partial Breast Irradiation (APBI) using interstitial brachytherapy at Tata Memorial Hospital: Limited role of ASTRO consensus statement guidelines in clinical application

- N=102
- 1998-2005
- Median age 57 years
- Median pTsize 2cm
- Dose 34 Gy in 10 fractions
- Intraop 66 and postop 36
- 2 dimensional planning
- **Median FU 125 months**



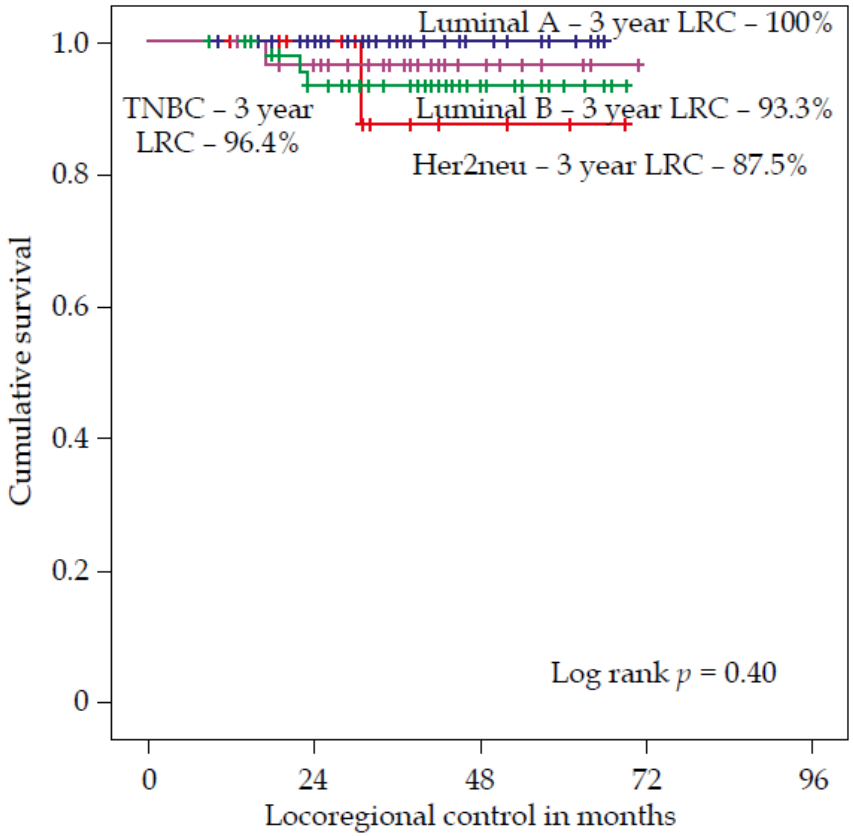
Wadasadawala et al, Proceedings of Breast Oncology Conference, Kochi, 2014

ASTRO-CS: Does not predict risk of LR

Author (ref)	N	Technique	Median FU (months)	Tsize (Median)	Histology	ASTRO CS group (Percent/LR)			p value
						Suitable	Cautionary	Unsuitable	
Ferraro DJ, 2012	202	IBT	64	1.0 cm	IDC/DCIS/ ILC	28.7%	51.5%	19.8%	NS at 5 years, ASTRO CS failed to predict LR, LRR or DFS
						Overall 3.0%			
Wilkinson JB*, 2012	1813	All except IORT	60.6	1.0 cm	IDC/DCIS	36.5% 2.5%	46.9% 3.3%	16.7% 4.6%	NS at 5 years
Vicini FA 2011	**199**	**IBT**	**133**	**NR**	**IDC**	**47.7%** **2.6%**	**31.7%** **7.8%**	**20.6%** **2.5%**	**NS at 10 years, ASTRO CS did not predict LR**
MacHaffie DR, 2011	136	MammoSite	60	1.0 cm	IDC/DCIS	24.6% 1.6%	42.2% 4.8%	33.2% 6.6%	NS at 5 years
TMH, 2014	**112**	**IBT**	**91**	**2.0 cm**	**IDC**	**27.1%** **8.0%**	**62.5%** **1.7%**	**29.5%** **7.6%**	**10 year LR not as per ASTRO CS group**

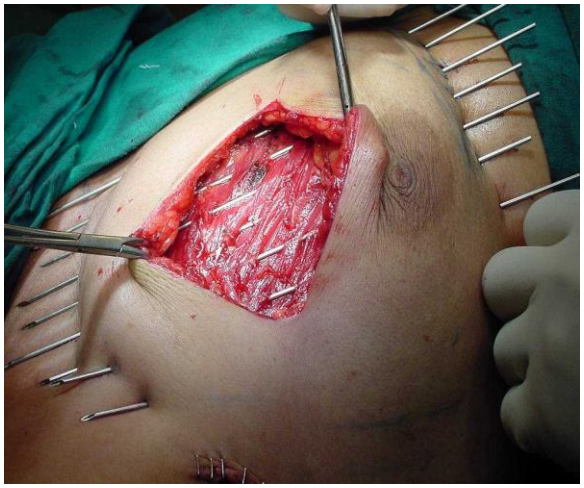
Recent cohort: impact of molecular sub-type

- N=157
- Median FU 35 months
- 2012-2016
- Median age 60 years
- Median tumor size 2.1 cm
- Molecular subtype:
  - Luminal A 34.4%
  - Luminal B 36.3%
  - TNBC 18.5%
  - Her2 10.8% (only one third patients received 12 weeks of trastuzumab)

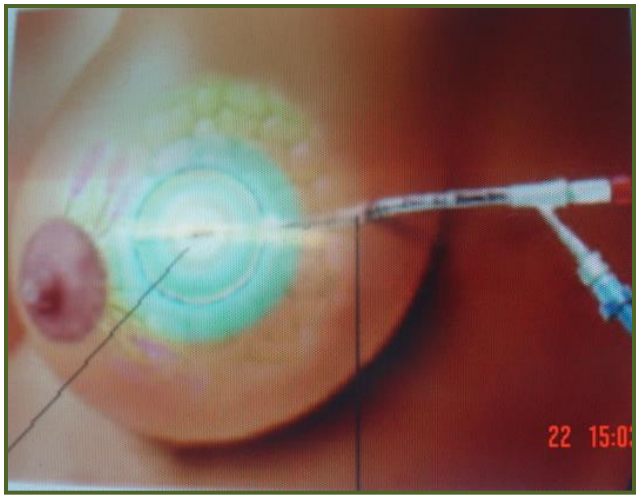


Wadasadawala et al, Journal Of Contemporary Brachytherapy, 2018

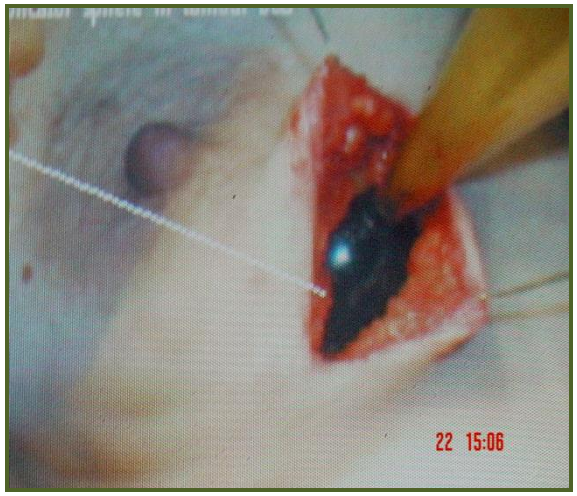
A range of External beam & Brachytherapy techniques for APBI



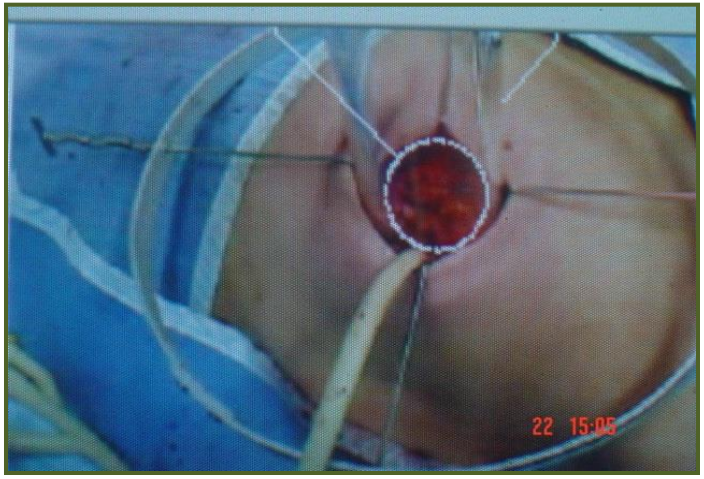
Interstitial Implant



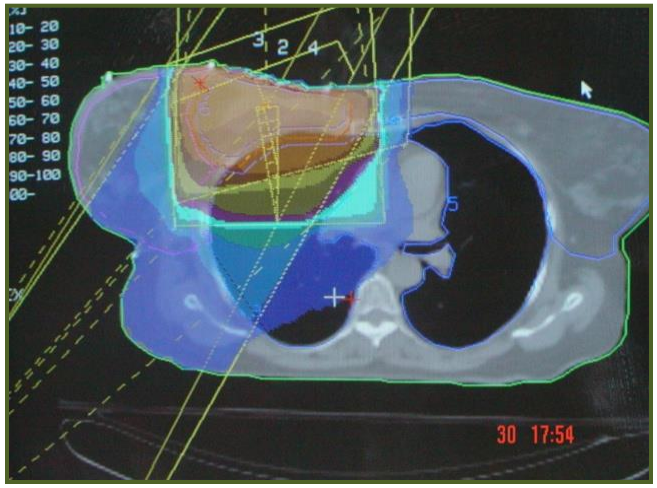
Mammosite



TARGIT



Intra op electrons [ELIOT]



