APBI in Breast Cancer: Rationale & Indications

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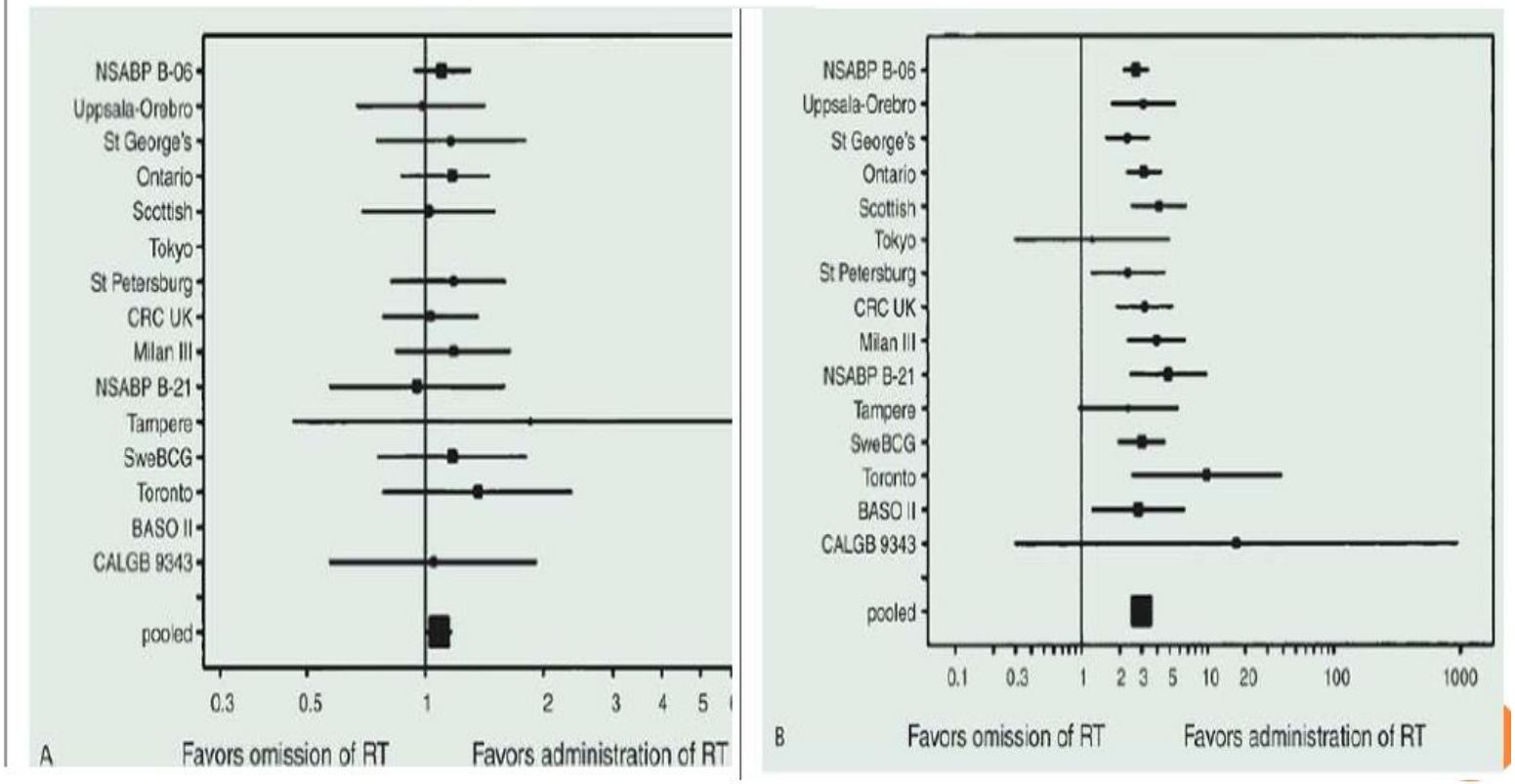
Radiotherapy in Ca Breast

