UC San Diego Health

Novel Approaches in Breast Radiotherapy: Ultra-hypofractionation and External Beam Partial Breast Radiotherapy

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Disclosures

- I have no conflicts of interest to disclose

Learning Objectives

- Reinforce moderate hypofractionation as the standard of care for whole breast radiotherapy
- Learn about newer, ultra-hypofractionated whole breast radiotherapy, described risks and identify patient selection
- Understand the options for external beam partial breast radiotherapy

Hypofractionation Nomenclature

• Conventional fractionation	1.8-2Gy/fraction	50Gy	5 weeks
• Moderate hypofractionation	>2Gy/fraction	40-42Gy	3 weeks
• Ultra-hypofractionation	≥5Gy/fraction	26Gy	1 week
		Lower Total Dose for equivalent biological effectiveness	Larger fraction size for shorter overall treatment duration

Benefits to Hypofractionation

- Improves access to care
- Convenience
- Better compliance with treatment
- Reduced toxicity/Improved cosmesis

Moderate Hypofractionation

Whole Breast

UC San Diego Health

Whole Breast Hypofractionation (Moderate Hypofx)

Trial	Years	N	Dose (Fraction Size)	Local Recurrence (10 yr)	OS
RMH/GOC	1986-1998	1410	50 Gy/25 fx (2 Gy) 42.9 Gy/13 fx (3.3 Gy) 39 Gy/13 fx (3 Gy)	12.1% 9.6% 14.8%	No diff.
OCOG	1993-1996	1234	50 Gy/25 fx (2 Gy) 42.5 Gy/16 fx (2.66 Gy)	7.5% 7.4%	No diff.
START A	1998-2002	2236	50 Gy/25 fx (2 Gy) 41.6 Gy/13fx – 5 wks (3.2 Gy) 39 Gy/13 fx – 5 wks (3 Gy)	7.4% 6.3% 8.8%	No diff.
START B	1999-2001	2215	50 Gy/25 fx (2 Gy) 40 Gy/15 fx – 3 wks (2.67 Gy)	5.5% 4.3%	No diff.

Yarnold el al, Radiation Oncology 2005; Haviland et al, Lancet 2013; Whelan et al, NEJM 2010

Toxicity/Cosmesis

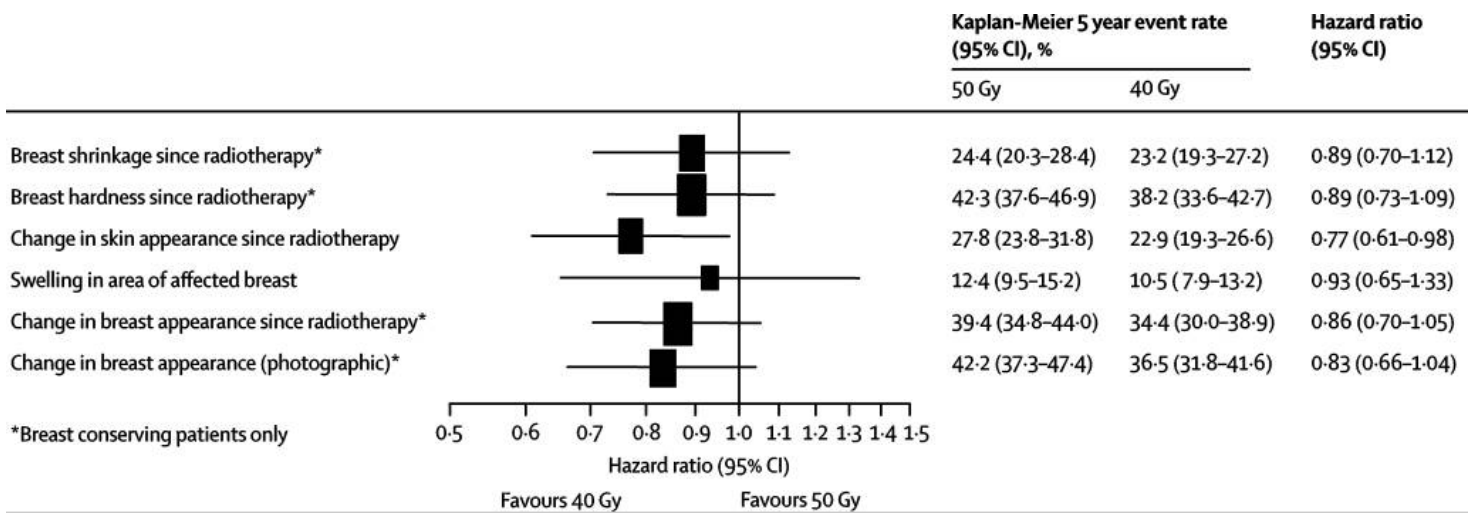
Trial	Years	N	Dose (Fraction Size)	Freedom from marked change (5† or 10 yr)	P-value
RMH/GOC	1986-1998	1410	50 Gy/25 fx (2 Gy) 42.9 Gy/13 fx (3.3 Gy) 39 Gy/13 fx (3 Gy)	90.2% 84.4% 93.4%	<0.001
OCOG	1993-1996	1234	50 Gy/25 fx (2 Gy) 42.5 Gy/16 fx (2.66 Gy)	71.3% 69.8%	NS
START A	1998-2002	2236	50 Gy/25 fx (2 Gy) 41.6 Gy/13fx – 5 wks (3.2 Gy) 39 Gy/13 fx – 5 wks (3 Gy)	60.1%† 58.4%† 66.1%†	NS
START B	1999-2001	2215	50 Gy/25 fx (2 Gy) 40 Gy/15 fx – 3 wks (2.67 Gy)	60.6% 65.6%	NS

