Accelerated Partial Breast Irradiation with brachytherapy: Targets and Techniques

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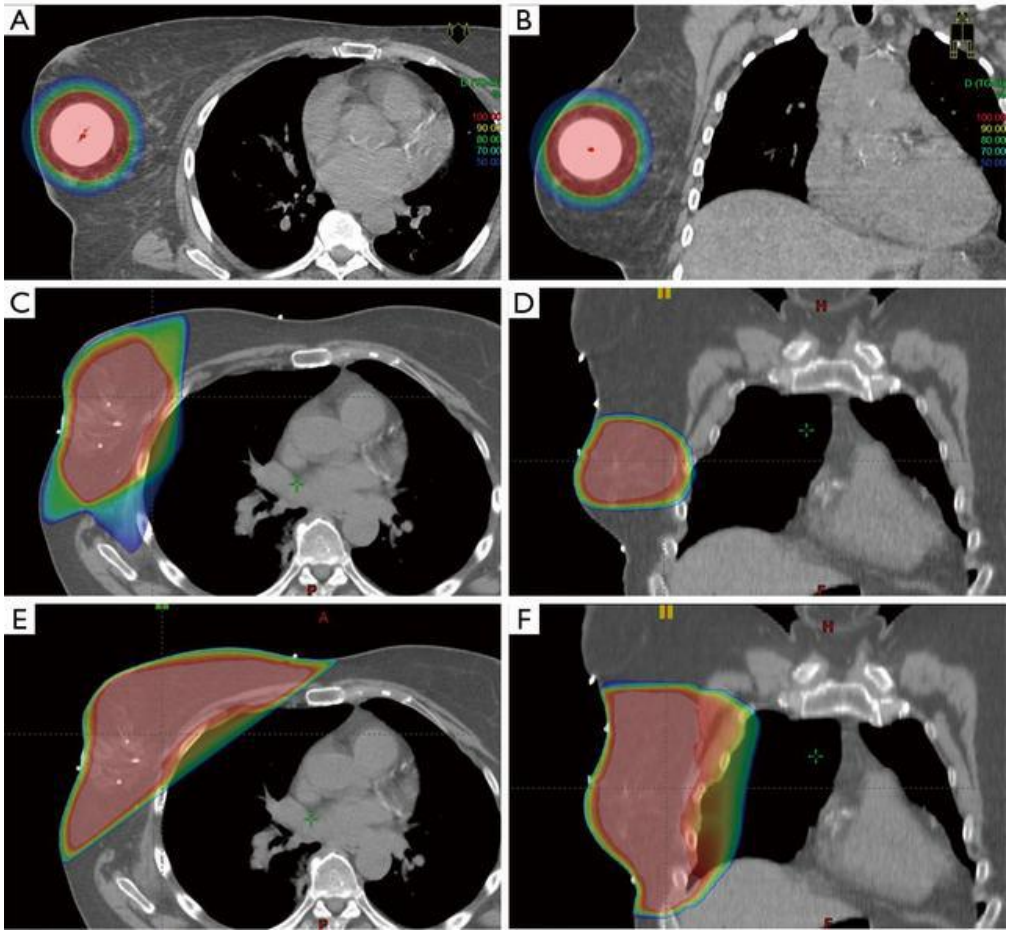
Flow of presentation

- Definition
- Rationale
- Modalities of brachytherapy
- Clinical evidence
- Practical considerations
  - Discuss the technique
  - Target delineation
  - Plan evaluation

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)

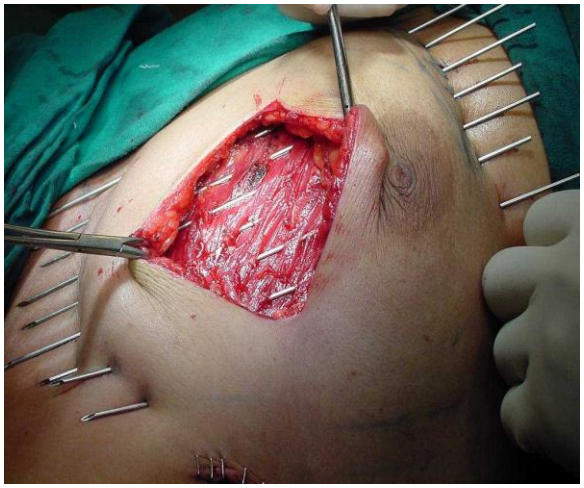
Women opt for mastectomy though eligible for BCS or never receive RT after BCS even in the west

Lazovich DA, JAMA, 1991

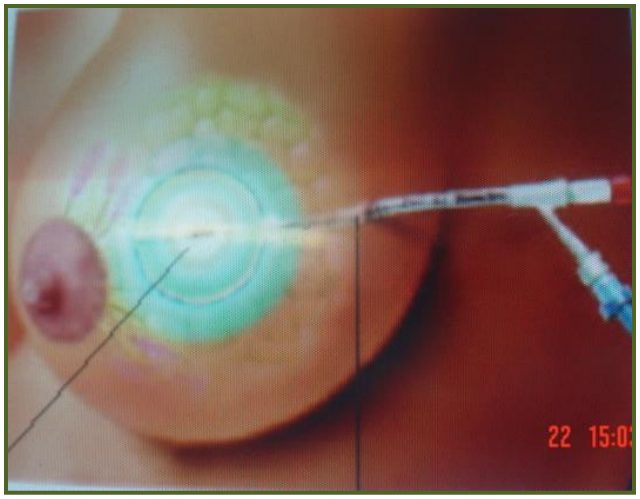
Advances in radiotherapy

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

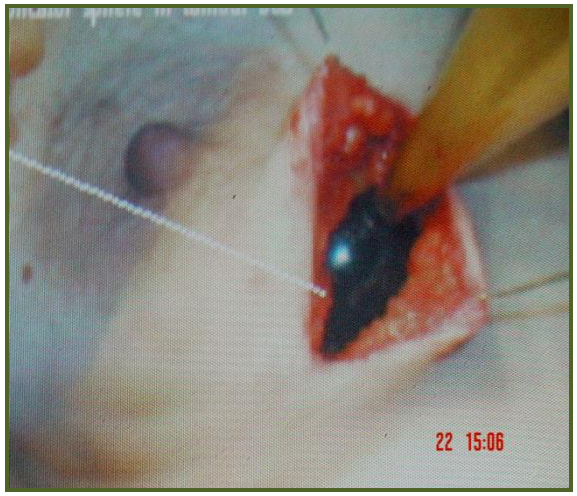
A range of External beam & Brachytherapy techniques for APBI



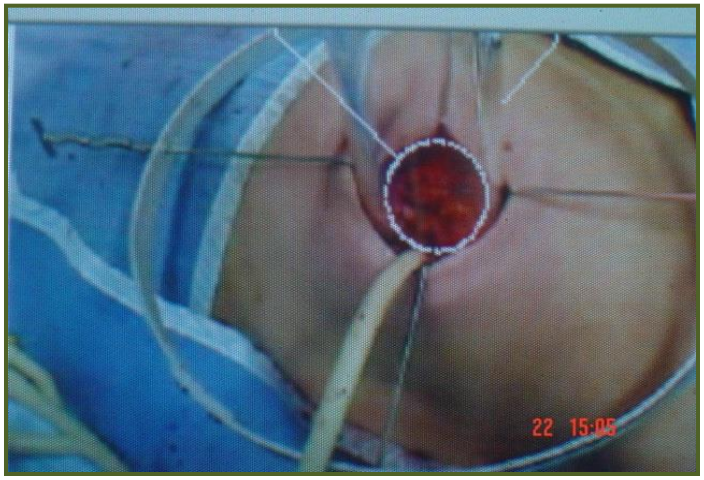
Interstitial Implant



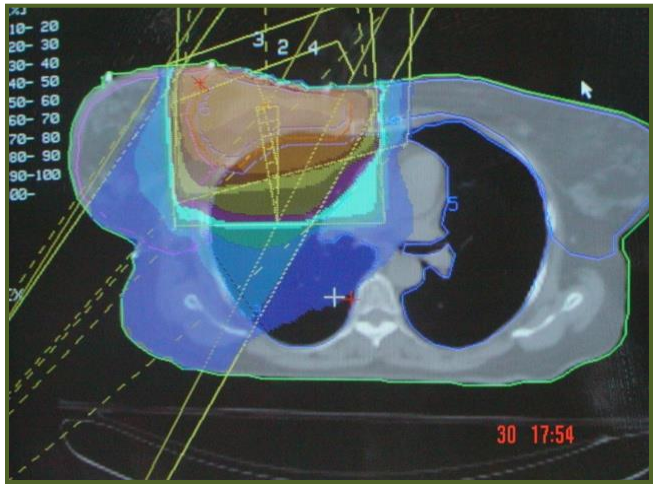
Mammosite



TARGIT



Intra op electrons [ELIOT]