Institute	IGR	Milan	NSABP B-06	NCI	EORTC	Danish
Stage	1	1	1,2	1,2	1,2	1,2,3
Surgery	2cm gross margin	Quad-rantectomy	Lump-ectomy	Gross excision	1 cm gross margin	Wide excision
Follow-up(y)	15	20	20	18	10	6
OS:BCS+RT(%)	73	42	46	59	65	79
M(%)	65	41	47	58	66	82
LR: BCS+RT(%)	9	9	14	22	20	3
M(%)	14	2	10	6	12	4

Radiotherapy in Ca Breast

BCS+RT vs BCS → The pooled meta-analysis of 15 RCTs shows a threefold reduction in local failure & a small but significant improvement in OS with RT after BCS



Vinh-Hung et al. JNCI (2004);96:115-121

Issues with Adjuvant RT

- After examination of 175 000 patients with early breast cancer (SEER database) it was found that in 1992-2003:
  - The percentage of BCS increased from 41% to 60%.
  - The proportion of patients irradiated after BCS decreased from 79% to 71%.
  - Lead to increased risk of local recurrences after BCS.

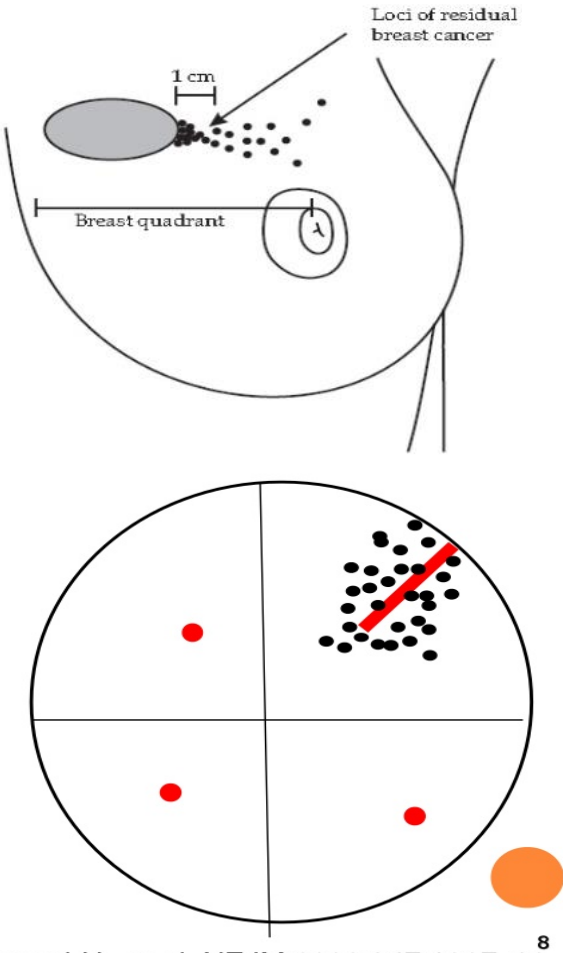
Issues with Adjuvant RT

- They exchanged the factors affecting to decide RT:
  - Convenience… 4-5 weeks of treatment,
  - Accessibility,
  - Cost,
  - Distance from the center of RT,
  - Lack of transportation,
  - Lack of social support,
  - Movement difficulties of patients
  - Doctor bias,
  - Age of the patient
  - Fear of radiation.

APBI: RATIONALE & GUIDELINES

IBTR pattern Post BCS

- A very large percentage of local recurrence arises in the immediate vicinity of the original location of the tumour.
- At least five prospective randomized studies examining the percentage of local recurrence after radiotherapy the whole breast were published and it was found that 69% to 90% recurrences occur in immediate vicinity of the primary tumour.