3DCRT / IMRT

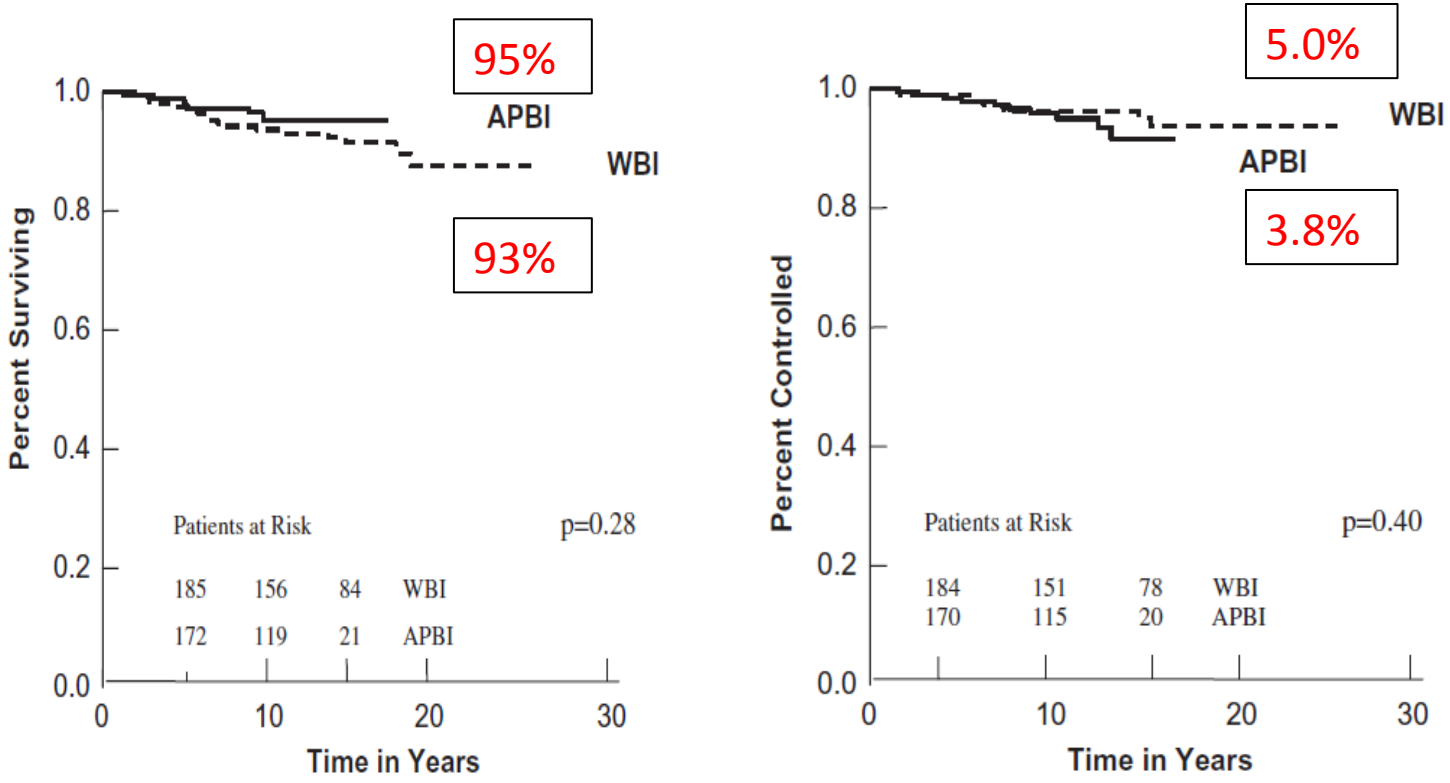
Classification of techniques

- **Brachytherapy:**
  - Multi-catheter Interstitial (MIB)
  - Intraluminal (Mammosite, SAVI, Contura, Clearpath)
  - Permanent breast seed implant (PBSI)
  - Electronic breast brachytherapy (EBB)
  - Non-invasive image guided breast brachytherapy (NIBB)

- **Intra-operative:**
  - ELIOT
  - TARGIT

- **External beam:**
  - Photons
  - Electrons
  - Protons

Interstitial brachytherapy: most *mature and safe* technique



Cause-specific survival for APBI and WBI patients. APBI = accelerated partial

Freedom from local failure for APBI and WBI patients. APBI = accelerated

Median follow up: **14.5** years in WBI arm and **10.7** years in APBI arm
N=199 matches

Vicini et al Radioth Oncol 2011

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Phase III randomised trial

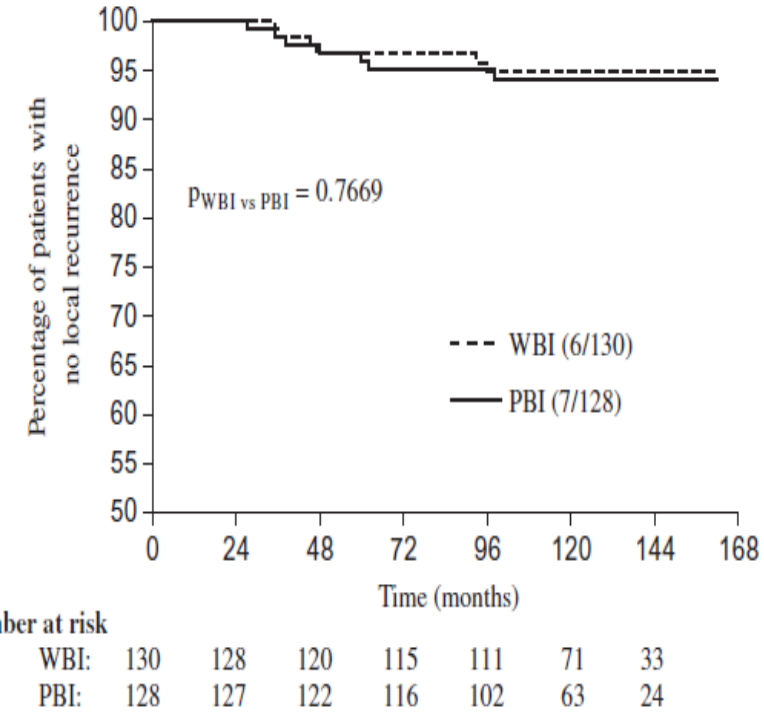
Breast-conserving therapy with partial or whole breast irradiation: Ten-year results of the Budapest randomized trial

Csaba Polgár [a,*], János Fodor [a], Tibor Major [a], Zoltán Sulyok [b], Miklós Kásler [c]

[a] Center of Radiotherapy; [b] Center of Surgery; [c] National Institute of Oncology, Budapest, Hungary

Local recurrence (primary endpoint)

5.9% vs. 5.1% at median follow up of **10.2 years**

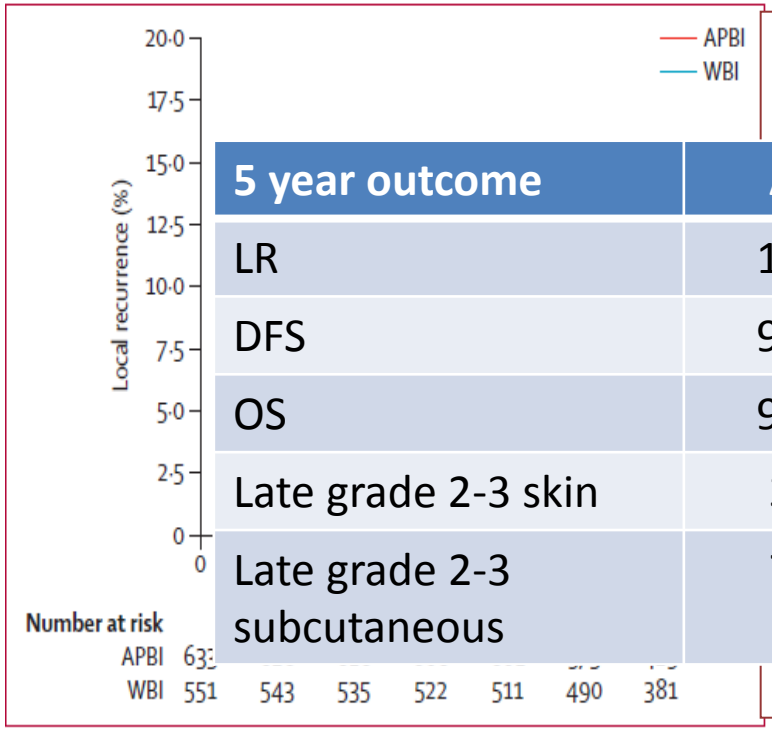


Cosmetic outcome.

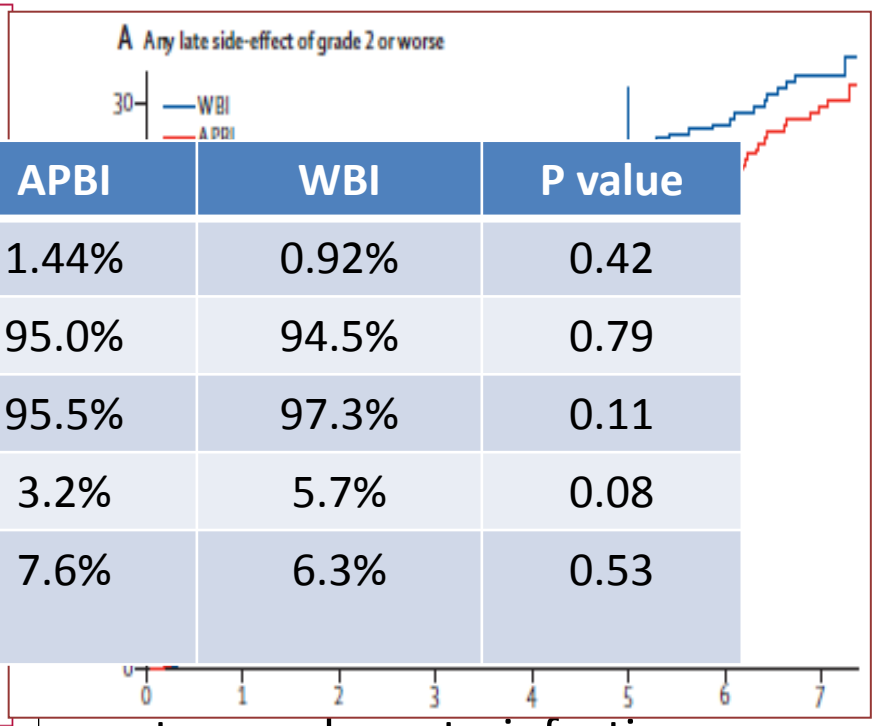
Harvard cosmetic score	PBI – HDR BT ($n = 85$)[a]	PBI – EB ($n = 40$)[a]	WBI – photons ($n = 93$)[a]	WBI – cobalt ($n = 23$)[a]
Excellent	29 (34.1)	7 (17.5)	16 (17.2)	3 (13.1)
Good	43 (50.6)	22 (55.0)	46 (49.5)	8 (34.8)
Fair	11 (12.9)	11 (27.5)	22 (23.6)	11 (47.8)
Poor	2 (2.4)	0 (0)	9 (9.7)	1 (4.3)

Radioth Oncol 2013

5-year results of accelerated partial breast irradiation using sole interstitial multicatheter brachytherapy versus whole-breast irradiation with boost after breast-conserving surgery for low-risk invasive and in-situ carcinoma of the female breast: a randomised, phase 3, non-inferiority trial



5 year outcome	APBI	WBI	P value
LR	1.44%	0.92%	0.42
DFS	95.0%	94.5%	0.79
OS	95.5%	97.3%	0.11
Late grade 2-3 skin	3.2%	5.7%	0.08
Late grade 2-3 subcutaneous	7.6%	6.3%	0.53



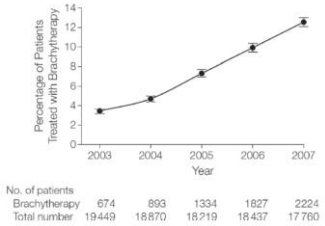
hematoma, breast infection

Figure 2: Ipsilateral breast tumour recurrence
APBI=accelerated partial breast irradiation. WBI=whole-breast irradiation.

