Brachytherapy in Ca Breast

Choosing wisely

Dr Prashanth Giridhar MD (AIIMS) DNB
Assistant Professor, MPMMCC/ HBCH Varanasi
Unit of Tata Memorial Centre, Govt of India

Specific learning objectives

- **Revise indications of RT in breast cancer**
- **Learn types of Brachytherapy in breast cancer**
- **Evolution of APBI in breast cancer**
- **Criteria for selection of patients for APBI**
- **Learn indications of brachytherapy boost in breast cancer**

Indications for radiotherapy in breast cancer

Breast	• **All cases post BCS (Patients should be checked for suitability for APBI)**
Chest wall **(Post breast implant RT indications remain the same)**	• T3-T4 disease (pathological) • N+ ve disease (pathological) • Margin positive (If re-surgery is not possible) • If NACT given, cT3 or higher, N1 or higher
Supraclavicular	• Clinical N2 or N3 disease (NACT received) • >4 +ve LN after axillary dissection • 1-3 +ve LN with high risk features (Age < 40 years, LVSI +, TNBC-2/3 positive) • N+ sentinel LN with no dissection • No dissection (After re-surgery opinion)
Axilla	• N+ with extensive ECE • SN + with no dissection • Inadequate axillary dissection (Less than 10 LN) • High risk with no dissection
Internal mammary **(Faculty call on case to case basis)**	• Positive axillary node with central or medial lesion • +SLN in IM chain • +SLN in axilla with drainage to IM on lymphosicntigraphy

Types of brachytherapy in breast cancer

- APBI – Accelerated partial breast irradiation (Early breast CA)
- IORT – Intra-operative radiotherapy (??Evidence of non-inferiority/ equivalence)
- Boost after whole breast RT

What is APBI?

*Accelerated partial breast irradiation (APBI) is the delivery of a shortened course of adjuvant radiation to the planning target volume (PTV) (lumpectomy cavity plus a 1- to 2-cm margin) after breast-conserving surgery. The treatment is completed in 4 to 5 days; thus the term accelerated treatment

**Michel Ghilezan, Alvaro A. Martinez, in Clinical Radiation Oncology (Third Edition), 2012*

Evolution of APBI

- **Breast-conserving therapy** (BCS + Whole breast RT) remains **standard of care** in early-stage breast cancer with long-term outcomes demonstrating equivalent local control and survival compared with mastectomy*(Level 1 evidence)
- A radiation schedule delivering 40 Gy in 15 fractions over 3 weeks offers **local-regional control and late adverse effects** at least as favorable as the standard schedule of 50 Gy in 25 fractions** (Level 1 evidence)

**Veronesi U., Cascinelli N., Mariani L., et. al.: Twenty-year follow-up of a randomized study comparing breast-conserving surgery with radical mastectomy for early breast cancer. N Engl J Med 2002; 347: pp. 1227-1232.*

***Bentzen, S. M., Bliss, J. M., Brown, et al(2008). The UK Standardisation of Breast Radiotherapy (START) Trial B of radiotherapy hypofractionation for treatment of early breast cancer: a randomised trial. Lancet (London, England), 371(9618), 1098–1107*

Evolution of APBI

- Adjuvant radiation therapy to whole breast after breast-conserving surgery (BCS) has demonstrated a reduction in local recurrence and breast cancer mortality (Level 1 evidence)*
- **Up to 80% of the ipsilateral breast cancer recurrences occur in close vicinity of the tumor bed****
- ??Whole breast needed

Randomized controlled trials for APBI

Brachytherapy

RTOG-9517 (Phase 2)
(HDR BT *vs* LDR BT)
Well tolerated with good control

GEC-ESTRO (Phase 3)
(HDR or PDR BT *vs* WBI)
Non-inferior IBTR. Increased toxicity

Budapest (Single institution RCT)
(HDR BT (70%) or Electron (30%) PBI *vs* WBI)
Equal IBTR outcomes. Better cosmesis

NSABP-39 / RTOG 0413 (Phase 3)
(MC-HDR (5%) or MamoCyte HDR (25%) or 3DC-APBI (70%) *vs* WBI)
APBI inferior IBRT though low, similar toxicity