Veronesi U, et al. NEJM 2002;347:1227–32

IBTR Pattern Post BCS

Trial (time of primary treatment)	Median follow-up (range)	Recurrence number/ Total number of patients	Pattern of IBTR
NSABP B-06 (1976-1984) [12]	39 (5-95) months	110 (1108)	86% within or close to the quadrant of the index cancer 14% more diffuse within the breast
Uppsala-Orebro (1981-1988) [13]	10 years	57 (381)	69% in the surgical field 3.6% in the cuticular scar 3.6% in the skin overlying the surgical field 23.6% in the breast parenchyma outside the field of surgery
Ontario Clinical Oncology Group (1984-1989) [14]	43 months	131 (837)	86% (83% with RT) at the site of primary surgery
Milan III (1987-1989) [15]	9 years	75 (579)	85% (84% with RT) in the scar area 15% (16% with RT) in other quadrants
SweBCG 91-RT (1991-1997) [16]	5 years	104 (1178)	90% in the same quadrant as the previous tumour 10% in other quadrants

IBTR Pattern Post BCS

Authors, studies	Median follow-up (range)	Local recurrence rate (%)	Recurrence rate outside of treated quadrant (%)	Recurrence rate in second breast (%)
Retrospective clinical trials (BCS + EBRT)				
Kurtz *et al.* [17]	11 (5-24) years	11	2	6
Freedman *et al.* [18]	5 years	3	1	3
	10 years	7	2	7
	15 years	13	6	13
Krauss *et al.* [19]	5 years	2	0.1	4
	10 years	7	2	9
	15 years	10	3	12
Veronesi *et al.* [20]	8.5 years	6.8	1.4	5
Prospective trials (BCS + EBRT)				
NSABP B-06 [21]	39 (5-95) months	2.7	0.7	9.4
Uppsala-Orebro trial [13]	10 years	8.5	2.1	10.5
Scottish trial [22]	5.7 years	5.8	1.4	1
Milan III [15]	9 years	5.4	1.3	3.4
NSABP B-21 [23]	8 years	9.3	2.3	5.4
SweBCG 91-RT [16]	61 (10-98) months	4.4	1.1	3.4
GBCSG trial [24]	5.9 years	4.2	1	2.1
ABCSG study 8 [25]	53.8 months	0.5	0.1	0.5

BCS – Breast Conserving Surgery, EBRT – External Beam Radiation Therapy

APBI: Pros & Cons

Benefits

- Larger dose can be delivered to a small area.
- Limited radiation exposure to normal tissue.
- Treatment completed in one week instead of 4-5 weeks

Limitations

- May require additional surgical procedure.
- Requires twice daily treatment.
- Newer modality with limited data.
- Selected patients can benefit.
- Technique and expertise may not be available everywhere.

APBI GUIDELINES

APBI Guidelines

- Why do we need them…
  - Need more numbers/ all patients enrolled in trial settings.
  - Need to strictly specify patient selection for this extremely specific treatment to have best outcomes.
  - Data from randomised trials is still trickling in… clear information from all of them have to be charted…

Need for Guidelines….

CLINICAL RESULTS OF APBI USING SUBOPTIMAL PATIENT SELECTION

Institution	Technique	Median FUP (years)	LR% (*n*)	Annual LR% (*n*)	Comments on patient selection
Uzsoki hospital [37]	MDR	12	24 (17 of 70)	2	Max. tumour size: 5 cm; 100% unknown margins; 30% unknown pathological axillary status (pNx); 4% node positive; 10% lobular ca.; multifocal tumours, LVI and EIC allowed; no patient age limitation
Christie hospital[a] [20]	EBI	8	20 (69 of 353)	2.5	Max. tumour size: 4 cm; 100% unknown margins; no surgical axillary staging; lobular ca., LVI and EIC allowed; no patient age limitation
Cookridge hospital[a] [11]	EBI	8	12 (10 of 84)	1.5	Max. tumour size: 4.5 cm; 41% node positive; lobular ca., LVI and EIC allowed; no patient age limitation
London Reg. Ca. C. [30]	HDR	7.6	15 (6 of 39)	2	Max. tumour size: 4.5 cm; 31% close margins; 15% node positive; 5% pNx; 8% EIC pos.; no patient age limitation
Tufts university [16]	HDR	7	9.1 (3 of 33)	1.30	45% Close margins; 9% node positive; 55% EIC pos.; no patient age limitation
Guy's hospital I [12]	LDR	6	37 (10 of 27)	6.2	Max. tumour size >4 cm; 56% positive margins; 44% node positive, 41% EIC positive; lobular ca. and LVI allowed; patient age >40 years
Guy's hospital II [13]	MDR	6.3	18 (9 of 49)	2.9	Max. tumour size: 4 cm; 43% positive margins; 45% node positive; 14% lobular ca., LVI and EIC allowed, no patient age limitation
Osaka Med. center [26]	HDR	4.3	5.0 (1 of 20)	1.15	15% Positive margins; 35% EIC pos.; 5% lobular ca.; 10% DCIS; no patient age limitation (25% with age ≤45 years)
Florence hospital [10]	LDR	4.2	6 (7 of 115)	1.4	Max. tumour size: 5 cm; 8% positive and 7% unknown margins; 38% node positive; 20% lobular ca.; LVI and EIC allowed, no patient age limitation
All patients		4.2–12	17 (132 of 790)	1.15–6.2	