Strnad Lancet 2015 & 2017

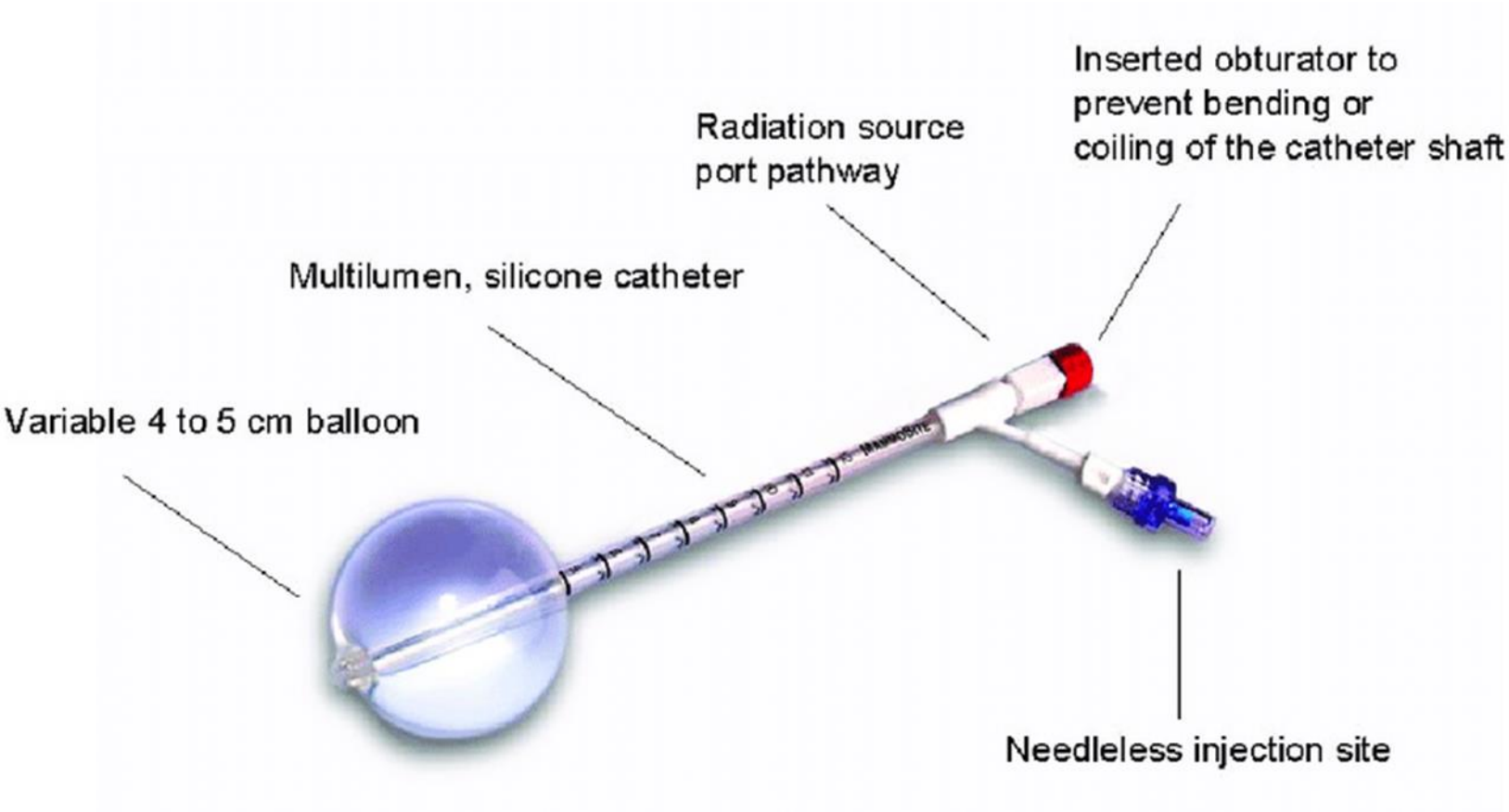
Intracavitary techniques: Tremendous popularity with Mammosite

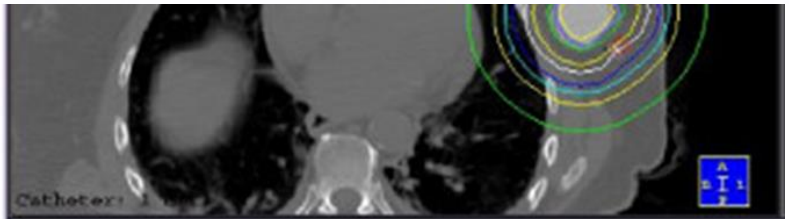
- Approval of MammoSite® (Hologic, Inc., Beford, MA) by the US FDA in May 2002
- The new device was adopted aggressively in non trial setting: better tolerated, reproducible and easy to implant
- Balloon is inflated with saline solution mixed with a small amount of contrast material (35 – 70 ml)
- Balloon is inflated to a size that would completely fill the lumpectomy cavity and ensures conformance of the tissue to the balloon.
- An Ir-192 radioactive source, connected to HDR remote after-loader, is inserted through the catheter into the balloon to deliver the prescription radiation dose
- **Dose prescription at 1 cm from the balloon surface in the plane transverse to the balloon's axis**

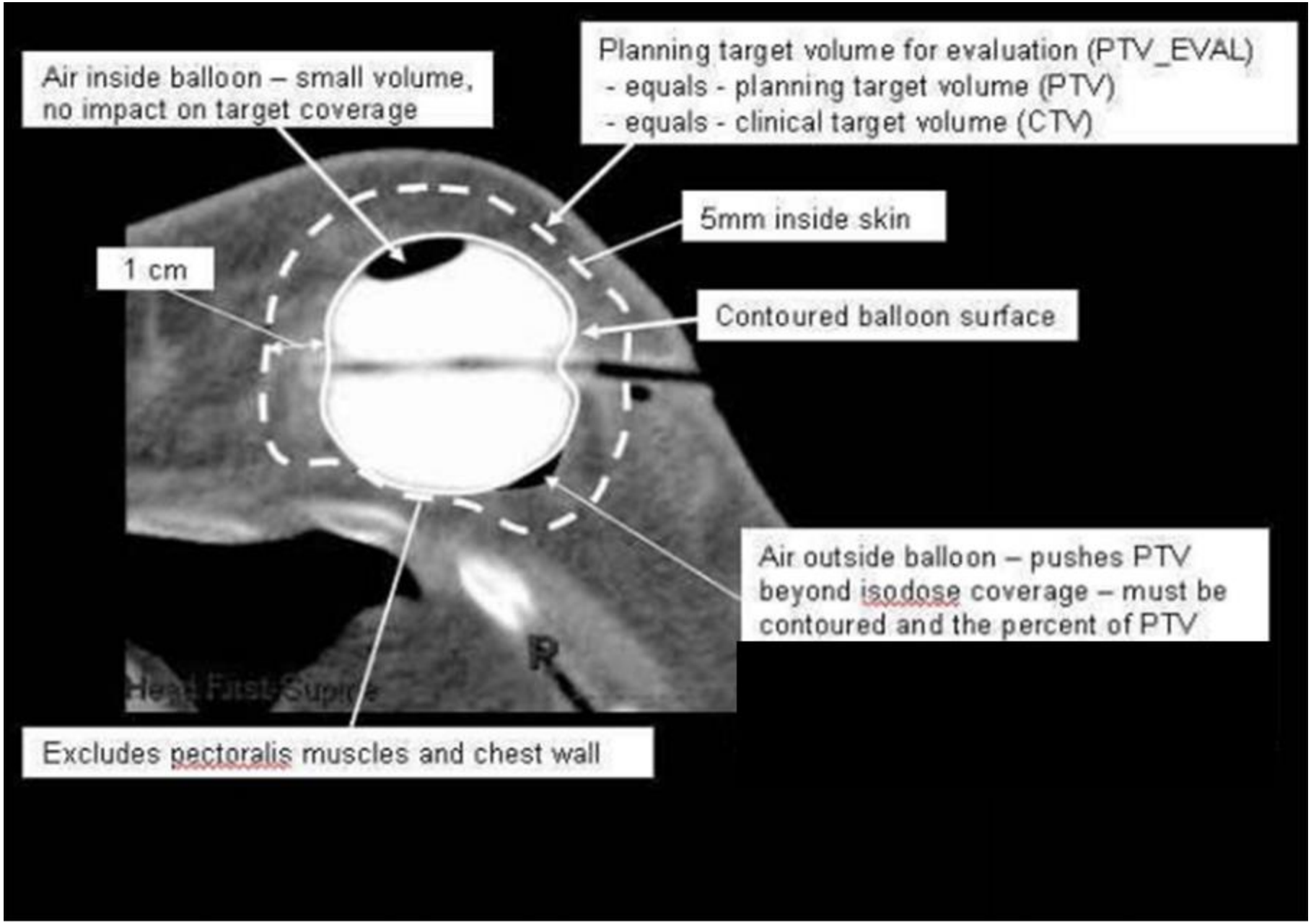


MammoSite Brachytherapy

INTRA-OPERATIVE **POST-OPERATIVE**



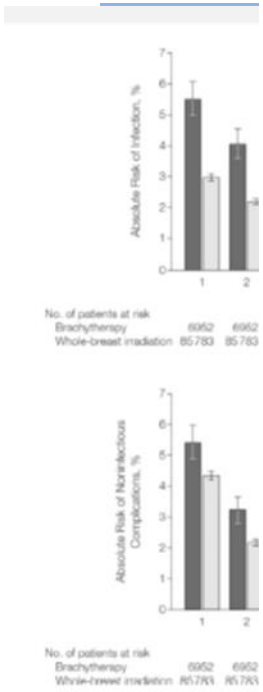


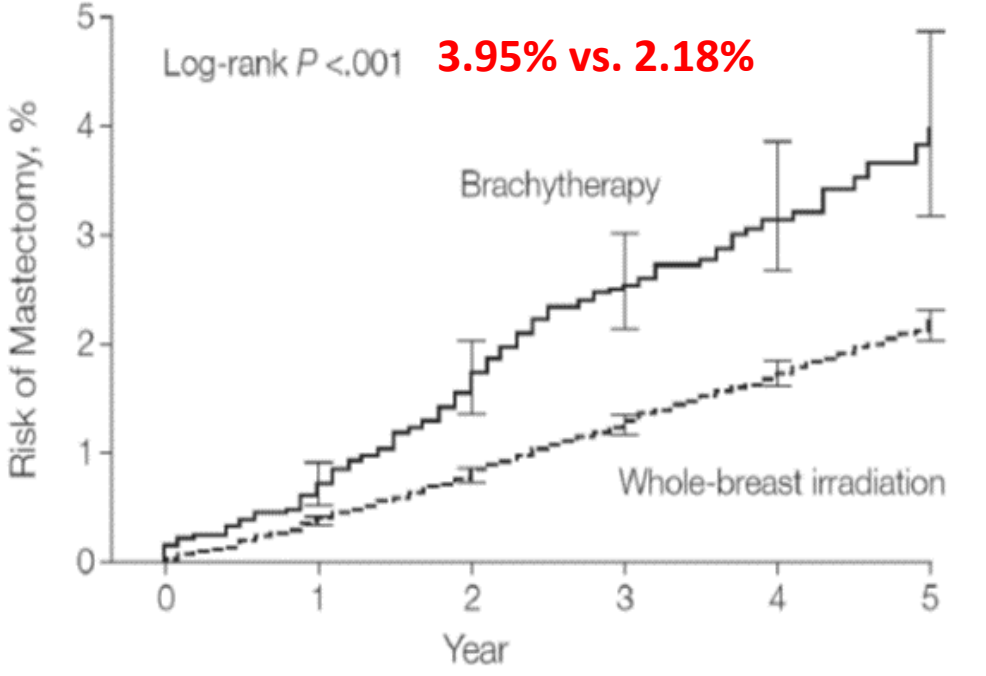

Air inside balloon – small volume, no impact on target coverage
Planning target volume for evaluation (PTV_EVAL)
- equals - planning target volume (PTV)
- equals - clinical target volume (CTV)
5mm inside skin
1 cm
Contoured balloon surface
Air outside balloon – pushes PTV beyond isodose coverage – must be contoured and the percent of PTV
R
Excludes pectoralis muscles and chest wall

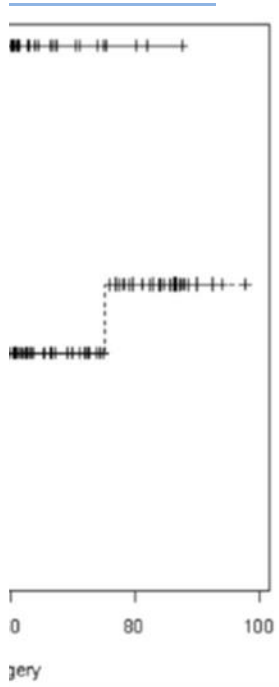
Pros and Cons: technical

- Advantages:
  - Relatively easier application
  - Less expertise required
  - Good to excellent cosmesis (In ASBS registry trial, RO, 2009)
  - Near symmetric geometric distribution
- Disadvantages:
  - Poor balloon conformance
  - Balloon rupture
  - Inadequate skin spacing-may not be suitable in patients with small breast or for tumours located in the upper-inner quadrant because of the requirement for skin-to-cavity distances.
  - Interposition of air or liquids
  - Limited sizes of balloons
  - Not suitable for irregular cavities