UK START B

Toxicity/Cosmesis

50Gy in 25 fx
vs
40Gy in 15 fx

- Photographic change and patient self assessments favored hypofractionation
- Less breast shrinkage, breast hardness, and edema with hypofractionation



Forest plot of late normal tissue effects assessed as moderate/marked by patients and mild/marked from photographs

NCCN Guidelines

Whole Breast Radiation

- **Target definition is the breast tissue at risk.**
- **RT dosing:**
  - **The whole breast should receive a hypofractionated dose of 40–42.5 Gy in 15–16 fractions; in selected cases 45–50.4 Gy in 25–28 fractions may be considered.**
  - **A boost to the tumor bed is recommended in patients at higher risk for recurrence. Typical boost doses are 10–16 Gy in 4–8 fractions.**

Short course of radiotherapy (15-16 fx) is the NCCN preferred option for whole breast only radiotherapy

ASTRO Consensus Guidelines- Hypofractionation

Factor	2011 Guideline	2018 Guideline
Age	≥50 years	Any
Stage	T1-2 N0	Any stage provided intent is to treat the whole breast without an additional field to cover the regional lymph nodes
Chemotherapy	None	Any chemotherapy
Dose homogeneity	±7% in the central axis	Volume of breast tissue receiving >105% of the prescription dose should be minimized regardless of dose-fractionation

Ultra-Hypofractionation

Whole breast

Ultra-Hypofractionation: UK FAST

25 fx vs 5 fx

- Randomized, Phase III trial
  - 50Gy/ 25 fx
  - 28.5Gy/5 fx or 30Gy/5fx (Once weekly)
- N = 915, 2004 – 2007, 10 yr follow-up
- Primary endpoint: Photographic breast appearance

