

An update in partial breast irradiation for breast cancer

Expert: **Prof Icro Meattini**, Florence University, Florence, Italy

Discussant: **Prof Pierfrancesco Franco**, University of Eastern Piedmont, Novara, Italy

Discussant: **Dr Orit Kaidar-Person**, Sheba Tel Hashomer, Ramat Gan, Israel

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Partial Breast Irradiation

Techniques, results, and patient selection

Prof. Icro Meattini, MD

University of Florence, Florence (IT)





Conflict of Interest Disclosure

- ***None related to the presented work.***
- *Icro Meattini declares occasional small fees received for advisory boards supported by Eli Lilly, Novartis, Seagen, Roche, Pfizer, Ipsen.*



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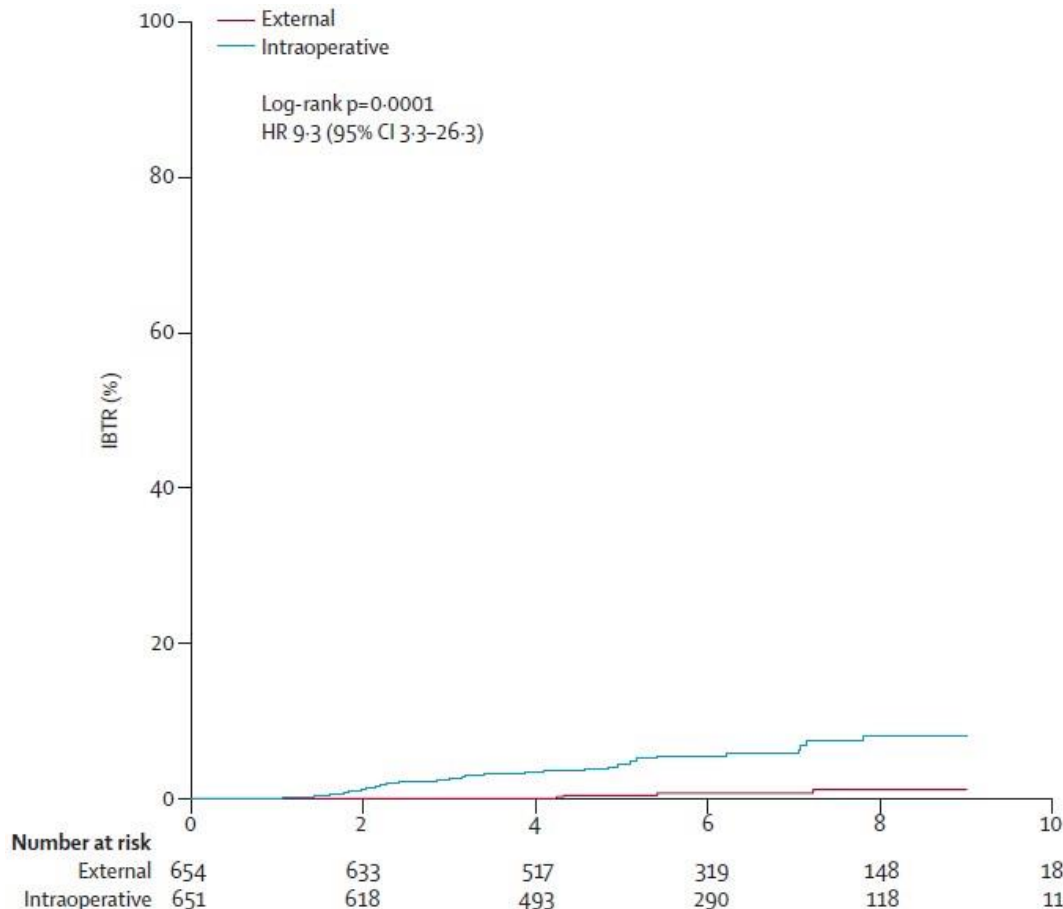
All the techniques are the same?

Intraoperative electrons radiation therapy – ELIOT trial

IOeRT **single fraction** 21 Gy

1305 patients (654 WBI vs. **651** IOeRT)

Equivalence trial 5-year difference (Δ): 7.5%



ELIOT vs WBI @5 years

IBTR	4.4% vs 0.4%	(HR 9.3)
True	2.5% vs 0.4%	(p=0.00003)
OS	96.8% vs 96.9%	(p=0.59)



All the techniques are the same?

Intraoperative electrons radiation therapy – ELIOT trial

@Multivariate analysis

5-year IBTR >10% (High risk factors)

Tumors >2 cm	(10.9%)
>4 positive nodes	(15.0%)
Grade 3 tumors	(11.9%)
ER negative	(14.9%)
TN tumors	(18.9%)

Patients with >1 factors (*ELIOT high risk*) vs patients with none factors

5-year IBTR → 11.3% vs 1.5%

ASTRO guidelines

Suitable	295/1822	(16%)	5-year rate 1.5%
Luminal A	118/295	(40%)	5-year rate 2.3%

ESTRO guidelines

Suitable	572/1822	(31%)	5-year rate 1.9%
Luminal A	206/572	(36%)	5-year rate 0%

Veronesi U, et al. *Lancet Oncol*, 2013
Silverstein MJ, et al. *Ann Surg Oncol*, 2014

	External radiotherapy	intraoperative radiotherapy with electrons	p value†
Any skin toxicity			
No	427	401	..
Yes, acute	32	5	..
Yes, chronic	5	6	0.0002
Erythema			
No	7	24	..
Grade 1-2	35	5	..
Grade 3	2	0	..
Grade 4	3	0	..
Grade 5	0	0	<0.0001
Dryness			
No	128	147	..
Grade 1-2	20	10	..
Grade 3-5	0	0	0.04
Hyper-pigmentation			
No	138	146	..
Grade 1-2	36	11	..
Grade 3-5	0	0	0.0004
Pruritus (scale 0-10)			
0	174	153	..
1-2	6	5	..
≥3	11	0	0.006
Overall p value	
Necrosis (radiological)			
Absent	136	129	..
Present	10	22	0.04

*Information available only for a subset of patients. †Overall p value.

Table 4: Skin side-effects (per-protocol analysis)*



All the techniques are the same?

Intraoperative radiation therapy – TARGIT-A trial

50 kV energy x-rays IORT **single fraction** 20 Gy

Randomized either before (*pre-pathology*) or after lumpectomy (*post-pathology by reopening the wound*)

TARGIT received supplemental EBRT in case of unforeseen adverse features (*risk-adapted RT*)

1721 TARGIT vs 1730 EBRT

Supplemental WBI after TARGIT in 15.2%
(21.6% pre-pathology, 3.6% post-pathology)

Median follow up: 2.5 years (*3451 patients*)
Median follow up: 5 years (*1222 patients*)

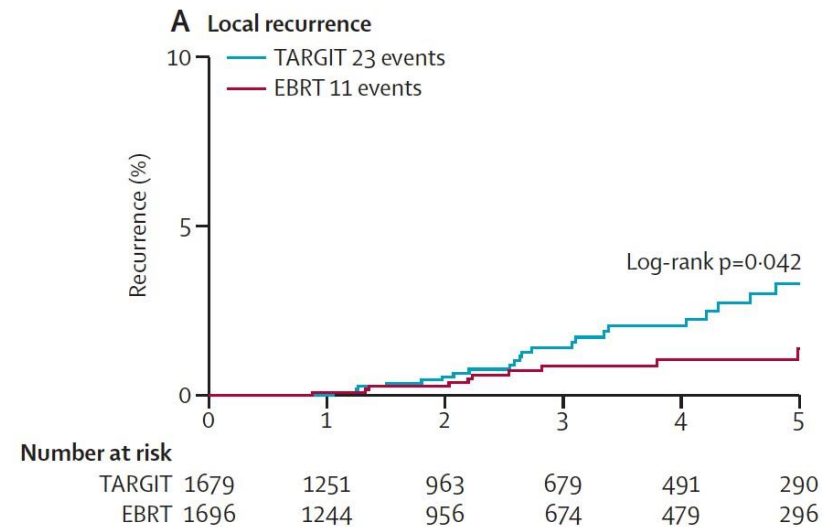
TARGIT vs EBRT @5 years (cumulative risk)

Local Recurrence 3.3% vs 1.3% (p=0.042)

Pre-pathology (n=2298) 2.1% vs 1.1% (p=0.31)

Post-pathology (n=1153) 5.4% vs 1.7% (p=0.069)

Breast cancer mortality 2.6% vs 1.9% (p=0.56)



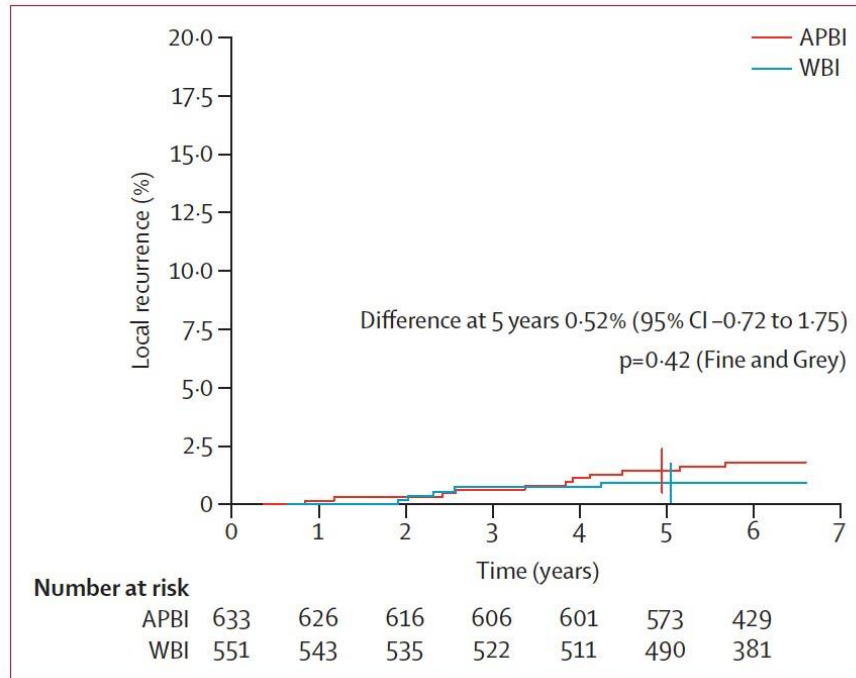
All the techniques are the same?

Brachytherapy – GEC/ESTRO trial

stage 0, I, IIA breast cancer

1184 patients **HDR 7-8 fractions**

633 **brachy** vs. 551 WBI



Strnad V, et al. Lancet 2016

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



APBI **brachy** vs WBI @5 years

IBTR 1.44% vs 0.92% $p=0.42$

DM 0.80% vs 0.93% $p=0.81$

OS 96.0% vs 94.0% $p=0.84$



All the techniques are the same?

Brachytherapy – GEC/ESTRO trial

stage 0, I, IIA breast cancer

1184 patients **HDR 7-8 fractions**

633 **brachy** vs. 551 WBI

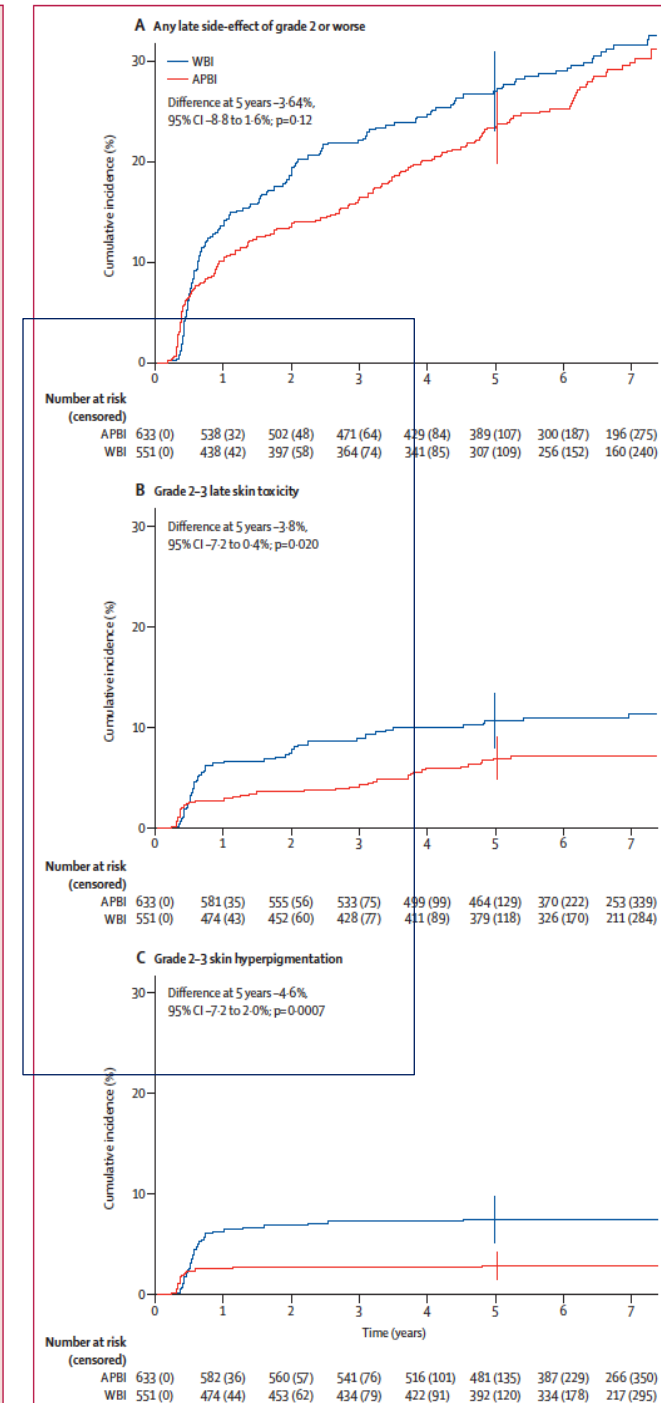
Late side-effects and cosmetic results of accelerated partial breast irradiation with interstitial brachytherapy versus whole-breast irradiation after breast-conserving surgery for low-risk invasive and in-situ carcinoma of the female breast: 5-year results of a randomised, controlled, phase 3 trial



Csaba Polgár, Oliver J Ott, Guido Hildebrandt, Daniela Kauer-Dorner, Hellen Knauerhase, Tibor Major, Jaroslaw Lyczek, José Luis Guinot, Jürgen Dunst, Cristina Gutierrez Miguelez, Pavel Slampa, Michael Allgäuer, Kristina Lössl, Bülent Polat, György Kovács, Arnt-René Fischeidick, Rainer Fietkau, Alexandra Resch, Anna Kulik, Leo Aribas, Peter Niehoff, Ferran Guedea, Annika Schlamann, Richard Pötter, Christine Gall, Wolfgang Uter, Vratislav Strnad, on behalf of the Groupe Européen de Curiethérapie de European Society for Radiotherapy and Oncology (GEC-ESTRO)

Polgar C, et al. Lancet Oncol 2017

	Accelerated partial breast irradiation group	Whole-breast irradiation group	p value*
Skin RTOG/EORTC			0.16
Grade 0	415/484 (86%)	324/393 (82%)	
Grade 1	50/484 (10%)	45/393 (12%)	
Grade 2	16/484 (3%)	17/393 (4%)	
Grade 3	3/484 (<1%)	7/393 (2%)	
Skin telangiectasia			0.93
Grade 0	434/483 (90%)	352/392 (90%)	
Grade 1	29/483 (6%)	22/392 (6%)	
Grade 2	16/483 (3%)	10/392 (3%)	
Grade 3	4/483 (<1%)	8/392 (2%)	
Skin hyperpigmentation			0.0087
Grade 0	457/484 (94%)	352/392 (90%)	
Grade 1	26/484 (5%)	36/392 (9%)	
Grade 2	1/484 (<1%)	4/392 (1%)	
Subcutaneous tissue RTOG/EORTC			0.097
Grade 0	281/485 (58%)	248/393 (63%)	
Grade 1	171/485 (35%)	126/393 (32%)	
Grade 2	33/485 (7%)	17/393 (4%)	
Grade 3	0	2/393 (<1%)	
Fibrosis			0.24
Grade 0	297/484 (61%)	254/392 (65%)	
Grade 1	156/484 (32%)	120/392 (31%)	
Grade 2	31/484 (6%)	16/392 (4%)	
Grade 3	0	2/392 (<1%)	
Fat necrosis			0.24
Grade 0	440/484 (91%)	366/393 (93%)	
Grade 1	37/484 (8%)	23/393 (6%)	
Grade 2	6/484 (1%)	3/393 (<1%)	
Grade 3	1/484 (<1%)	1/393 (<1%)	
Pain			0.99
Grade 0	379/484 (78%)	309/393 (79%)	
Grade 1	102/484 (21%)	75/393 (19%)	
Grade 2	3/484 (<1%)	7/393 (2%)	
Grade 3	0	2/393 (<1%)	
Arm lymphoedema			0.17
Grade 0	472/483 (98%)	377/393 (96%)	
Grade 1	10/483 (2%)	16/393 (4%)	
Grade 2	1/483 (<1%)	0	
Data are n/N (%). RTOG/EORTC–Radiation Therapy Oncology Group/European Organisation for Research and Treatment of Cancer. *Calculated with an exact two-sided Wilcoxon-Mann-Whitney Test.			
Table 2: 5-year prevalence of late side-effects			



All the techniques are the same?

External beam radiation therapy - IMPORT LOW trial

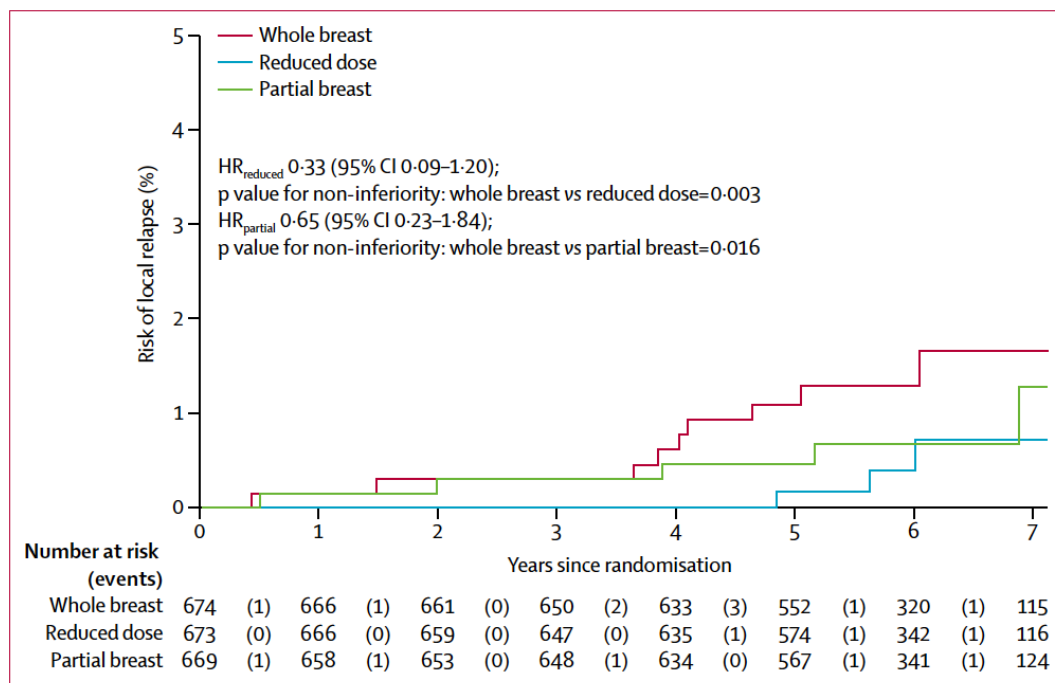
>90% T1N0 HR+/HER2-

40 Gy in 15 fractions to the partial breast

669 PBI vs. 674 WBI



Partial-breast radiotherapy after breast conservation surgery for patients with early breast cancer (UK IMPORT LOW trial): 5-year results from a multicentre, randomised, controlled, phase 3, non-inferiority trial



PBI EBRT 40/15 vs WBI @5 years

IBTR	0.5%	vs	1.1%	$p=0.42$
DM	1.6%	vs	1.4%	$p=0.83$
OS	96.3%	vs	95%	$p=0.69$

All the techniques are the same?