EBRT

RTOG-0319 (Phase 2)
(3DC-APBI *vs* WBI)
Safe and reproducible

Florence (Phase 3)
(IMRT-APBI *vs* WBI)
Equal IBTR, Better toxicity and cosmesis

IMPORT LOW (Phase 3)
(IMRT-PBI *vs* WBI)
Non-inferior IBTR. Same QOL, cosmesis

RAPID (Phase 3)
(IMRT-PBI *vs* WBI)
Non-inferior IBTR. Acute better. Late worse

IORT

TARGIT
(Intrabeam IORT *vs.* WBI)
Non-inferior IBTR. Lower G3. More seromas

ELIOT
(e-IORT *vs.* WBI)
Worse IBTR. Lower toxicity

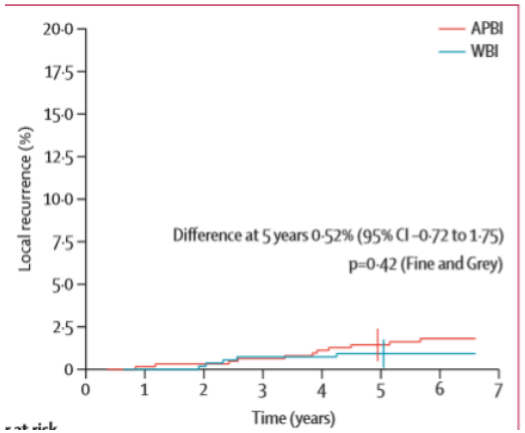
Brachytherapy: GEC ESTRO

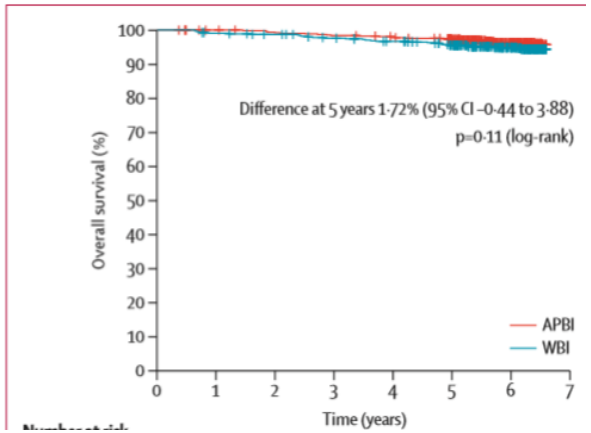
- Phase III, randomized, **non-inferiority** comparison of APBI via HDR BT vs WBI
- Methods:
  - *Inclusion Criteria:*
    - >40 years, Invasive or DCIS, Stage 0-IIA, ≤3cm in size, no LVSI
    - BCT with negative margins (≥2 mm, 5 mm for ILC) and ALND with pN0 or pN1mi
  - *RT:*
    - APBI: Either HDR (80%) or PDR (20%)
      - HDR: 32 Gy in 8 fractions given BID or 30.1 Gy in 7 fractions BID
      - PDR: 0.6-0.8 Gy/pulse up to 50 Gy (1 pulse/h, 24h/day)
      - Target: Tumor bed + 2cm
    - WBI: 50-50.4 Gy in 1.8-2 Gy/fx, QD, with 10 Gy electron boost.

Brachytherapy: GEC ESTRO

- 1183 women, well balanced between arms

- Toxicity (WBI vs APBI-BT)
  - Early Skin Reaction: 93% vs 21%
  - Hematoma: 2% vs 20%
  - Infection: 2% vs 5%
- No difference in IBTR, DFS, or OS
  - ***5 year IBTR: 1.44% APBI vs 0.92% WBI***





Brachytherapy: GEC ESTRO

Conclusion:

APBI via BT as compared with WBI was non-inferior with regards to IBTR.