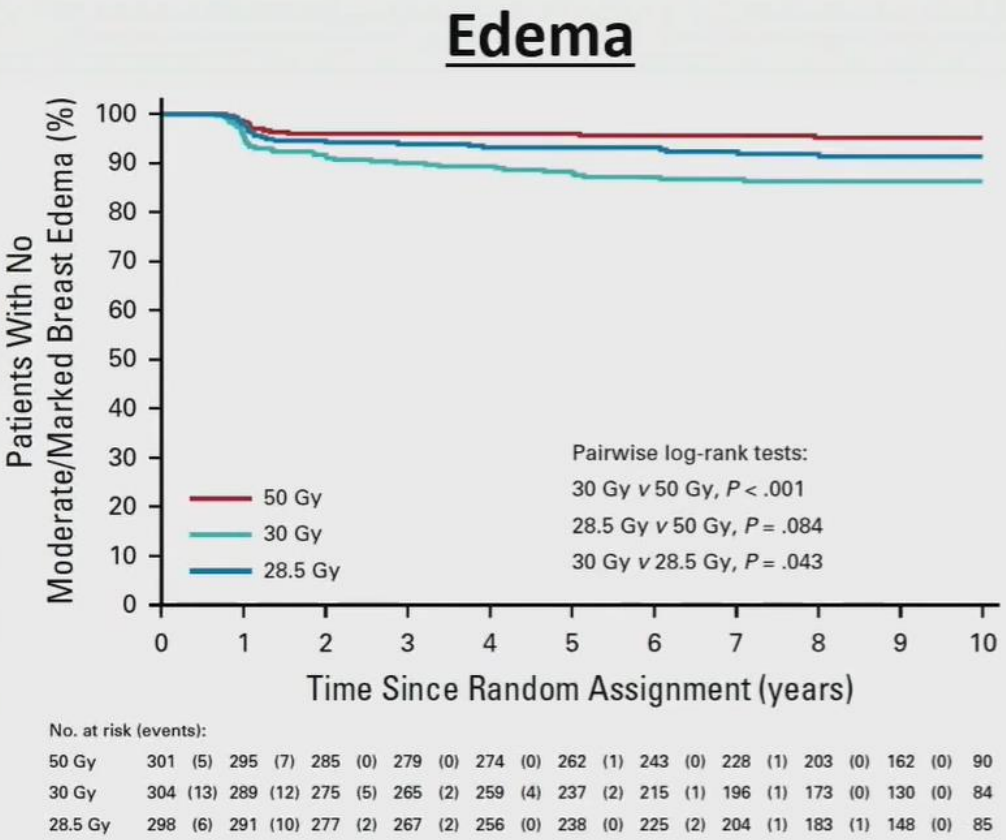
Local Control

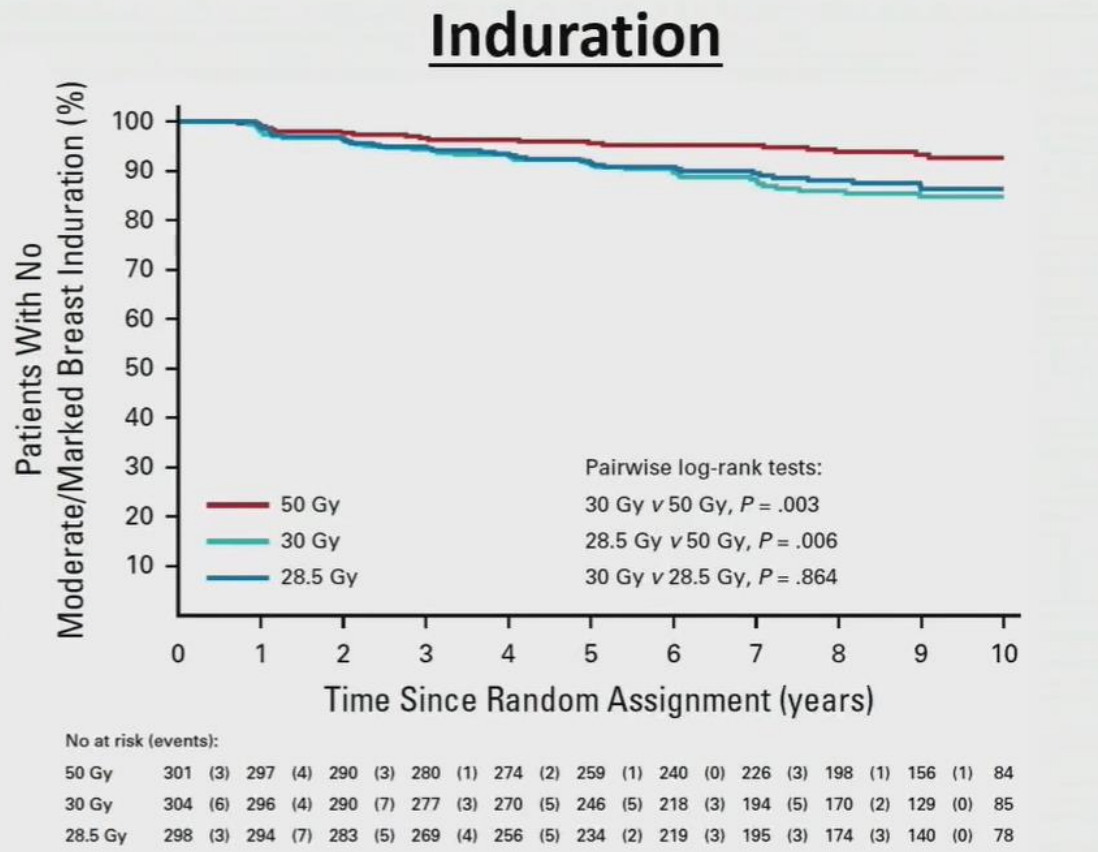
UK FAST

Fractionation Schedule	Ipsilateral Breast Event[a]/Total (%)	KM Estimate (95% CI) of Cumulative Incidence (%)		Hazard Ratio (95% CI)
		5 Years	10 Years	
All patients	11/915 (1.2)	0.7 (0.3 to 1.6)	1.3 (0.7 to 2.3)	—
50 Gy	3/302 (1.0)	0.7 (0.2 to 2.8)	0.7 (0.2 to 2.8)	1
30 Gy	4/308 (1.3)	1.0 (0.3 to 3.2)	1.4 (0.5 to 3.8)	1.36 (0.30 to 6.06)
28.5 Gy	4/305 (1.3)	0.4 (0.05 to 2.6)	1.7 (0.6 to 4.4)	1.35 (0.30 to 6.05)