3DCRT / IMRT

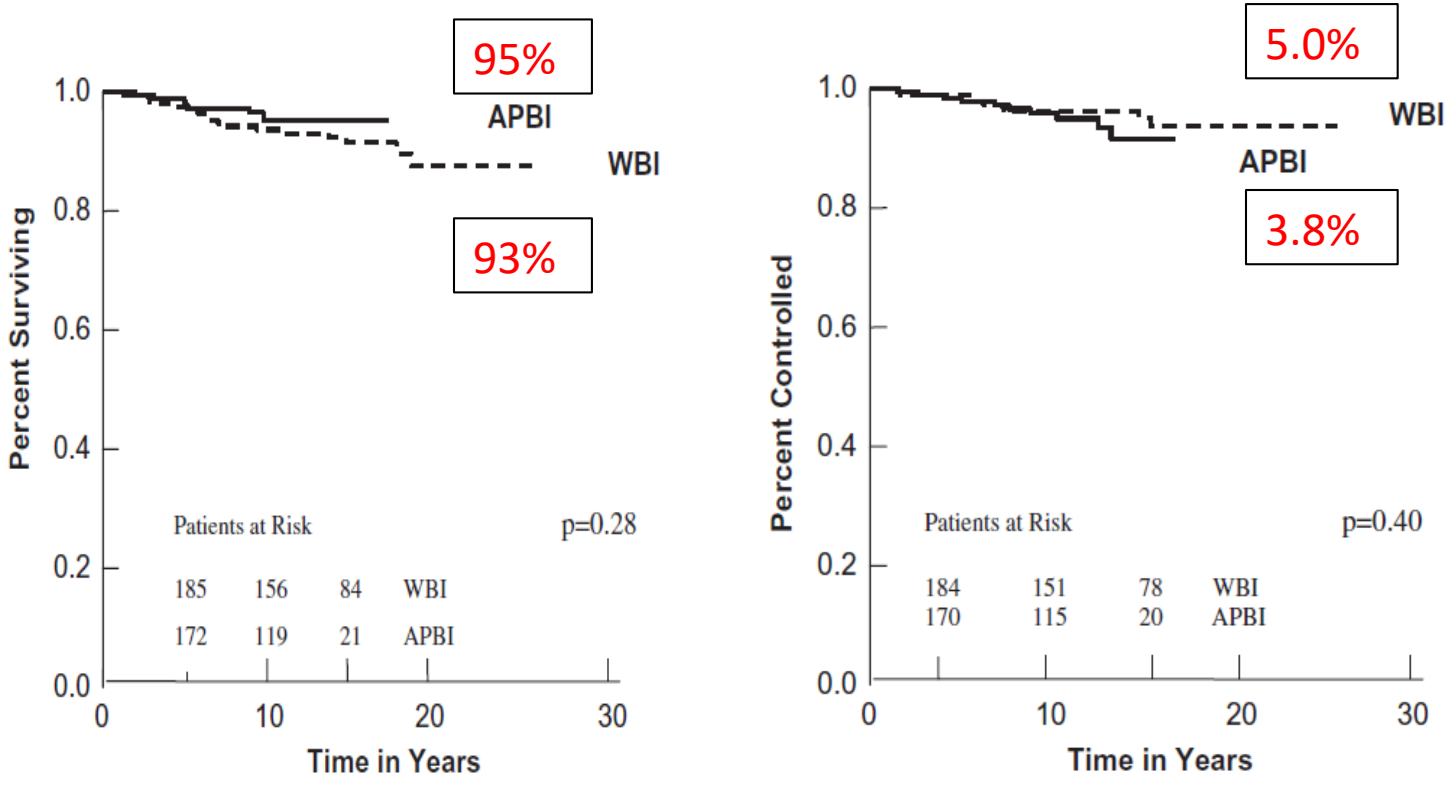
Classification of techniques

- **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:**
  - Intraoperative radiotherapy with electrons (ELIOT)
  - Targeted intraoperative radiotherapy (TARGIT)

- **External beam:**
  - Photons (3DCRT, IMRT, SBRT)
  - 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

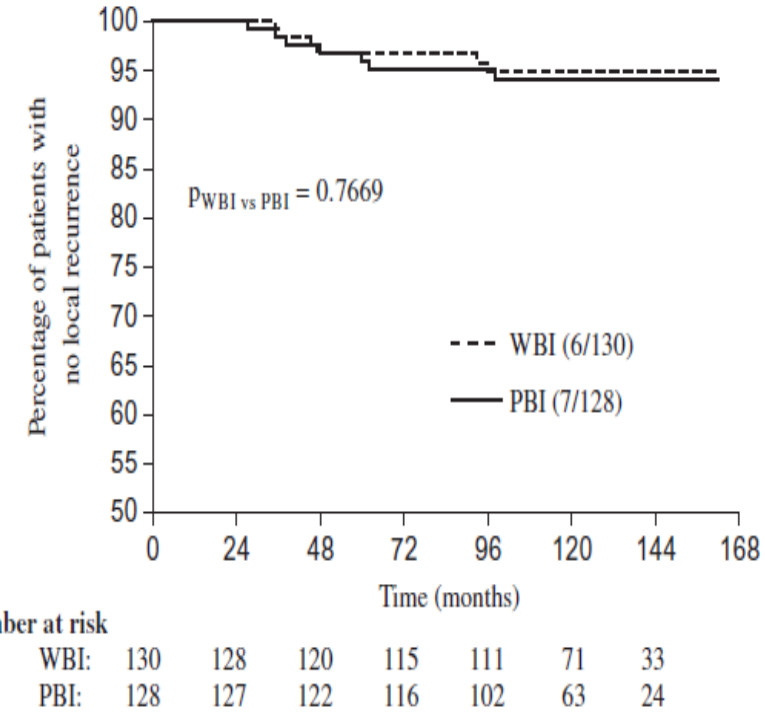
Breast-conserving therapy with partial or whole breast irradiation: Ten-year results of the Budapest randomized trial

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**

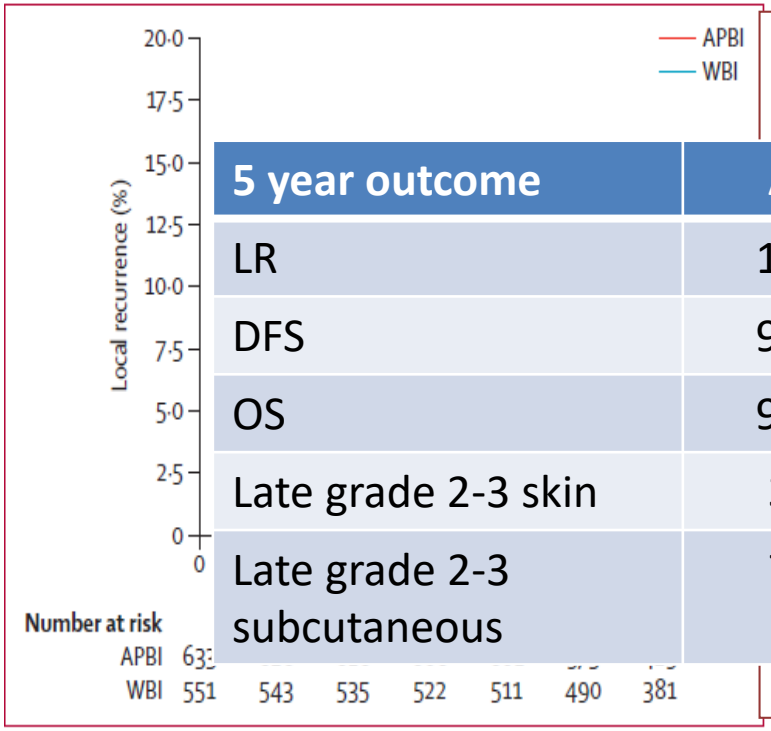


Cosmetic outcome.

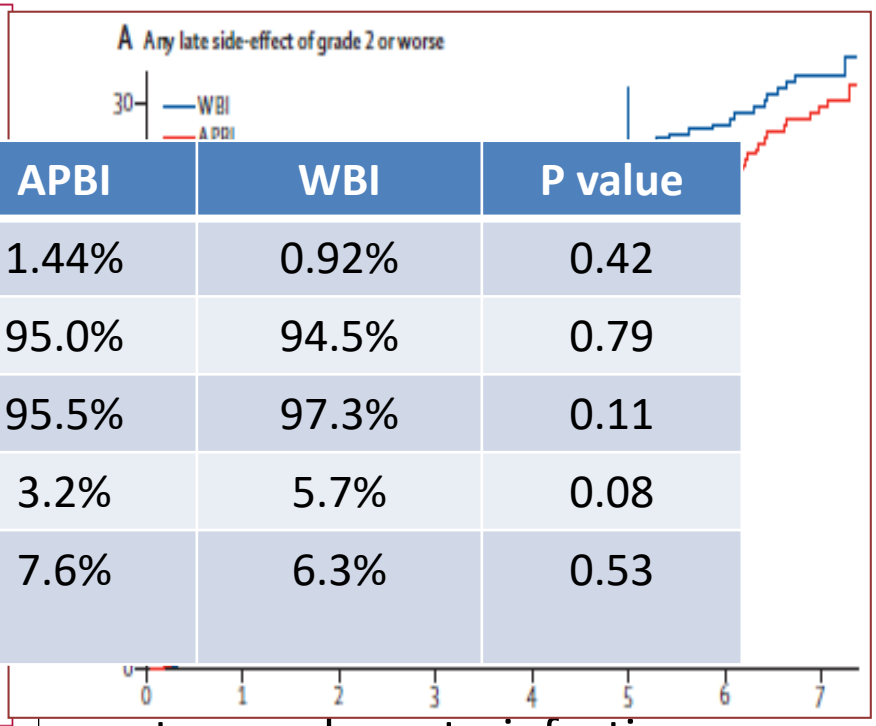
Harvard cosmetic score	PBI – HDR BT ($n = 85$)[a]	PBI – EB ($n = 40$)[a]	WBI – photons ($n = 93$)[a]	WBI – cobalt ($n = 23$)[a]
Excellent	29 (34.1)	7 (17.5)	16 (17.2)	3 (13.1)
Good	43 (50.6)	22 (55.0)	46 (49.5)	8 (34.8)
Fair	11 (12.9)	11 (27.5)	22 (23.6)	11 (47.8)
Poor	2 (2.4)	0 (0)	9 (9.7)	1 (4.3)