APBI reduced skin toxicity at the expense of increased risk of hematoma

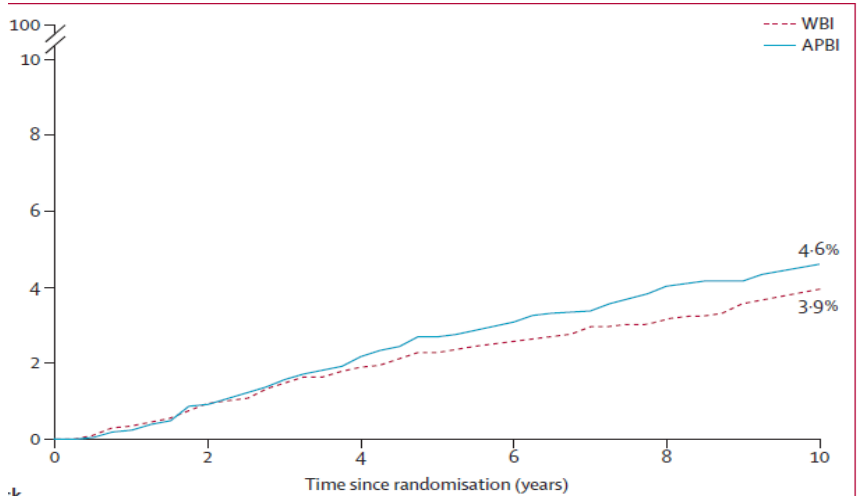
EBRT/HDR BT: NSABP B39

- Phase III, equivalence trial of APBI via HDR or EBRT vs WBI
- >18 yo, any histology, ≤ 3 cm size (0-II), **≤3 positive nodes**, negative margins
  - Included all histologies and **multifocal breast cancer**
- WBI: 50 in 25 ± 10 Gy boost
- APBI: via HDR-BT or EBRT as chosen by treating Rad Onc
  - HDR: 34 Gy via multicatheter interstitial (MCI) or Mammosite
  - EBRT: 38.5 in 10 fx given BID over 5 days w/i 8 day period via **3DCRT**
- Primary Outcome: IBTR
- Secondary Outcomes: DFS, OS, QOL, toxicity
- **Equivalence margin: 50% increase in HR for IBTR**

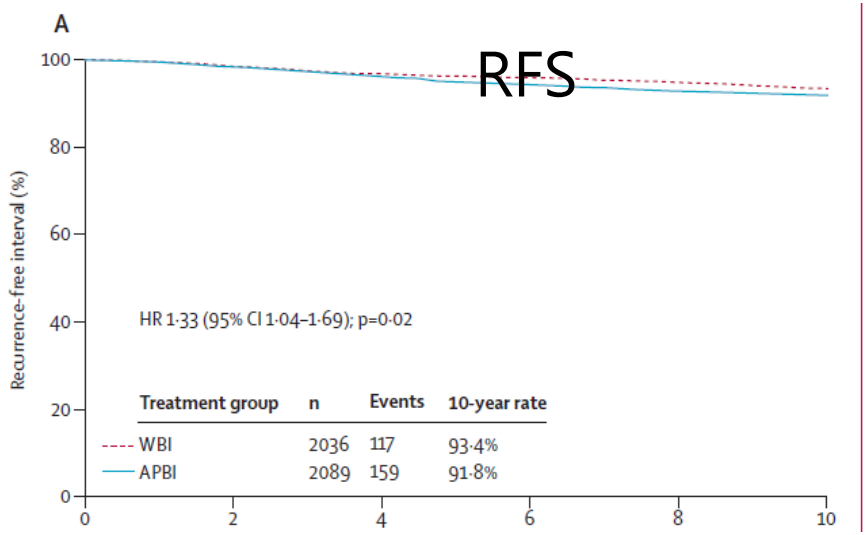
NSABP B39

- 4216 patients, well balanced, good adherence
- Median f/u: 10.2 years
- APBI: 73% EBRT, 21% Mamosite BT, 6% MCI
- APBI did not meet criteria for equivalence to WBI
  - HR of 1.22 (90% CI: 0.94-1.58)
  - 10 year IBRT: 4.6% APBI vs 3.9% WBI
  - <1% difference
- APBI had lower recurrence free survival
  - 10 year RFS: 91.8% APBI vs 93.4% WBI
- No difference in DM or OS