External beam radiation therapy - IMPORT LOW trial

>90% T1N0 HR+/HER2-

40 Gy in 15 fractions to the partial breast

669 PBI vs. 674 WBI

Analysis by treatment group showed average number of AEs per person was lower in PBI (95% CI, 0.71 to 0.84; $P < .001$) and reduced-dose (95% CI, 0.76 to 0.90; $P < .001$) versus WBI and decreased over time in all groups

Bhattacharya I, et al. JCO 2018

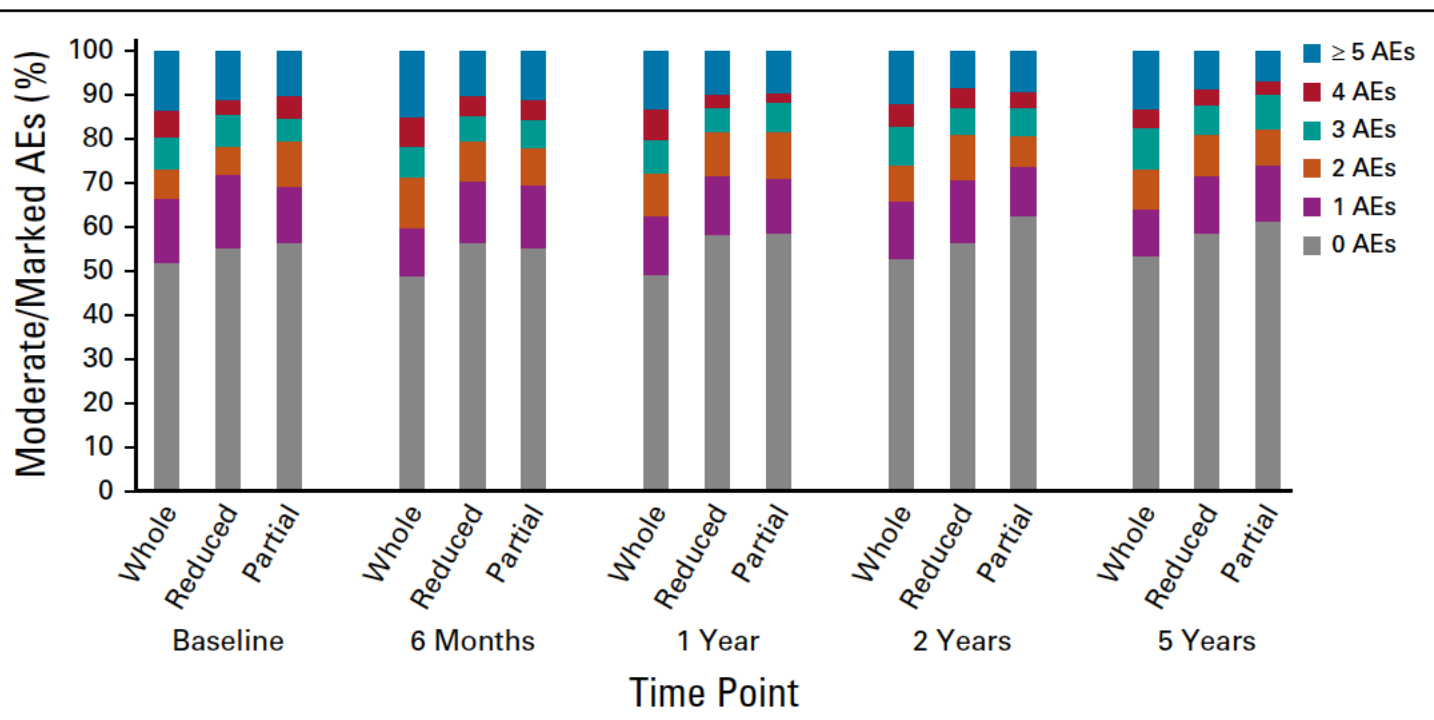


FIG 3. Number of moderate/marked adverse effects (AEs) reported per person over time by treatment group.

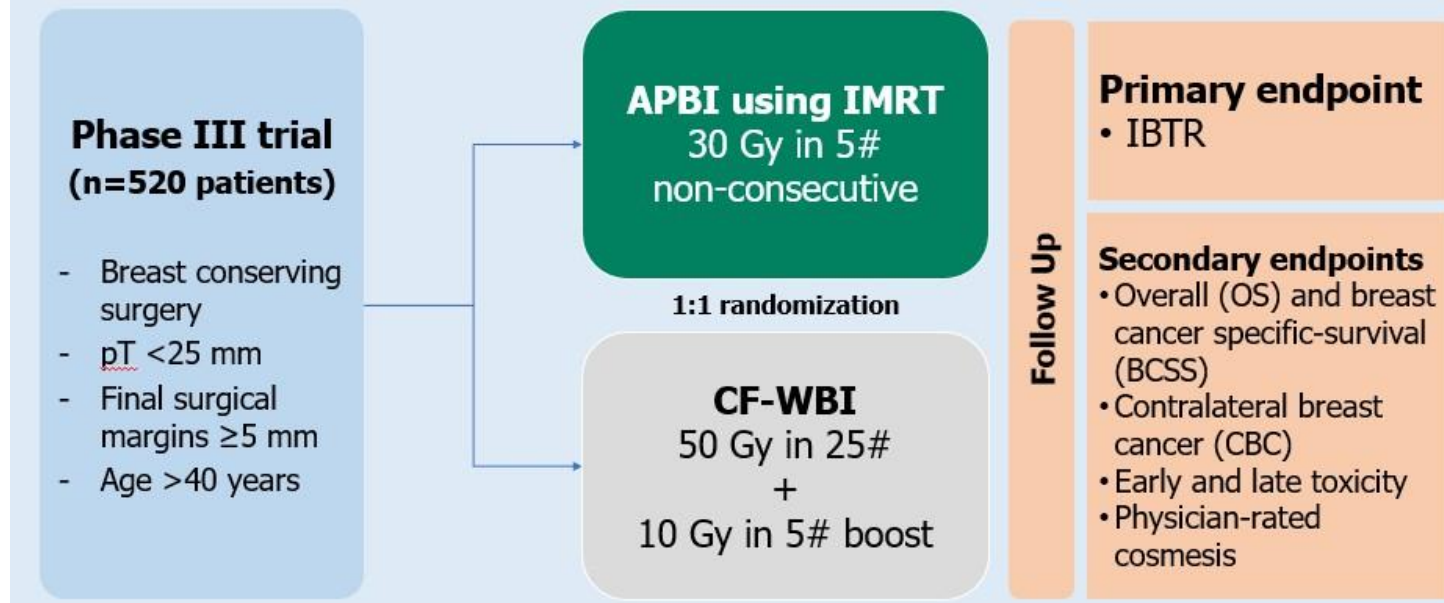
All the techniques are the same?

External beam radiation therapy – APBI-IMRT Florence trial

APBI-IMRT 30 Gy in 5 fractions vs. **WBI 50 Gy+10 Gy** boost

520 patients (1:1 randomized)

Trial design – APBI IMRT Florence (NCT 02104895)



Available at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejcancer.com



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



APBI-IMRT **EBRT** vs WBI @5 years

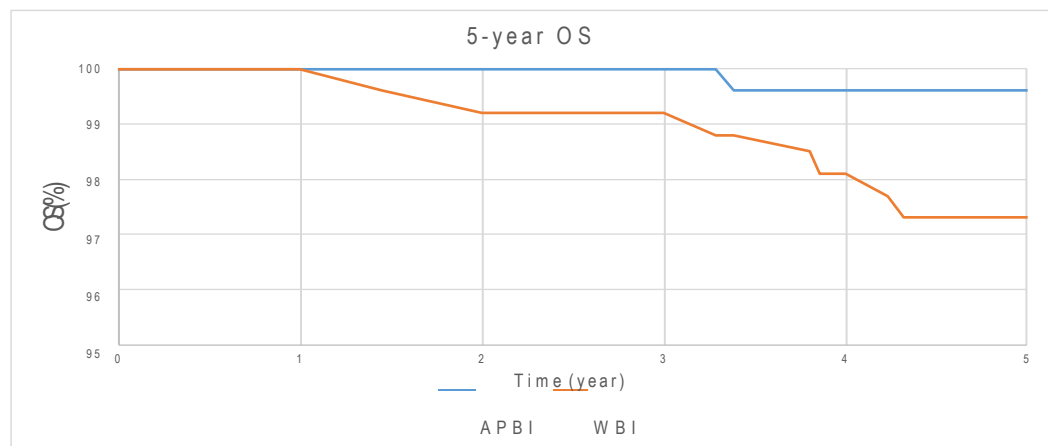
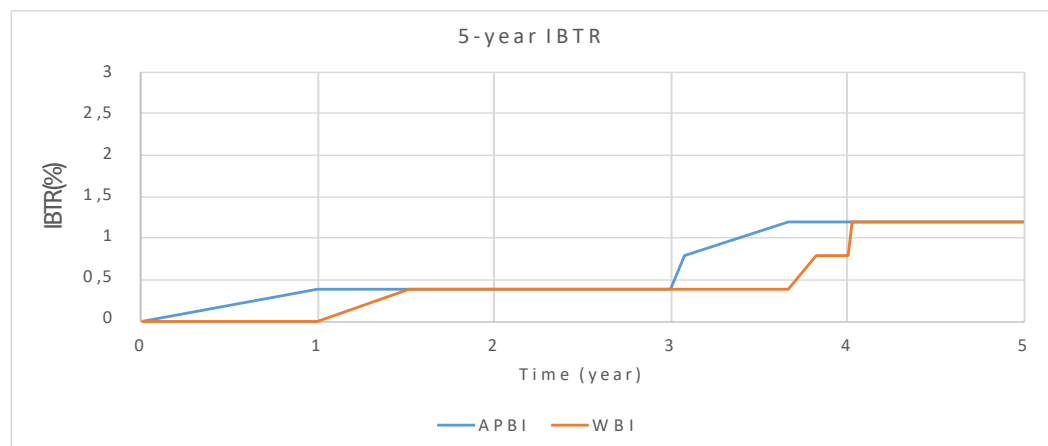
IBTR	1.5% vs 1.4%	$p=0.86$
DM	1.5% vs 1.8%	$p=0.87$
OS	99.4% vs 96.6%	$p=0.057$

All the techniques are the same?

External beam radiation therapy – APBI-IMRT Florence trial

APBI-IMRT

30 Gy in 5 fractions vs. WBI 50 Gy+10 Gy boost



Subgroup	IBTR	%	DM	%	OS	%
Luminal A (n:169)	2	1.7	0	0	0	100
ASTRO suitable (n:133)	0	0	1	1.0	1	98.9
ESTRO low risk (n:190)	1	0.8	1	0.7	0	100

Luminal-A patients (n=320)

61% of the whole series

151 WBI vs 169 APBI

IBTR rate @5 years

0.9% vs 1.7% $p=0.53$

Endocrine therapy (around 70%)

No impact on:

- IBTR $p=0.11$
- LRR $p=0.28$
- DM $p=0.55$



All the techniques are the same?

External beam radiation therapy – APBI-IMRT Florence trial

APBI-IMRT

30 Gy in 5 fractions vs. WBI 50 Gy+10 Gy boost

original reports

Accelerated Partial-Breast Irradiation Compared With Whole-Breast Irradiation for Early Breast Cancer: Long-Term Results of the Randomized Phase III APBI-IMRT-Florence Trial



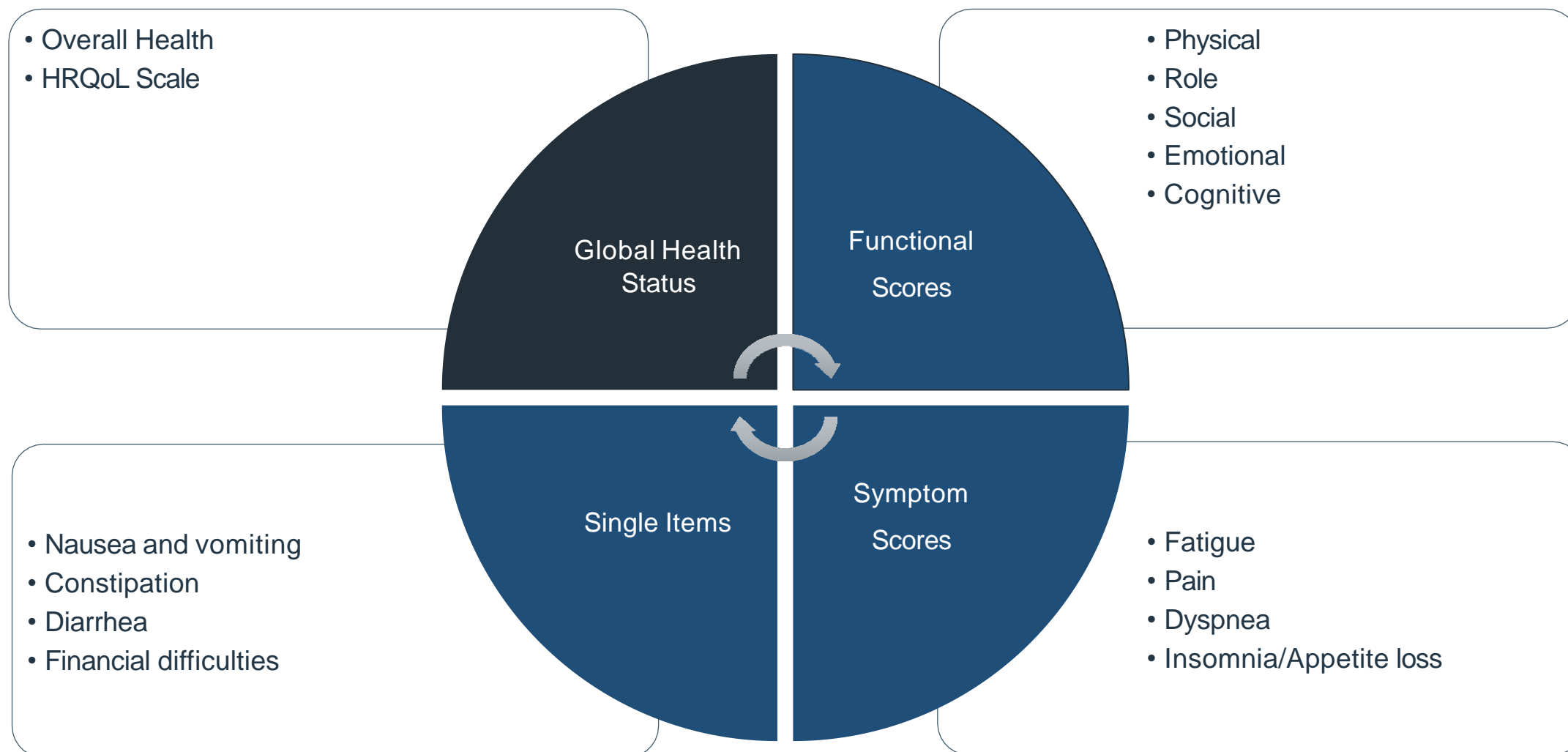
Icro Meattini, MD^{1,2}; Livia Marrazzo, MS²; Calogero Saieva, MD³; Isacco Desideri, MD^{1,2}; Vieri Scotti, MD²; Gabriele Simontacchi, MD²; Pierluigi Bonomo, MD²; Daniela Greto, MD²; Monica Mangoni, MD, PhD^{1,2}; Silvia Scoccianti, MD²; Sara Lucidi, MD¹; Lisa Paoletti, MD⁴; Massimiliano Fambrini, MD^{1,2}; Marco Bernini, MD, PhD²; Luis Sanchez, MD²; Lorenzo Orzalesi, MD^{1,2}; Jacopo Nori, MD²; Simonetta Bianchi, MD^{1,2}; Stefania Pallotta, MS^{1,2}; and Lorenzo Livi, MD^{1,2}

Meattini I, et al. JCO 2020

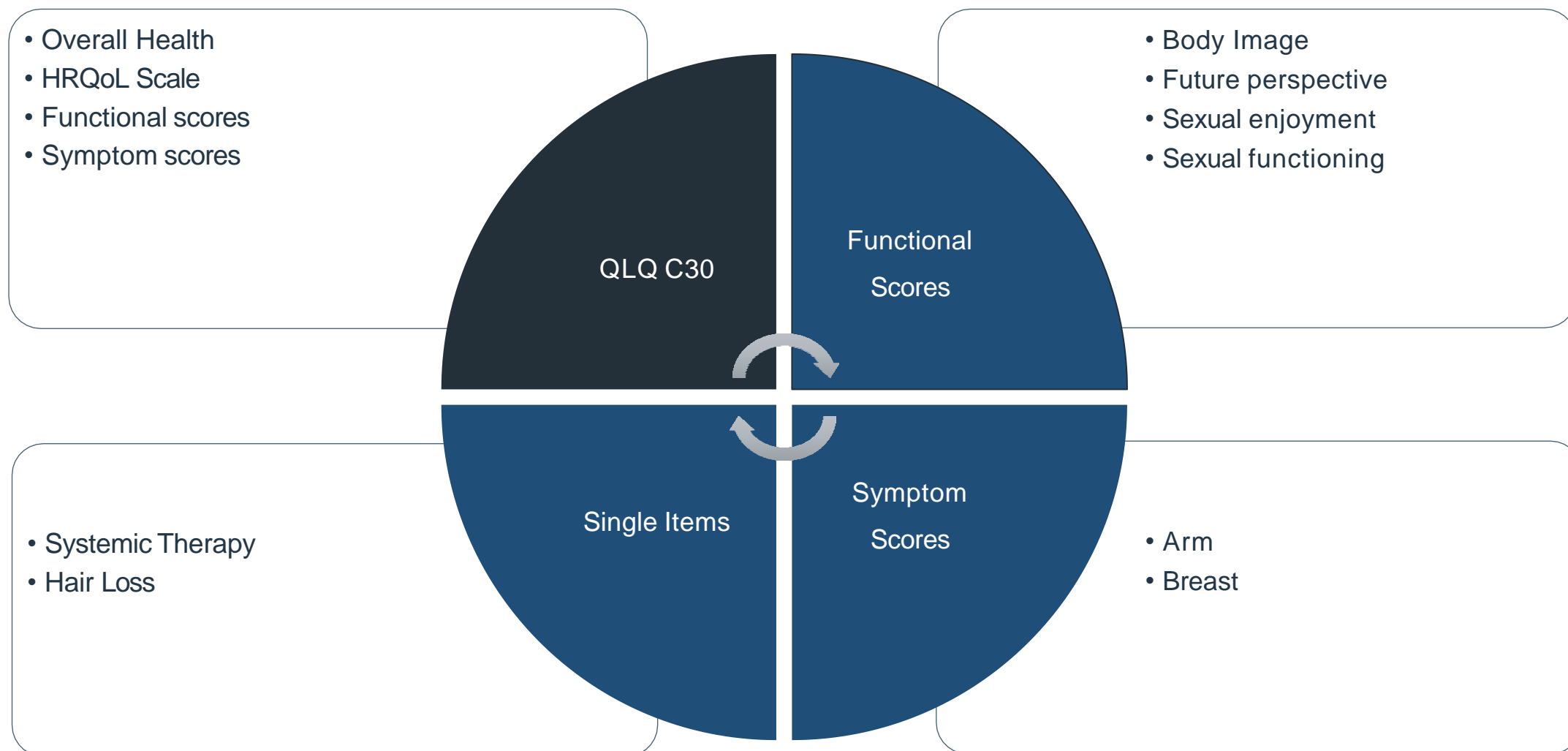
TABLE 3. Treatment-Related Adverse Events, Physician- and Patient-Rated Cosmesis Assessments Stratified by Treatment Arm and Period (per protocol)