Toxicity – Increased Risk of Edema and Induration

UK FAST

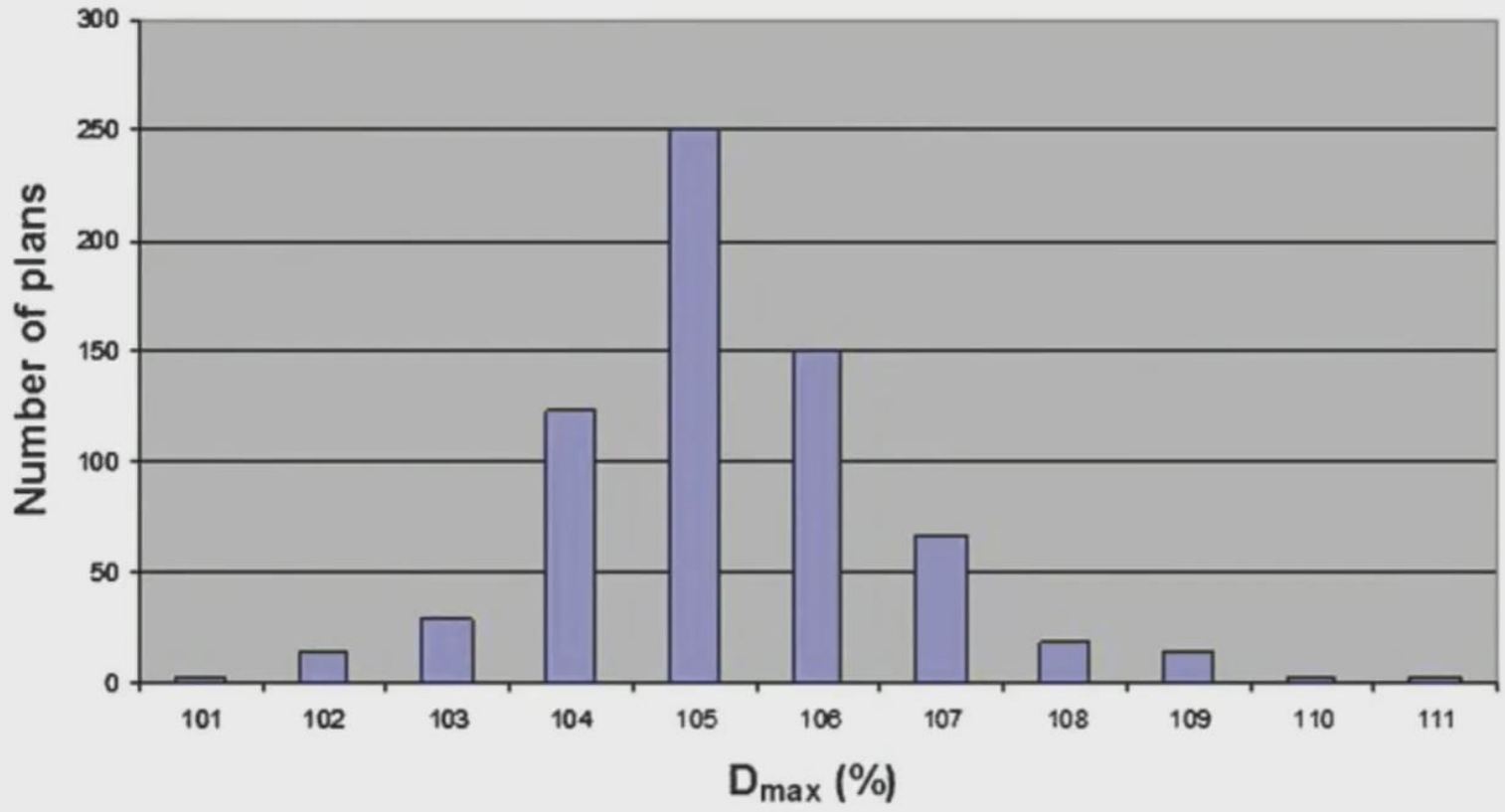




Brunt et al. Ten-Year Results of FAST: A Randomized Controlled Trial of 5-Fraction Whole-Breast Radiotherapy for Early Breast Cancer. J Clin Oncol. 2020; 38:3261-3272.

Dosimetry – Dmax (Hot Spots)

UK FAST



11% V105%>5%

~1/3 D_{max}>105%

100% = 28.5 Gy (5.7 Gy/fx)

105% = 29.9 Gy (6.0 Gy/fx)

107% = 30.5 Gy (6.1 Gy/fx)

110% = 31.4 Gy (6.3 Gy/fx)

Tsang et al. Quality assurance analysis of participating centres' protocol compliance to a UK multicenter hypofractionated breast (FAST) trial. BJR. 2012.

Ultra-Hypofractionation: UK FAST FORWARD

3 weeks vs 1 week

- Phase III Randomized Trial
  - 40Gy in15 fx
  - 27Gy in 5fx (one week)
  - 26Gy in 5fx (one week)
- N= 4096; pT1-3, N0-1, M0
- s/p lumpectomy (93%) or mastectomy with SLNB (if + ALND)
- 2011-2014, 5 yr follow-up
- Primary Endpoint: IBTR