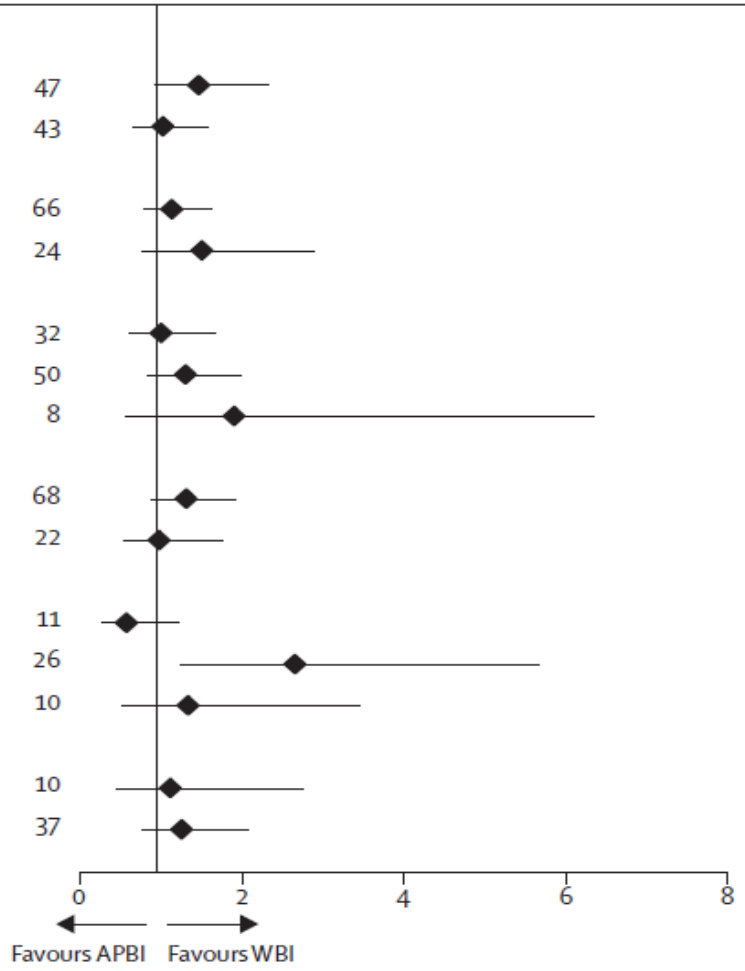
IBTR



RFS



	Number of patients		Number of events		Hazard ratio (95% CI)	10-year cumulative incidence		$p_{interaction}$
	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%	