Assessment	APBI (n = 246)	WBI (n = 260)	P
Acute period adverse events ^a			
None	194 (78.9)	87 (33.5)	.0001
Yes, any grade	52 (21.1)	173 (66.5)	
Grade 1	47 (19.1)	75 (28.8)	.0001
Grade 2	5 (2.0)	81 (31.2)	
Grade 3	—	17 (6.5)	
Grade 4	—	—	
Grade 0-1	241 (98.0)	162 (62.3)	.0001
Grade ≥ 2	5 (2.0)	98 (37.7)	.0001
Late period adverse events ^a			
None	235 (95.5)	182 (70.0)	.0001
Yes, any grade	11 (4.5)	78 (30.0)	.0001
Grade 1	11 (4.5)	71 (27.3)	.0001
Grade 2	—	7 (2.7)	
Grade 3	—	—	
Grade 4	—	—	
Grade 0-1	246 (100)	253 (97.3)	.015
Grade ≥ 2	0	7 (2.7)	
Physician-rated cosmesis ^b			
Excellent	233 (94.7)	189 (72.7)	.0001
Good	13 (5.3)	66 (25.4)	
Fair	—	5 (1.9)	
Poor	—	—	
Patient-rated cosmesis ^b			
Excellent	44 (17.9)	13 (5.1)	.0001
Good	200 (81.3)	209 (80.3)	
Fair	2 (0.8)	38 (14.6)	
Poor	—	—	

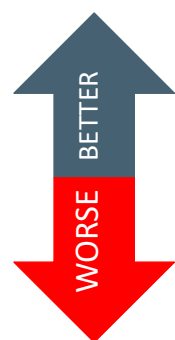
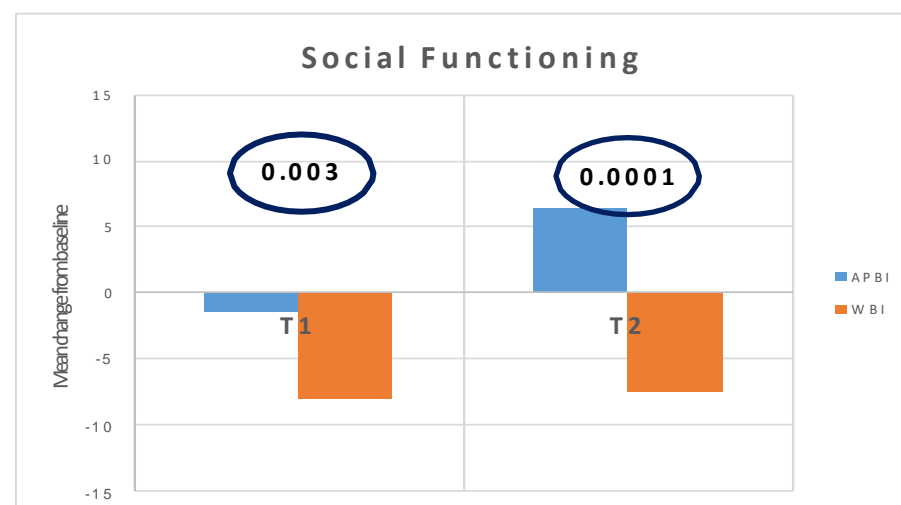
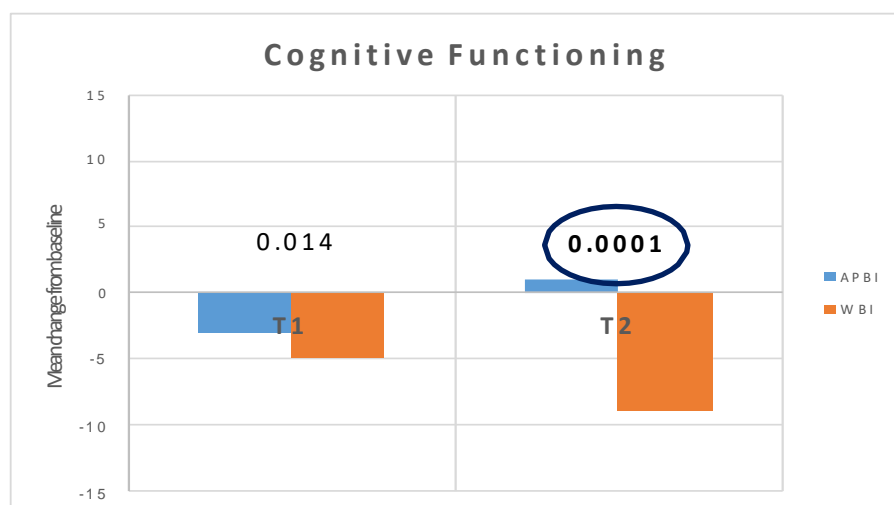
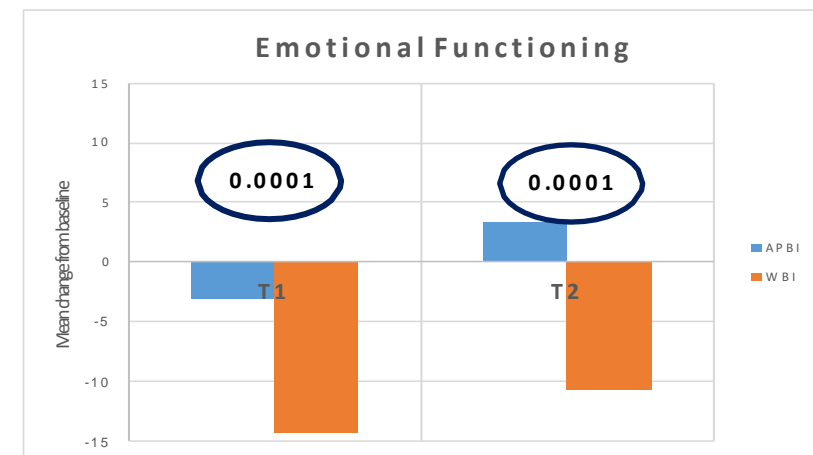
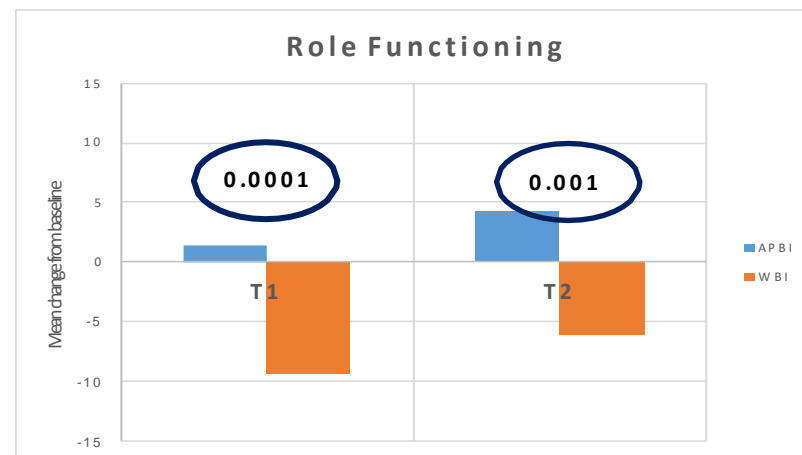
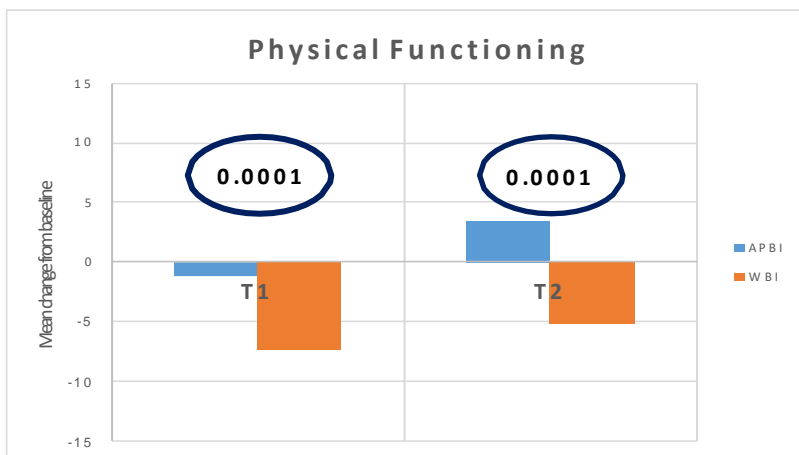
HRQoL Analysis Assessments: QLQ C30



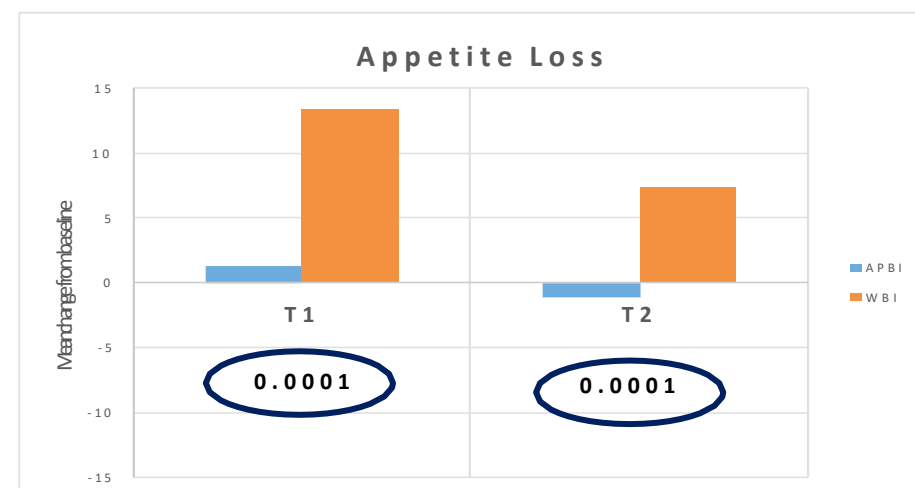
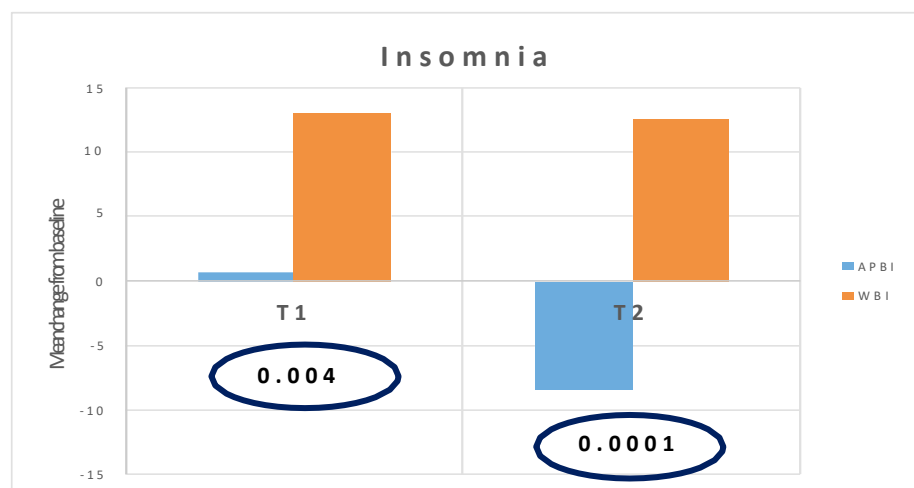
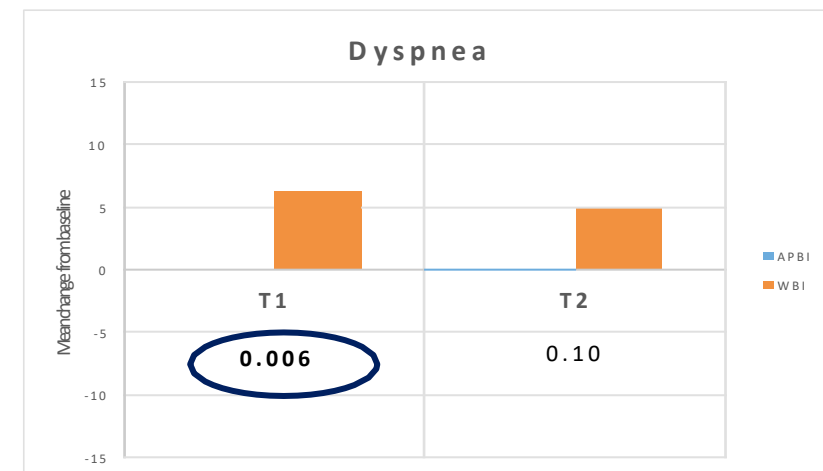
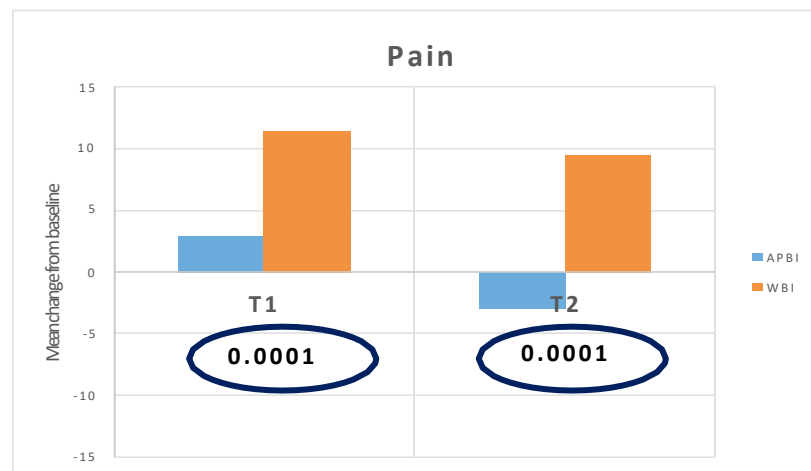
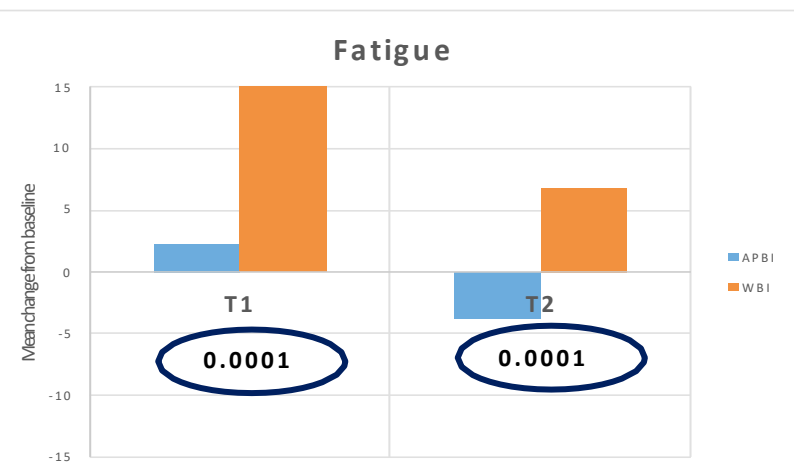
HRQoL Analysis Assessments: QLQ BR23