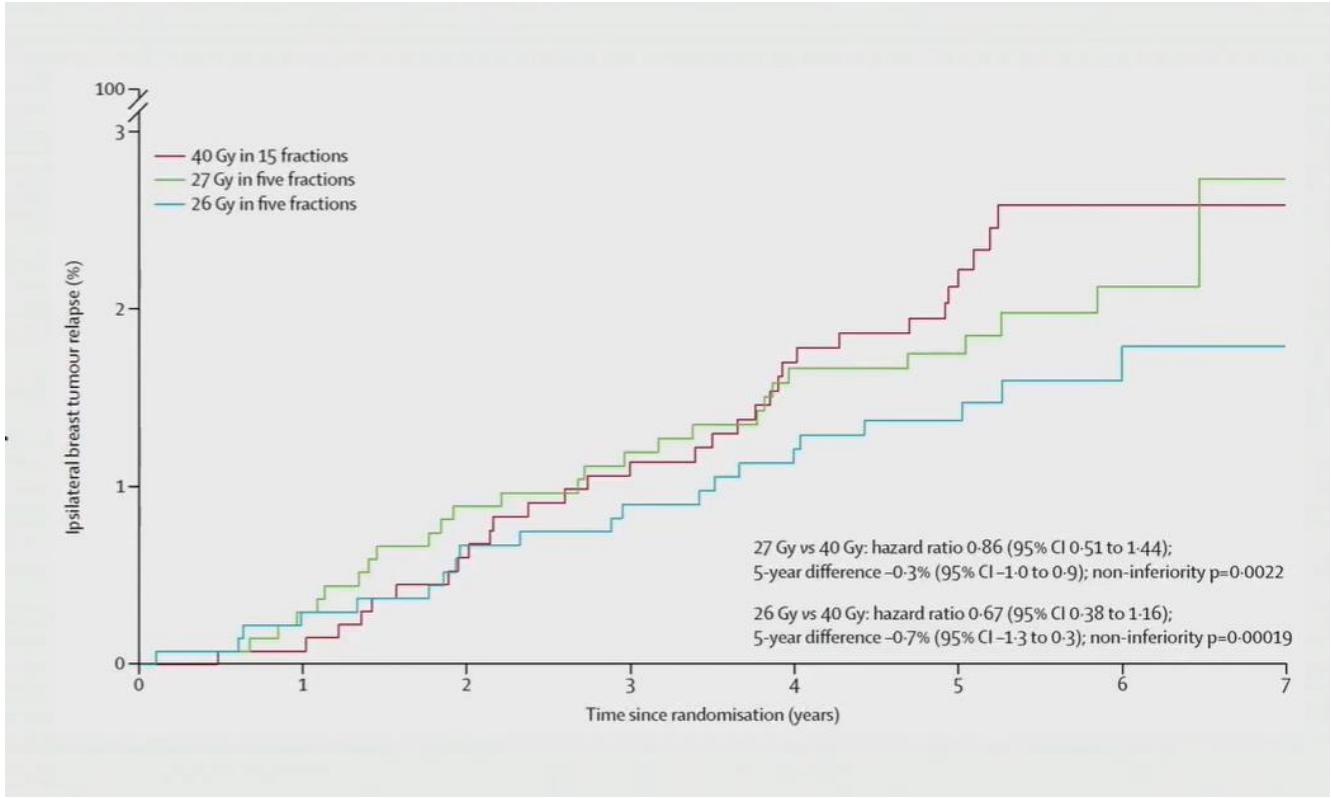
Patient Population

age	%
< 40	1-2
40-50	13
51-60	30
61-70	37
71-80	12

	%
T1a	5
T1b	19
T1c	45
T2	28
T3	1.5
ER+H+	7.5
ER+H-	81
ER-H+	2.4
ER-H-	8

UK FAST FORWARD

5 Year Results



IBTR: 26Gy and 27Gy are not inferior to 40Gy

Brunt et al, Lancet 2020, 395:1613-26

UK Fast Forward

Toxicity

- The absolute incidence of late toxicities was higher in the Ultra-Hypofx arms (most pronounced in the 27Gy arm)

Outcome	40 Gy	27 Gy	26 Gy	P-Value
Induration	0.8%	2.3%	1.6%	0.013
Edema	1.5%	3.4%	2.4%	0.032
Marked hardness	20.4%	27.5%	24.7%	0.048

Ultra-Hypofractionated Whole Breast RT

- The data for ultra-hypofractionated whole breast radiotherapy is promising and shows the 26 Gy in 5 fraction regimen is not inferior to 40Gy in 15fx for local tumor control; however, the data is not as robust as with other fractionations with limited follow-up.

- The incidence of late toxicities such as breast induration, edema and marked hardness does appear to be higher with ultra-hypofx

- We need to emphasize plan homogeneity and minimize hot spots:

$$D_{max} \leq 105\%$$

- Patient selection considerations
  - Given the limited data, the ultra-hypofractionated whole breast regimen is used very selectively
  - Need to be very careful in patients with large breasts/large separations due to increases in hot spots
  - Main consideration is in older patients who have limited access to care and are burdened by a longer duration of treatment.

NCCN Guidelines – Ultra-Hypofractionation

- Ultra-hypofractionated WBRT of 28.5 Gy in 5 (once-a-week) fractions may be considered for selected pts over 50 yrs following BCS with early-stage, node-negative disease, particularly those in whom a boost is not intended.a,b

  - a Alternatively, 26 Gy in 5 daily fractions over one week may be considered, though data beyond 5 years for local relapse or toxicity are not yet available for this regimen. [Murray Brunt A, Haviland JS, Wheatley DA, et al. Hypofractionated breast radiotherapy for 1 week versus 3 weeks (FAST-Forward): 5-year efficacy and latenormal tissue effects results from a multicentre, non-inferiority, randomised, phase 3 trial. Lancet 2020;395:1613-1626.]

  - b Brunt AM, Haviland JS, Sydenham M, et al. Ten-year results of FAST: A randomized controlled trial of 5-fraction whole-breast radiotherapy for early breast cancer. J Clin Oncol 202, 38:3261-3272

Partial Breast Irradiation

External Beam

ASTRO Consensus Guidelines (2017)

APBI

Important to select patients for partial breast RT properly

	Suitable (Pt meets all criteria)	Cautionary (Pt meets all criteria)	Unsuitable (Pt meets any criteria)
Age	≥ 50	40-49	< 40
Tumor Size, T stage	≤ 2 cm, Tis or T1	2.1 – 3 cm, T0 or T2	> 3 cm, T3-T4
N stage, surgery	pN0 (SNBx or ALND)		pN1-3 or no nodal surgery
Margins	Negative (≤ 2 mm)	Close (< 2 mm)	Positive
LVSI	No	Limited/focal	Extensive
ER status	Positive	Negative	
Centricity	Unicentric	Microscopic multi-centricity	Present
Histology	Invasive ductal or favorable histology	Invasive lobular	
EIC or Pure DCIS	If screen detected, low to intermediate grade, size ≤2.5 cm, resected with margins negative at >3mm	≤ 3 cm and does not meet criteria for suitable	> 3 cm
Associated LCIS	Allowed		
Neoadjuvant Tx	Not allowed		Received

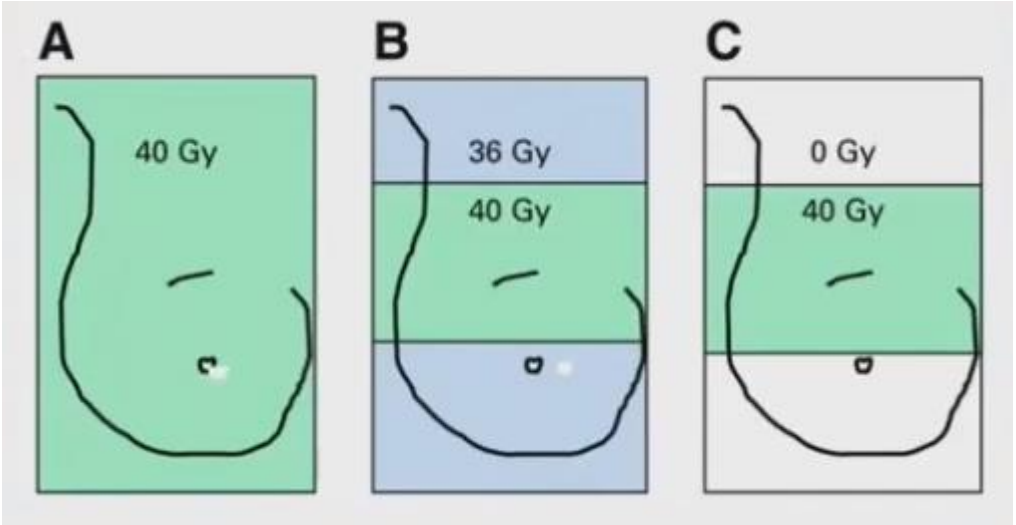
Partial Breast Irradiation (PBI)