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



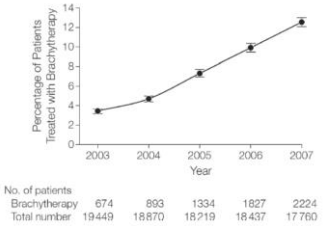
hematoma, breast infection

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

Strnad Lancet 2015 & 2017

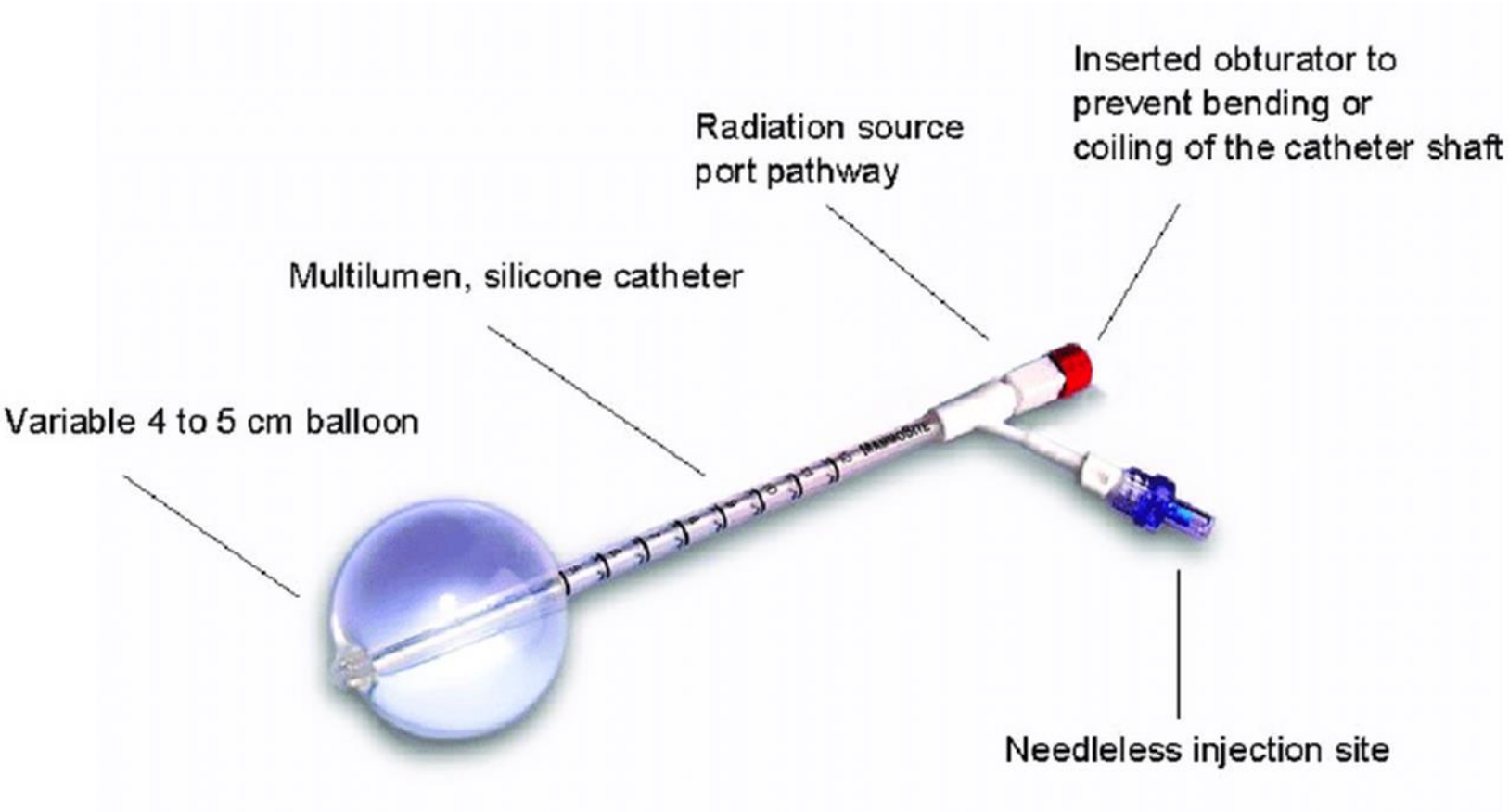
Intracavitary techniques: Tremendous popularity with Mammosite

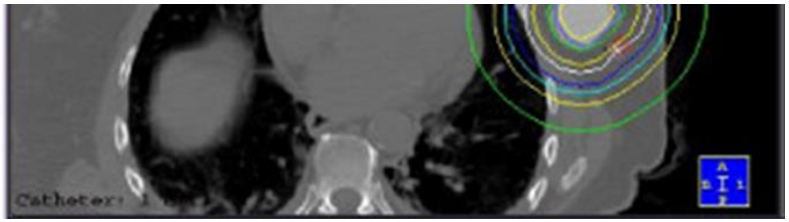
- Approval of MammoSite® (Hologic, Inc., Beford, MA) by the US FDA in May 2002
- The new device was adopted aggressively in non trial setting: better tolerated, reproducible and easy to implant
- Balloon is inflated with saline solution mixed with a small amount of contrast material (35 – 70 ml)
- Balloon 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**

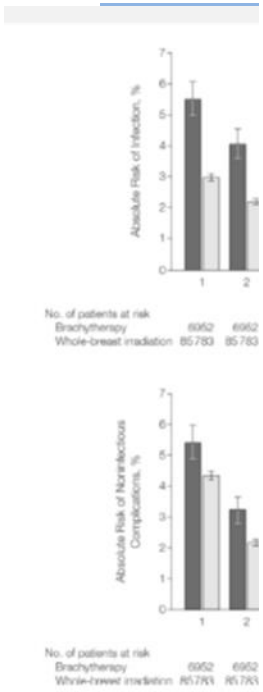


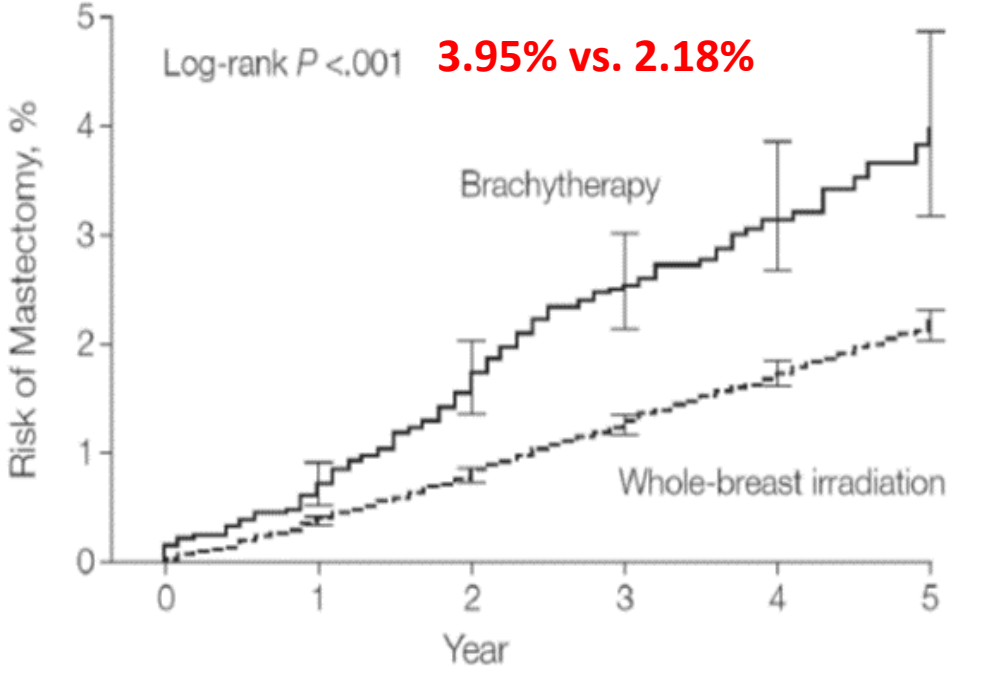


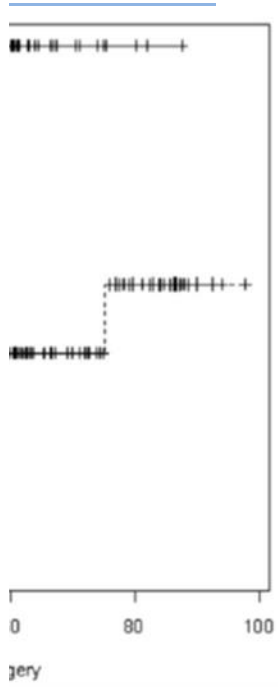
Pros and Cons: technical

- 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

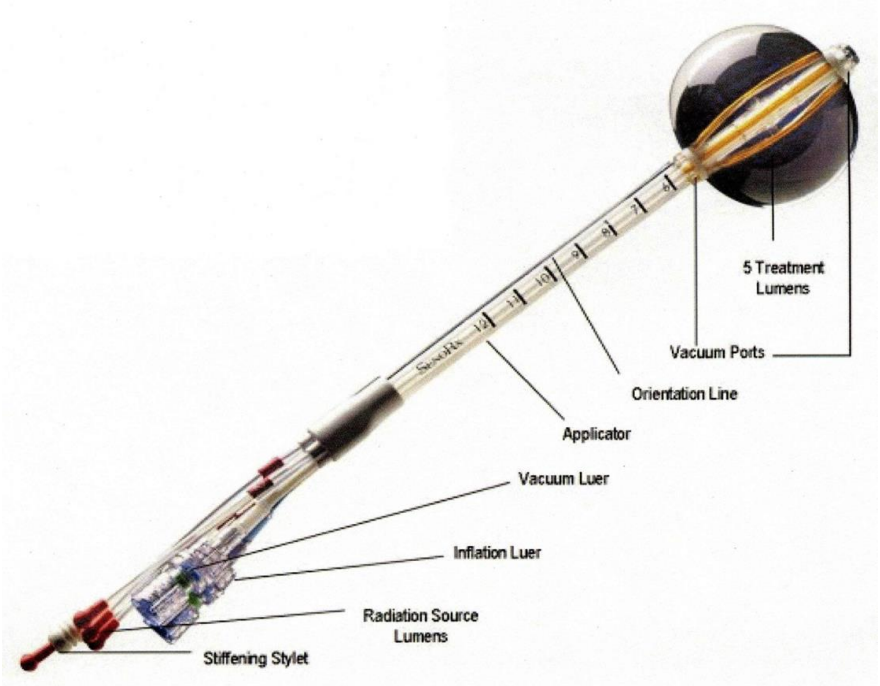
Brachytherapy	6952	6746	4287	2419	1176	442
Whole-breast irradiation	85 783	81 651	62 268	43 704	26 991	11 735