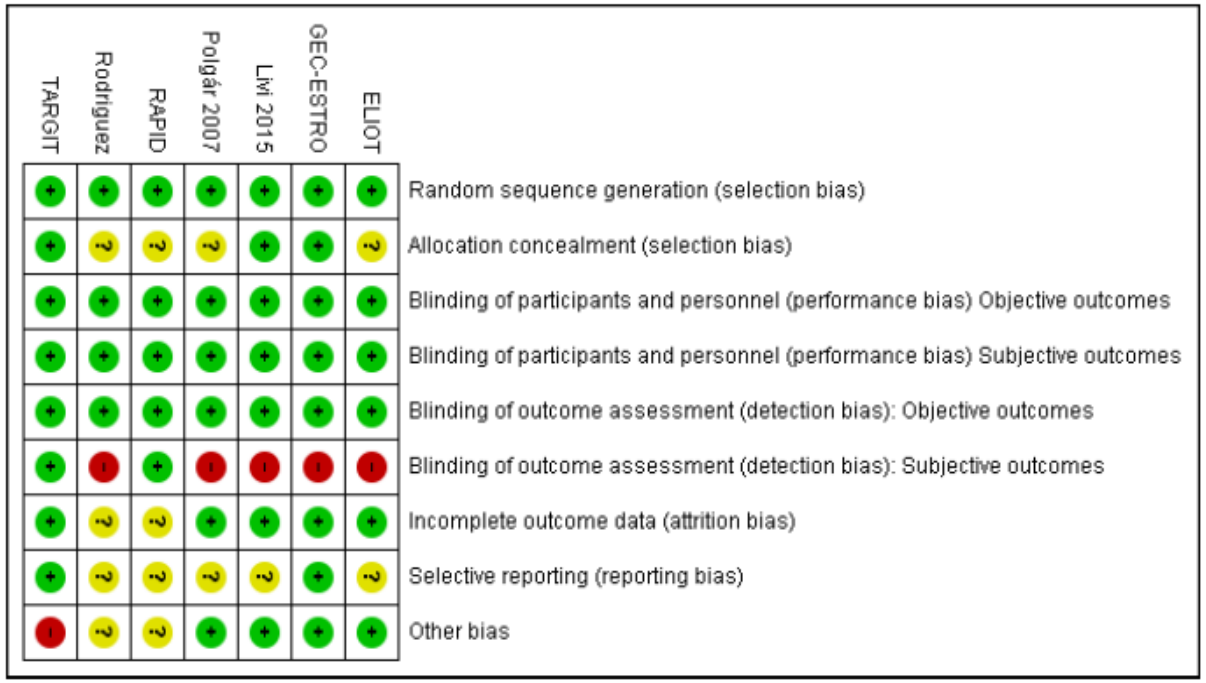
NSABP 39

Conclusion:

- APBI via EBRT or HDR did not meet criteria for equivalence to WBI with regards to IBTR but still very low, with an absolute increase of 0.7% at 10 years, with similar rates of treatment related toxicity
- ***More broad selection criteria than import-LOW and RAPID***