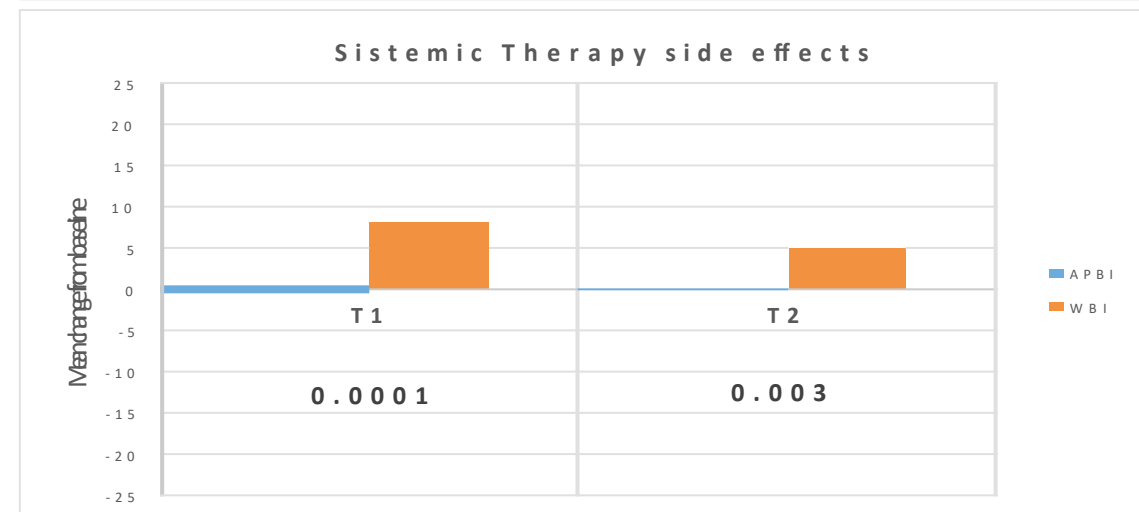
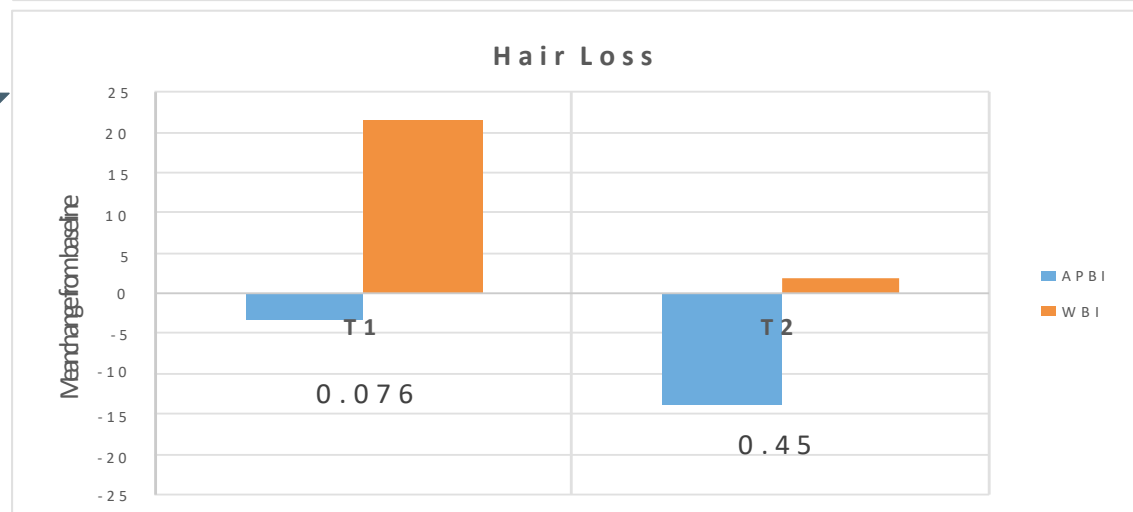
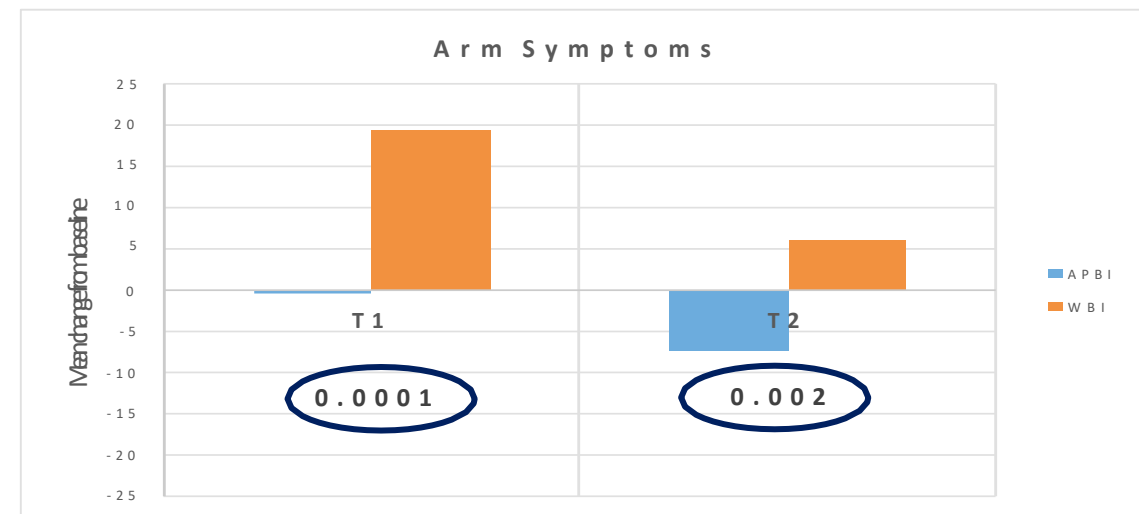
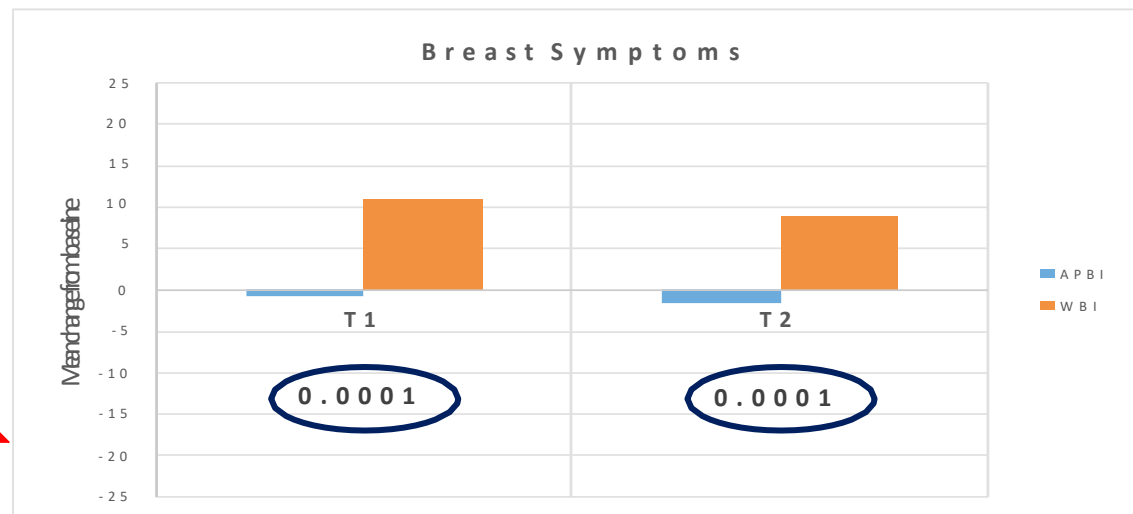
HRQoL QLQ C30 functional scales



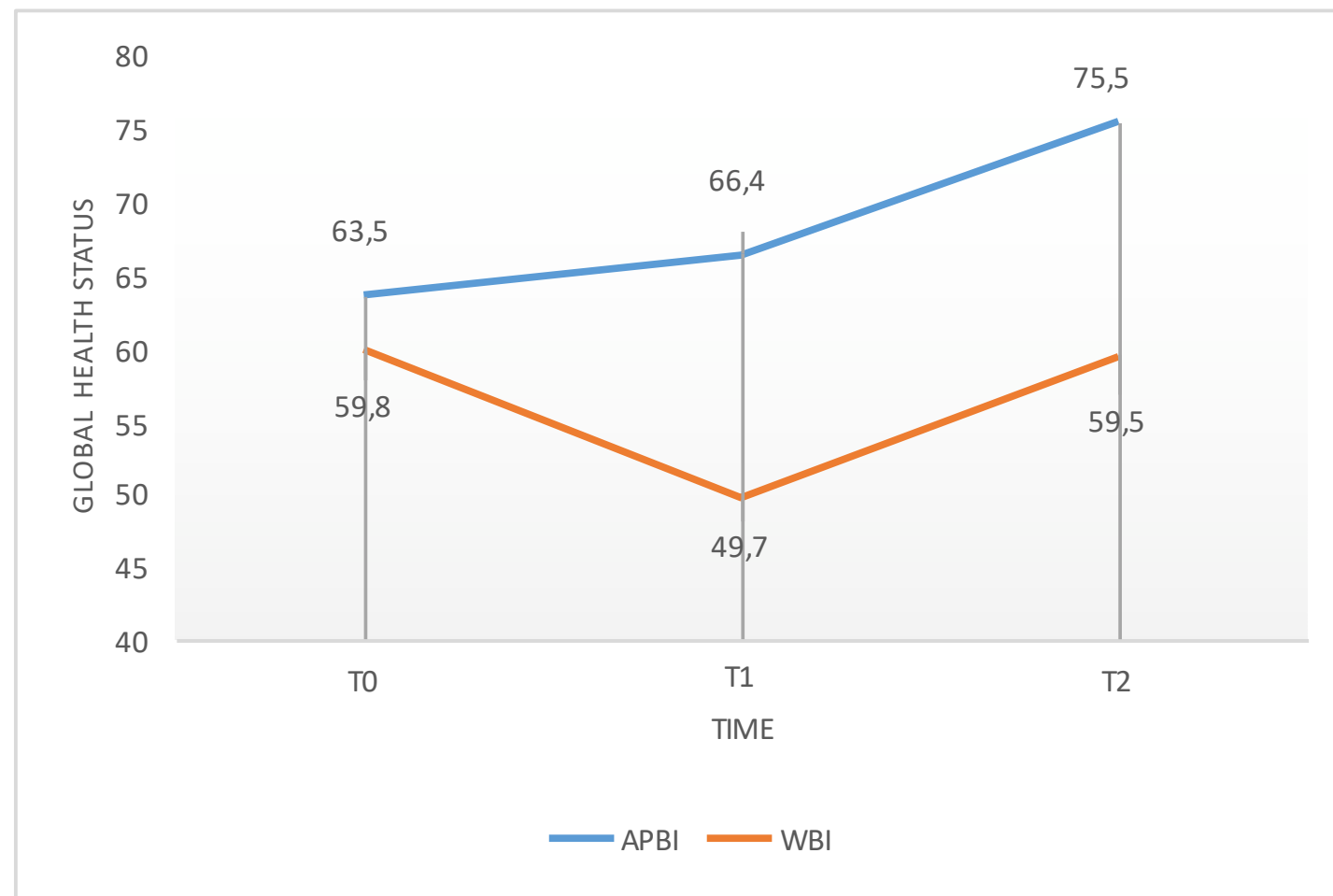
HRQoL QLQ C30 symptom scales



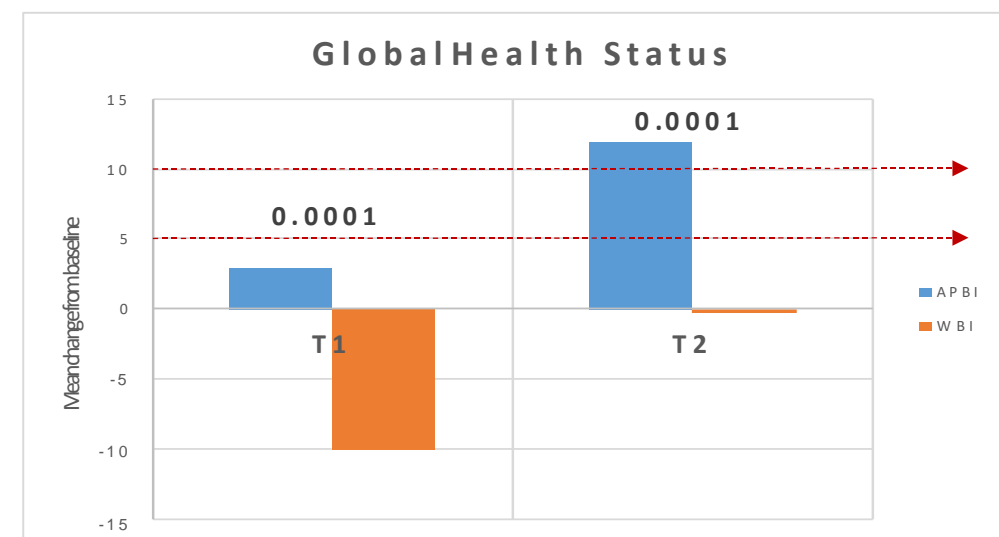
HRQoL QLQ BR23 symptom scales



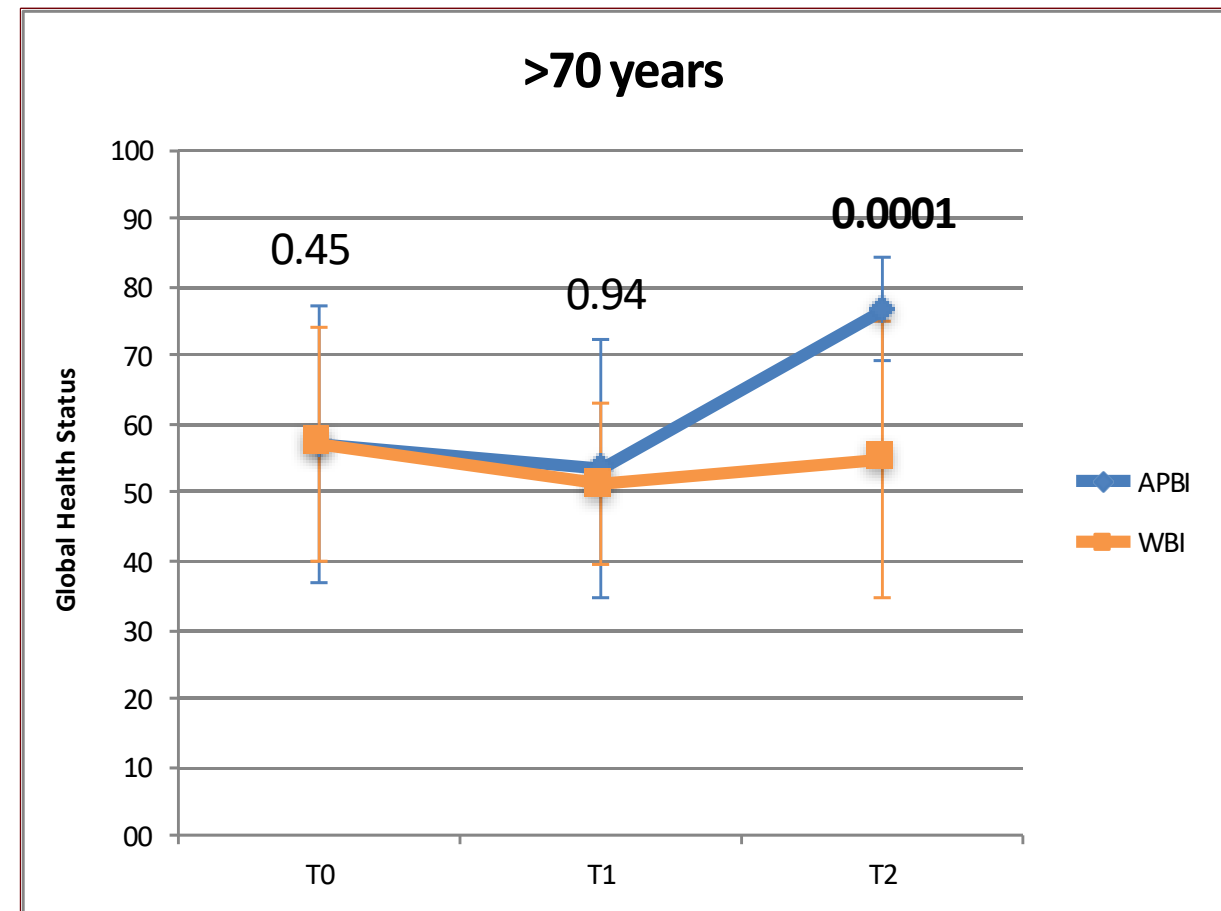
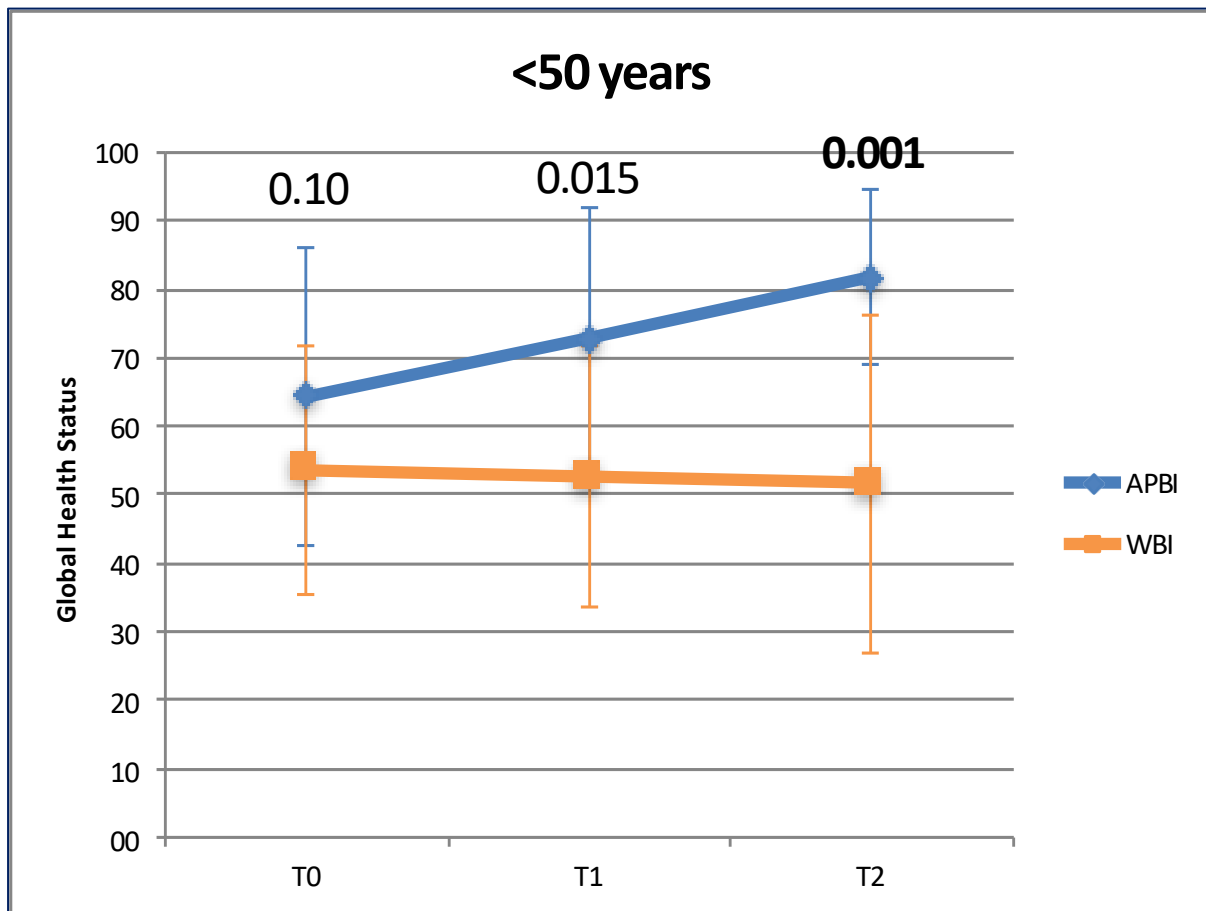
GHS trend over time



Wilcoxon signed rank test			
	T0-T1	T0-T2	T1-T2
	P-value	P-value	P-value
APBI	0.32	0.0001	0.0001
WBI	0.0001	0.92	0.0001

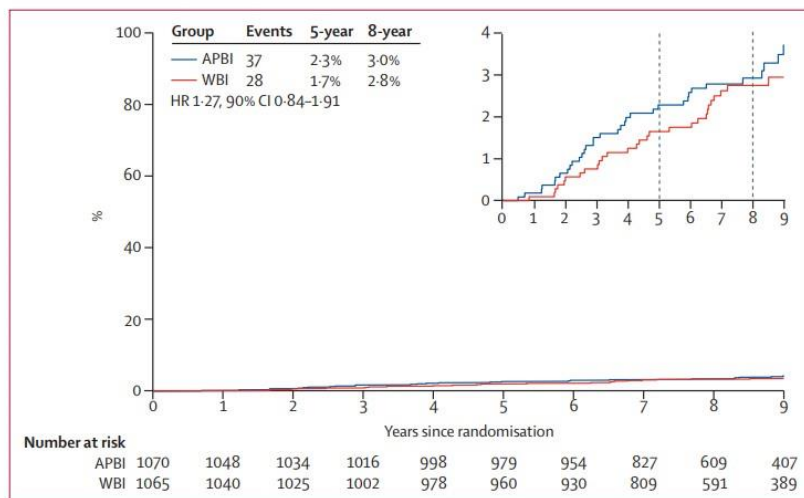


Impact of age on HRQoL GHS



All the techniques are the same?