Sur 2013

Smith et al, JAMA 2012

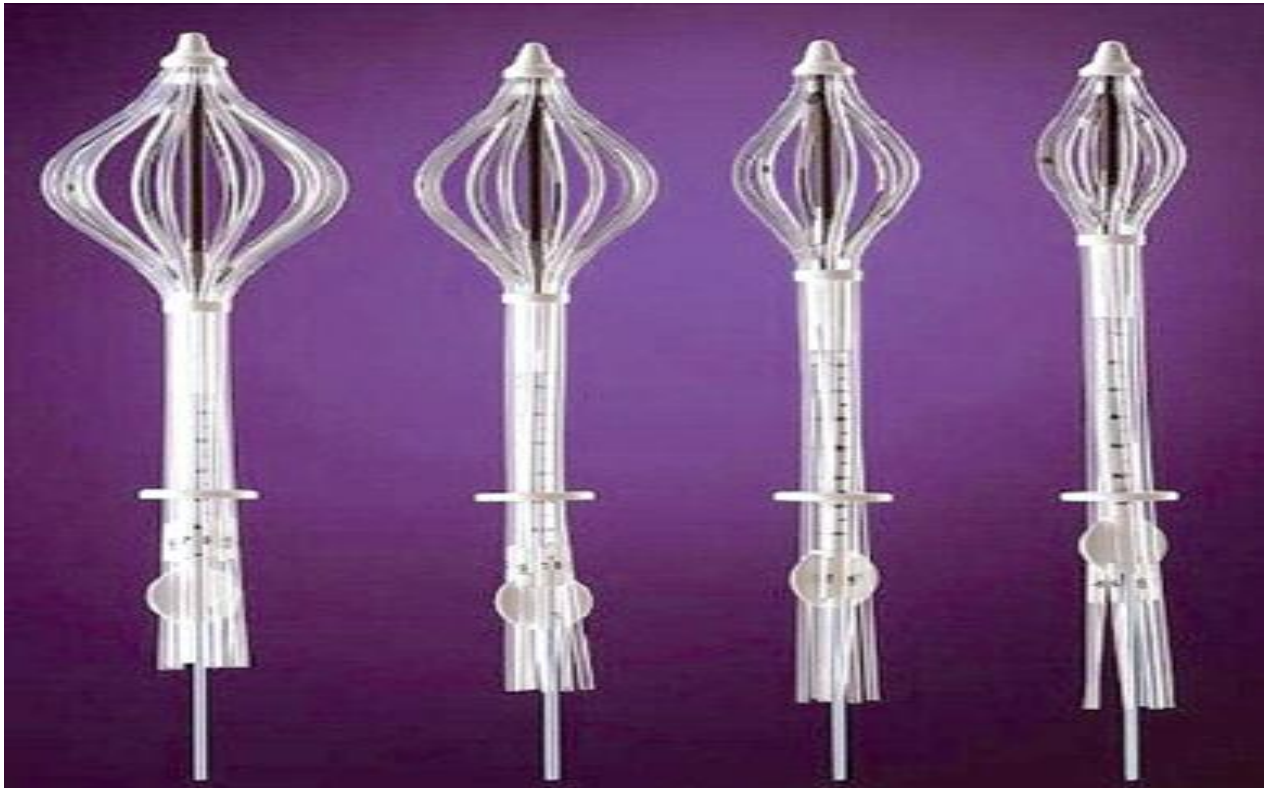
Multi-lumen balloon devices

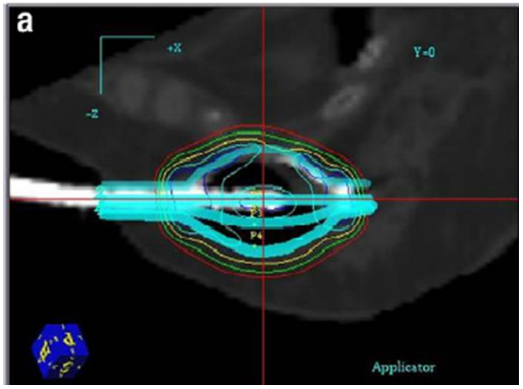
- Next generation balloon applicators to improve upon fixed geometry and inflexible dosimetry of single lumen ones
- 2 such devices:
- A. Contura: has one central lumen with 4 peripheral arched lumens
- B. MammoSite Multi-Lumen: has one central lumen with 3 peripheral lumens

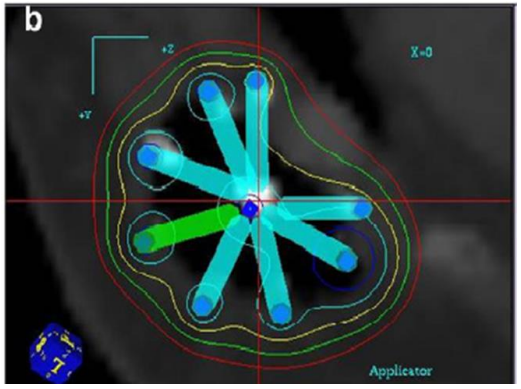


Multi-lumen Cage like device

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

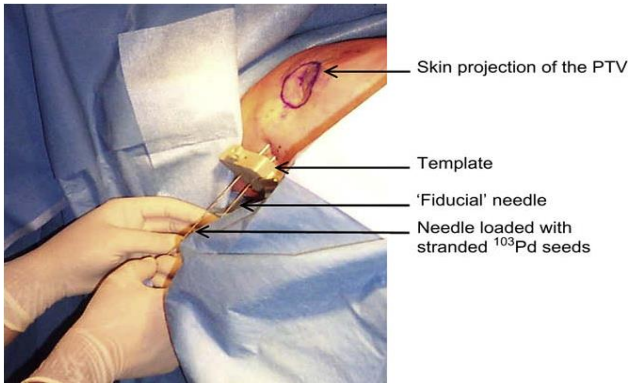


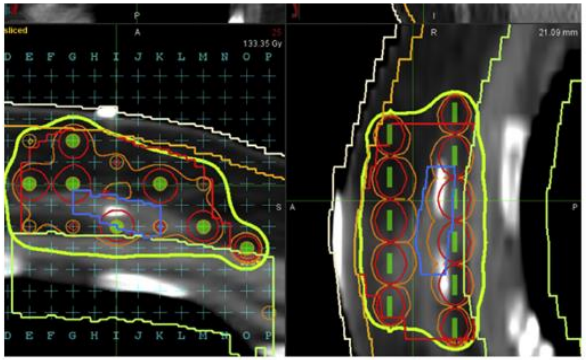


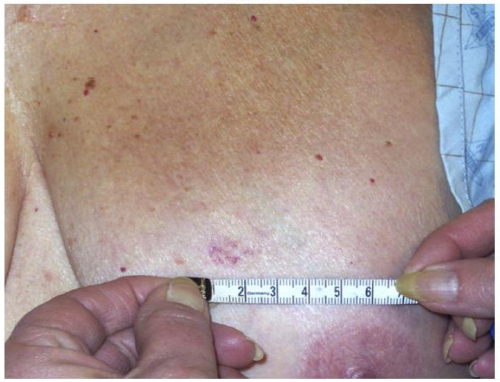


Seed Brachytherapy: Palladium 103

- 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%)



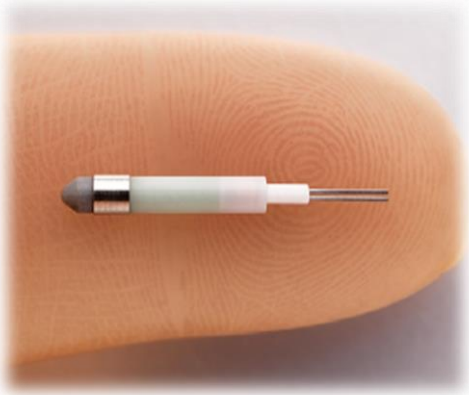


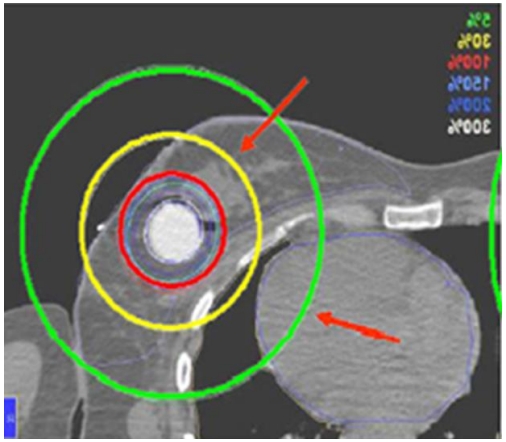


Crook et al, Brachytherapy 2019
Pignol et al, IJROBP 2015)