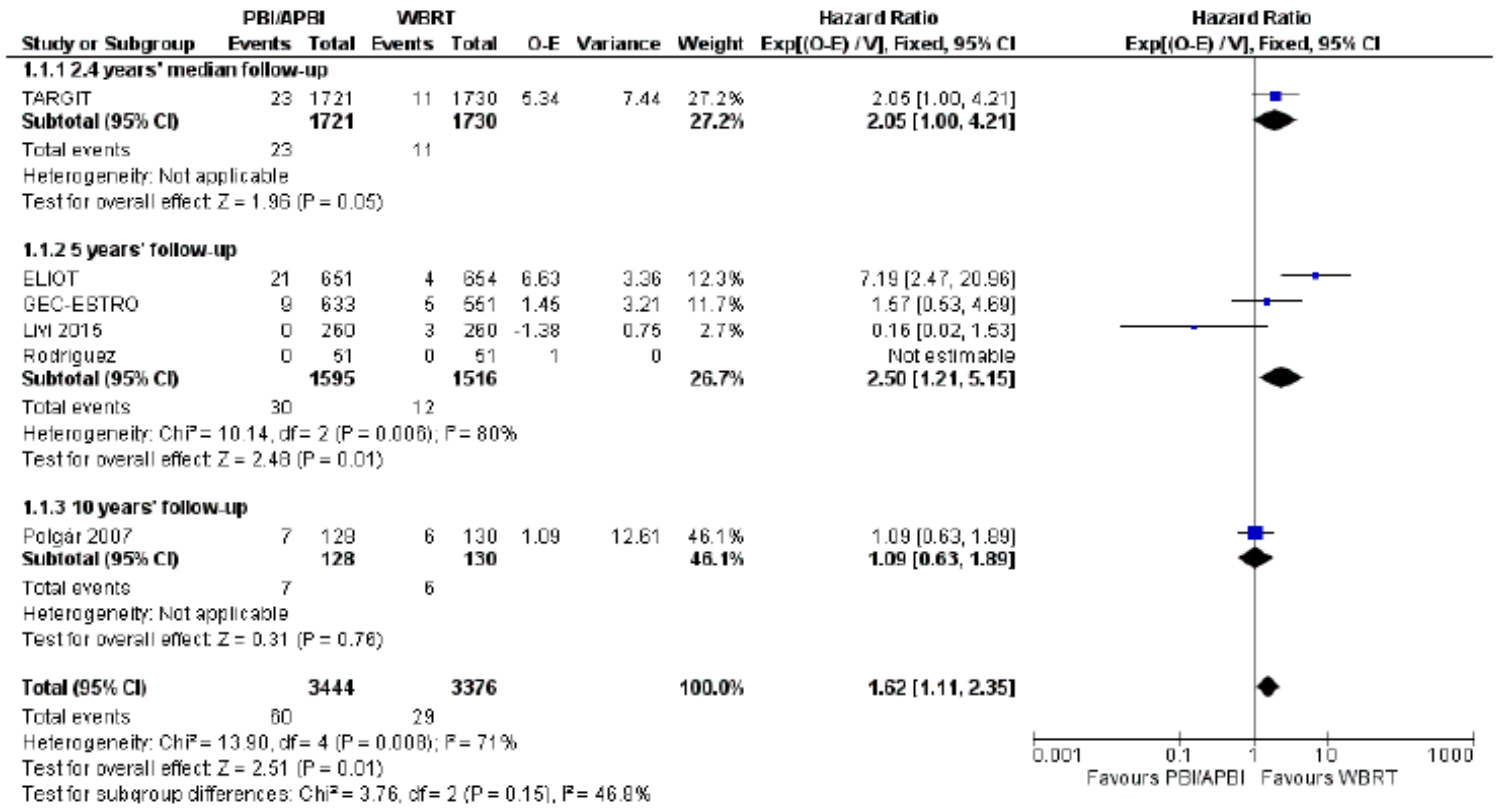
Meta-analyses for APBI

- *Cochrane database systematic reviews*
- *Included data from **7 RCTs** with **8955 participants***



Meta-analyses for APBI

Local recurrence free survival

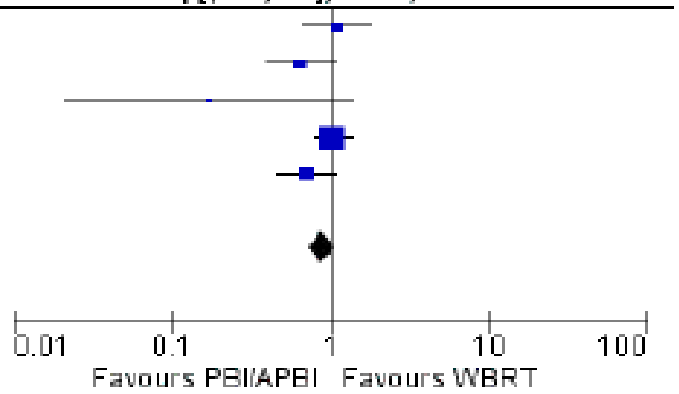


Meta-analyses for APBI

Overall survival

Study or Subgroup	PBI/APBI Events	PBI/APBI Total	WBRT Events	WBRT Total	O-E	Variance	Weight	Hazard Ratio Exp[(O-E) / V], Fixed, 95% CI
ELIOT	34	651	31	664	1.47	15.41	15.6%	1.10 [0.67, 1.81]
GEC-ESTRO	27	633	32	551	-6.12	14.64	14.8%	0.66 [0.39, 1.10]
Livi 2015	1	260	7	280	-1.55	0.88	0.9%	0.17 [0.02, 1.39]
Polgár 2007	25	128	23	130	2.29	46.93	47.5%	1.05 [0.79, 1.40]
TARGIT	37	1721	51	1730	-7.04	21.044	21.3%	0.72 [0.47, 1.10]
Total (95% CI)		**3393**		**3325**			**100.0%**	**0.90 [0.74, 1.09]**
Total events	124		144					

Heterogeneity: Chi² = 6.68, df = 4 (P = 0.15); I² = 40%
Test for overall effect: Z = 1.10 (P = 0.27)



- Summary till now:

- APBI appears to provide similar survival outcomes with slightly higher local recurrence rates

Selection of patients for APBI

Histology

- Most randomized, prospective, and retrospective studies evaluating APBI have predominantly included patients with invasive ductal carcinoma
- Patients with invasive lobular carcinomas (ILCs) remain under-represented in trials evaluating APBI
- Data from the PROMIS study found the 10 - year IBTR to be 7.3%
- When evaluating outcomes for patients with ILC undergoing BCS and WBI, no difference in outcomes are noted with modern techniques