External beam radiation therapy – RAPID and NSABP B-39 trials



Whelan T, et al. Lancet 2019

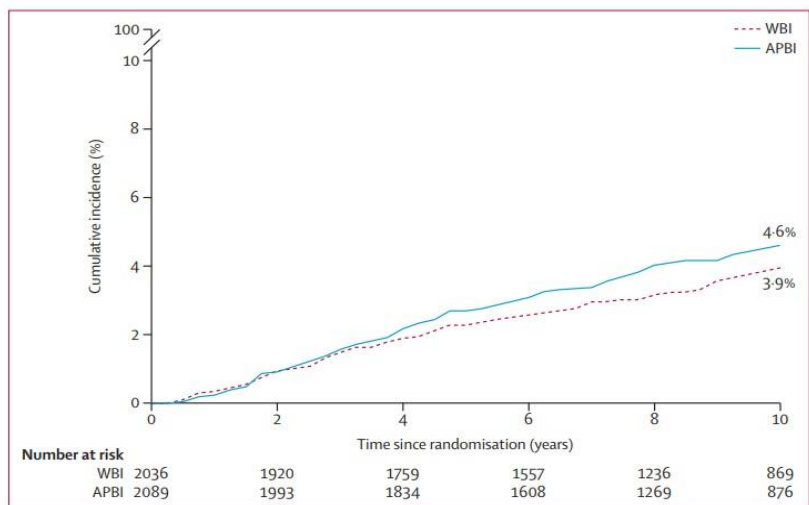
RAPID trial

2135 patients – 38.5 Gy in 10 td fractions

EBRT-APBI (*3DCRT and IMRT*)

5-year IBTR events: 2.3% (APBI) vs. 1.7% (WBI)

APBI not inferior to WBI ($HR=1.27$, 90%CI, 0.84-1.91)



Vicini F, et al. Lancet 2019

NSABP B-39/RTOG 0413 trial

4216 patients – 38.5 Gy in 10 td fractions

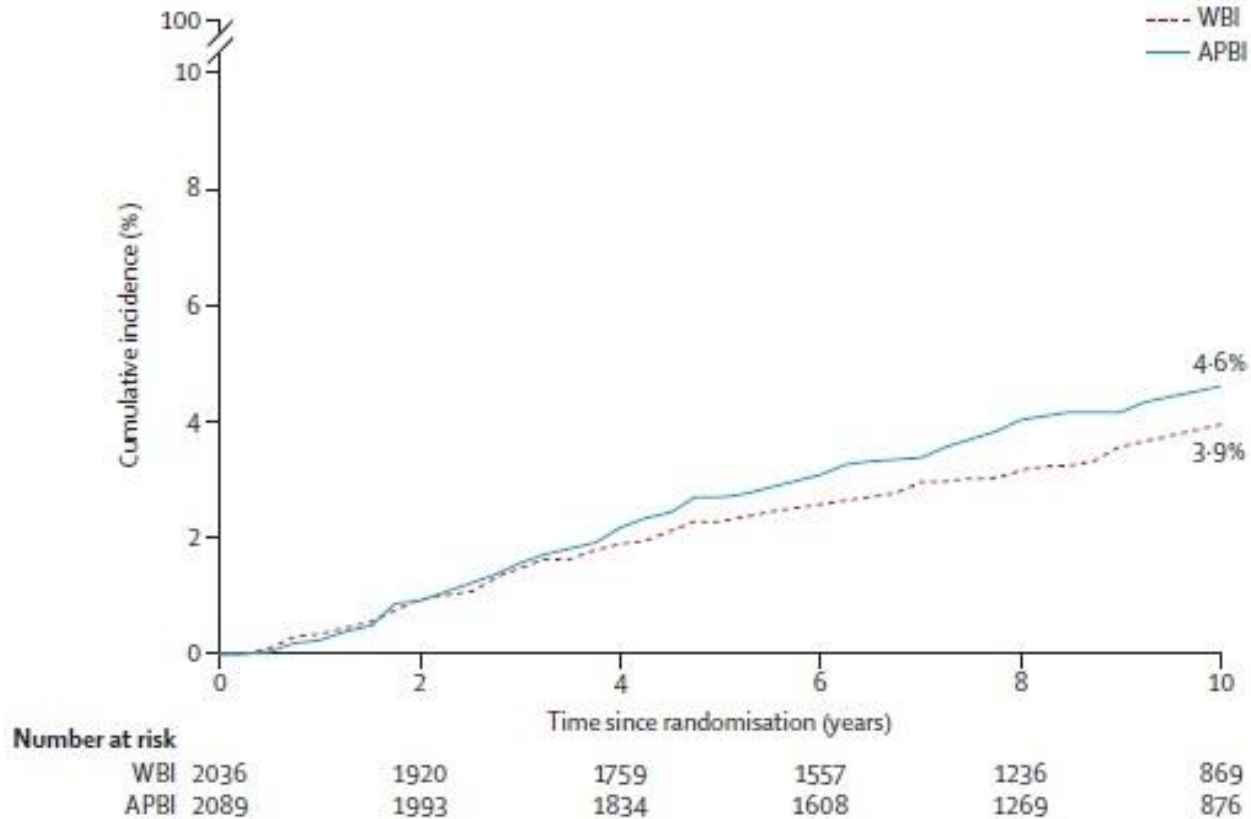
APBI (71% 3DCRT / 23.3% balloon-single entry device / 6% brachytherapy)

10-year difference IBTR: 0.7%

(4.6% PBI vs 3.9% WBI) ($HR 1.22$; 90%CI 0.94-1.58)

NSABP B39/RTOG 0413

4216 patients (2109 WBI vs 2107 APBI)



APBI vs WBI

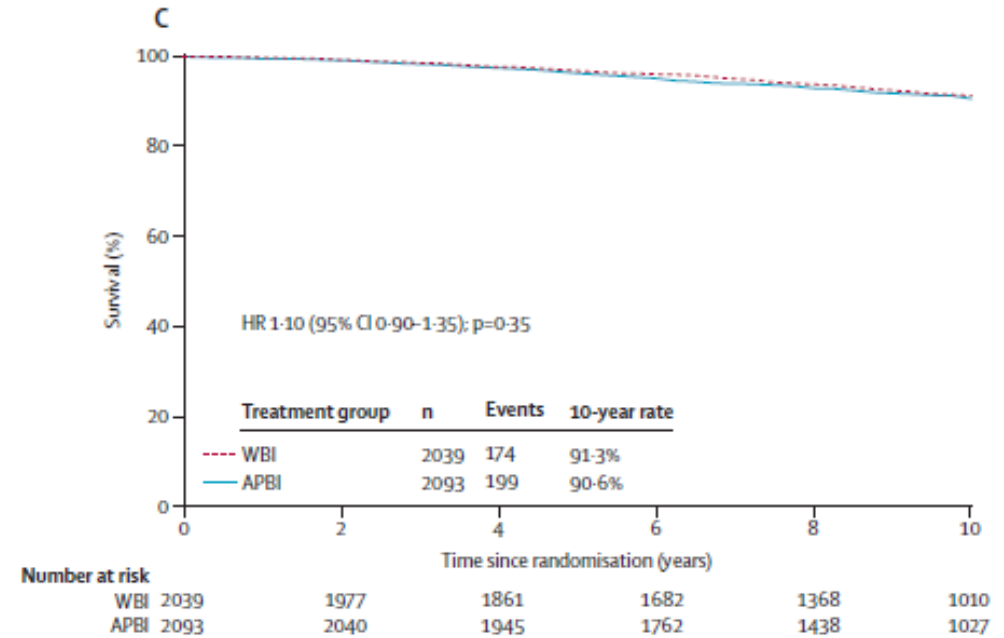
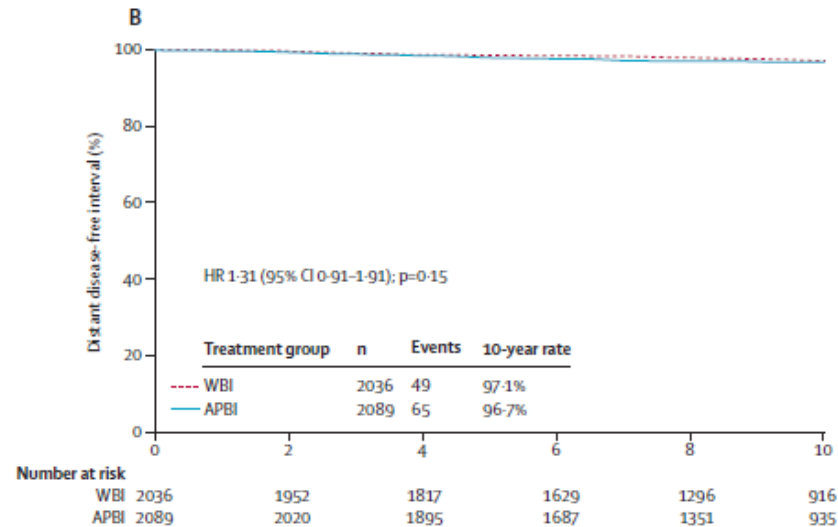
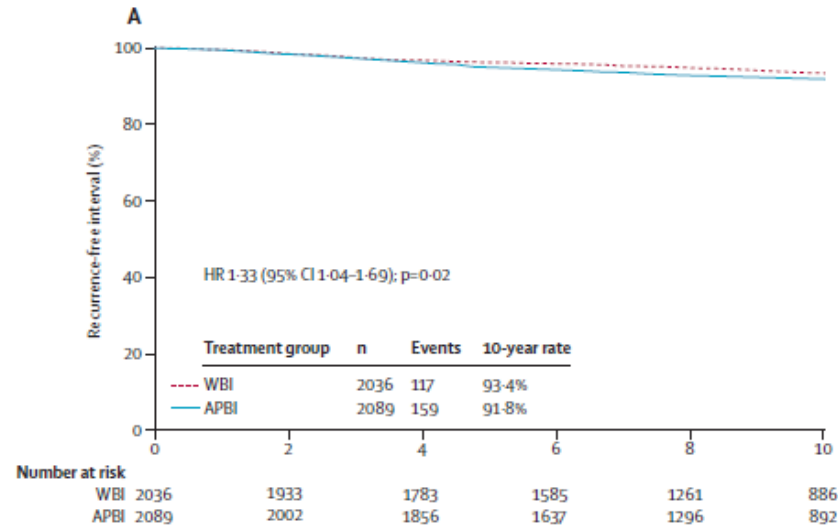
IBTR 90 (4%) vs 71 (3%)

(HR 1.22, 90% CI 0.94–1.58)

[equivalency test on the basis of a 50% margin increase in the HR (90% CI for the observed HR between 0.667 and 1.5 for equivalence)]

10-year cumulative incidence of IBTR was 3.9% (95% CI 3.1–5.0) in the WBI group and 4.6% (3.7–5.7) in the APBI group for an absolute difference of 0.7%

NSABP B39/RTOG 0413



APBI vs WBI

DFS 96.7% vs 97.1%

OS 90.6% vs 91.3%

No significant differences between APBI and WBI



NSABP B39/RTOG 0413

Adverse events (highest toxicity)

available for 4109 (97%) of all enrolled patients

APBI

CTCAE toxicity Grade 1 in 845 (40%), grade 2 in 921 (44%), and grade 3 in 201 (10%) patients

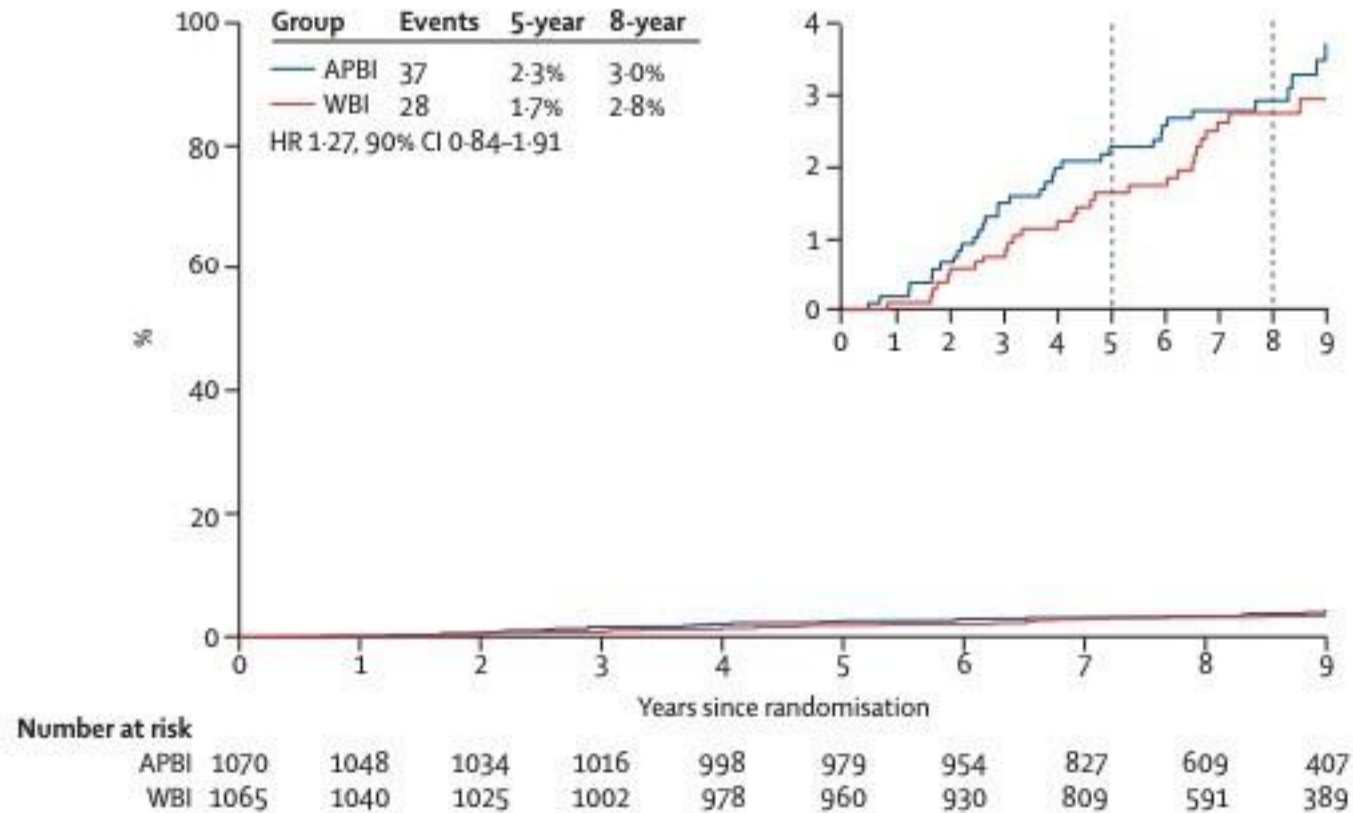
WBI

CTCAE toxicity Grade 1 in 626 (31%), grade 2 in 1193 (59%), and grade 3 in 143 (7%) patients

Grades 4 and 5 toxicities were low: 10 (<1%) patients in the APBI and 6 (<1%) in the WBI group

There were **no significant differences** in the number of patients with **second primary cancers** reported between the two groups

Rates of IBTR over time



APBI vs WBI @8-year

IBTR 3.0% vs 2.8%

	APBI	WBI
Total patients	1070	1065
Ipsilateral breast tumour recurrence	37 (3.5%)	28 (2.6%)
Regional recurrence	4 (0.4%)	2 (0.2%)
Distant recurrence	20 (1.9%)	18 (1.7%)
Contralateral breast cancer	29 (2.7%)	38 (3.6%)
Non-breast second cancer*	84 (7.9%)	57 (5.4%)
Death	25 (2.3%)	27 (2.5%)
Any event	199 (19%)	170 (16%)

Data are n (%) unless otherwise specified. APBI=accelerated partial breast irradiation. WBI=whole breast irradiation. *Site of second cancers are provided in the appendix (p 8).

Characteristic	Adverse cosmesis at 3 y:		Deterioration of cosmesis from baseline to 3 y:	
	Multivariable model (events/n = 249/1083*)		Multivariable model (events/n = 291/1033*)	
	OR (95% CI)	P	OR (95% CI)	P
Treatment: APBI vs WBI	2.30 (1.65-3.21)	<.001	1.93 (1.45-2.59)	<.001
Tumor location		.004		.69
Central vs outer	1.98 (1.24-3.17)		1.19 (0.74-1.91)	
Inner vs outer	1.53 (1.07-2.17)		1.11 (0.80-1.55)	
Comorbidities: Yes vs no	1.02 (0.74-1.42)	.89	0.98 (0.72-1.33)	.89
Breast infection: Yes vs no	2.02 (1.22-3.32)	.006	0.80 (0.47-1.34)	.39
Current smoker: Yes vs no	2.42 (1.56-3.75)	<.001	1.58 (1.01-2.46)	.04
Hormonal therapy: Yes vs no	1.14 (0.84-1.55)	.40	1.04 (0.78-1.34)	.80
Chemotherapy: Yes vs no	1.19 (0.57-2.48)	.65	1.69 (0.85-3.37)	.14
Dose homogeneity: Yes vs no	0.69 (0.46-1.02)	.06	0.85 (0.57-1.26)	.42
Seroma volume (per 10 cm ³)	1.18 (1.09-1.28)	<.001	1.12 (1.04-1.21)	.004
Breast volume (per 500 cm ³)	0.86 (0.75-0.99)	.04	1.09 (0.96-1.23)	.18
Age (per 10 y)	1.30 (1.08-1.54)	.004	1.11 (0.94-1.31)	.23
Weeks from surgery to RT	1.03 (0.98-1.05)	.15	1.02 (0.99-1.06)	.26
Maximum isodose	1.07 (0.98-1.15)	.10	1.00 (0.98-1.02)	.68

RAPID trial

V95/whole-breast volume ratio <0.15 was associated with a **lower risk of cosmetic deterioration** (p .04), but this accounted for only 11% of patients

For all subjects, factors associated with **adverse cosmesis** at 3 years were older age, central/inner tumor location, breast infection, smoking, seroma volume, breast volume, and use of APBI

Factors associated with **cosmetic deterioration** were smoking, seroma volume, and use of APBI (P<.05)

For APBI subjects, tumor location, smoking, age, and seroma volume were associated with **adverse cosmesis** (P<.05), and smoking was associated with **cosmetic deterioration** (P .02)

	APBI (n=1070)			WBI (n=1065)		
	Grade 2	Grade 3	Total	Grade 2	Grade 3	Total
Acute period						
Radiation dermatitis	101 (9.4%)	1 (<0.5%)	102 (9.5%)	322 (30.2%)	6 (0.6%)	328 (30.8%)
Fatigue	130 (12.1%)	9 (0.8%)	139 (13.0%)	146 (13.7%)	5 (0.5%)	151 (14.0%)
Breast swelling	63 (5.9%)	1 (<0.5%)	64 (6.0%)	90 (8.5%)	1 (<0.5%)	91 (8.5%)
Breast pain	69 (6.4%)	2 (<0.5%)	71 (6.6%)	78 (7.3%)	4 (<0.5%)	82 (7.7%)
Pneumonitis	2 (<0.5%)	0	2 (<0.5%)	7 (0.7%)	1 (<0.5%)	8 (0.8%)
Any acute toxicity	281 (26.3%)	19 (1.8%)	300 (28.0%)	466 (43.8%)	18 (1.7%)	484 (45.4%)
Late period						
Induration or fibrosis	214 (20.0%)	31 (2.9%)	245 (22.9%)	48 (4.5%)	1 (<0.5%)	49 (4.6%)
Telangiectasia	86 (8.0%)	13 (1.2%)	99 (9.3%)	39 (3.7%)	0	39 (3.7%)
Breast pain	48 (4.5%)	3 (<0.5%)	51 (4.8%)	19 (1.8%)	1 (<0.5%)	20 (1.9%)
Chest wall pain	26 (2.4%)	4 (<0.5%)	30 (2.8%)	3 (<0.5%)	0	3 (<0.5%)
Fatty necrosis	24 (2.2%)	5 (0.5%)	29 (2.7%)	2 (<0.5%)	2 (<0.5%)	4 (<0.5%)
Any late toxicity	298 (27.9%)	48 (4.5%)	346 (32.3%)	131 (12.3%)	11 (1.0%)	142 (13.3%)

Data are n (%) unless otherwise specified. APBI=accelerated partial breast irradiation. WBI=whole breast irradiation.
 *Worst grade experienced by patients in the acute period (within 3 months from start of radiotherapy), and in the late period (beyond 3 months).