Electronic Brachytherapy

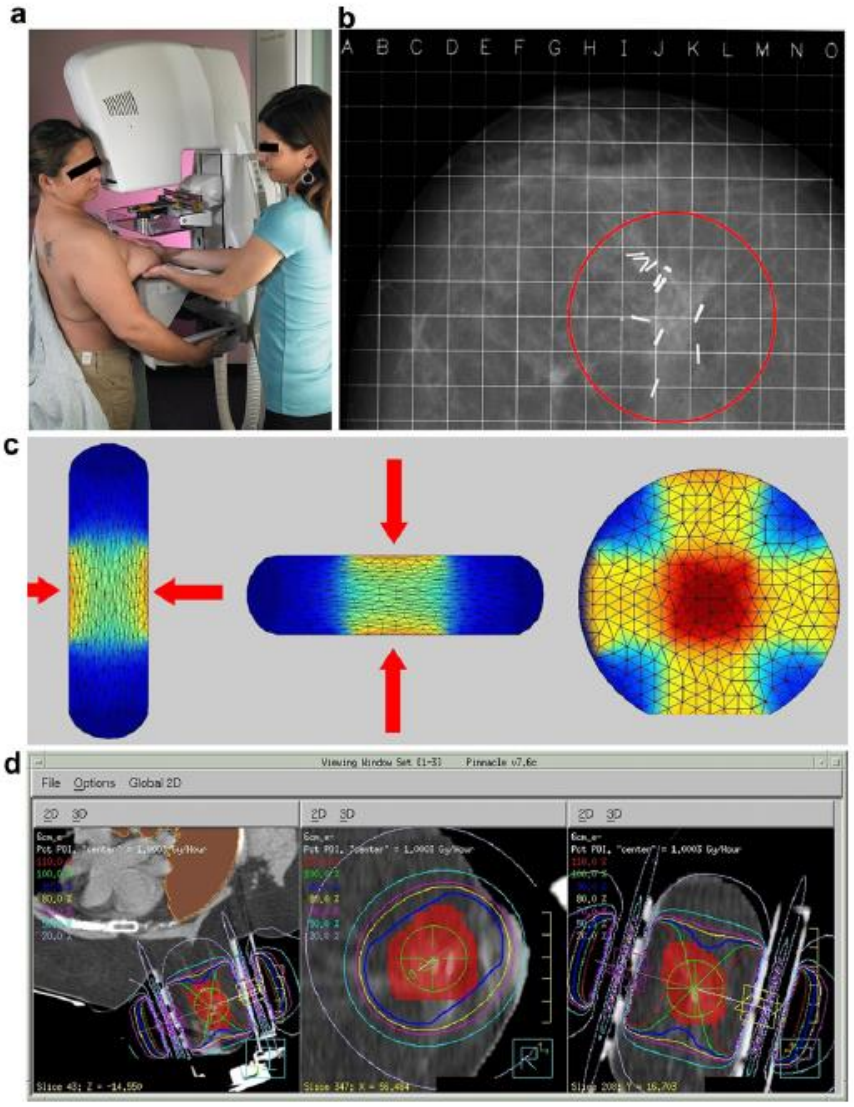
- Utilises electronic generation of kV X-rays instead of a radioactive source
- Example: Axxent X-Ray Source (Xoft) approved by FDA in 2009
- An electronic microminiature X-ray tube: 50 kV X rays are used in breast BT, translating to average energy of 28 keV with radial dose function
- It is a disposable 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)



Accelerated partial-breast irradiation technique summary and guidelines

	Pros	Cons	Recommendation	Utilization
Multicatheter interstitial brachytherapy	Long-term followup Randomized data Cost-effective	Technical complexity	Strong	Off and on protocol
External beam: IMRT	Randomized data—equivalent outcomes, lower toxicity	Increased cost vs. 3D-CRT APBI	Strong	Off and on protocol
Applicator brachytherapy	Ease of use Prospective data Low rates of toxicity	Cost Lack of randomized data	Moderate	Off and on protocol
External beam: 3D-CRT	Least costly APBI technique Noninvasive	Worse cosmesis Increased subcutaneous toxicity/fibrosis	Moderate	Off and on protocol
Proton therapy	Noninvasive Updated results show low rates of toxicities	Small number of patients treated High rates of acute toxicity in initial studies	Weak	On protocol
Intraoperative radiation therapy	Single treatment	Higher rates of local recurrence Up to 20% require whole-breast irradiation Low-energy: question of volume coverage	Weak	On protocol
Electronic brachytherapy	Single treatment	Small number of patients treated Lack of long-term clinical outcomes Lack of mature toxicity outcomes	Weak	On protocol

IMRT = intensity-modulated radiation therapy; 3D-CRT = three-dimensional conformal radiotherapy; APBI = accelerated partial-breast irradiation.

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

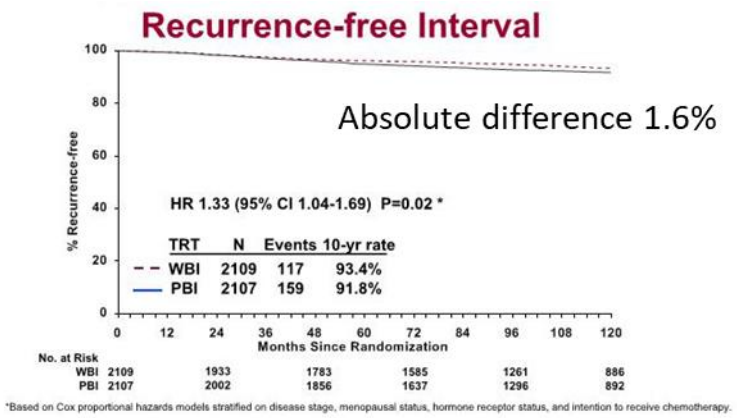
Partial Breast Irradiation prior to Adjuvant Chemotherapy

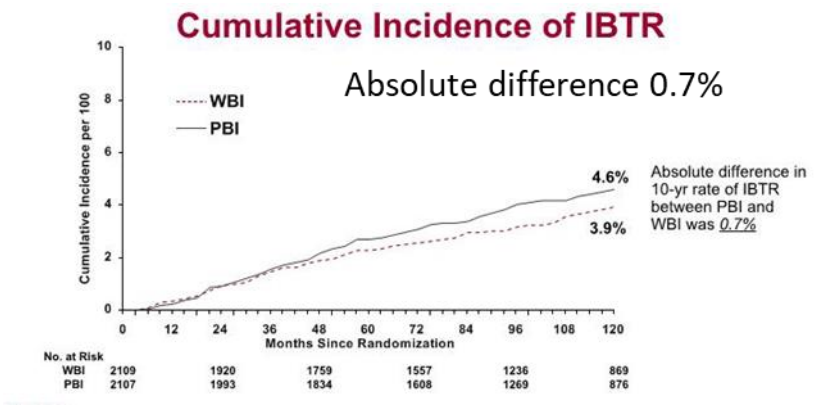
For a total of 10 treatments given on 5 days over 5 to 10 days:

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

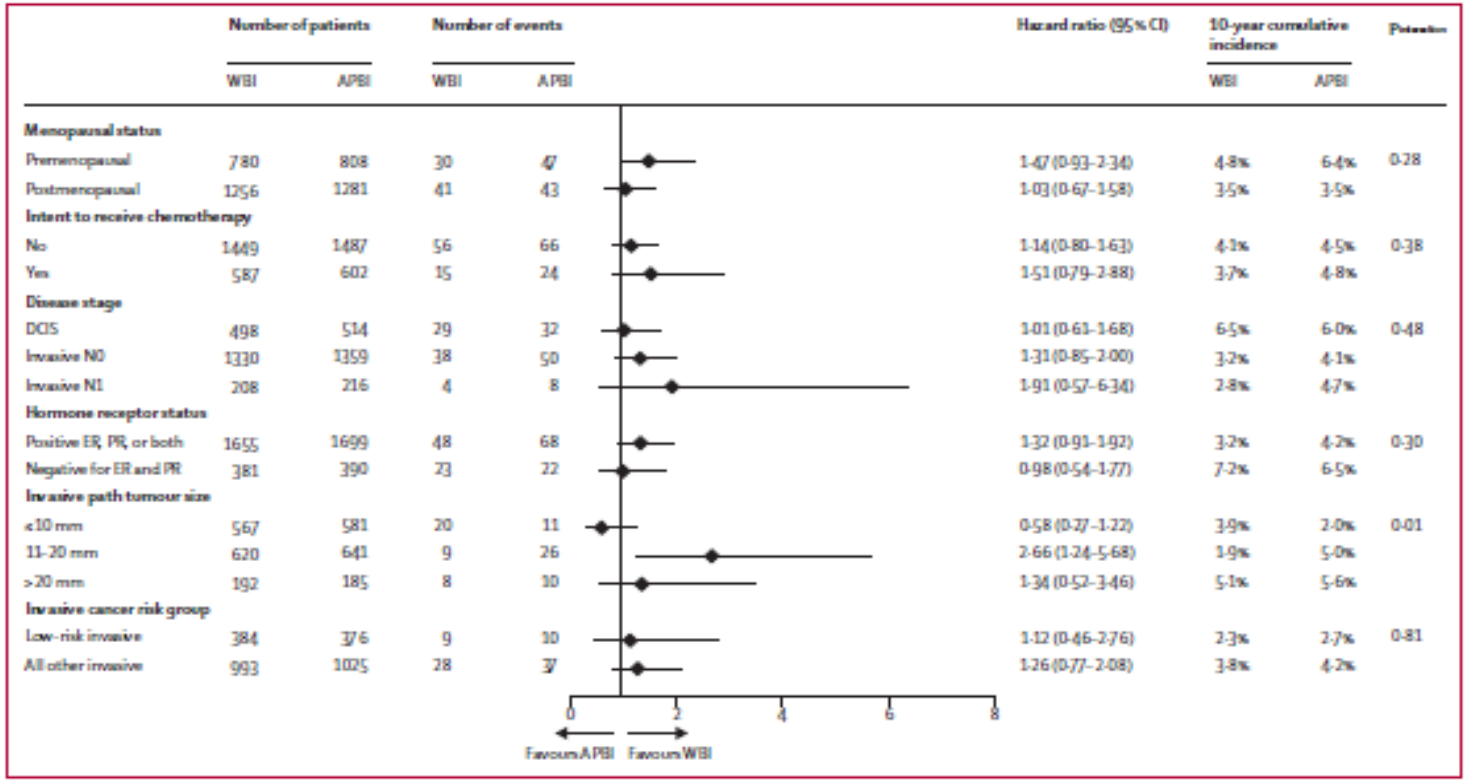
Primary: Ipsilateral Breast Tumor Recurrence (IBTR), both invasive and DCIS, as a first recurrence