Clinical outcome: a word of caution







No. of patients at risk

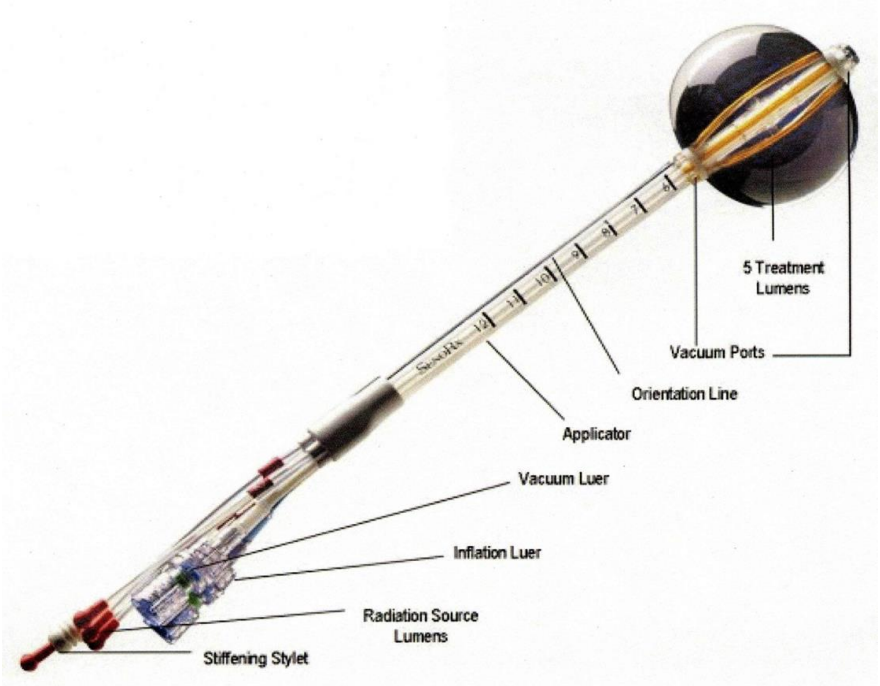
Brachytherapy	6952	6746	4287	2419	1176	442
Whole-breast irradiation	85 783	81 651	62 268	43 704	26 991	11 735

Sur 2013

Smith et al, JAMA 2012

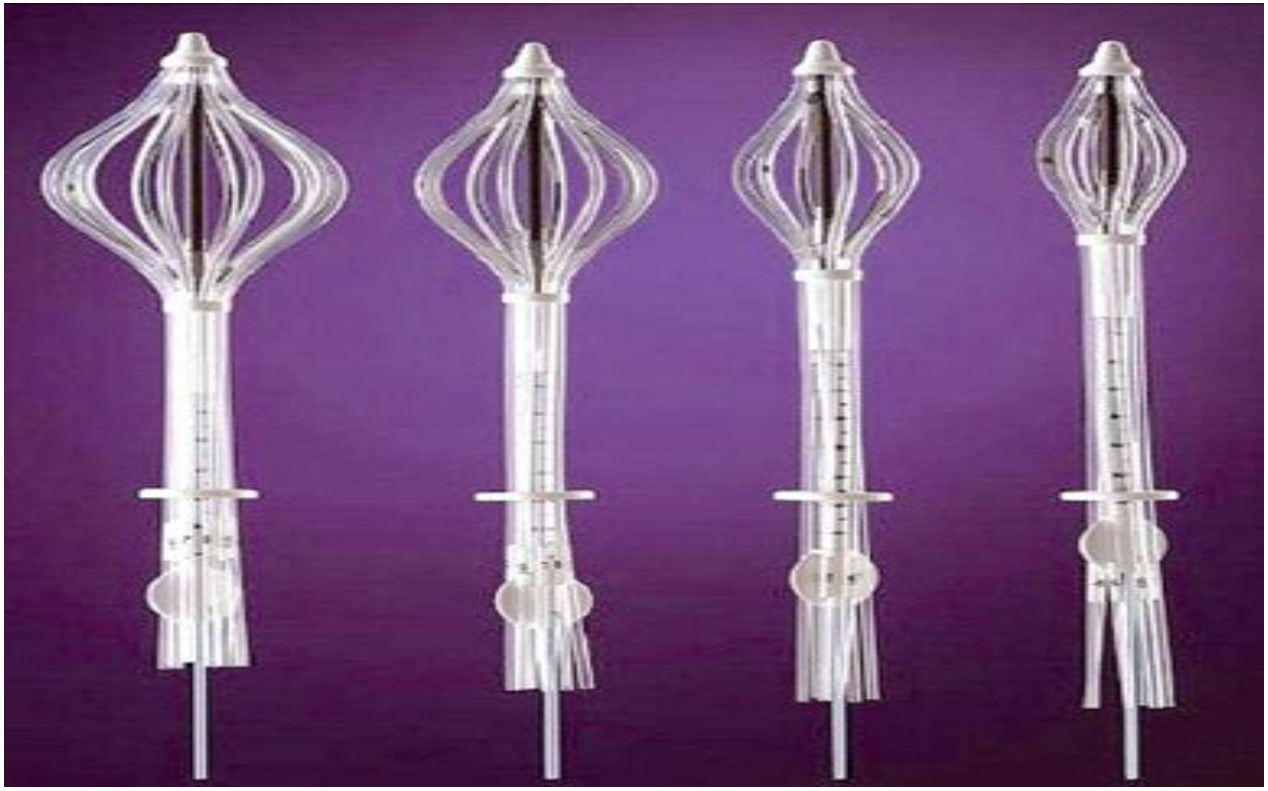
Multi-lumen balloon devices

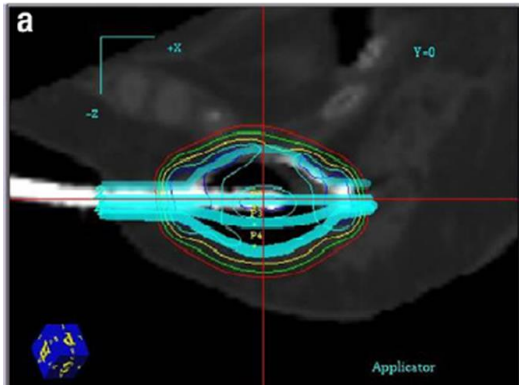
- Next generation balloon applicators to improve upon fixed geometry and inflexible dosimetry of single lumen ones
- 2 such devices:
- A. Contura: has one central lumen with 4 peripheral arched lumens
- B. MammoSite Multi-Lumen: has one central lumen with 3 peripheral lumens

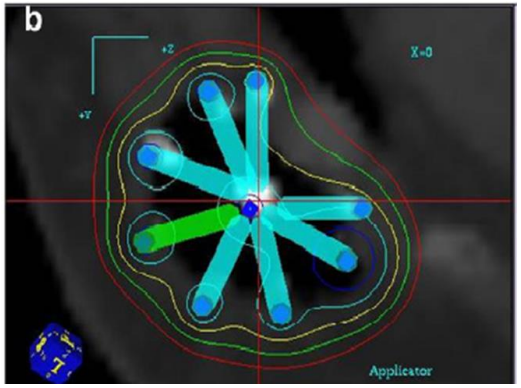


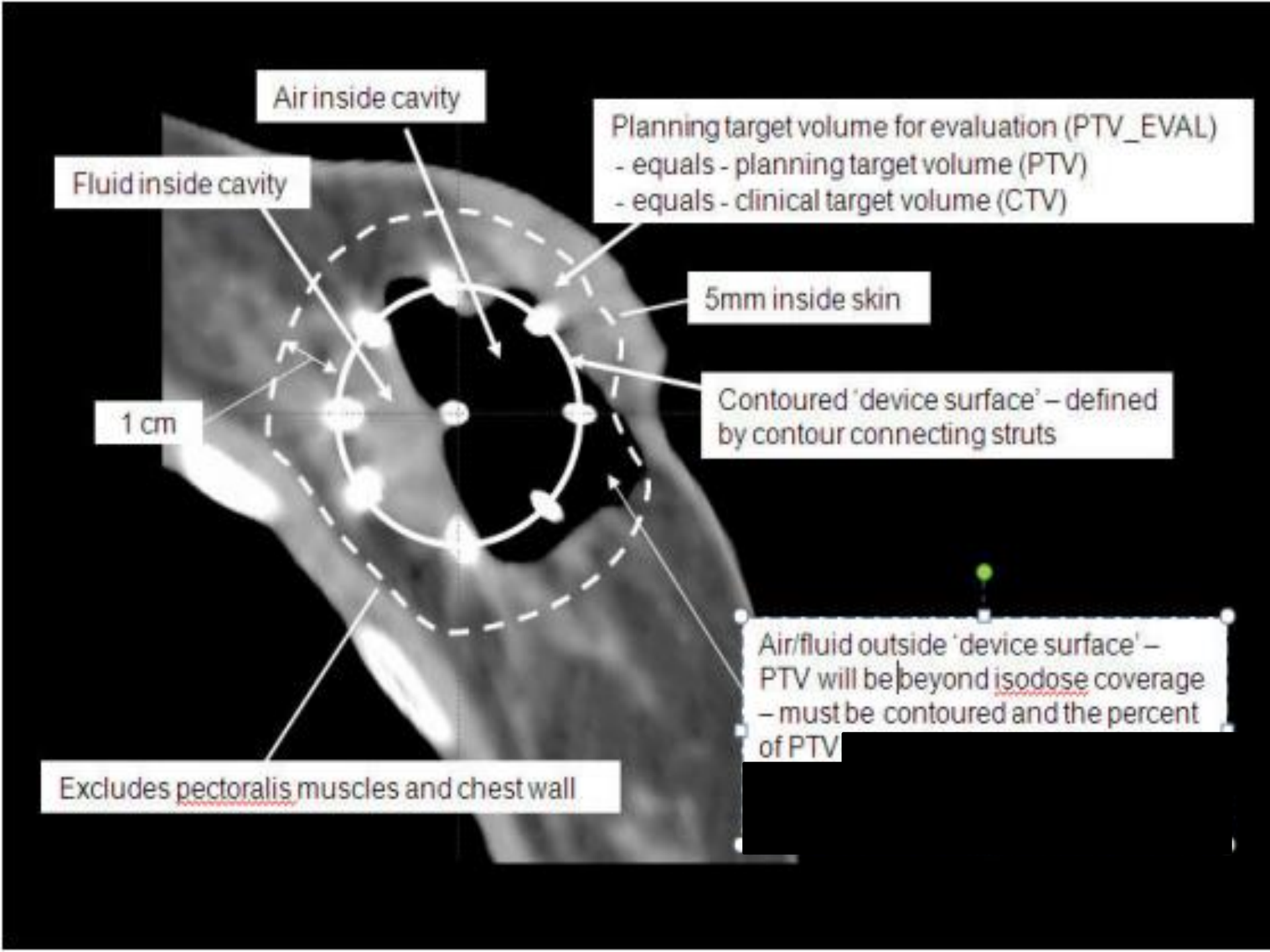
Multi-lumen Cage like device

STRUT ADJUSTED VOLUME IMPLANT (SAVI) : Central strut and 6,8 or 10 peripherally positioned struts/lumen