Results were poor, with high LR rates exceeding 1% per year

Polgar et al,Radiotherapy and Oncology 94 (2010) 264–273

ASTRO Consensus Guidelines: Old Vs Updated

Patient group	Risk factor	Original	Update
Suitability	Age	≥60 y	≥50 y
	Margins	Negative by at least 2 mm	No change
	T stage	T1	Tis or T1
	DCIS	Not allowed	If all of the below: • Screen-detected • Low to intermediate nuclear grade • Size ≤2.5 cm • Resected with margins negative at ≥3 mm
Cautionary	Age	50-59 y	• 40-49 y if all other criteria for "suitable" are met • ≥50 y if patient has at least 1 of the pathologic factors below and does not have any "unsuitable" factors *Pathologic factors:* • Size 2.1-3.0 cm [a] • T2 • Close margins (<2 mm) • Limited/focal LVSI • ER(-) • Clinically unifocal with total size 2.1-3.0 cm [b] • Invasive lobular histology • Pure DCIS ≤3 cm if criteria for "suitable" not fully met • EIC ≤3 cm
	Margins	Close (<2 mm)	No change
	DCIS	≤3 cm	≤3 cm and does not meet criteria for "suitable"
Unsuitable	Age	<50 years	• <40 y • 40-49 y and do not meet the criteria for cautionary
	Margins	Positive	No change
	DCIS	>3 cm	No change

[a] The size of the invasive tumor component.
[b] Microscopic multifocality allowed, provided the lesion is clinically unifocal (a single discrete lesion by physical examination and ultrasonography/mammography) and the total lesion size (including foci of multifocality and intervening normal breast parenchyma) falls between 2.1 and 3.0 cm.

Correa et al, Pract Rad Onco: Mar-Apr, 2017
Br J Radiol;91:20170565

ASTRO: Unsuitable Candidates

- Any of the following criteria:
  - T> 3 cm/ T4 or N +
  - BRCA Mutated
  - High Grade
  - LVSI Extensive
  - EIC + (> 3 cm)
  - Multifocal disease
  - Margin positive
  - Post NACT

GEC- ESTRO GUIDELINES

Characteristic	A) Low-risk group – good candidates for APBI	B) Intermediate-risk group – possible candidates for APBI	C) High-risk group – contraindication for APBI
Age	> 50 years	40-50 years	< 40 years
Histology	IDC, mucinous, tubular, medullary, and colloid cc.	IDC, ILC, mucinous, tubular, medullary, and colloid cc	–
ILC	not allowed	not allowed	–
Associated LCIS	allowed	allowed	–
DCIS	not allowed	allowed	–
HG	any	any	–
Tumour size	pT1-2 (< 30 mm)	pT1-2 (< 30 mm)	pT2 (> 30 mm), pT3, T4
Surgical margin	negative (> 2 mm)	negative, but close (< 2 mm)	positive
Multicentricity	unicentric	unicentric	multicentric
Multifocality	unifocal	multifocal (limited within 2 cm of the index lesion)	multifocal (> 2 cm from the index lesion)
EIC	not allowed	not allowed	present
LVI	not allowed	not allowed	present
ER, PR status	any	any	–
Nodal status	pN0 (SLNB or ALND*)	pN1mi, pN1a (by ALND*)	pNx; PpN2a (4 or more positive nodes)
Neoadjuvant chemotherapy	not allowed	not allowed	if used