Selection of patients for APBI

Nodal status

- As level I data demonstrated a benefit with regional nodal irradiation in patients with limited nodal involvement, APBI should not be offered to node-positive patients off trial

Selection of patients for APBI

- ***Receptor status***
- Estrogen receptor negativity and Her 2 neu positivity has been associated with increased rates of local recurrence
- No data suggest higher rates of local recurrence for estrogen receptor negative patients treated with APBI compared with WBI

Selection of patients for APBI

- ***Margin status***
- Pooled analysis shows that close (< 2 mm) or positive margins have a trend towards increased IBTR
- It should be noted that differences in assessment of margins exist, which make defining an optimal margin challenging

Selection of patients for APBI

- ***Age***
- Analysis of the ASBS MammoSite Registry did not find age to be associated with IBTR
- GEC-ESTRO randomized trial included patients 40 years and older (15% < 50) with no difference in rates of IBTR noted
- University of Florence randomized trial included patients 40 years and older (18.5% < 45 years) with age not associated with IBTR

Selection of patients for APBI

- ***Tumor size***
- To date, limited data have suggested an association between IBTR and tumor size in patients undergoing APBI
- when faced with tumors greater than 3 cm, a concern is the larger cavities associated and therefore, the larger volume of normal breast tissue irradiated

Selection of patients for APBI

- ***DCIS***
- RTOG 9804 randomized low-risk patients with DCIS (low-intermediate grade, tumor size < 2.5 cm, margins ≥3 mm) to adjuvant whole breast radiotherapy or observation after lumpectomy.
- Adjuvant radiotherapy reduced the rate of local failure (7 year local failure 0.9% vs. 6.7%)
- Numerous studies demonstrated excellent outcomes for patients with DCIS treated with APBI

Summary of criteria for selection

Expert group/organization (year)	Age	Histology/LVSI[b]	Tumor size	N status	Estrogen receptor status	Surgical margins
ABS Shah (53) 2018	≥45 years	All invasive histologies and ductal carcinoma *in situ*/LVSI negative[b]	≤3 cm	Node negative	Positive/negative	Negative surgical margins
RCR (57) 2016	≥50 years	Nonlobular invasive breast cancer, grade 1–2, HER2 negative	≤3 cm	Node negative	Positive	Negative surgical margins ≥2 mm
ASTRO Correa (55) 2017 (updated from 2009)	≥50 years (suitable)	All invasive histologies and low-risk ductal carcinoma *in situ*[c]	pTis or pT1–2 (≤3 cm), clinically unifocal	Node negative	Positive	Negative surgical margins ≥2 mm
GEC-ESTRO Polgár (35) 2010 Strnad (56) 2018	≥50 years	Nonlobular invasive breast cancer; no EIC[a]/LVSI[b] negative	pT1–2 (≤3 cm), unifocal/unicentric	Node negative (pN0)	Positive	Negative surgical margins ≥2 mm

[a]Extensive intraductal component (EIC).
[b]Lymphovascular invasion (LVSI).
[c]Screen-detected and low-to-intermediate nuclear grade and size ≤2.5 cm and surgical margins negative at ≥3 mm.

Why APBI at all in the era of FAST FORWARD?

- FAST FORWARD protocol completes whole breast RT in 5 days (26 Gy/ 5#/ 5 days)
- But, no long term data available on control/ cardiac toxicity (10 year data)
- 5 days machine time on LINAC can be saved

IORT

- Delivery of a single intraoperative dose directly to lumpectomy cavity
  - Pro: Patient convenience, skin sparing
  - Con: No pathological confirmation, logistics, equipment
- Two common techniques
  - Electrons via NOVAC 7 as in ELIOT
  - Photons via IntraBeam as in TARGIT

IORT: ELIOT

- Single institutional, randomized trial of electron IORT v WBI
- 48-75 yo, maximum 2.5 cm, suitable for BCT, any histology
- **Equivalence margin of 7.5% local recurrence in IORT arm**
  - Single dose of 21 Gy via NOVAC 7 or Liac electron IORT
  - 90% isodose line to tumor bed
  - Al and Pb chips for chest wall protection
- WBI: 50 Gy in 25 fx followed by 10 Gy boost
- Primary: Ipsilateral Breast Tumor Recurrence (IBTR)
- Secondary: OS and Toxicity