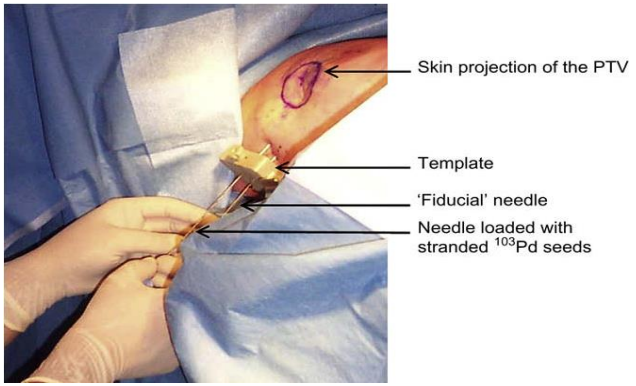


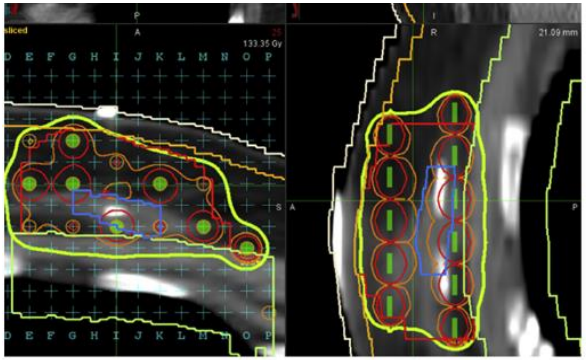


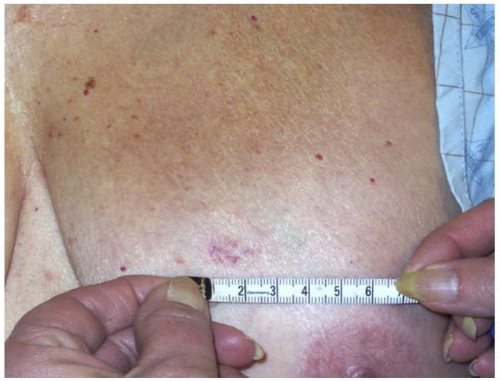

Air inside cavity
Fluid inside cavity
Planning target volume for evaluation (PTV_EVAL)
- equals - planning target volume (PTV)
- equals - clinical target volume (CTV)
5mm inside skin
Contoured 'device surface' – defined by contour connecting struts
1 cm
Air/fluid outside 'device surface' – PTV will be beyond isodose coverage – must be contoured and the percent of PTV
Excludes pectoralis muscles and chest wall

Seed Brachytherapy: Palladium 103

- Patient undergoes a pre-planning CT scan followed by surface marking of the representative points for insertion of seeds
- Size of PTV restricted to 125 cc (median 61 cc)
- Average 75 seeds needed
- Seed activity: 2.5 U/seed (range 2.3-2.7 U)
- Prescribed minimum peripheral dose is 90 Gy.
- Homogeneity criteria: V150 of 60-65% and V200 <25%.
- Planned skin dose is limited to <90% of prescription over 1 cm2.
- Seed insertion is done under ultrasound guidance and general anesthesia using a template
- Discharged next day and advised not to sleep on the same side as well as use Xenoprene shield under the bra for 3 weeks
- Repeat CT at 4 weeks, 6 months and annually
- Main late toxicity is induration (23-40%) and telangiectasia (22-24%)



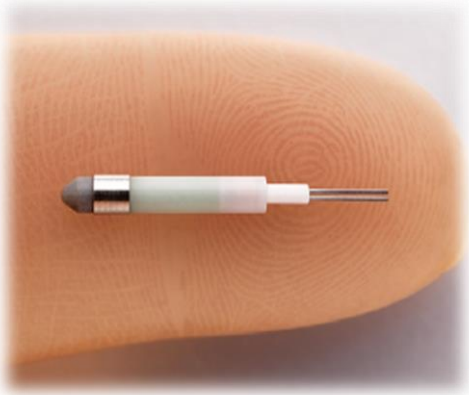


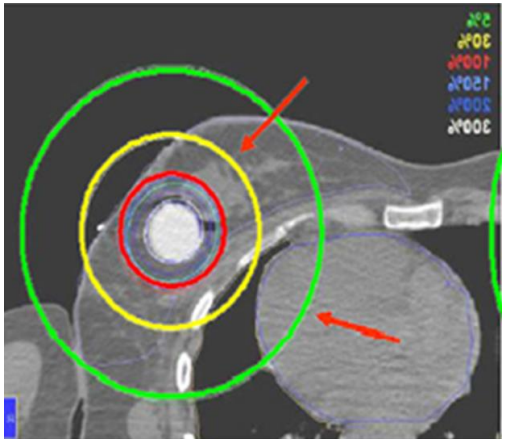


Crook et al, Brachytherapy 2019
Pignol et al, IJROBP 2015)

Electronic Brachytherapy

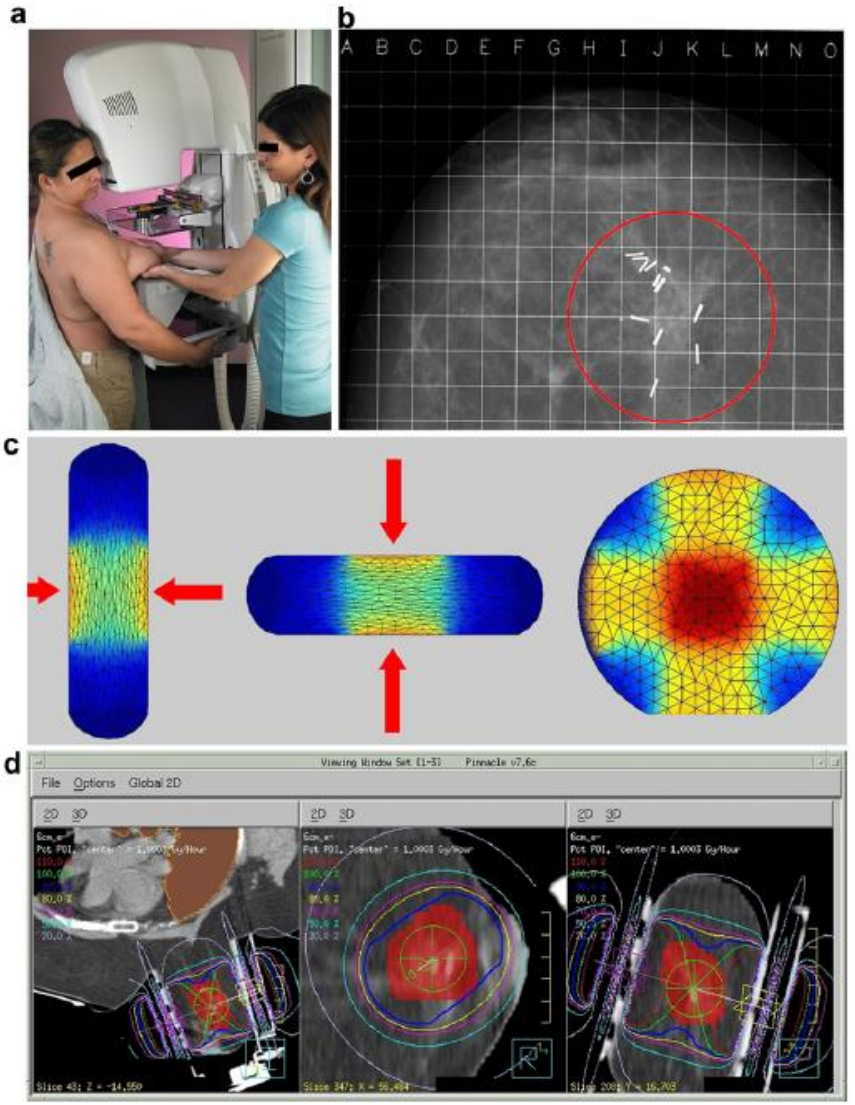
- Utilises electronic generation of kV X-rays instead of a radioactive source
- Example: Axxent X-Ray Source (Xoft) approved by FDA in 2009
- An electronic microminiature X-ray tube: 50 kV X rays are used in breast BT, translating to average energy of 28 keV with radial dose function
- It is a disposable source intended to be used for maximum 10 fractions
- Dosimetric analysis by Dickler et al 2010: Lung and heart doses lower due to rapid dose fall-off. V200 and V300 are higher, approaching constraints for fat necrosis
- ABS guidelines do not recommend this as a modality for APBI (Tom et al, Brachytherapy 2018)





NIBB: Accuboost

- Completely non invasive technique
- Limited clinical experience
- Three-step process:
  - Breast immobilization (compression between two MMG paddles)
  - Imaged-guided target delineation (30kVp X rays)
  - Treatment with collimated photon emission using 192Ir HDR brachytherapy (from two orthogonal angles)



Comparison of APBI brachytherapy techniques

APBI technique	Advantages	Disadvantages
IMB	• Mature clinical experience • Flexible to conform to complex tumor bed geometry	• Invasive—catheters in place for 1 wk • Multiple percutaneous catheters not acceptable to some patients • Placement of catheters is technically demanding and requires specialized expertise
Single-lumen IBB	• Simple insertion technique • Simple spherical dosimetric geometry • Large clinical experience, just beginning to mature	• Invasive—catheter in place for 1 wk • Fixed dosimetric geometry, not flexibility to shape dose especially when skin or chest wall close to balloon
Multilumen IBB	• Simple insertion technique • Simple spherical dosimetric geometry • Improved flexibility to shape dose but limited	• Invasive—catheter in place for 1 wk • Improved flexibility to shape dose but limited • Limited clinical experience
Multilumen cage-like intracavitary brachytherapy	• Simple insertion technique • Flexibility to shape dose	• Invasive—catheter in place for 1 wk • Multiple hotspots at catheter-tissue interface (unclear clinical significance) • Limited clinical experience
EBB	• Simple insertion technique • Simple spherical dosimetric geometry • No vault shielding required • Reduced heart, lung and nontarget breast dose	• Invasive—catheter in place for 1 wk • Fixed dosimetric geometry • Increase surface dose (unclear clinical significance) • Higher RBE (unclear clinical significance) • Limited clinical experience
PBSI	• Single 1-day procedure • Increased convenience • Increased access in remote areas • Flexible to conform to complex tumor bed geometry • LDR may improve therapeutic ratio	• Invasive—single procedure without indwelling catheters • Permanent seeds may not be acceptable to some patients • Not appropriate for large CTV volumes • Not appropriate for large seroma cavities • Limited clinical experience
NIBB	• Noninvasive • Breast immobilization and image guidance • Sparing of nontarget breast tissue compared with external beam techniques	• Skin dose may be increased if there is significant skin overlap between orthogonal axes (exclusion criteria) • Limited clinical experience

APBI = accelerated partial breast irradiation; IMB = interstitial multicatheter brachytherapy; IBB = intracavitary balloon brachytherapy; EBB = electronic balloon brachytherapy; PBSI = permanent breast seed implant; NIBB = noninvasive image-guided breast brachytherapy; LDR = low-dose rate; RBE = radiobiologic effect; CTV = clinical tumor volume.