ESTRO – IORT ACROP Guidelines

- Criteria according to APBI guidelines:
  - Age ≥50 years;
  - Ductal and other favourable histologies;
  - Unicentric and unifocal;
  - Positive receptor status;
  - pN0 (i-/i+); to integrate with grade 1/2; tumour size ≤2 cm; Luminal A.

ABS Guidelines

Criteria	
Age	≥45 years
Size	≤3 cm
Histology	All invasive subtypes and DCIS
Estrogen receptor	Positive/negative
Surgical margins	Negative (no tumor on ink for invasive, ≥2 mm for DCIS)
Lymphovascular space invasion	Not present
Nodal status	Negative

DCIS = ductal carcinoma *in situ*.

To Summarise…

- ***Tumour Size:***
  - ABS - > 3 cms
  - ASTRO - > 2.5 cms
  - GEC- ESTRO - > 3cms
- ***Age:***
  - ABS - > 45 yrs
  - ASTRO - > 50 yrs
  - GEC-ESTRO - > 50 yrs

To Summarise…

- ***Multifocality:***
  - ABS – Not Allowed
  - ASTRO – Not Allowed
  - GEC- ESTRO – Not Allowed
- ***Estrogen Receptors:***
  - ABS – Positive/ Negative
  - ASTRO – Positive
  - GEC- ESTRO – Positive/ Negative

To Summarise…

- ***LVSI:***
  - ABS – Not Allowed
  - ASTRO – Not Allowed
  - GEC- ESTRO – Not Allowed
- ***Surgical Margins:***
  - ABS – > 2mm for DCIS, tumor on inked margin for invasive
  - ASTRO – > 2 mm, >3 mm for DCIS
  - GEC- ESTRO – > 2 mm

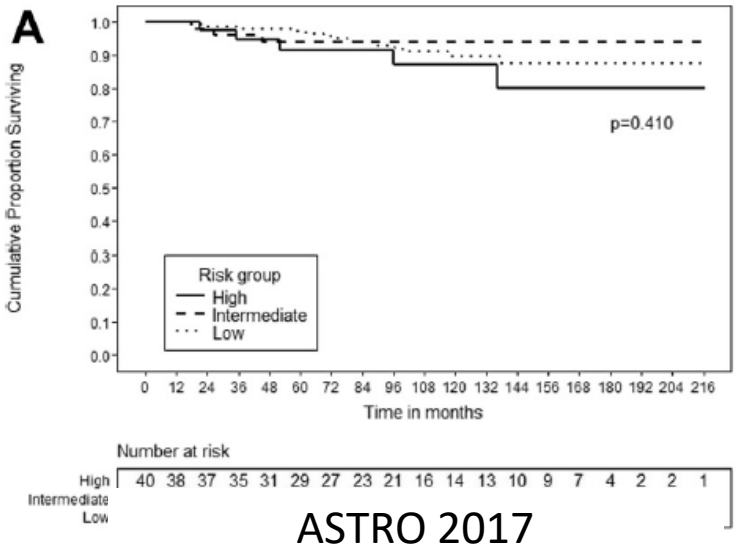
To Summarise…

- ***Histology/ Grade:***
  - ABS – Any
  - ASTRO – Any
  - GEC- ESTRO – Any
- ***DCIS:***
  - ABS – Allowed
  - ASTRO – Tumor < 2.5 cms, low to intermediate grade, margin > 3 mm
  - GEC- ESTRO – Not allowed