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 DFS and OS, grade 3 and above toxicity (10.5% vs 7.4%) or second cancers



	Number of patients		Number of events		Hazard ratio (95% CI)	10-year cumulative incidence		Interaction
	WBI	APBI	WBI	APBI		WBI	APBI	
Menopausal status								
Premenopausal	780	808	30	47	1·47 (0·93–2·34)	4·8%	6·4%	0·28
Postmenopausal	1256	1281	41	43	1·03 (0·67–1·58)	3·5%	3·5%	
Intent to receive chemotherapy								
No	1449	1487	56	66	1·14 (0·80–1·63)	4·1%	4·5%	0·38
Yes	587	602	15	24	1·51 (0·79–2·88)	3·7%	4·8%	
Disease stage								
DCIS	498	514	29	32	1·01 (0·61–1·68)	6·5%	6·0%	0·48
Invasive N0	1330	1359	38	50	1·31 (0·85–2·00)	3·2%	4·1%	
Invasive N1	208	216	4	8	1·91 (0·57–6·34)	2·8%	4·7%	
Hormone receptor status								
Positive ER, PR, or both	1655	1699	48	68	1·32 (0·91–1·92)	3·2%	4·2%	0·30
Negative for ER and PR	381	390	23	22	0·98 (0·54–1·77)	7·2%	6·5%	
Invasive path tumour size								
<10 mm	567	581	20	11	0·58 (0·27–1·22)	3·9%	2·0%	0·01
11–20 mm	620	641	9	26	2·66 (1·24–5·68)	1·9%	5·0%	
>20 mm	192	185	8	10	1·34 (0·52–3·46)	5·1%	5·6%	
Invasive cancer risk group								
Low-risk invasive	384	376	9	10	1·12 (0·46–2·76)	2·3%	2·7%	0·81
All other invasive	993	1025	28	37	1·26 (0·77–2·08)	3·8%	4·2%	

Figure 4
DCIS=d

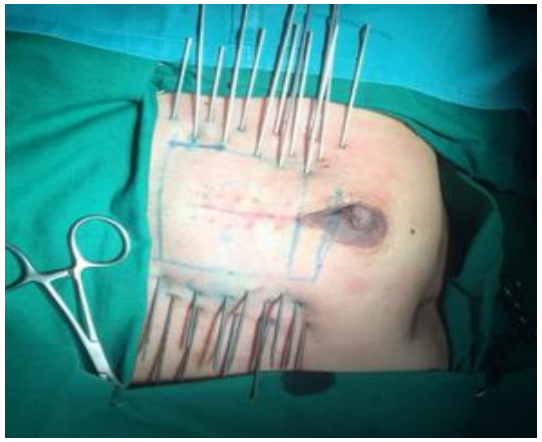
IBTR by PBI Method

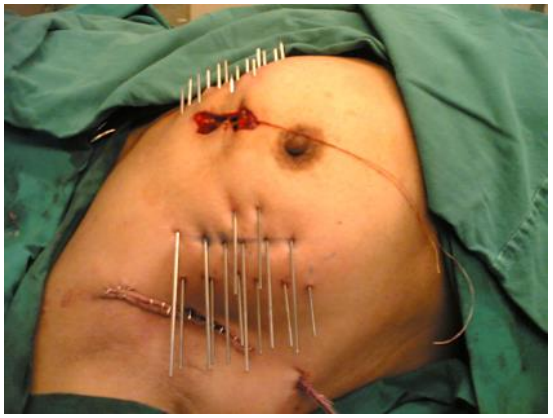
Treatment Group	# of Pts	# of Events	Hazard Ratio (HR)	HR 95% Confidential Interval	10-yr Cum Incidence	
WBI	2,011	67	REF		3.8%	
PBI						
Multi-catheter brachytherapy	130	9	2.21	1.10 – 4.46	7.7%	6%
Single-entry brachytherapy device	358	24	2.15	1.34 – 3.44	7.8%	21%
3DCRT (external beam)	1,535	55	1.04	0.73 – 1.49	3.7%	73%

Practical considerations: implant technique

- Implant quality is critical: dose optimization cannot compensate for poorly done implant
- Implant to cover the tumor bed with adequate margin (1-2 cm).
- The catheters need to be equally and evenly spaced (1-1.5 cm apart) within each implant plane
- Number and spacing between implant planes as well as the total number of catheters to be used depends on individual patient's tumor bed location and anatomic geometry
- Preimplant CT scan will be helpful to decide the implant geometry
- Implant orientation:
  - Comfortable exit
  - Entry site where implant marks will be less visible (important for cosmetic outcome)
  - Ensure adequate coverage

Practical considerations: implant technique





POST-OPERATIVE

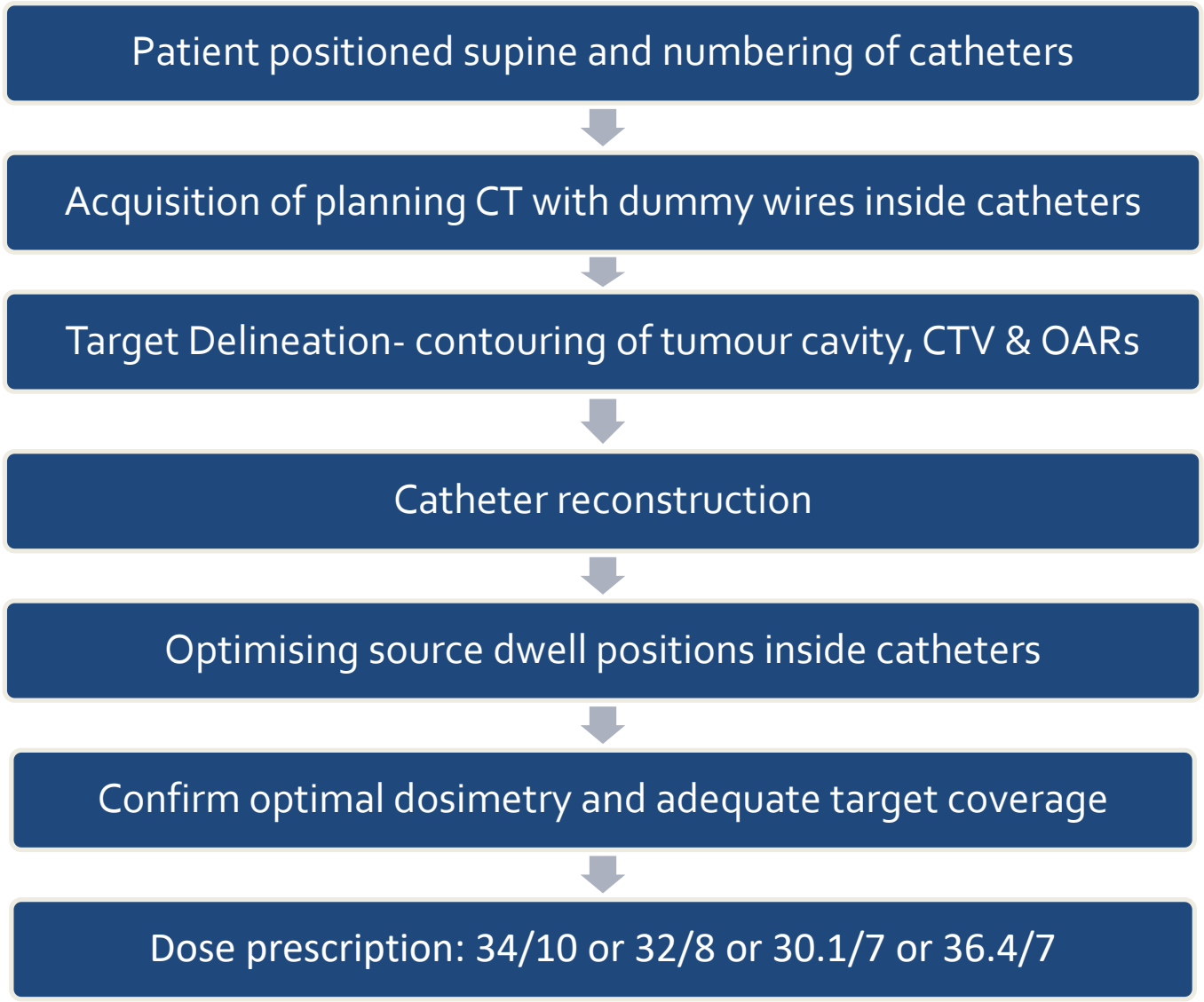
- Done after wound healing and final HPR
- Image guidance necessary for placing the adequate number of catheters in the right geometry elative to the cavity volume

INTRA-OPERATIVE

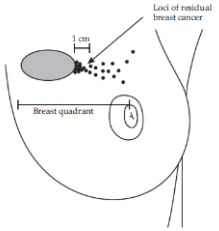
- Direct visualization (no geographical miss) and easy to implant
- Choose an orientation with least resistance to avoid tension after skin closure
- Cooperation between surgeon, pathologist, and radiation oncologist is crucial

Free-hand or template-based implantation can be done

CT Based Planning



What is the optimal CTV margin?