Intra-operative radiotherapy

- Intra-operative radiation therapy (IORT) refers to the delivery of a single fractional dose of irradiation directly to the tumor bed during surgery.
- Post surgery tissue has rich vascularization, with aerobic metabolism, more sensitive to the action of the radiation (oxygen effect).
- Accurate dose delivery: by permitting delivery of the radiation dose directly to the surgical margins, NO RISK OF GEOGRAPHICAL MISS
- Decreasing healthcare cost because it is one fraction as opposed to 25 fractions.
- Disadvantages: Final pathology not available, extra shielding required, resource intense, expensive technology, inadequate coverage
- Available in two forms: Electron based (ELIOT- Mobetron, NOVAC & LIAC) and X-ray based (TARGIT-Intarbeam)

Dosimetric concerns

- Treatment time ranges from 20-40 mins
- The pyramid shaped lumpectomy is made spherical by wrapping the breast tissue around the applicator
- Movement of the X-ray source by a mm in TARGIT or bevel angle in ELIOT can change the dosimetry significantly

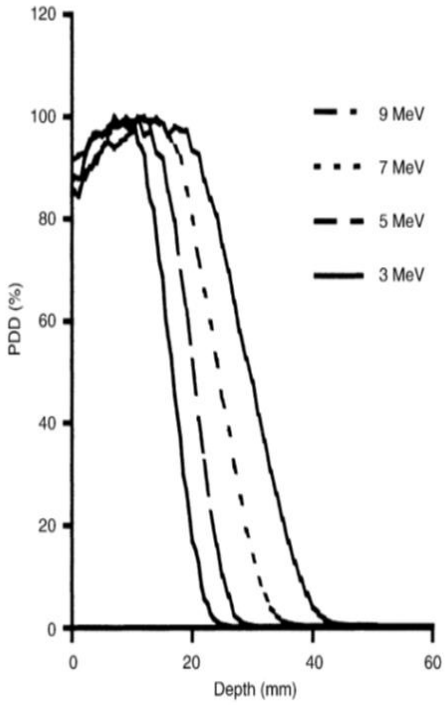


Fig. 2. Percent depth dose curves (PDD) measured in a water phantom for a flat applicator (10 cm diameter).

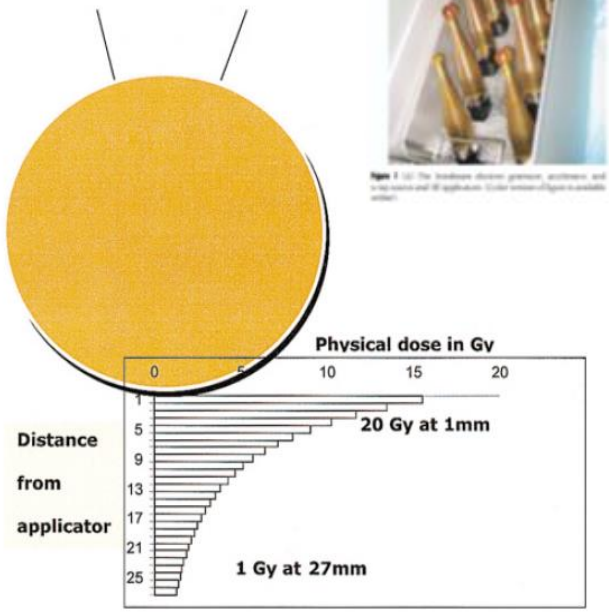
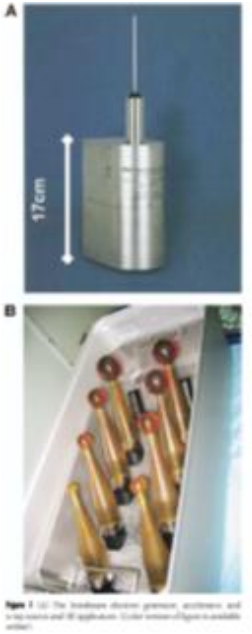


Figure 2 Dosimetry around a 3.5 cm applicator in terms of physical dose with a prescription of 5 Gy at 1 cm.



ELIOT **TARGIT**

Vaidya et al, EJSO 2002
Veronesi et al, EJC 2001

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

Lancet 2014; 383: 603–13

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

- Randomised, 2000- 2012, 3451 patients

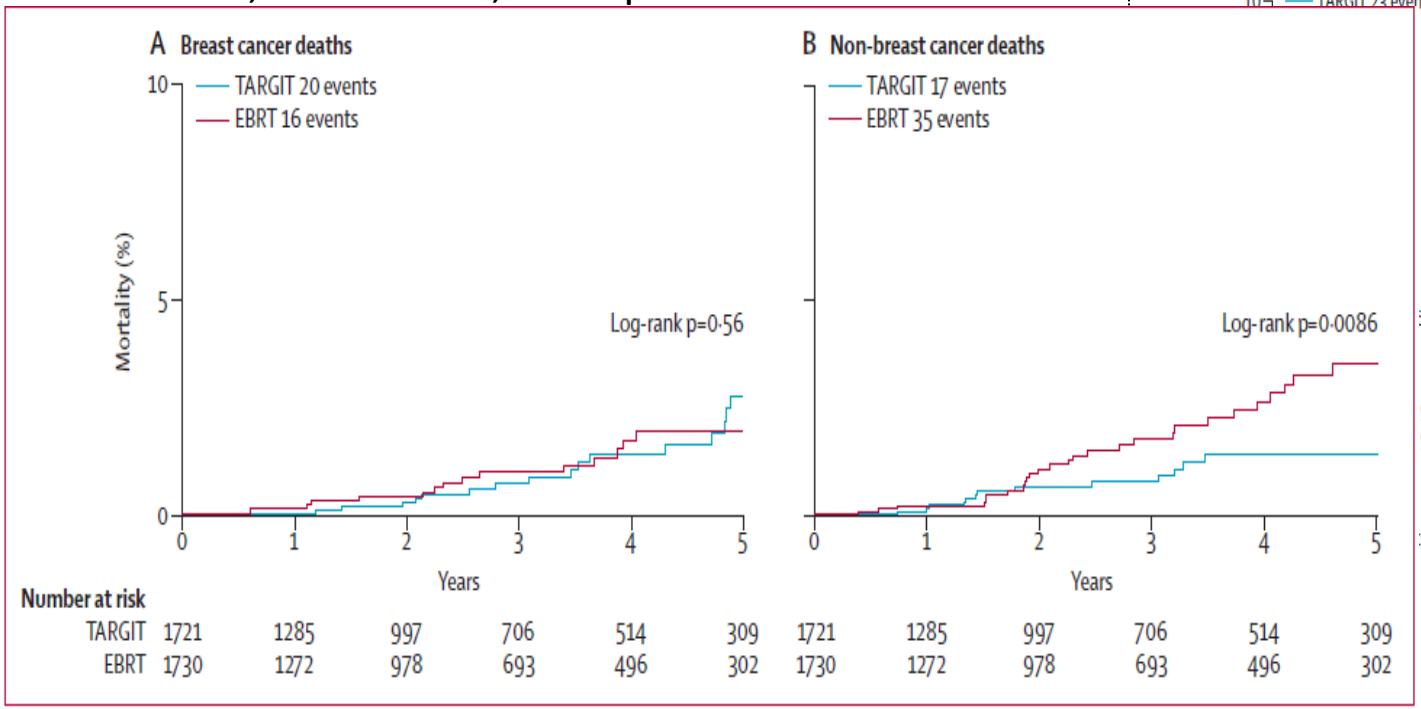
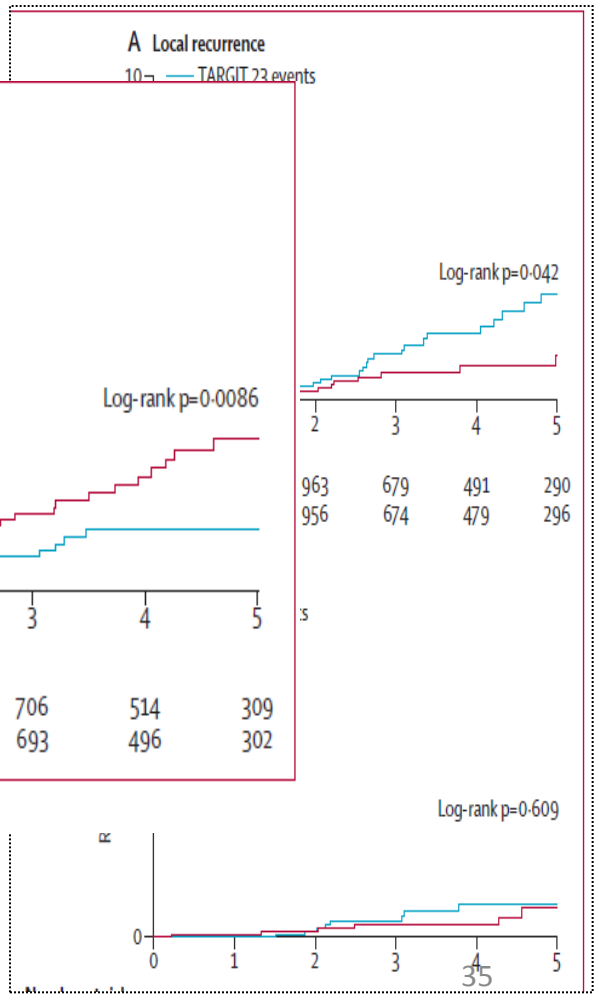
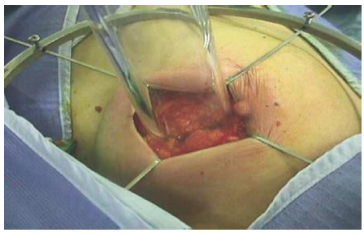


Figure 1: Kaplan-Meier analysis of breast cancer deaths and non-breast-cancer deaths



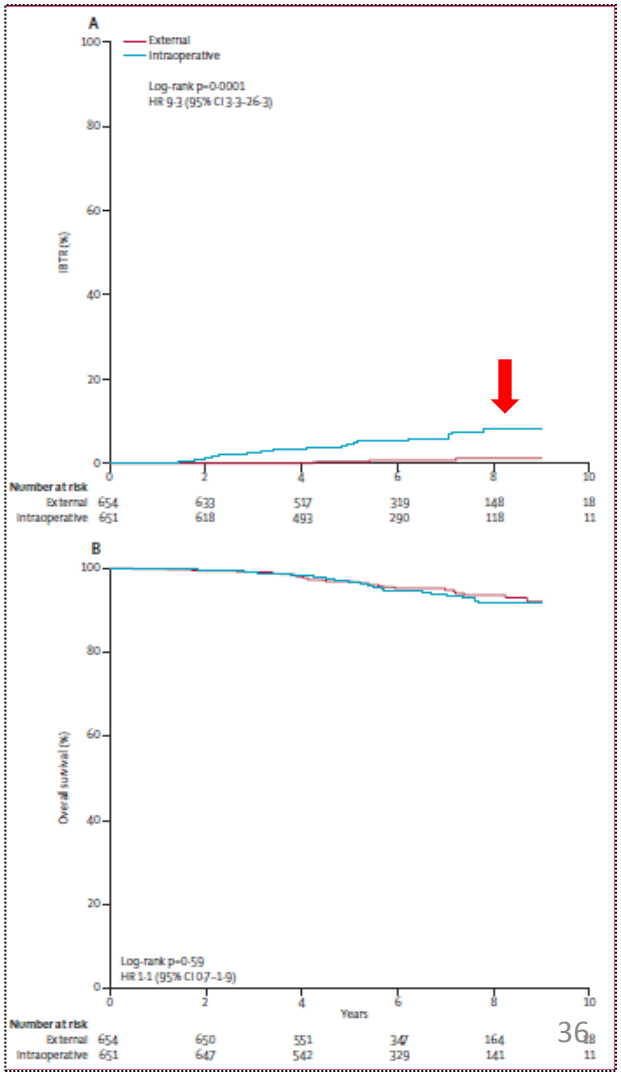
Intraoperative radiotherapy versus external radiotherapy for early breast cancer (ELIOT): a randomised controlled equivalence trial

Lancet Oncol 2013; 14: 1269–77



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, Bettina Ballardini

- 2000-2007, 1305 pts aged 48–75 years
- Medium FU 5.8 years
- Max diameter 2・5 cm
- 1 dose 21Gy during surgery vs WBI
- 35 pts in IORT and 4 in ERT had IBTR (p<0・0001)
- 5-year event rate 4.4% vs 0.4% (HR 9.3)
- 5-year OS 96.8% vs 96.9%
- Fewer skin SE with IORT (p=0·0002)
- Pulmonary fibrosis- 4 in IORT and 38 in ERT (p<0.0001).