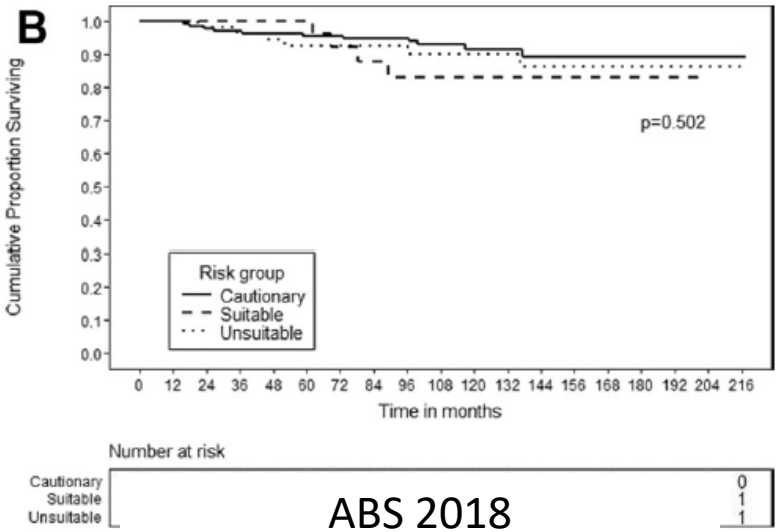
GUIDELINES… CRITIQUE

Comparative Local Contol Rates

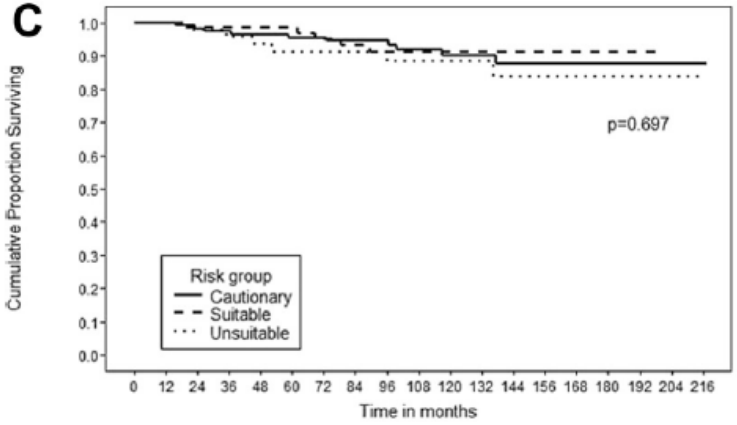
ESTRO 2010



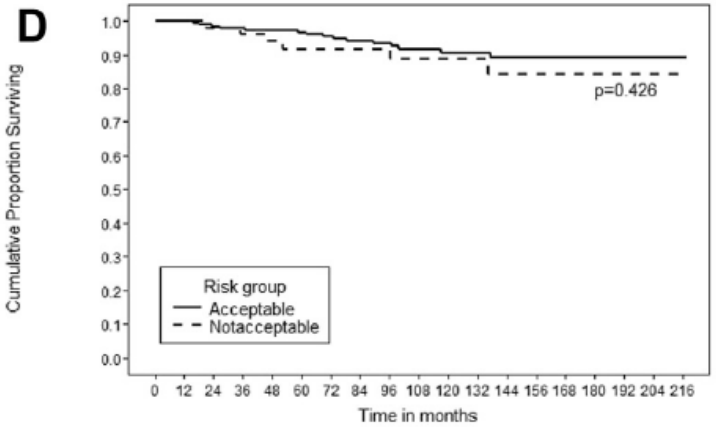
ASTRO 2009



ASTRO 2017



ABS 2018



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Comparative Survival Values

Table 4
Long-term survival outcomes of 239 patients stratified as per GEC-ESTRO, ASTRO, updated ASTRO, and ABS guidelines