APBI vs WBI @8-year

Acute radiation toxicity (grade ≥ 2) 28% vs 45%

($p < 0.0001$)

Late radiation toxicity (grade ≥ 2) 32% vs 13%

($p < 0.0001$)

	Baseline	3 years	5 years	7 years
Nurse assessment APBI				
Excellent	354	275	231	148
Good	484	413	360	291
Fair	180	240	225	196
Poor	16	35	57	55
Fair + poor	196 (19%)	275 (29%)	282 (32%)	251 (36%)
Total	1034	963	873	690
Nurse assessment WBI				
Excellent	373	389	335	246
Good	474	377	363	263
Fair	161	149	115	101
Poor	12	11	16	16
Fair + poor	173 (17%)	160 (17%)	131 (16%)	117 (19%)
Total	1020	926	829	626
Patient self-assessment APBI				
Excellent	314	313	244	175
Good	469	387	358	294
Fair	203	188	189	158
Poor	42	64	66	56
Fair + poor	245 (24%)	252 (27%)	255 (30%)	214 (31%)
Total	1034	963	873	690
Patient self-assessment WBI				
Excellent	289	370	329	250
Good	518	378	343	279
Fair	184	131	119	71
Poor	37	31	25	21
Fair + poor	221 (22%)	162 (18%)	114 (18%)	92 (15%)
Total	1028	910	816	621

Data are n or n (%). APBI=accelerated partial breast irradiation. WBI=whole breast irradiation. *Global cosmetic outcome assessed by the nurse and by the patient using the European Organisation for Research and Treatment of Cancer Breast Cancer Cosmetic Rating System.

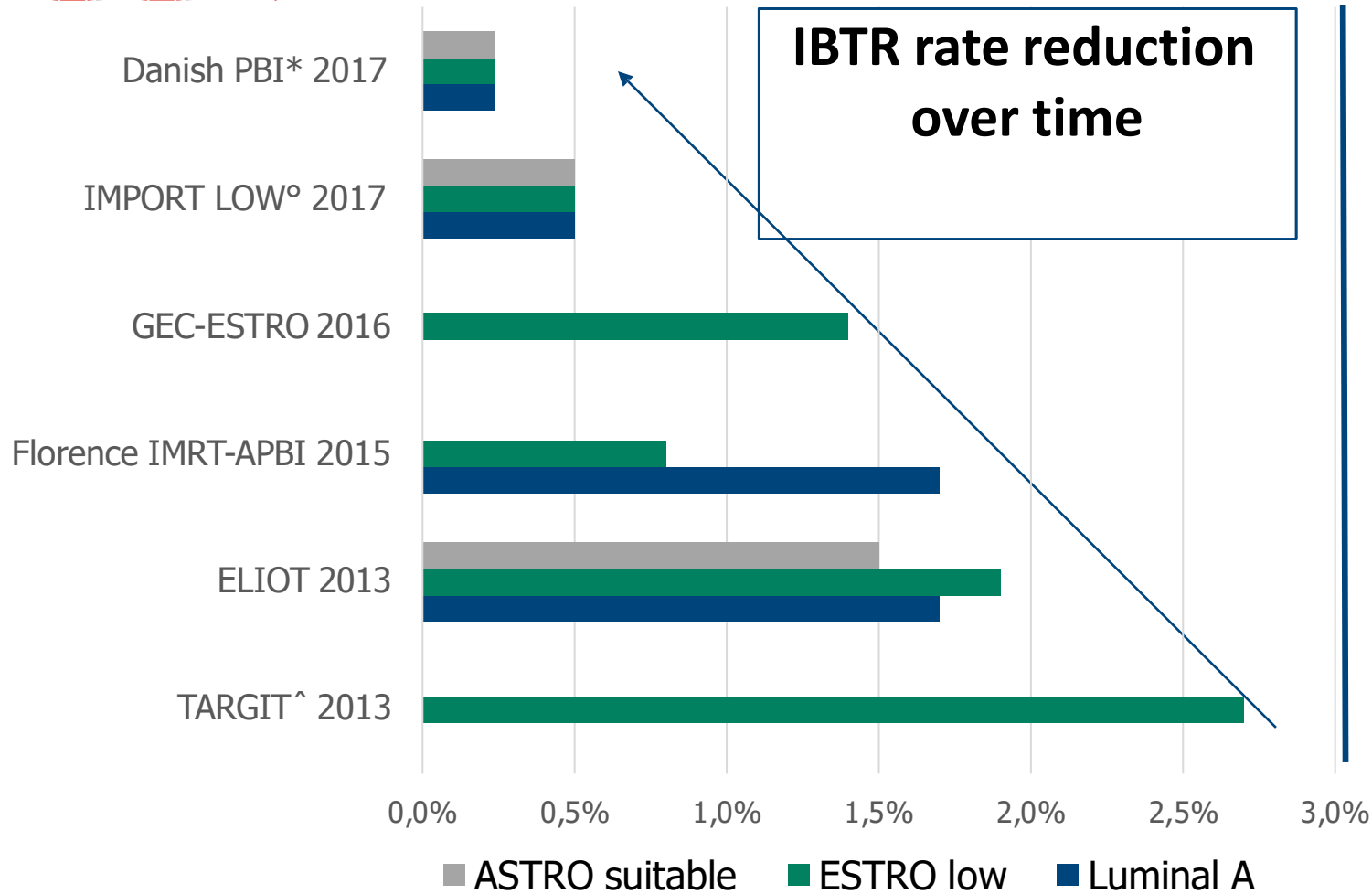
Adverse cosmesis (defined as fair or poor) @3 years

absolute difference
11.3%, 95% CI 7.5–15

5 years (**16.5%**, 12.5–20.4)
7 years (**17.7%**, 12.9–22.3)

All the techniques are the same? **Yes, in case of adequate selection of patients.**

5-year IBTR rate stratified by low risk-groups



RAPID trial

8-year IBTR

3.0% vs 2.8%

NSABP B39/RTOG 0413 trial

10-year IBTR

4.6% vs 3.9%

- Very low long-term IBTR rates
- Safety concerns on twice-daily schedule (RAPID)

Vicini F, et al. Lancet 2019
Whelan T, et al. Lancet 2019

* 3-year IBTR rate

° 5-year estimated rate

^ Pre-pathology group

Adapted from
Meattini I, et al. Breast 2018

Maybe at a longer follow up these difference will change?

original reports

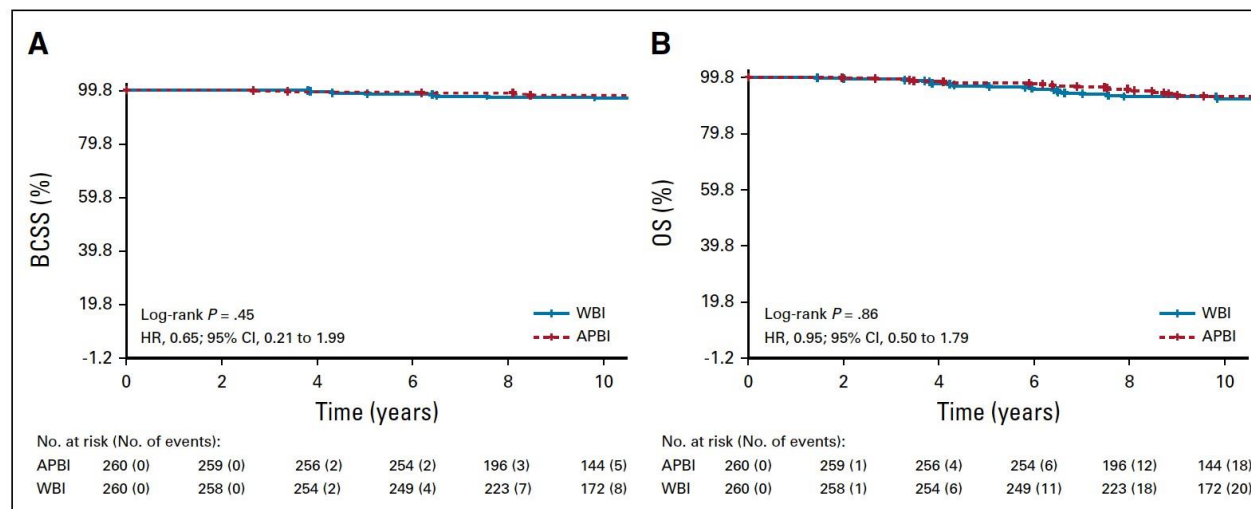
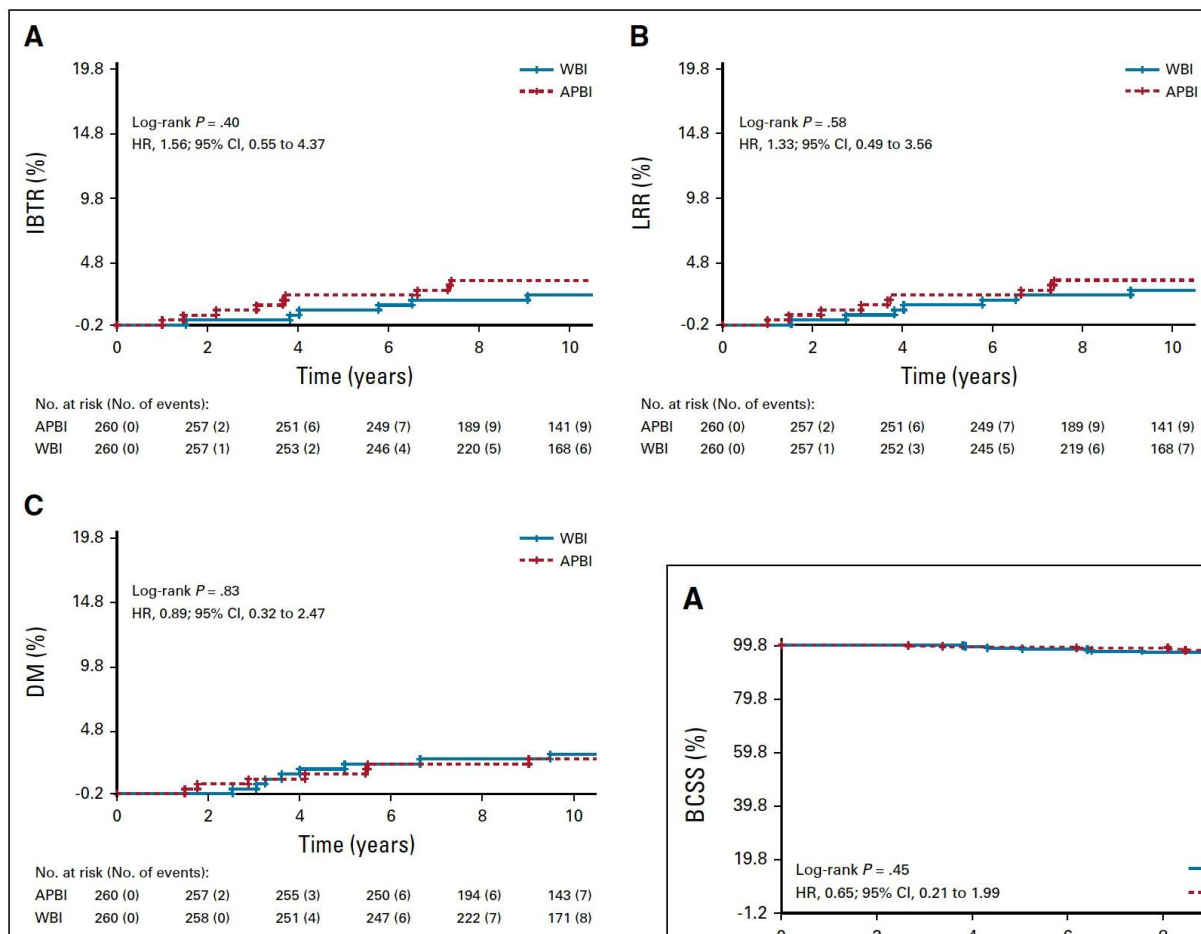
Accelerated Partial-Breast Irradiation Compared With Whole-Breast Irradiation for Early Breast Cancer: Long-Term Results of the Randomized Phase III APBI-IMRT-Florence Trial

Icro Meattini, MD^{1,2}; Livia Marrazzo, MS²; Calogero Saieva, MD³; Isacco Desideri, MD^{1,2}; Vieri Scotti, MD²; Gabriele Simontacchi, MD²; Pierluigi Bonomo, MD²; Daniela Greto, MD²; Monica Mangoni, MD, PhD^{1,2}; Silvia Scoccianti, MD²; Sara Lucidi, MD¹; Lisa Paoletti, MD⁴; Massimiliano Fambrini, MD^{1,2}; Marco Bemini, MD, PhD²; Luis Sanchez, MD²; Lorenzo Orzalesi, MD^{1,2}; Jacopo Nori, MD²; Simonetta Bianchi, MD^{1,2}; Stefania Pallotta, MS^{1,2}; and Lorenzo Livi, MD^{1,2}

Median follow-up: **10.7 years**

10-year cumulative **IBTR** incidence: **2.5% (WBI) vs. 3.7% (APBI)** (*HR 1.56; P = 0.40*)

10-year **BCSS**: **96.7% (WBI) vs. 97.8% (APBI)** (*HR 0.65; P = 0.45*)

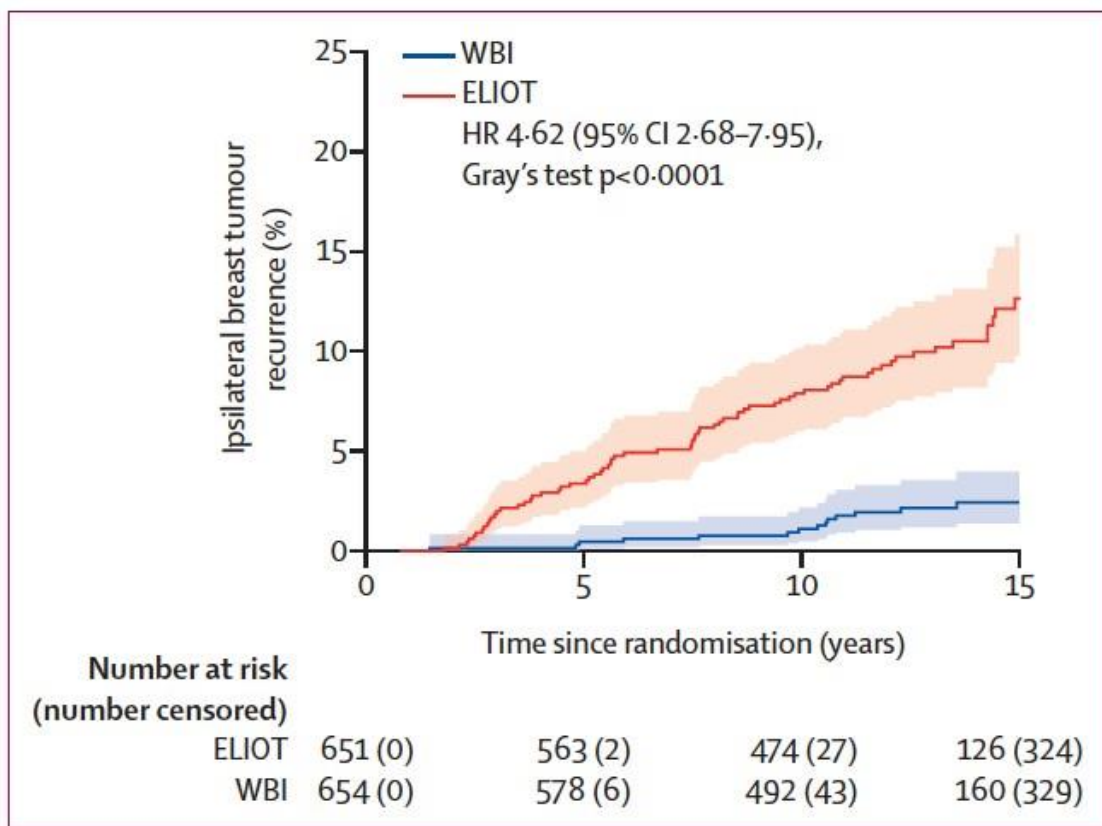


Maybe at a longer follow up these difference will change?

Intraoperative irradiation for early breast cancer (ELIOT): long-term recurrence and survival outcomes from a single-centre, randomised, phase 3 equivalence trial



Roberto Orecchia, Umberto Veronesi*, Patrick Maisonneuve, Viviana Enrica Galimberti, Roberta Lazzari, Paolo Veronesi, Barbara Alicja Jereczek-Fossa, Federica Cattani, Claudia Sangalli, Alberto Luini, Pietro Caldarella, Marco Venturino, Daniele Sances, Stefano Zurrida*, Giuseppe Viale, Maria Cristina Leonardi†, Mattia Intra†



Median follow-up: **12.4 years**

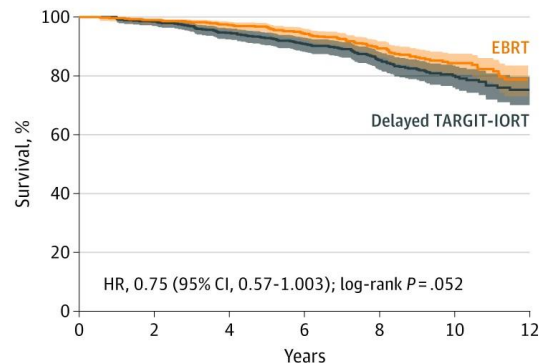
IBTR 11% (ELIOT) vs. **2%** (WBI) ($HR 4.62, p < 0.0001$)

10-year rate 8.1% (ELIOT) vs. **1.1%** (WBI)

15-year rate 12.6% (ELIOT) vs. **2.4%** (WBI)

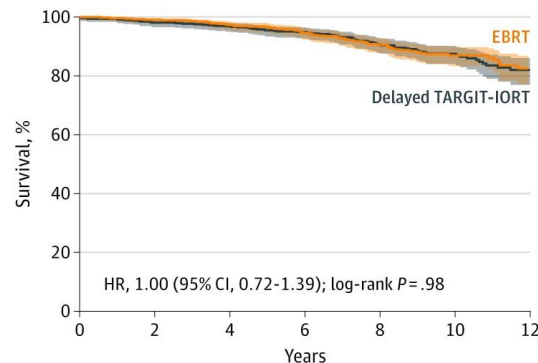
Maybe at a longer follow up these difference will change?