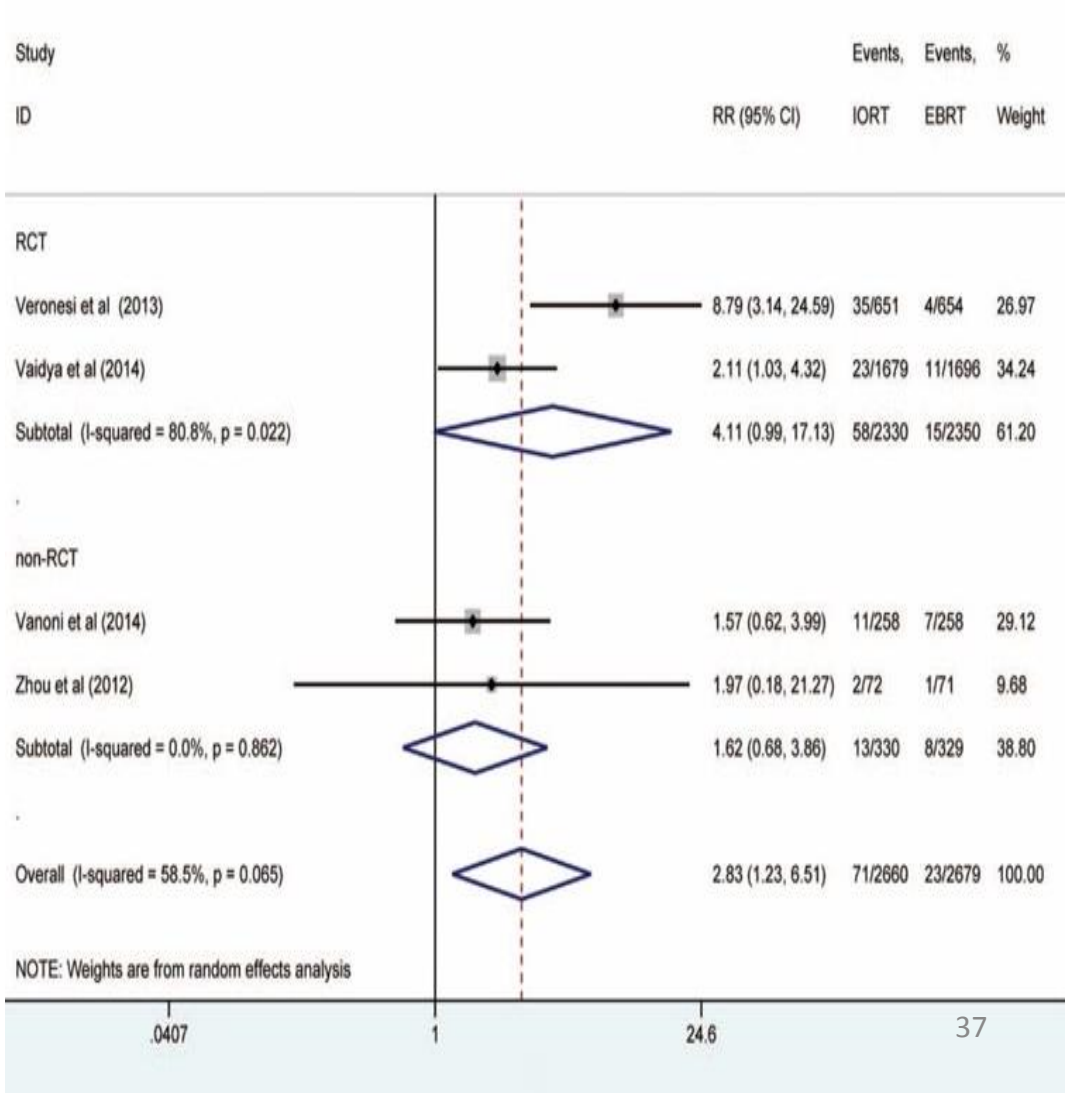
Medicine (Baltimore). 2015 Jul;94(27):e1143. doi: 10.1097/MD.0000000000001143.

Intraoperative Radiotherapy Versus Whole-Breast External Beam Radiotherapy in Early-Stage Breast Cancer: A Systematic Review and Meta-Analysis.

Zhang L[1], Zhou Z, Mei X, Yang Z, Ma J, Chen X, Wang J, Liu G, Yu X, Guo X.

Author information

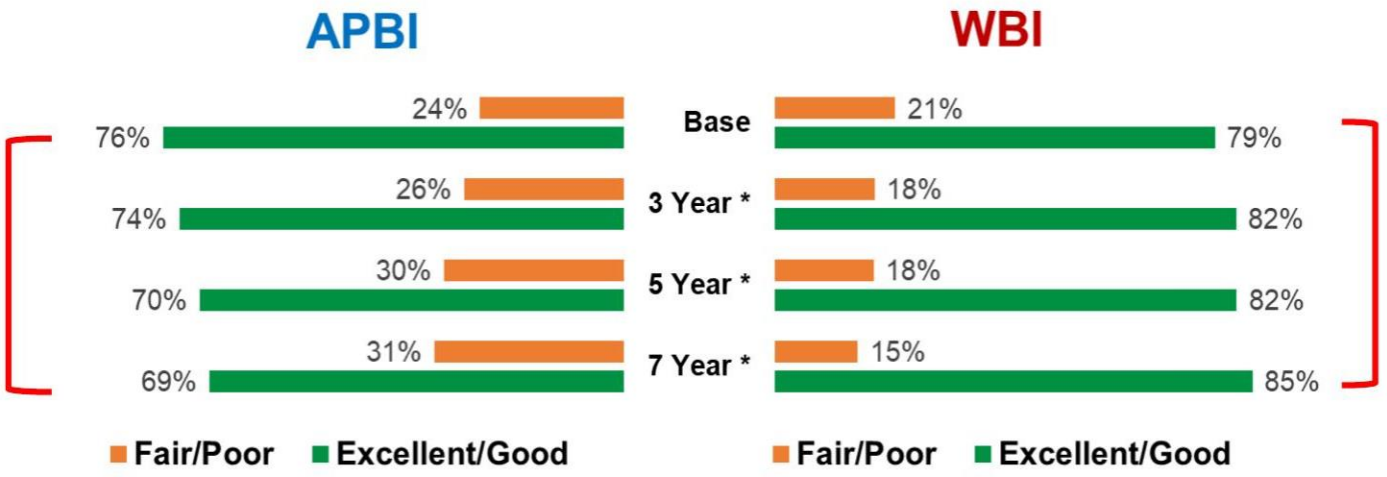
- 4 studies 5415patients (2 RCTs and 2 non-RCTs)
- **IBTR significantly higher IORT vs WBI (RR 2.83)**
- Overall mortality did not differ significantly
- **Prudent selection of suitable patients with low risk of LR necessary**



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

Ivo A. Olivotto, Timothy J. Whelan, Sameer Parpia, Do-Hoon Kim, Tanya Berrang, Pauline T. Truong,

- Median FU 36 months, 2135 patients
- Grade 1/2 toxicities increased with APBI (p 0.001) 35% *v* 17%
- Grade 3 toxicity 4.5% vs. 1% (p <0.001)
- Telangiectasia, breast induration, breast pain increased
- Fat necrosis significantly more likely after APBI (3% *v* 0.9%; *P* .01).
- Inferior cosemsis
- **Conclusion-** Cautioned against the use of 3D-CRT APBI due to increased toxicity



J Clin Oncol 31:4038-4045. © 2013

Accelerated partial breast irradiation using intensity-modulated radiotherapy versus whole breast irradiation: 5-year survival analysis of a phase 3 randomised controlled trial

European Journal of Cancer (2015)

Lorenzo Livi [a], Icro Meattini [a,*], Livia Marrazzo [b], Gabriele Simontacchi [a],

- Increase in dose conformity with more normal tissue sparing.
- >40 yrs, ≤25 mm
- 30 Gy to tumour bed in five non consecutive #
- 520 patients 2004-2013, LR and survival as endpoint
- Median follow-up of 5.0 years
- IBTR rate was 1.5% in both
- 5-year OS 96.6% for WBI vs 99.4% for APBI
- *Better* results considering acute (66.5% vs 19.9%, p = 0.0001), late (11.2% vs 4.5%, p = 0.004), and cosmetic outcome (89.6% vs 95.1%, p = 0.045) with APBI

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

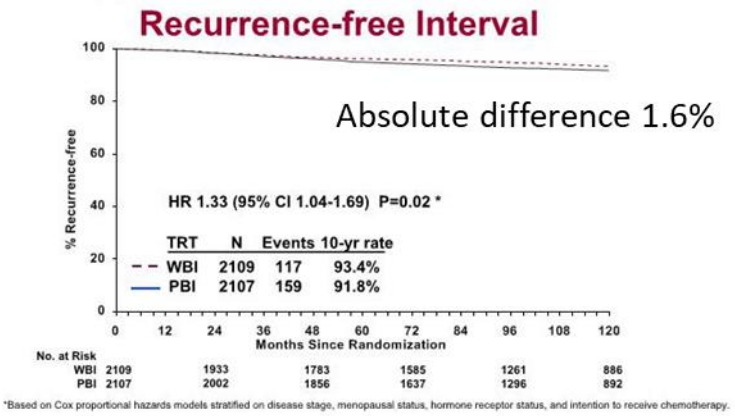
Partial Breast Irradiation prior to Adjuvant Chemotherapy

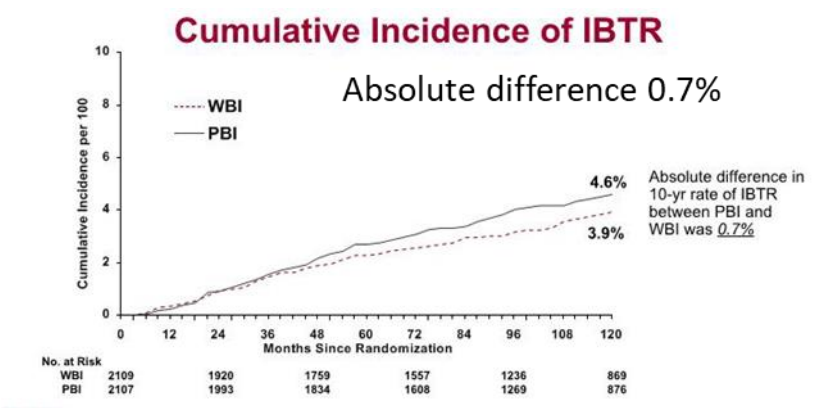
For a total of 10 treatments given on 5 days over 5 to 10 days:

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

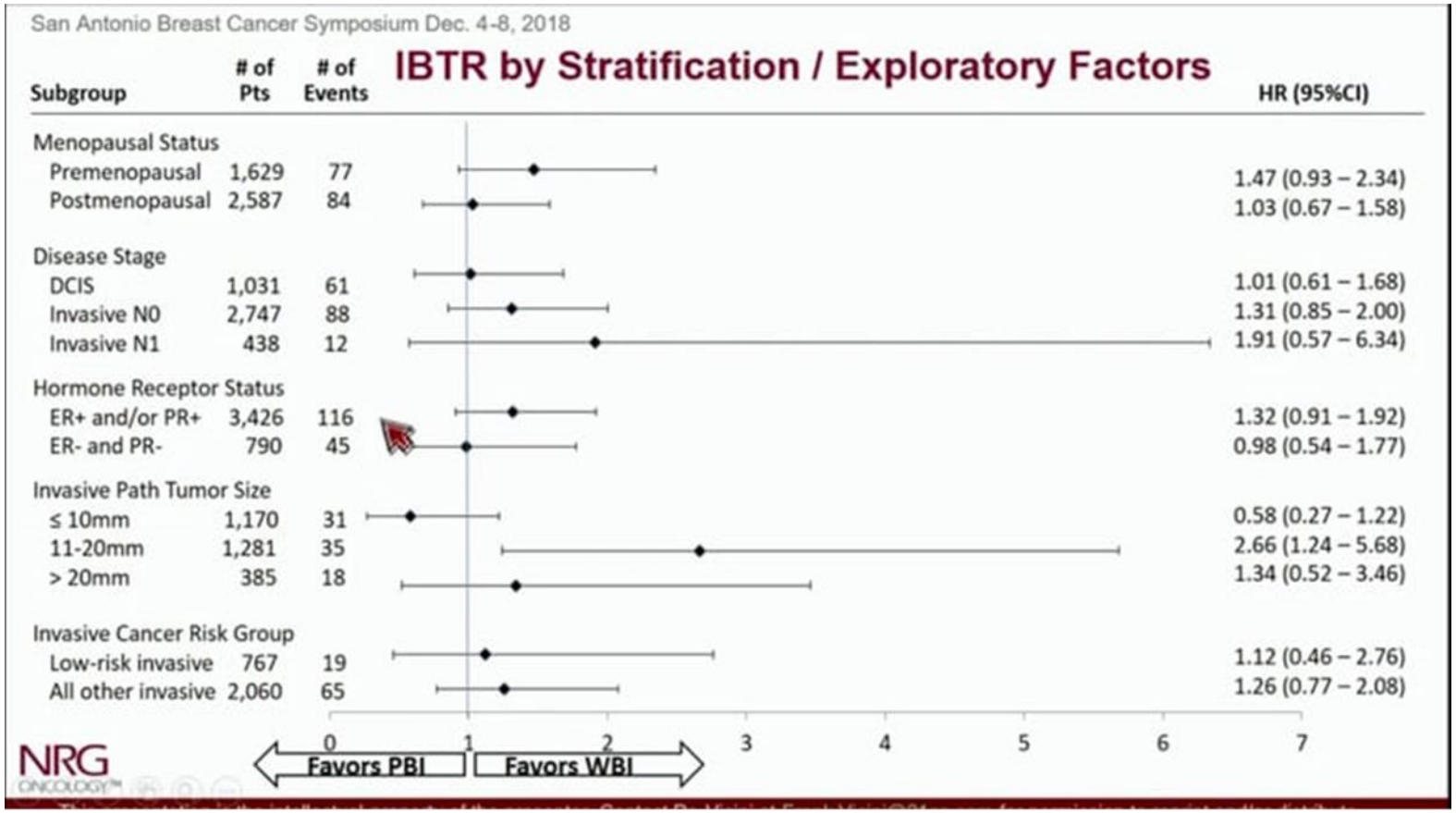
Primary: Ipsilateral Breast Tumor Recurrence (IBTR), both invasive and DCIS, as a first recurrence

Equivalence design with 50% increase in hazard ratio chosen as acceptable margin
Definitive analysis was planned to occur after 175 IBTRs or at 10 years of median FU





No difference in grade 3 and above toxicity 10.5% vs 7.4% or second cancers



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

Take home message

- PBI did not meet the criteria for equivalence to WBI in controlling IBTR on the upper limit of the HR CI (1.58 instead of 1.5)
- The trial results favour the use of PBI for early stage breast cancer as the difference in the absolute rates of local recurrence and any first recurrence are clinically acceptable
- It may be worthwhile not offer PBI to younger women and those with node positive disease till further results on sub-group analysis are available
- The decision on the appropriate PBI technique cannot be made in view of imbalance of numbers across the three techniques
- We already have the safety data for interstitial brachytherapy from another recently published trial of GEC-ESTRO (Lancet 2015)

Radiotherapy and Oncology 118 (2016) 199–204

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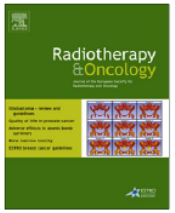

GEC ESTRO breast cancer recommendations

Recommendations from GEC ESTRO Breast Cancer Working Group (II): Target definition and target delineation for accelerated or boost partial breast irradiation using multicatheter interstitial brachytherapy after breast conserving open cavity surgery

Radiotherapy and Oncology xxx (2015) xxx–xxx

Contents lists available at ScienceDirect

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journal homepage: www.thegreenjournal.com

Original article

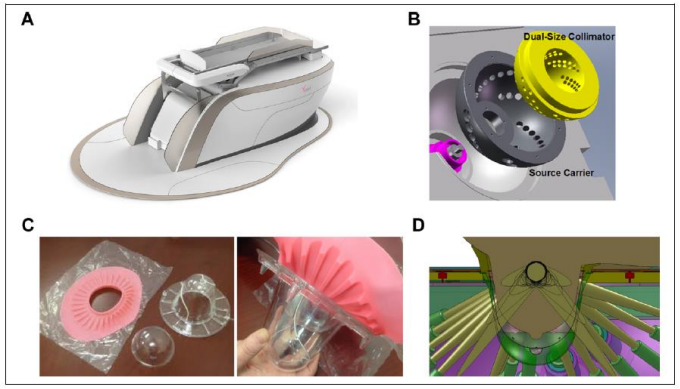
Recommendations from GEC ESTRO Breast Cancer Working Group (I): Target definition and target delineation for accelerated or boost Partial Breast Irradiation using multicatheter interstitial brachytherapy after breast conserving closed cavity surgery

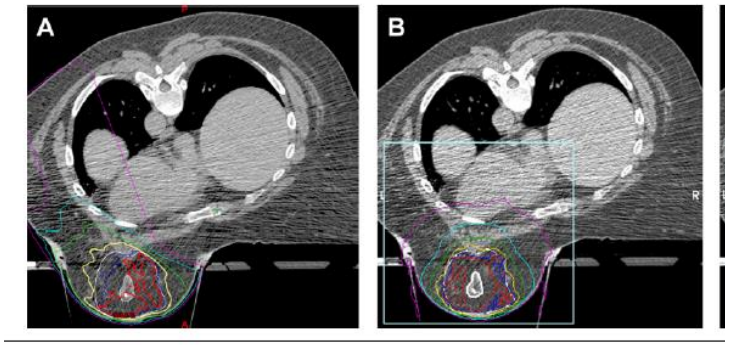
Vratislav Strnad [a,*], Jean-Michel Hannoun-Levi [b], Jose-Luis Guinot [c], Kristina Lössl [d], Daniela Kauer-Dorner [e], Alexandra Resch [e], György Kovács [f], Tibor Major [g], Erik Van Limbergen [h], On behalf of Working Group Breast Cancer of GEC-ESTRO

	MIB (32 Gy in 8 fractions BID) (Strnad , RO 2018)	IMRT (30 Gy in 6 fractions over 2 wks) (Livi, EJC 2015)
PTV coverage	V100 ≥90%	V100% ≥95%
Maximal dose	V150 < 65 cm3 (PTV) V200 < 15 cm3 (PTV) COIN 0.65 (PTV) V_{PD} 300 cm3 (Implant) DNR 0.35 (Implant)	<105%
Minimal dose	NA	>93% (28 Gy)
Uninvolved breast	V90% < 10% V50% < 50%	V15Gy(V50%) <50%
Ipsilateral lung	MLD < 8% D0.1cm3 < 60%	V10Gy <20%
Contralateral lung	NA	V5Gy <10%
Contralateral breast	NA	Dmax <1Gy
Heart	MHD < 8% D0.1cm3 < 50%	V3Gy < 10%
Skin (5 mm shell below the body)	D1cm3 < 90% D0.2cm3 < 100%	NA
Ribs	D0.1cm3 < 90% D1cm3 < 80%	NA

Future Directions

- Newer modalities: Stereotactic radiotherapy (Cyberknife, Gamma pod)
- Protons
- Further acceleration: 1-3 fractions (Hannoun Levi et al, Brachy 2017, Khan et al, IJROBP 2019)
- Pre-operative approach





Ongoing trials of APBI

Trial	Design	N	Inclusion	Control	Experimental	Status
IRMA	Non inferiority	983	≥ 49 years pT1-2 (< 3 cm) invasive carcinoma, pN0- N1 Margins ≥ 2 mm	WBI 45 Gy/18 fractions, or 50 Gy/25 fractions, or 50,4 Gy/ 28 Fractions	3D CRT 38.5 Gy total in 10 fractions (3.85 Gy per fraction), twice a day with an interval of at least 6 Hours over 5 days	Ongoing
SHARE	Equivalence	2796	≥ 50 years, invasive adenoca, T ≤ 2 cm, margin ≥ 2 mm, pNO-pNmi	Standard WBI: 50Gy/25 fractions + 16 Gy boost Hypofractionated WBI: 42.5 Gy/16 fractions or 40Gy/15 fractions over 3 weeks	3DCRT: 40 Gy total in 10 fractions (4 Gy per fraction), twice a day with an interval of at least 6 Hours over 5-7 days	Ongoing

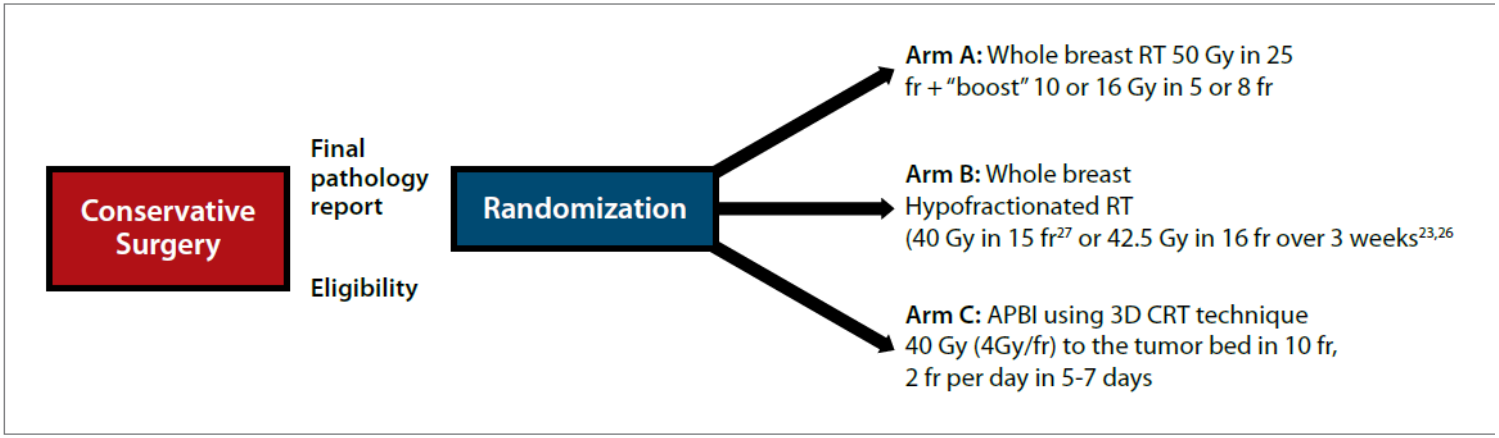


Figure 1. Design of the SHARE trial. APBI=accelerated partial breast irradiation; fr=fractions; HER2=human epidermal growth factor receptor 2; HR=hormone receptor; rt=radiotherapy.

Conclusion: APBI

- Randomized and prospective data from interstitial brachytherapy series: reassuring and can be considered standard in selected women in centers having expertise for the same
- A word of caution for intra-operative techniques
- IMRT better than 3DCRT for APBI
- Adherence to contouring guidelines and dosimetric constraints can be in excellent outcome
- ASTRO-CS not useful for patient selection
- There is still a scope for further acceleration