Study	N	Median Age (range)	Size	Node+	ER+	Her2+	G1-2	Median FU (years)	LR	Cosmesis
RAPID (50/25 or 42.5/16 vs 38.5/10 BID)	2135	61 [IQ 54-68]	71% <1.5 cm	<1%	91%	6%	84%	8.6	2.8% 3%	PBI worse
NSABP B39 (50/25 vs 38.5/10 BID)	4216	54 (38% <50)	58% <2 cm	10%	81%	---	63%	10.2	3.9% 4.6%	PBI worse
IMPORT-LOW (40/15 WBI vs PBI)	2018	62 (57-67)	1.2 cm (0.8-1.6 cm)	2-4%	95%	4%	90%	6.2	1.1% 0.5%	PBI better
Florence 50/25 vs 30/5 QOD	520	63 (40-85)	82-85% <2 cm	7-12%	95%	3-6%	87-90%	10.7	2.5% 3.7%	PBI better

IMPORT LOW

PBI

- Partial breast radiotherapy after breast conserving surgery for patients with early breast cancer in the UK
- Randomized Phase III Non-Inferiority Trial
  - 40Gy in 15 whole breast
  - 36Gy in 15 fx whole breast (reduced dose) with 40Gy to partial breast
  - 40Gy in15 fx partial breast



- N = 2016, 2007-2016

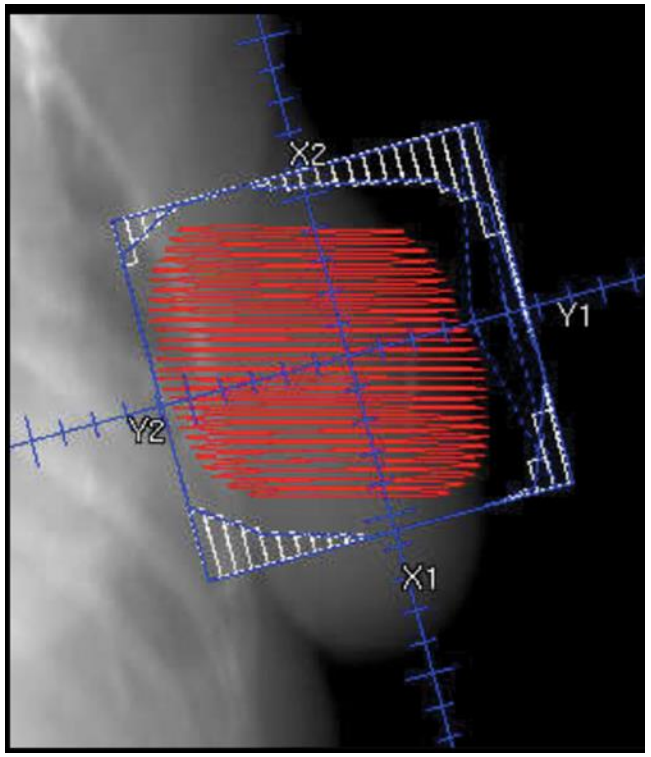
- > 50 yo, IDC, ≤3cm, 0-3 nodes, margin ≥ 2mm
  - 97% pN0
  - >90% LVI neg
  - 95% ER+
  - 94-96% Her2 neg
  - ~90% Grade 1 or 2

- Primary endpoint was IBTR;
- Secondary endpoint: NTE, regional and distant mets, DFS, OS