Outcomes	ESTRO guideline				ASTRO guideline (2009)				Updated ASTRO guideline (2017)				ABS 2018		
10 years	Low	Intermediate	High	*p* Value	Suitable	Cautionary	Unsuitable	*p* Value	Suitable	Cautionary	Unsuitable	*p* Value	Acceptable	Not acceptable	*p* Value
LC	89%	94%	87%	0.41	93%	91%	90%	0.50	91%	90%	88%	0.69	91%	89%	0.42
DFS	75%	88%	60%	0.02	78%	74%	75%	0.86	79%	75%	71%	0.29	78%	67%	0.01
CSS	93%	93%	70%	<0.001	88%	91%	84%	0.29	93%	90%	81%	0.08	93%	76%	<0.001
OAS	86%	93%	62%	0.001	84%	86%	78%	0.39	85%	87%	74%	0.11	88%	69%	0.001

LC = local control; DFS = disease-free survival; CSS = cause-specific survival; OAS = overall survival; GEC-ESTRO = Groupe Européen de Curie-thérapie and the European Society for Radiotherapy & Oncology; ASTRO = American Society for Radiation Oncology; ABS = American Brachytherapy Society.

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Do we need more factors…

- The TMH analysis showed statistically insignificant difference amongst variables in various risk groups classified by guidelines.
- This suggests there might be few more variables which would help us in categorising our variables more scientifically.

Do we need more factors…

- Among the high-risk group, most common risk factor was LVI positivity (87.5%), and among the intermediate group most common risk factor was age between 40-50 years (70%).
- There was no statistical significant difference between the 3-year actuarial LC and LRC rates among the molecular subtypes, or according to ER, PR, Her2neu status, three cases of IBTR occurred in luminal B subtype.
- This can be possibly explained by the fact that luminal B subtype had a higher percentage of T2 tumors, in this study.
- There was no statistically significant increased risk of local recurrence within TNBC subgroup