A Local recurrence-free survival



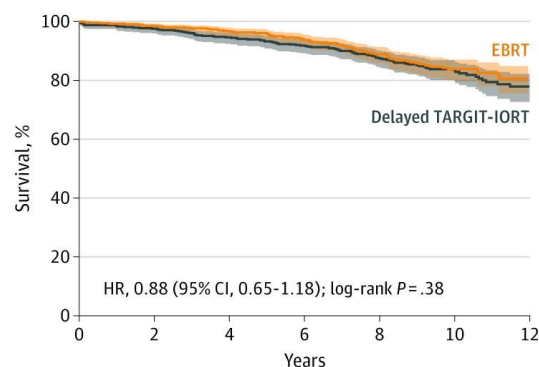
No. at risk								
Delayed TARGIT-IORT	581	567	544	513	378	178	78	
EBRT	572	559	547	520	370	161	57	

B Distant disease-free survival



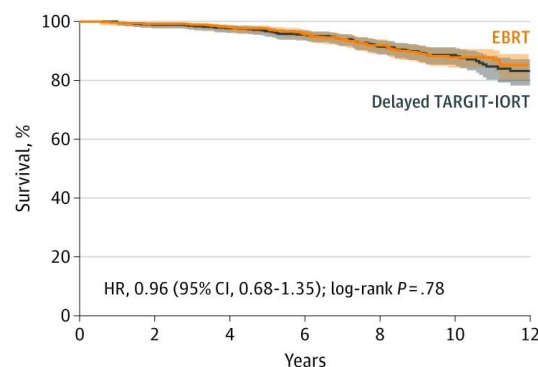
No. at risk								
Delayed TARGIT-IORT	581	565	557	538	399	193	81	
EBRT	572	559	546	519	374	165	61	

C Mastectomy-free survival



No. at risk								
Delayed TARGIT-IORT	581	563	545	521	387	186	78	
EBRT	572	557	543	517	367	159	57	

D Overall survival



No. at risk								
Delayed TARGIT-IORT	581	570	562	542	402	197	83	
EBRT	572	560	550	526	379	167	63	

Effect of Delayed Targeted Intraoperative Radiotherapy vs Whole-Breast Radiotherapy on Local Recurrence and Survival: Long-term Results from the TARGIT-A Randomized Clinical Trial in Early Breast Cancer

At 5-year complete follow-up the LR rates were:

TARGIT-IORT 3.96% vs EBRT 1.05%

difference of 2.9% which crossed the non inferiority margin of 2.5%



Maybe at a longer follow up these difference will change?
Long-term results – TARGIT-A trial

Delayed targeted IORT is not non-inferior and actually **significantly inferior** compared to EBRT (5-years LR rates reported of **3.96% vs 1.05%**)

Delayed targeted IORT showed **5-years local recurrence rates comparable to the no-RT arm in PRIME trial (3.96% vs 4.1%)** as comparable were results from the respective EBRT arms in both trials



Maybe at a longer follow up these difference will change? **Maybe not.**

Patients selection at baseline is the key

Patients selection is a **not-modifiable feature** over time

Pathology parameters are crucial for PBI patient selection



Patient selection

Intraoperative electrons radiation therapy – ELIOT trial

@Multivariate analysis

5-year IBTR >10% (High risk factors)

Tumors >2 cm	(10.9%)
>4 positive nodes	(15.0%)
Grade 3 tumors	(11.9%)
ER negative	(14.9%)
TN tumors	(18.9%)

Patients with >1 factors (*ELIOT high risk*) vs patients with none factors (*ELIOT low risk*, 69.4%)

5-year IBTR → 11.3% vs 1.5%

ASTRO guidelines

Suitable	295/1822	(16%)	5-year rate 1.5%
Luminal A	118/295	(40%)	5-year rate 2.3%

ESTRO guidelines

Suitable	572/1822	(31%)	5-year rate 1.9%
Luminal A	206/572	(36%)	5-year rate 0%



Patient selection

Intraoperative radiation therapy – TARGIT-A trial

50 kV energy x-rays IORT **single fraction** 20 Gy

Randomized either before (*pre-pathology*) or after lumpectomy (*post-pathology by reopening the wound*)

TARGIT received supplemental EBRT in case of unforeseen adverse features (*risk-adapted RT*)

1721 TARGIT vs 1730 EBRT

Supplemental WBI after TARGIT in 15.2%
(21.6% pre-pathology, 3.6% post-pathology)

Median follow up: 2.5 years (3451 patients)
Median follow up: 5 years (1222 patients)

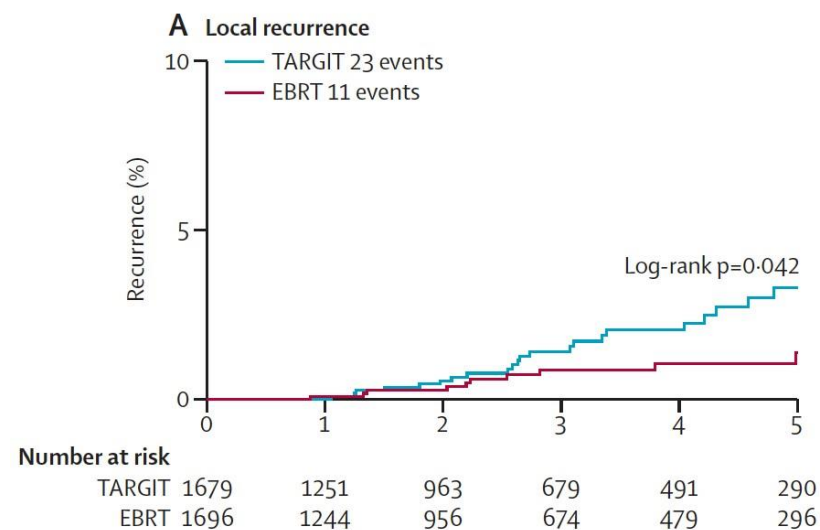
TARGIT vs EBRT @5 years (cumulative risk)

Local Recurrence 3.3% vs 1.3% (p=0.042)

Pre-pathology (n=2298) 2.1% vs 1.1% (p=0.31)

Post-pathology (n=1153) 5.4% vs 1.7% (p=0.069)

Breast cancer mortality 2.6% vs 1.9% (p=0.56)





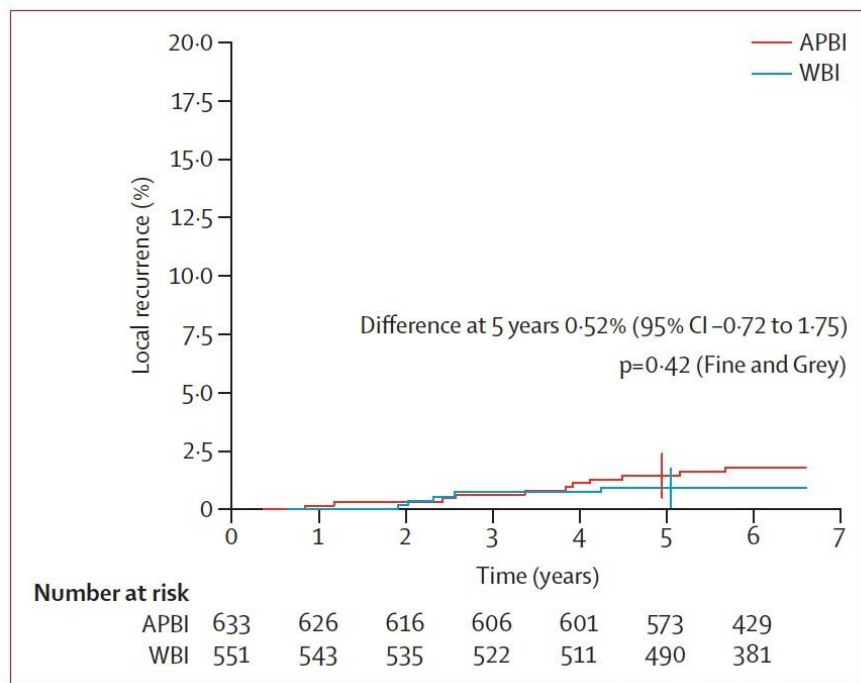
Patient selection

Brachytherapy – GEC/ESTRO trial

stage 0, I, IIA breast cancer

1184 patients **HDR 7-8 fractions**

633 **brachy** vs. 551 WBI



Strnad V, et al. Lancet 2016

	APBI group (n=633)	WBI group (n=551)
Age (years)		
Median (IQR)	62 (54–67)	62 (54–68)
>40–50	91 (14%)	91 (17%)
>50–60	192 (30%)	162 (29%)
>60–70	256 (40%)	202 (37%)
>70	94 (15%)	96 (17%)
Menopausal status		
Premenopausal	108 (17%)	92 (17%)
Postmenopausal	525 (83%)	459 (83%)
Performance status		
0	604 (95%)	520 (94%)
1–2	26 (4%)	30 (5%)
Unknown	3 (<1%)	1 (<1%)
Tumour size and resection margins		
Tumour diameter (mm)	12 (9–17)	12 (9–17)
Surgical free margins (mm, range)	8 (2–40)	7 (2–25)
T stage		
pTis (DCIS)	36 (6%)	24 (4%)
pT1mi	0	4 (1%)
pT1a	30 (5%)	21 (4%)
pT1b	187 (30%)	182 (33%)
pT1c	313 (49%)	262 (48%)
pT2 (≤3 cm)	67 (11%)	58 (11%)
N stage		
pN0	127 (20%)	118 (21%)
pN0 sn	470 (74%)	408 (74%)
pN1 mi	5 (1%)	5 (1%)
No data	31 (5%)	20 (4%)
Grading		
1	248 (39%)	217 (39%)
2	319 (50%)	288 (52%)
3	57 (9%)	42 (8%)
No data	9 (1%)	4 (1%)
Histological subtype		
Ductal	453 (72%)	424 (77%)
Lobular	85 (13%)	49 (9%)
Tubular	38 (6%)	36 (7%)
Mucinous	14 (2%)	13 (2%)
Papillary	5 (1%)	4 (1%)
Medullary	2 (<1%)	1 (<1%)
Unknown	36 (6%)	24 (4%)
Hormone receptor status		
ER+/PR+	510 (81%)	447 (81%)
ER-/PR+	5 (1%)	6 (1%)
ER+/PR-	69 (11%)	56 (10%)
ER-/PR-	34 (5%)	29 (5%)
Unknown	15 (2%)	13 (2%)
Systemic treatment		
Yes	572 (90%)	505 (92%)
No	59 (9%)	46 (8%)
No data	2 (<1%)	0

	APBI group (n=633)	WBI group (n=551)
(Continued from previous column)		
Antihormonal treatment		
Yes	549 (87%)	482 (87%)
No	82 (13%)	69 (13%)
No data	2 (<1%)	0
Chemotherapy		
Yes	63 (10%)	65 (12%)
No	568 (90%)	486 (88%)
No data	2 (<1%)	0

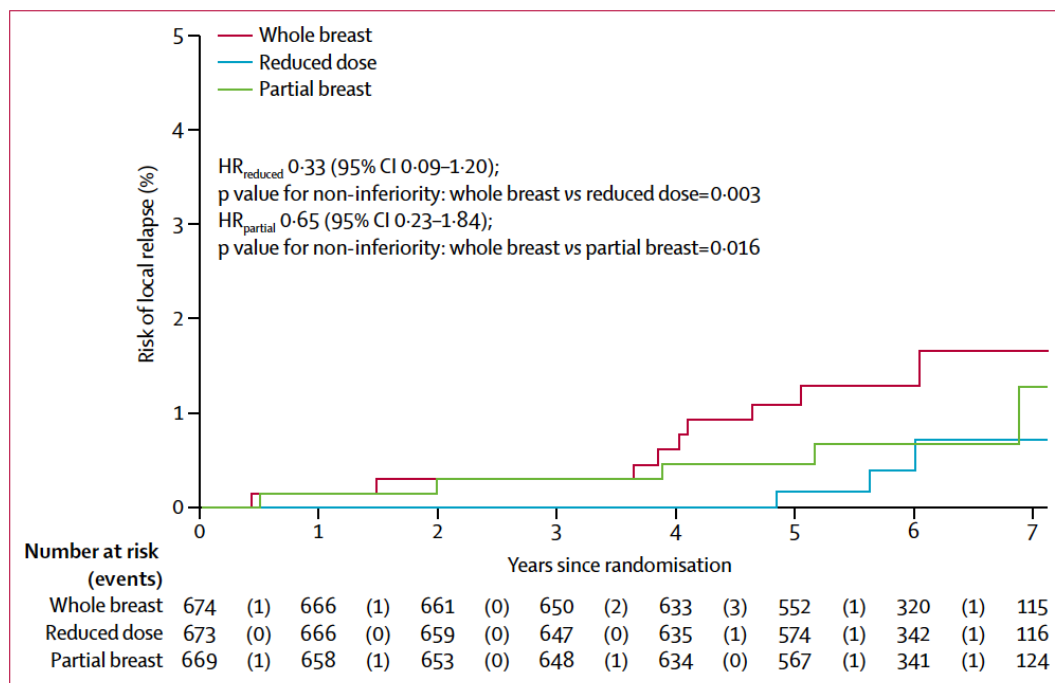
6 vs 94.0%

p=0.84

>90% T1N0 HR+/HER2-

40 Gy in 15 fractions to the partial breast

669 PBI vs. 674 WBI



Coles CE, et al. Lancet 2017

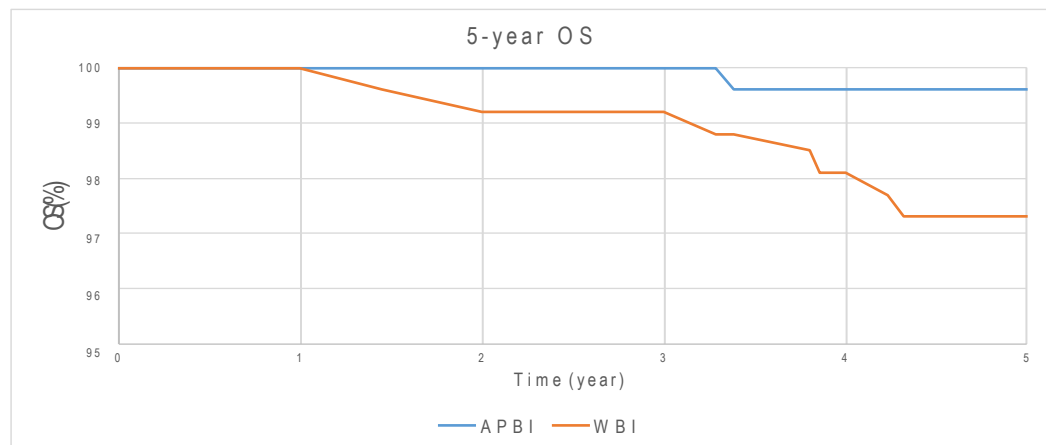
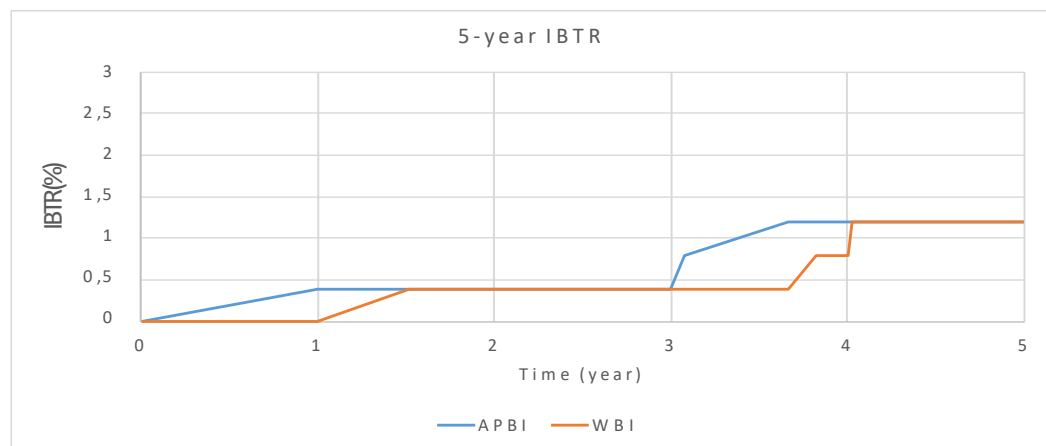
	Whole-breast radiotherapy (n=674)	Reduced-dose radiotherapy (n=673)	Partial-breast radiotherapy (n=669)
Age, years	62 (57–67)	63 (57–67)	62 (57–67)
Side of primary tumour			
Left breast	336/674 (50%)	344/673 (51%)	348/669 (52%)
Right breast	338/674 (50%)	329/673 (49%)	321/669 (48%)
Pathological tumour size, cm†	1.2 (0.8–1.5)	1.1 (0.8–1.6)	1.2 (0.8–1.6)
Tumour grade‡			
1	298/672 (44%)	272/673 (40%)	284/668 (43%)
2	310/672 (46%)	328/673 (49%)	320/668 (48%)
3	64/672 (10%)	73/673 (11%)	63/668 (9%)
Re-excision			
Yes	93/673 (14%)	78/673 (12%)	87/667 (13%)
No	580/673 (86%)	595/673 (88%)	580/667 (87%)
Axillary surgery			
Yes	672/673 (>99%)	673/673 (100%)	666/667 (>99%)
No	1/673 (<1%)	0	1/667 (<1%)
Pathological node status			
Positive	24/674 (4%)	19/673 (3%)	16/669 (2%)
Negative	650/674 (96%)	654/673 (97%)	653/669 (98%)
Histological type			
Infiltrating ductal	578/671 (86%)	581/672 (86%)	563/665 (85%)
Mixed	14/671 (2%)	18/672 (3%)	22/665 (3%)
Other	79/671 (12%)	73/672 (11%)	80/665 (12%)
Lymphovascular invasion			
Present	34/493 (7%)	47/492 (10%)	35/494 (7%)
Absent	459/493 (93%)	445/492 (90%)	459/494 (93%)
ER status			
Positive	640/672 (95%)	638/672 (95%)	633/667 (95%)
Poor§	32/672 (5%)	34/672 (5%)	34/667 (5%)
PR status			
Positive	400/493 (81%)	393/477 (82%)	380/475 (80%)
Poor§	93/493 (19%)	84/477 (18%)	95/475 (20%)
HER2 status			
Negative	599/622 (96%)	603/628 (96%)	580/614 (94%)
Positive	23/622 (4%)	25/628 (4%)	34/614 (6%)
Adjuvant therapy received¶			
Chemotherapy	29/673 (4%)	42/670 (6%)	33/665 (5%)
Endocrine therapy	610/673 (91%)	614/670 (92%)	602/665 (91%)
Trastuzumab	7/673 (1%)	15/670 (2%)	14/665 (2%)