Coles et al, Lancet 2017

IMPORT LOW

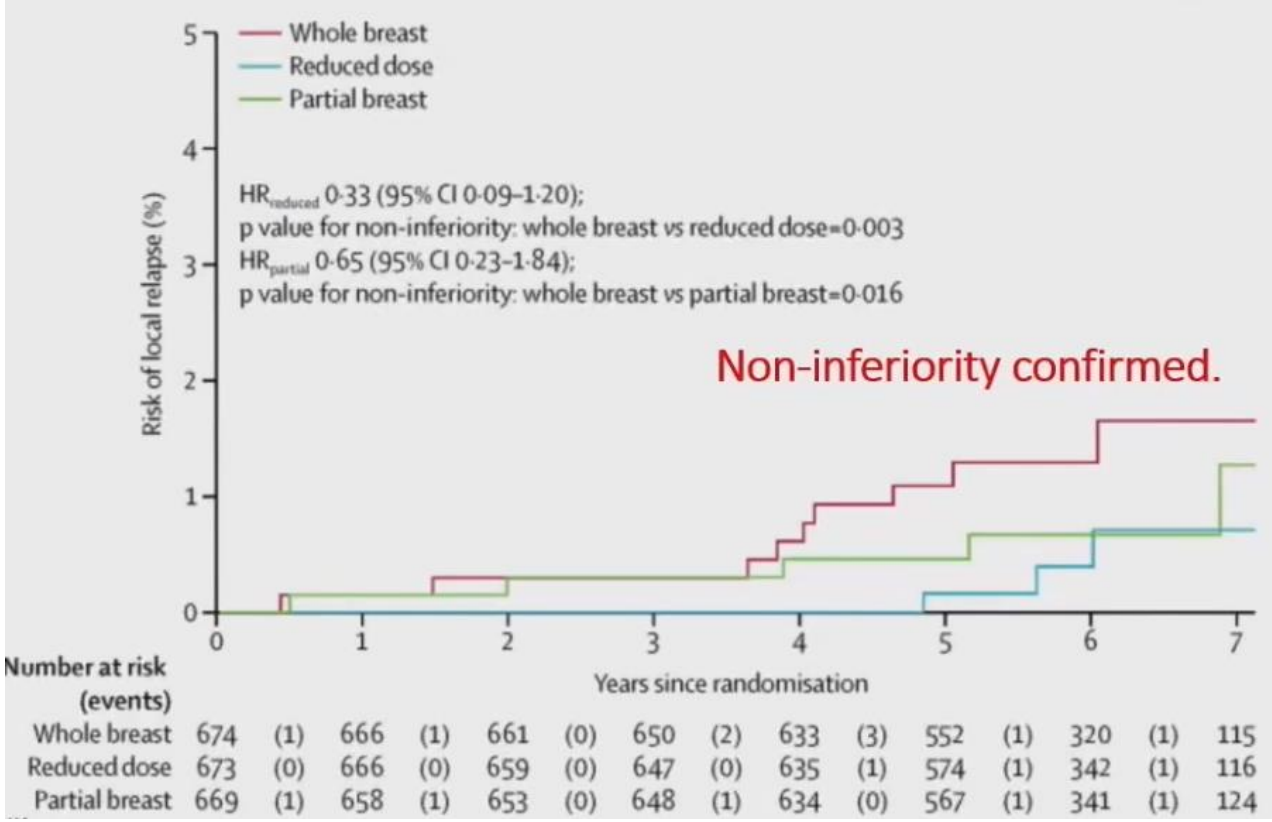
- Radiotherapy Target Volumes for Partial Breast Group
  - CTV = Tumor bed + 1.5cm
  - PTV = CTV + 5-10mm



IMPORT LOW

- 5 Year of IBTR (Lancet 2017)
  - 1.1% vs 0.2% vs 0.5%

- 10 Year IBTR (ASTRO Oct 2023, Abstract)
  - 2.8% vs 1.9% vs 2.8%



IMPORT LOW

Toxicity

5 Year Toxicity: Photographic, patient, and clinical assessments recorded similar adverse effects after reduced-dose or partial-breast radiotherapy, including two patient domains achieving statistically significantly lower adverse effects

-change in breast appearance [p=0·007 for partial-breast]

-breast harder or firmer [p=0·002 for reduced-dose and p<0·0001 for partial-breast]) compared with whole-breast radiotherapy.

10 Year NTE-free estimates per clinician assessment

70.5% vs 75.3% vs 75.5%

"*Based on data from the 10-year analysis of IMPORT LOW, Kirby said 15 fractions of 40 Gy external beam partial-breast radiotherapy remains the standard of care in the UK for patients with lower-risk breast cancer who are more than 50 years of age, have grade 1/2 disease, are T≤30 mm, are node negative, and are HER2-negative*."

This is NOT the standard of care in the USA

Florence Trial

APBI

- Phase III Trial of Accelerated Partial-Breast Irradiation Compared With Whole-Breast Irradiation for Early Breast Cancer
  - Whole Breast Irradiation (WBI): 50Gy in 25 fx
  - APBI: 30Gy in 5 fx qod IMRT
- N = 520
- Eligibility: Age ≥ 40, tumor size ≤2.5cm, neg margins, pN0, DCIS not allowed
- Median Follow-up of 10.7 yrs

Meattini et al, JCO 2020

Florence Trial

APBI

Modality	N	Median f/u	10-year failure rates		Survival rates
			Ipsilat. br	Contralat. br	Overall
WBI (50Gy / 25fx)	260	10.7 yrs	2.50%	3.20%	91.90%
APBI (30Gy / 5fx) IMRT	260	10.7 yrs	3.70%	0.80%	91.90%

Similar rates of breast tumor recurrence and survival

Toxicity/Cosmesis

Florence Trial

- APBI had less acute and late toxicity
- APBI had better cosmesis rated by patient and MD

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	—	—	

Florence Trial

APBI

Acute Toxicity

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 Toxicity

Assessment	APBI (n = 246)	WBI (n = 260)	P
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)	

Florence Trial Update: Daily treatment (not qod)