Do we need more factors…

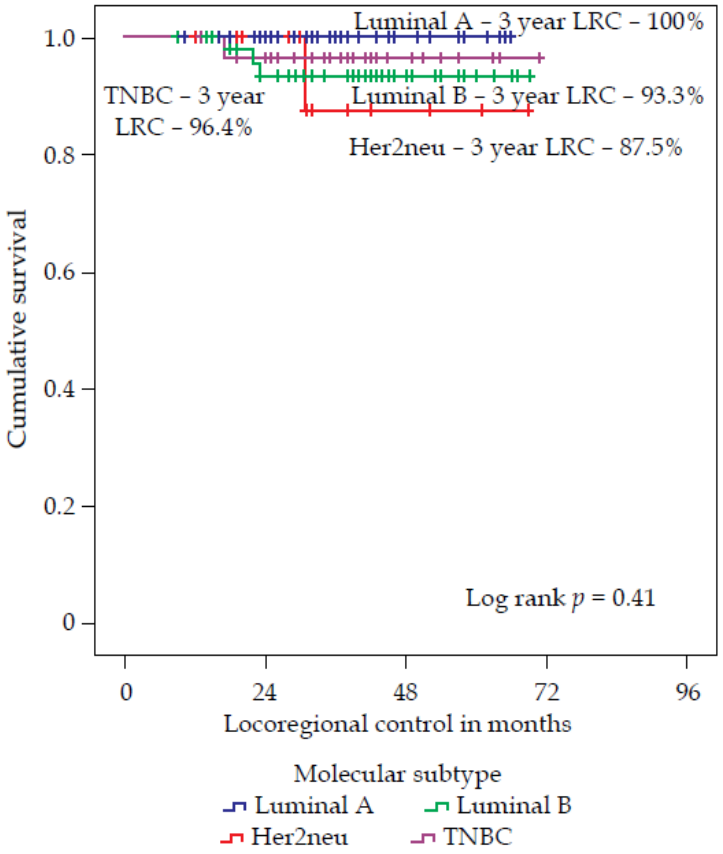

Fig. 2. Actuarial locoregional control (LRC) by molecular subtype

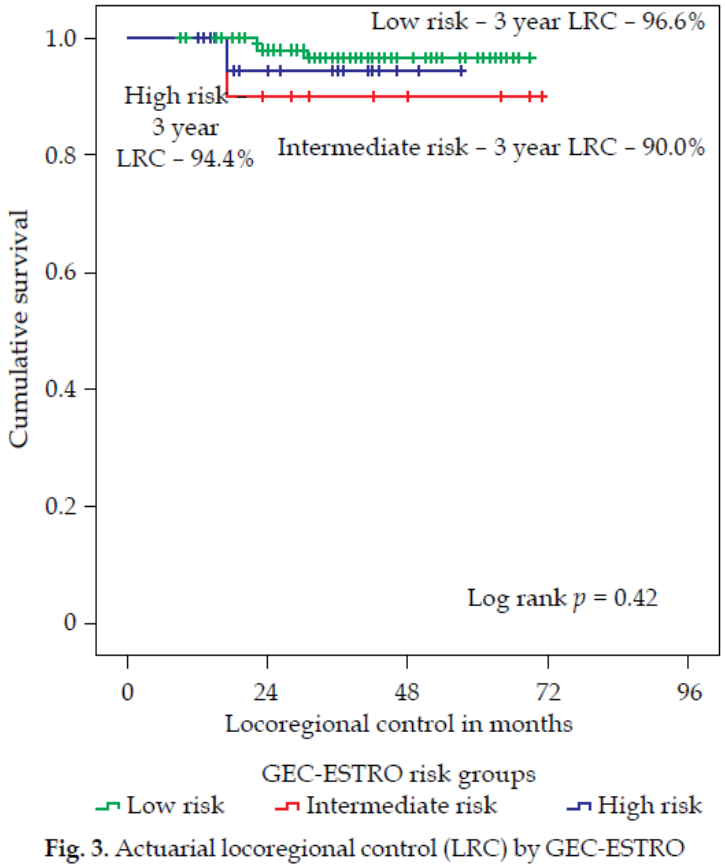

Fig. 3. Actuarial locoregional control (LRC) by GEC-ESTRO risk category

Journal of Contemporary Brachytherapy (2018/volume 10/number 1)

Do we need more Variables…

Table 5. Three-years actuarial outcome by molecular subtype, updated ASTRO category and GEC- ESTRO risk groups. As the number of unsuitable cases ASTRO Consensus was only five, unsuitable and cautionary analyzed as one category for statistical purpose. Clinical outcomes that were studied included local control (LC), locoregional control (LRC), distant metastasis-free survival (DMFS), disease-free survival (DFS), cause specific survival (CSS), and overall survival (OS). All the time to event data were calculated from the date of surgery. Bold numerals show statistically significant data, $p < 0.05$

		LC (%)	*p*-value	LRC (%)	*p*-value	DMFS (%)	*p*-value	DFS (%)	*p*-value	CSS (%)	*p*-value	OS (%)	*p*-value
Overall		96.5		96.5		95.6		93.1		98.3		97.6	
Molecular subtype	Luminal A	100	0.19	100	0.41	100	**0.01**	100	**0.007**	100	**0.006**	98.1	**0.05**
	Luminal B	93.3		93.3		97.6		93.3		100		100	
	Her2neu	87.5		87.5		71.6		61.4		82.0		82.0	
	TNBC	100		96.4		96.4		96.4		92.9		92.9	
Updated ASTRO category	Suitable	97.1	0.80	97.1	0.61	100	0.27	97.1	0.38	100	0.13	100	0.21
	Cautionary	96.1		95.1		93.5		91.0		97.4		96.5	
GEC-ESTRO risk group	Low	96.6	0.56	96.6	0.42	97.5	0.20	94.4	0.49	99.2	**0.007**	98.4	0.11
	Inter-mediate	100		90.0		87		78.8		85.7		85.7	
	High	94.4		94.4		100		94.4		100		100	

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Do we need more Variables…

- Budrukkar et al reported Her 2 neu as the only significant negative factor affecting LC.
- Clarke et al also showed Grade III affecting local control rates negatively.
- Wilkinson et al also reported no significant difference amongst various molecular markers (Luminal A/ B/ Her 2 neu).
- No significant difference was seen in outcomes of TNBC patients also

Take Home Message

- Careful selection of patients for APBI is absolutely essential for favourable outcomes.

THANK YOU