- 70-90% 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
- Intracavitary techniques employ 1 cm margin while interstitial brachy studies use 1-2 cm margin (NSABP trial used 1.5 cm)
- A uniform expansion ensures that at least 1.5 cm of the normal breast tissue is treated beyond the lumpectomy cavity
- In case of wide surgical margins, this is at the expense of treating unnecessary additional normal tissue without added benefit.
- To avoid the potential overtreatment, the GEC-ESTRO multicenter trial used differential CTV margin in accordance to the margin width in each direction

Skowronek J, JCB 2012, Faverly DR Cancer 2001, Vicini IJROBP 2004

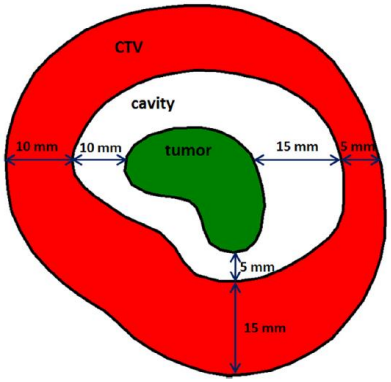
GEC ESTRO breast cancer recommendations

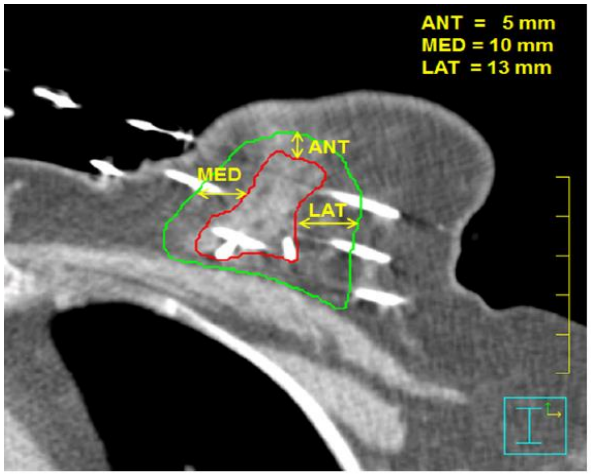
Recommendations from GEC ESTRO Breast Cancer Working Group (II): Target definition and target delineation for accelerated or boost partial breast irradiation using multicatheter interstitial brachytherapy after breast conserving open cavity surgery

Radiother Oncol 2016

Tibor Major [a,*], Cristina Gutiérrez [b], Benjamin Guix [c], Erik van Limbergen [d], Vratislav Strnad [e], Csaba Polgár [a], On behalf of Breast Cancer Working Group of GEC-ESTRO

- CTV delineated with a non-isotropic expansion taking into account the size of the free resection margin
- The total size of safety margin is always 20 mm, which is the sum of the surgical and added safety margins.
- If the surgical resection margin is larger than 20 mm, instead of zero margin a 5 mm margin is recommended to be used.
- CTV should be limited to chest wall/ pectoral muscles and 5 mm below the skin surface.



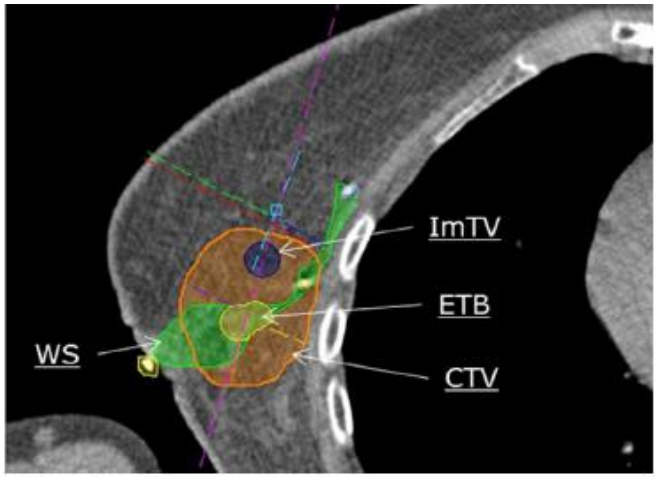


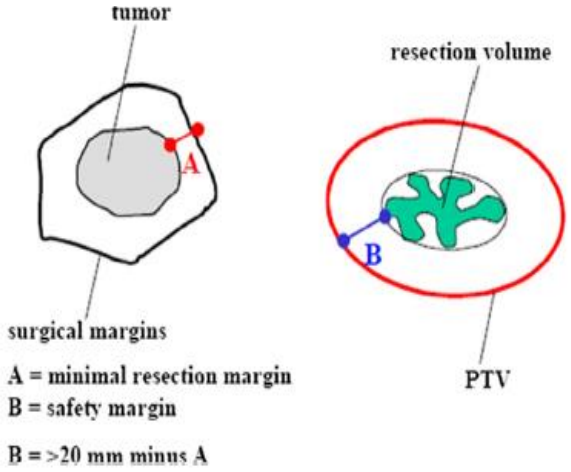
Recommendations from GEC ESTRO Breast Cancer Working Group (I): Target definition and target delineation for accelerated or boost Partial Breast Irradiation using multicatheter interstitial brachytherapy after breast conserving closed cavity surgery

Radiother Oncol 2015

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

- Acquisition of CT scan with wire on the scar
- Delineation of the clips: parenchymal and base
- Delineation of whole surgical scar (WS)
- Delineation imaging corelated targeted volume (ImTV)
- Delineation of estimated TB: clips+ WS + ImTV (formimg part of tumor bed)
- Delineation of CTV (20 mm – individual margin but minimum 10mm)
- Delineation of PTV