Patient selection

External beam radiation therapy – APBI-IMRT Florence trial

APBI-IMRT

30 Gy in 5 fractions vs. WBI 50 Gy+10 Gy boost



Ki67 index, %

< 20	193 (72.2)	174 (72.2)
≥ 20	50 (20.6)	67 (27.8)

Molecular subtype^a

Luminal A-like	169 (79.3)	151 (72.6)
Luminal B-like	33 (15.6)	42 (20.2)
HER2 positive (nonluminal)	6 (2.8)	13 (6.2)
Triple negative	5 (2.3)	2 (1.0)

Systemic treatment

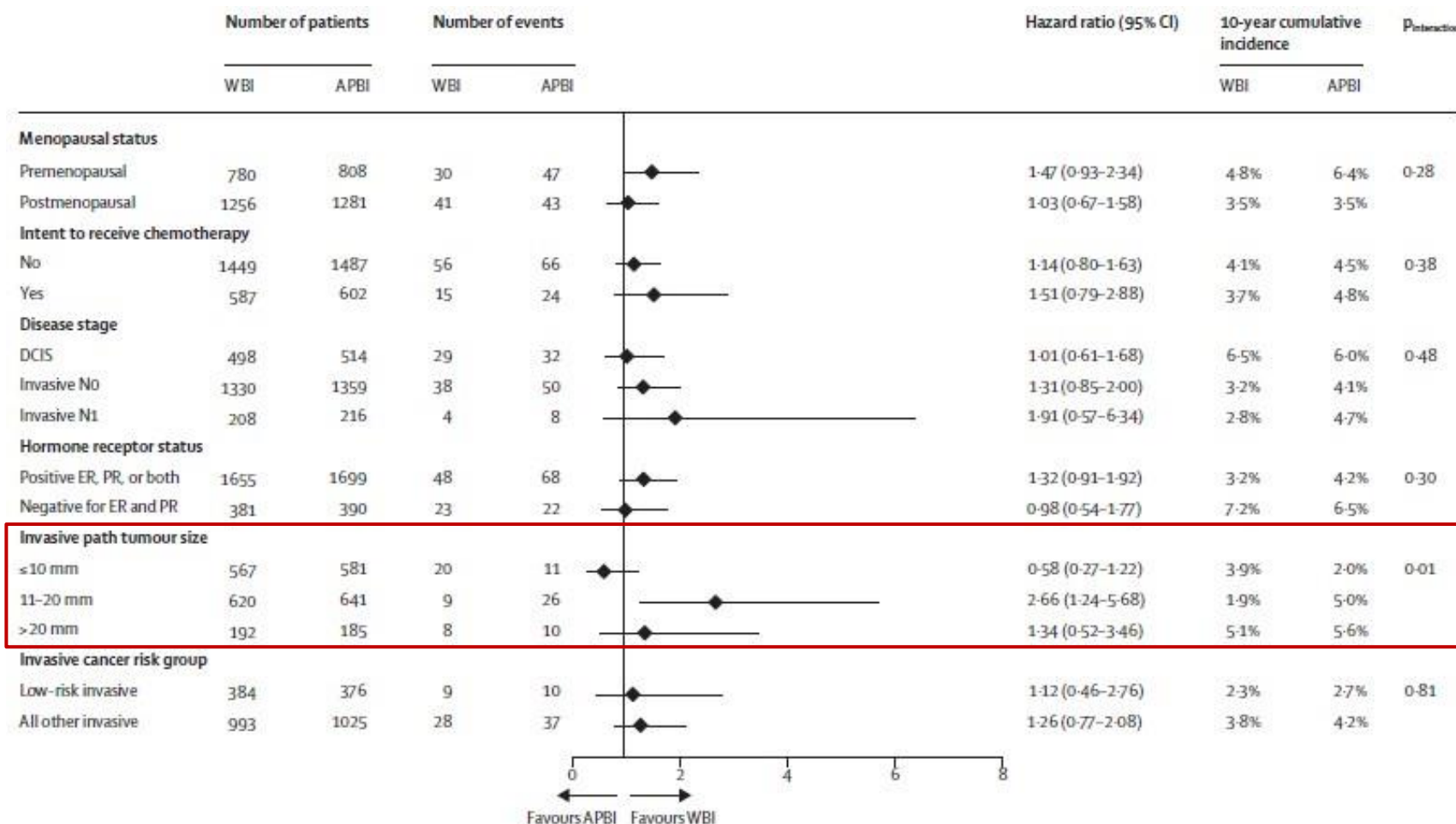
None	93 (35.8)	75 (28.8)
Endocrine therapy only	155 (59.6)	162 (62.3)
Chemotherapy only	5 (1.9)	3 (1.2)
Chemotherapy and endocrine therapy	7 (2.7)	20 (7.7)

Risk class

ASTRO suitable	133 (51.2)	113 (43.5)
ASTRO cautionary	74 (28.5)	79 (30.4)
ASTRO unsuitable	53 (20.3)	68 (26.1)
ESTRO low	190 (73.1)	166 (63.8)
ESTRO intermediate	41 (15.8)	47 (18.1)
ESTRO high	29 (11.1)	47 (18.1)

Patient selection

NSABP B39/RTOG 0413



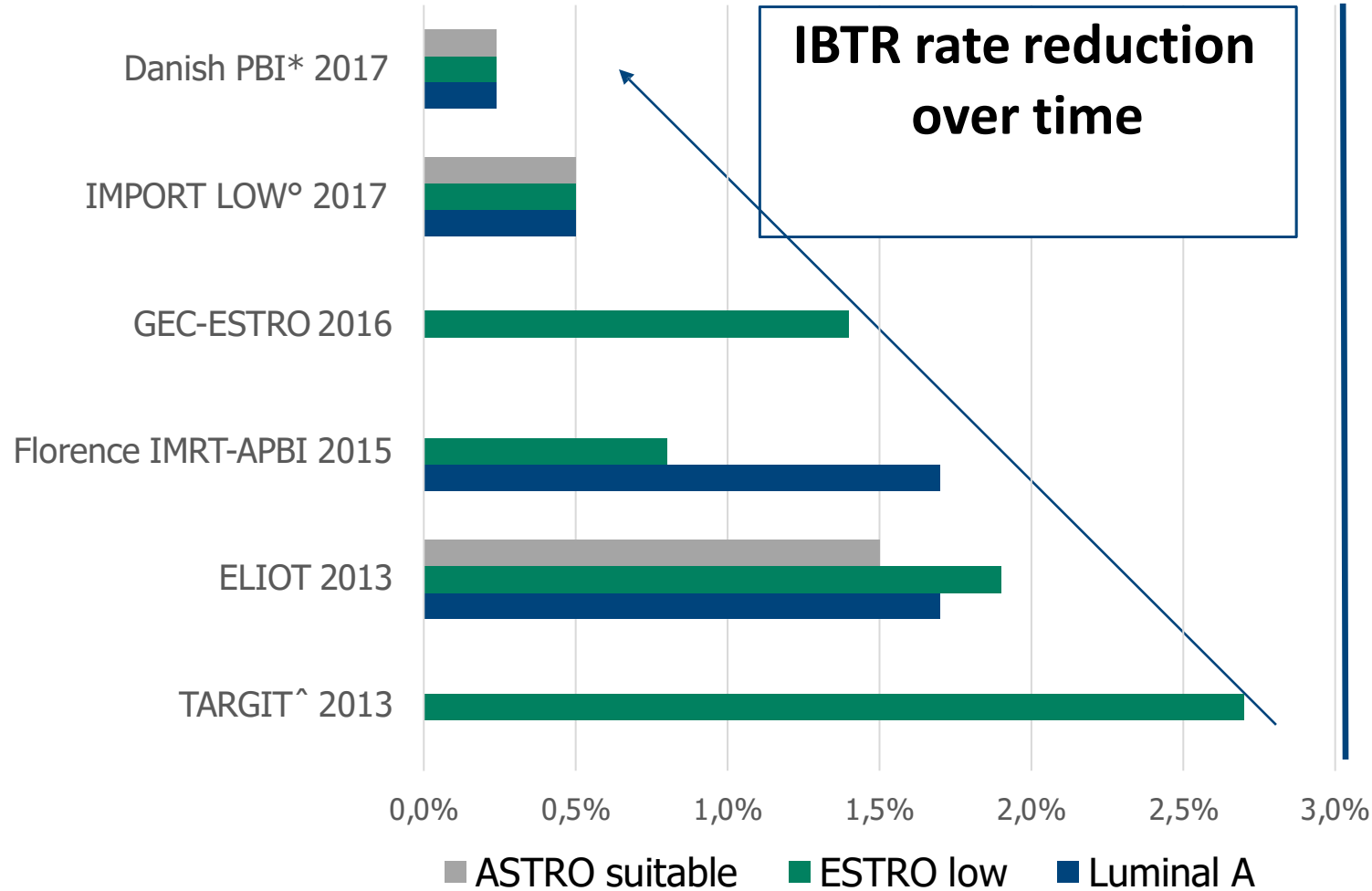
APBI vs WBI

Subgroups defined by invasive tumour size and risk group

There were no differences in the treatment effects between any of the subgroups except **invasive pathological tumour size**, for which APBI was favourable in patients with invasive tumours sized **10 mm or smaller**

All the techniques are the same? **Yes, in case of adequate selection of patients.**

5-year IBTR rate stratified by low risk-groups



RAPID trial

8-year IBTR

3.0% vs 2.8%

NSABP B39/RTOG 0413 trial

10-year IBTR

4.6% vs 3.9%

- Very low long-term IBTR rates
- Safety concerns on twice-daily schedule (RAPID)

Vicini F, et al. Lancet 2019
Whelan T, et al. Lancet 2019

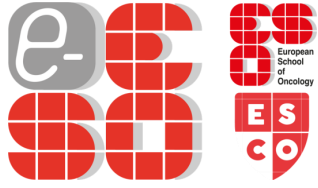
* 3-year IBTR rate
° 5-year estimated rate
^ Pre-pathology group

All the techniques are the same? **Yes, although not all studies were the same.**

ESTRO and ASTRO recommendations identified **suitable** patients for PBI outside clinical trials

Patient Group	Risk Factor	2009	2016 Update
ASTRO Suitable	Age	≥60	≥50
	Margins	≥2 mm	≥2 mm
	Nodal status	pN0	pN0
	T stage	T1	Tis or T1
	ER/PgR	Positive	
	DCIS Lobular invasive	Not allowed Not allowed	G1-2; ≤2.5 cm

Patient Group	Risk Factor	2010
ESTRO Low Risk	Age	≥50
	Margins	≥2 mm
	Nodal status	pN0
	T stage	T1-2
	ER/PgR	Any
	DCIS Lobular Invasive	Not allowed Not allowed



Royal College of Radiologists online repository of clinical advisory documents recommending strategies



Editorial

Moving Forward Fast with FAST-Forward

P. Lewis*, A.M. Brunt†, C. Coles‡, S. Griffin§, I. Locke¶, T. Roques§, on behalf of the Breast Radiotherapy Consensus Working Group

Lewis P, et al. Clin Oncol (R Coll Radiol)

Consensus statement 1

- Offer 26 Gray (Gy) in five fractions over one week for whole breast radiotherapy.

Consensus statement 2

- Offer 26 Gy in five fractions over one week for chest wall radiotherapy.

Consensus statement 3

- Consider 26 Gy in five fractions over one week for chest wall radiotherapy with reconstruction.

Consensus statement 4

- Offer 26 Gy in five fractions over one week for partial breast radiotherapy.

Consensus statement 5

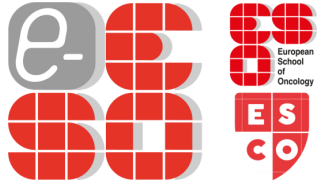
- Consider 28.5 Gy in five fractions over five weeks instead of 26 Gy in five fractions over one week for patients with significant co-morbidities and/or frailty that make daily radiotherapy difficult.

Consensus statement 6

- Fifteen fractions over three weeks is the current standard of care for breast nodal radiotherapy. Consider 26 Gy in five fractions for nodal radiotherapy (excluding the internal mammary chain [IMC]) only for patients with significant co-morbidities while awaiting the two-year normal tissue results of the FAST-Forward nodal sub-study (due to report in 2021).

Consensus statement 7

- For patients requiring a boost, offer:
 - 26 Gy in five fractions whole breast radiotherapy plus either a sequential normofractionated boost or a hypofractionated boost (delivered in no more than five fractions as per the RCR *Postoperative radiotherapy for breast cancer: UK consensus statements*, 2016)
 - or
 - 15 fraction simultaneous integrated boost (SIB), for example, 48 Gy to boost volume and 40 Gy to rest of breast all over three weeks.



ESTRO-ACROP EBRT consensus statements 2022

PBI selection criteria

4. Partial breast irradiation–suitable patient selection for external beam radiotherapy

I. Luminal-like subtypes small tumour (≤ 3 cm)	91.3%	Strong consensus
II. Clear surgical margins (> 2 mm)	95.6%	Strong consensus
III. Nodal status
IIIa. Node negative	100%	Unanimous consensus
IIIb. Node negative (including isolated tumour cells)	82.6%	Consensus
IV. Absence of lymph vascular space invasion	87.0%	Consensus
V. Non-lobular invasive carcinoma	87.0%	Consensus
VI. Tumour grade 1–2	91.3%	Strong consensus
VII. Low-to-intermediate grade DCIS, sized ≤ 2.5 cm, clear surgical margins (≥ 3 mm)	78.2%	Consensus
VIII. Age 50 years or more	87.0%	Consensus
IX. Unicentric or unifocal	100%	Unanimous consensus
X. Primary systemic therapy and neoadjuvant chemotherapy is considered an exclusion criterion for partial breast irradiation	78.2%	Consensus

Treatment groups		Disease-free survival rates at 5, 8, and 10 years (%)	Overall survival rates at 5, 8, and 10 years (%)	Local relapse rates at 5, 8, and 10 years (%)	Cosmetic outcome (fair to poor)	
					Physician-rated (%)	Patient-rated (%)
APBI-IMRT-Florence ⁴⁴	PBI: IMRT 30 Gy in 5 fractions vs WBI: IMRT 50 Gy in 25 fractions plus TBB 10 Gy in 5 fractions	98%/-/97%	99%/-/92% vs 96%/-/92%	2.3%/-/3.7% vs 1.2%/-/2.5%	0% at 5 years; 0% at 10 years vs 0.8% at 5 years; 1.9% at 10 years	0.8% at 10 years vs 14.6% at 10 years
NSABP B-39/RTOG 0413 ⁵⁶	PBI: HDR brachytherapy 34 Gy or 3DCRT 38.5 Gy in 10 fractions, twice a day vs WBI: EBRT 50 Gy in 25 fractions	-/-/78% vs -/-/80%	-/-/ 91%	-/-/4.6% vs -/-/3.9%
RAPID trial ¹⁴	PBI: 3DCRT or IMRT 38.5 Gy in 10 fractions, twice a day vs WBI: EBRT 42.5 Gy in 16 fractions or 50 Gy in 25 fractions with or without TBB 10 Gy in 5 fractions	96%/95%/- vs 97%/95%/-	96%/97%/- vs 97%/94%/-	2.3%/3%/- vs 1.7%/2.8%/-	29% at 3 years; 32% at 5 years; 36% at 7 years vs 17% at 3 years; 16% at 5 years; 19% at 7 years	27% at 3 years; 30 at 5 years; 31% at 7 years vs 18% at 3 years; 18% at 5 years; 15% at 7 years
UK IMPORT LOW trial ⁴⁵	PBI: IMRT 40 Gy in 15 fractions vs WBI: IMRT 40 Gy in 15 fractions	0.5%/-/- vs 1.1%/-/-
GEC-ESTRO ⁵⁷	PBI: HDR brachytherapy 32 Gy in 8 fractions or 30.1 Gy in 7 fractions, twice a day vs PBI: PDR brachytherapy 50 Gy, pulses of 0.6–0.8 Gy per h, 24 h per day vs WBI: (4-10 MV) EBRT 50–50.4 Gy in 25–28 fractions with or without TBB 10 Gy in 5 fractions	95%/-/- vs .. vs 94%/-/-	97%/-/- vs .. vs 96%/-/-	1.44%/-/- vs .. vs 0.9%/-/-	7% at 5 years vs .. vs 10% at 5 years	8% at 5 years vs .. vs 9% at 5 years

Meattini I, Becherini C, Poortmans P, Coles C, et al. Lancet Oncol 2022

European Society for Radiotherapy and Oncology Advisory Committee in Radiation Oncology Practice consensus recommendations on patient selection and dose and fractionation for external beam radiotherapy in early breast cancer



Icro Meattini, Carlotta Becherini, Liesbeth Boersma, Orit Kaidar-Person, Gustavo Nader Marta, Angel Montero, Birgitte Vrou Offersen, Marianne C Aznar, Claus Belka, Adrian Murray Brunt, Samantha Dicunzio, Pierfrancesco Franco, Mechthild Krause, Mairead MacKenzie, Tanja Marinko, Livia Marrazzo, Ivica Ratosa, Astrid Scholten, Elżbieta Senkus, Hilary Stobart, Philip Poortmans, Charlotte E Coles**

Statement 4. Low risk-features suitable for partial breast irradiation are:

- luminal-like subtypes small tumour (≤ 3 cm)
- absence of lymph vascular space invasion
- non-lobular invasive carcinoma
- tumour grade 1-2
- low to intermediate grade DCIS (sized ≤ 2.5 cm with clear surgical margins ≥ 3 mm)
- age at diagnosis 50 years or more
- unicentric/unifocal lesion
- clear surgical margins (> 2 mm)
- node negative (including isolated tumour cells)
- no use of primary systemic therapy/neoadjuvant chemotherapy

European Society for Radiotherapy and Oncology Advisory Committee in Radiation Oncology Practice consensus recommendations on patient selection and dose and fractionation for external beam radiotherapy in early breast cancer



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Statement 5. Partial breast irradiation—dose and fractionation:

- a. Moderate hypofractionation (40 Gy in 15 fractions) and ultrahypofractionation (26–30 Gy in five fractions) represent acceptable schedules for external beam partial breast irradiation
- b. Twice a day external beam partial breast irradiation dose and fractionations similar to those used in the RAPID trial should not be offered



Conclusions

- Every patient should be assessed individually:
 - tumour characteristics
 - comorbidity/frail scores (*i.e.*, Charlson score, G8)
 - patient's choice
 - assessment of **benefits and risks** of treatments (*i.e.*, PROMS, HRQoL)
- **Patient selection** for partial breast irradiation is crucial and should follow ESTRO, ESTRO-ACROP and ASTRO recommendations
- Multidisciplinary discussion
- Where available strongly consider an optimisation (former de-escalation) ongoing clinical trial

Icro Meattini, MD, Associate Professor
University of Florence, Florence, IT

Thank you!

Contacts

icro.meattini@unifi.it



@Icro_Meattini

ESTRO

European Society
for Radiotherapy & Oncology

Rue Martin V, 40
1200 Brussels
Belgium

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WWW.ESTRO.ORG



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