APBI

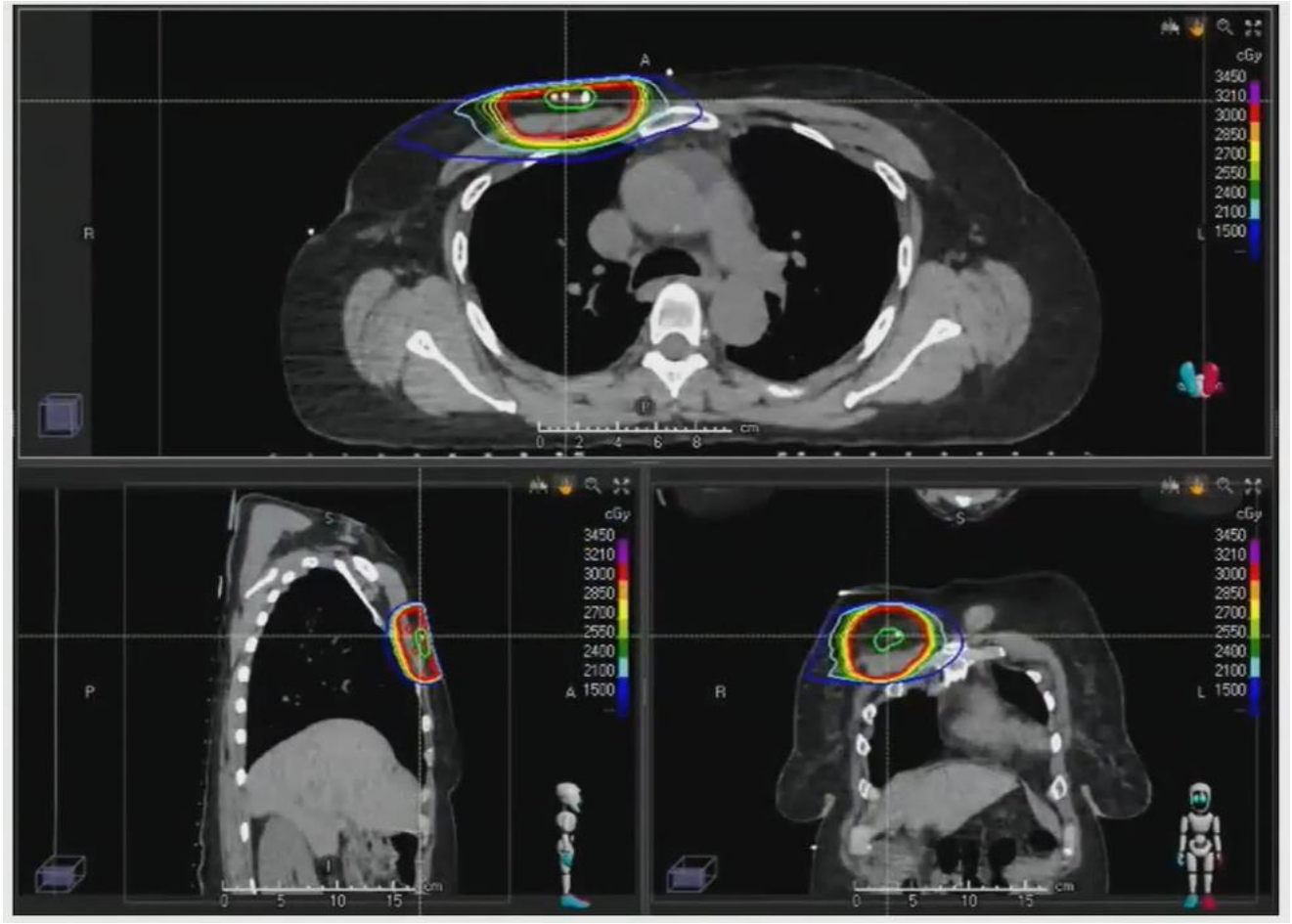
- Update on the Florence Trial Technique
- N = 50, treated on consecutive days, VMAT, CTV = 1.5cm, PTV = 0.5cm
- Median follow-up 4.5 yrs showed similar excellent toxicity profile

	Grade 1	Grade 2+
Acute	32% (N=16)	0%
Late	16% (N=8)	0%

Marrazzo et al, Practical Radiation Onc, 2023

Florence Trial IMRT

APBI



PRINCIPLES OF RADIATION THERAPY

Accelerated Partial Breast Irradiation (APBI)/Partial Breast Irradiation (PBI)

- **APBI/PBI offers comparable local control to WBRT in selected low-risk patients with early-stage breast cancer. However, the optimal external beam-APBI/PBI technique/fractionation for minimizing long-term cosmesis effects has not been determined.**
  - **Patients are encouraged to participate in clinical trials.**
  - **The NCCN Panel recommends APBI/PBI for any patient who is *BRCA* negative and meets the 2016 ASTRO criteria.**
    The 2016 ASTRO criteria define patients aged ≥50 years to be considered "suitable" for APBI/PBI if:
    - **Invasive ductal carcinoma measuring ≤2 cm (pT1 disease) with negative margin widths of ≥2 mm, no LVI, and ER-positive**
      or
    - **Low/intermediate nuclear grade, screening-detected DCIS measuring size ≤2.5 cm with negative margin widths of ≥3 mm.**
- **RT dosing:**

Regimen	Method	Reference
30 Gy/5 fractions QOD (preferred)	**External beam RT (EBRT)[e]**	Livi L, Meattini I, Marrazzo L, et al. Accelerated partial breast irradiation using intensity-modulated radiotherapy versus whole breast irradiation: 5-year survival analysis of a phase 3 randomised controlled trial. Eur J Cancer 2015;51:451-463. Meattini I, Marrazzo L, Saieva C, et al. 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. J Clin Oncol 2020;38:4175-4183.
40 Gy/15 fractions	**EBRT**	Coles CE, Griffin CL, Kirby AM, et al. 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. Lancet 2017;390:1048-1060.
34 Gy/10 fractions BID	**Balloon/ Interstitial**	Vicini FA, Cecchini RS, White JR, et al. Long-term primary results of accelerated partial breast irradiation after BCS for early-stage breast cancer: a randomised, phase 3, equivalence trial. Lancet 2019;394:2155-2164.
38.5 Gy/10 fractions BID	**EBRT**	Whelan TJ, Julian JA, Berrang TS, et al. External beam accelerated partial breast irradiation versus whole breast irradiation after breast conserving surgery in women with ductal carcinoma in situ and node-negative breast cancer (RAPID): a randomised controlled trial. Lancet 2019;394:2165-2172.