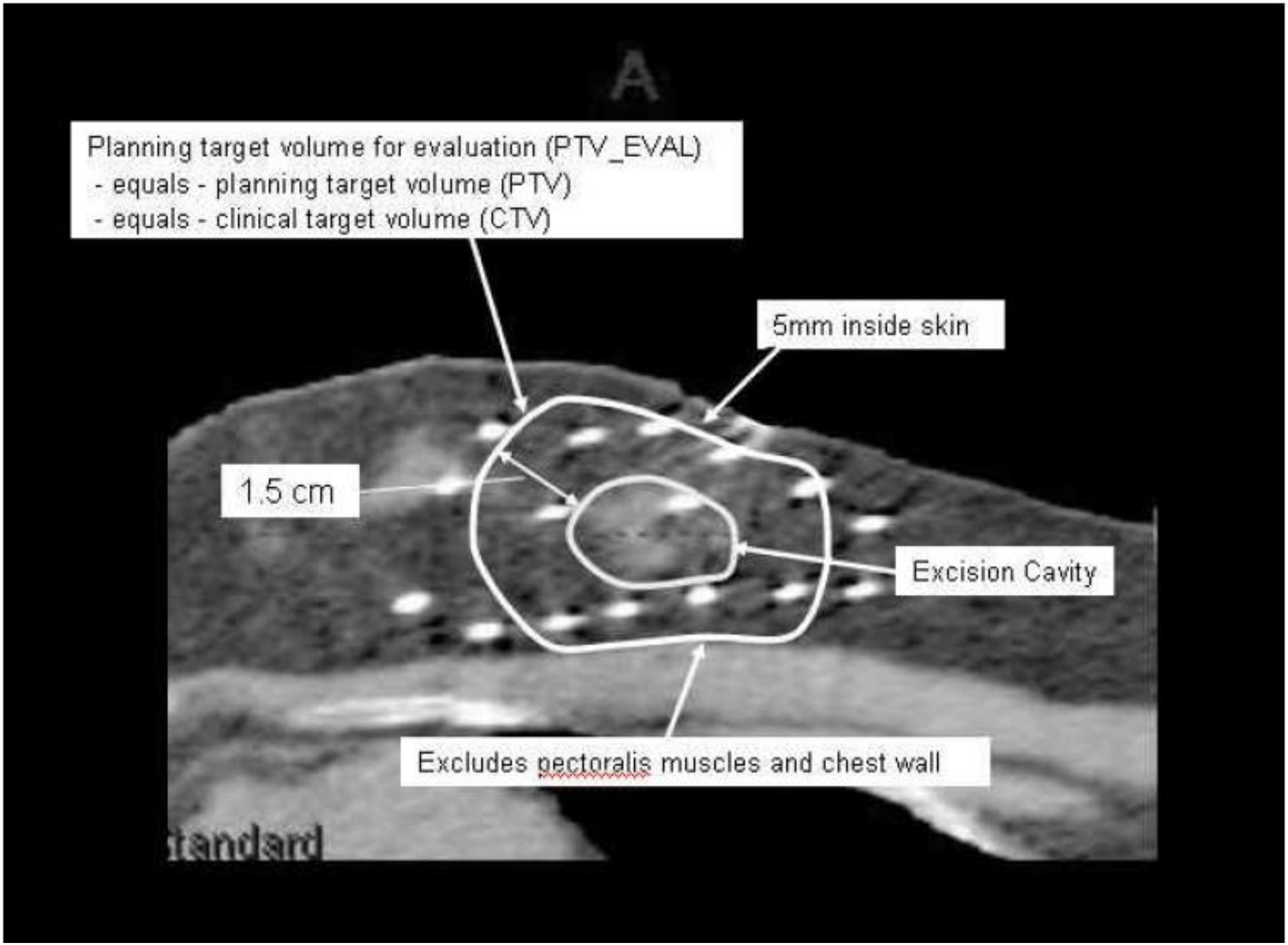


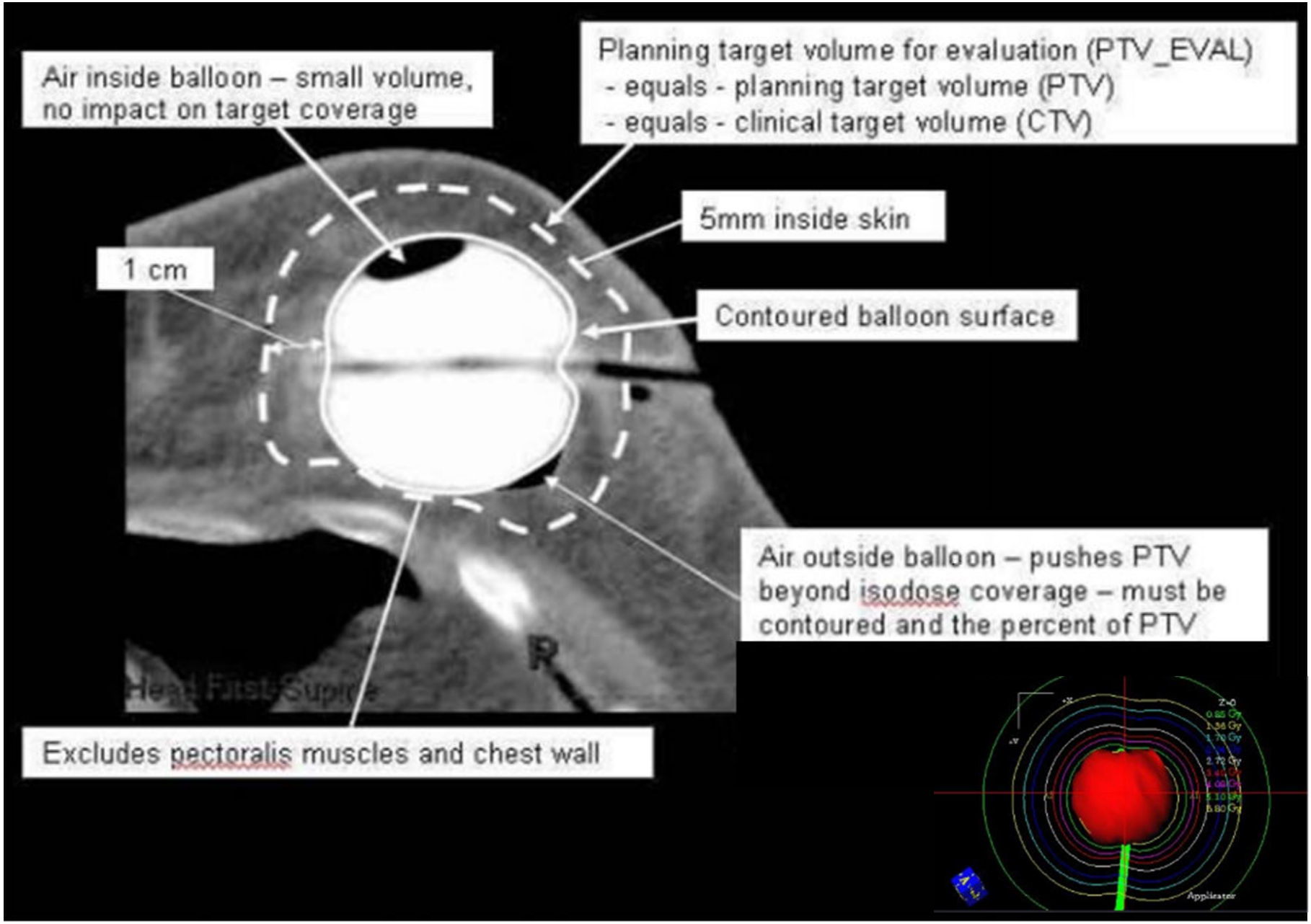
Impact of iso vs anisotropic margins on implant dosimetry

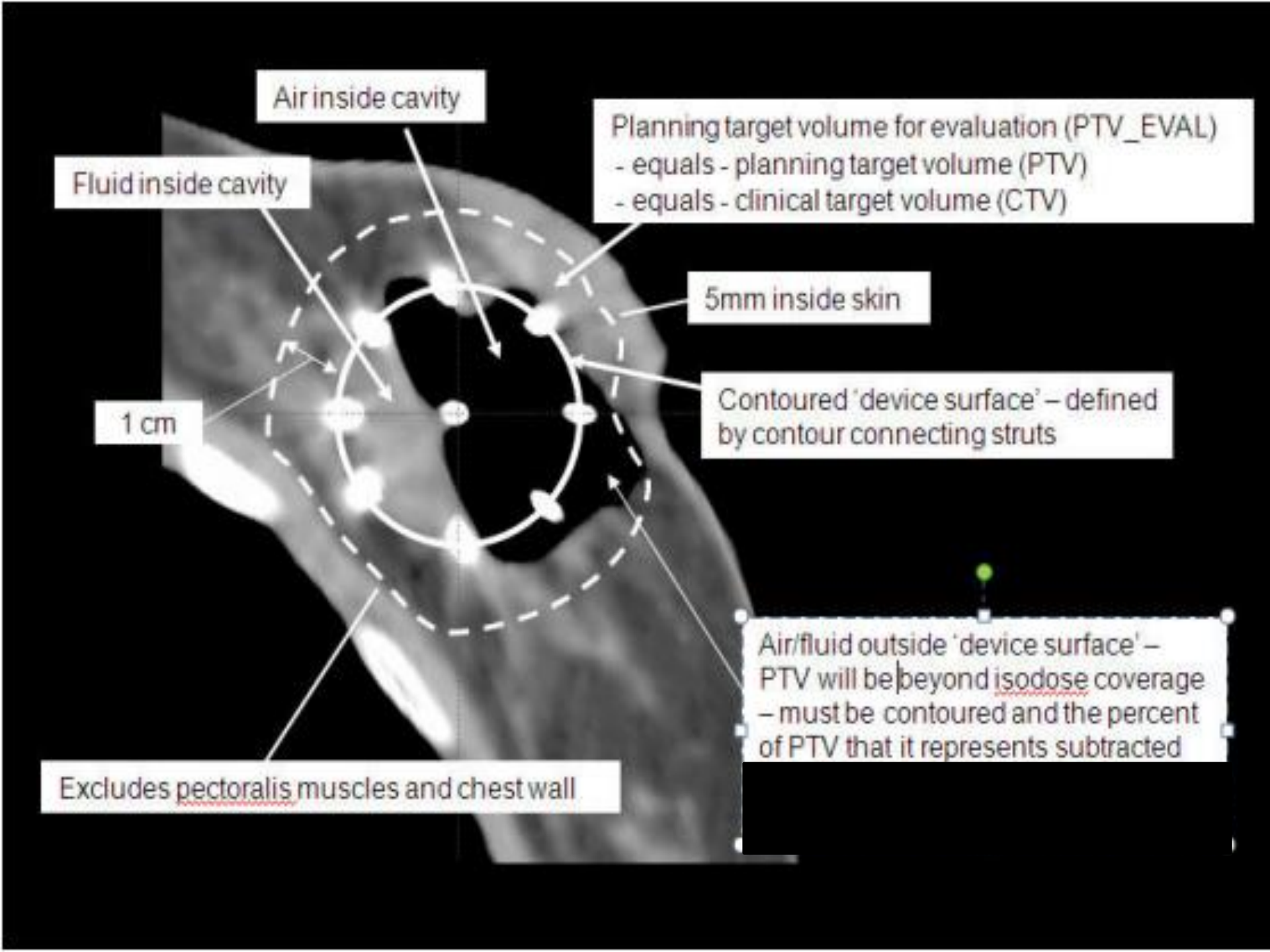
- N=100, 2015-2020
- Median TBV 37 cc and CTV (iso as well as gec) 116 cc
- Median margin width: 1.2 cm in A/M/L, 1.0 cm P/S and 0.9 in I directions
- Impact was more pronounced for smaller implants (<35 cc)

PARAMETER	CTV_ISO	CTV_GEC	P VALUE	Clinically acceptable
TB Coverage	0.94	0.93	0.667	Yes
CTV Coverage	0.86	0.84	0.001	Yes
DHI	0.77	0.75	<0.001	Yes
COIN	**0.66**	**0.64**	**<0.001**	**No**

Wadasadawala et al, Brachy 2020


A
Planning target volume for evaluation (PTV_EVAL)
- equals - planning target volume (PTV)
- equals - clinical target volume (CTV)
5mm inside skin
1.5 cm
Excision Cavity
Excludes pectoralis muscles and chest wall


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


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 that it represents subtracted
Excludes pectoralis muscles and chest wall

DOSE CONSTRAINTS	ESTRO guidelines (Strnad , RO 2018)	ABS guidelines (Hepel et al, Brachy 2017)
PTV coverage	V100 ≥90%	
Maximal dose	V150 < 65 cm3 (PTV) V200 < 15 cm3 (PTV) COIN 0.65 (PTV) V_{PD} 300 cm3 (Implant) DNR 0.35 (Implant)	V150 < 45 cm3 (PTV) V200 < 14 cm3 (PTV) DHI >0.75 (>0.85 preferred)
Uninvolved breast	V90% < 10% V50% < 50%	V50% < 60%
Ipsilateral lung	MLD < 8% D0.1cm3 < 60%	
Heart	MHD < 8% D0.1cm3 < 50%	
Skin	D1cm3 < 90% D0.2cm3 < 100% to 5 mm shell below the body	≤100% of prescription dose (≤60-70% preferred) at skin surface
Ribs	D0.1cm3 < 90% D1cm3 < 80%	≤125% of prescribed dose

Conclusion: APBI

- Randomized and prospective data from interstitial brachytherapy series prove safety and efficacy and hence can be considered an alternative in selected women
- MIB is labour intensive and high quality assurance is mandatory
- Guidelines also recommend MIB strongly over intra-luminal techniques
- Adherence to contouring guidelines and dosimetric constraints achieve excellent outcome
- Electronic brachytherapy and accuboost are currently considered investigational