IORT: ELIOT

- 1305 women, well balanced
- Median f/u: 5.8 years
- IBTR higher in IORT arm
  - ***5 year IBTR: 4.4% vs 0.4%, p=0.001***
  - ***However, met criteria for equivalence***
- “True” recurrence also higher in IORT
  - 5 year rate: 2.5% vs 0.4%, p=0.0003
- No difference in OS

IORT: ELIOT

Conclusion:

- IORT via electrons has increased risk of ipsilateral breast tumor recurrence. IORT provides a lower rate of treatment toxicity (skin).
- Consider for a suitable subset of patients. Have to weigh risk of IBTR with side effect profile. No OS difference.

IORT: TARGIT

- Randomized, non-inferiority trial comparing IORT and WBI
- 45+ yo, IDC, DCIS, unifocal
- 2.5% non-inferiority margin
- IORT: 20 Gy to depth of 1 cm via Intrabeam
    - Low energy (50 kV) X-rays
- WBI: 40-56 Gy with or without boost
- Primary: Local recurrence in ipsilateral breast
- Secondary: Toxicity or morbidity

IORT: TARGIT

- 2232 women, well balanced
  - 20% of IORT arm recived additonal WBI
  - 60 years, small tumors, G1/G2, N0
- Median f/u: 8.6 years
- **Local Recurrence was non-inferior with IORT**
  - **5 year LR: 2.11% IORT vs 0.95% WBI**
- No difference in LRFS, mastectomy free survival, distant DFS, OS, breast cancer mortality
- Mortality from other causes significantly LOWER with IORT

IORT: TARGIT

Conclusion:

- IORT via Intrabeam in favorable risk patients is not inferior to WBI. IORT has lower rate of mortality from other causes.

Summary of APBI

- Level 1 evidence present for APBI use in suitable patients (Strong recommendation) – No OS difference; Possible mild increase in risk of IBTR

Expert group/organization (year)	Age	Histology/LVSI[b]	Tumor size	N status	Estrogen receptor status	Surgical margins
ABS Shah (53) 2018	≥45 years	All invasive histologies and ductal carcinoma *in situ*/LVSI negative[b]	≤3 cm	Node negative	Positive/negative	Negative surgical margins
RCR (57) 2016	≥50 years	Nonlobular invasive breast cancer, grade 1–2, HER2 negative	≤3 cm	Node negative	Positive	Negative surgical margins ≥2 mm
ASTRO Correa (55) 2017 (updated from 2009)	≥50 years (suitable)	All invasive histologies and low-risk ductal carcinoma *in situ*[c]	pTis or pT1–2 (≤3 cm), clinically unifocal	Node negative	Positive	Negative surgical margins ≥2 mm
GEC-ESTRO Polgár (35) 2010 Strnad (56) 2018	≥50 years	Nonlobular invasive breast cancer; no EIC[a]/LVSI[b] negative	pT1–2 (≤3 cm), unifocal/unicentric	Node negative (pN0)	Positive	Negative surgical margins ≥2 mm

[a]Extensive intraductal component (EIC).
[b]Lymphovascular invasion (LVSI).
[c]Screen-detected and low-to-intermediate nuclear grade and size ≤2.5 cm and surgical margins negative at ≥3 mm.

- APBI with IORT still controversial

Brachytherapy boost

- Tumour bed boost after whole breast RT improves local control
- Most patients are boosted with photons or electrons (EBRT)
- *In deep seated tumors where in electrons may lead to a high skin dose and photons may lead to additional lung dose, brachytherapy boost may be considered*

ASSOCIATION OF RADIATION ONCOLOGISTS OF INDIA

MPMMCC, VARANASI

SERVICE RESEARCH EDUCATION

एम.पी.एम.एम.सी.सी., वाराणसी

UNIT OF DEPARTMENT ... ERGY, GOVT. OF INDIA